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CONTINUING MEDICAL EDUCATION

Acquired syphilis: update on clinical, diagnostic and therapeutic aspects*☆

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Abstract Syphilis, an infection caused by *Treponema pallidum*, transmitted predominantly through sexual contact, affects several organs, causing skin, mucous membranes and systemic lesions. Despite being a secular disease, it still poses a major challenge for the public health system, since the number of cases continues to increase after years of warnings from the scientific community. Recognizing the clinical manifestations is essential for formulating the clinical hypothesis and diagnostic confirmation with complementary exams. However, recognizing skin lesions is not always simple, given the diversity of clinical manifestations which resemble other diseases. This review presents an overview of the disease, with current epidemiological data, a representation of the various clinical manifestations, a description of the pertinent diagnostic methods for laboratory confirmation, and appropriate therapeutic approaches for each clinical form.
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Introduction

Since it was first described, syphilis has been considered a stigmatizing disease. Each country whose population was affected blamed neighboring nations, or those considered enemies, for spreading the disease. Thus, syphilis has been

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called the French or Gallic disease, the Neapolitan disease, the Polish disease, and the Turkish disease. In the 16th century, the term ''*lues venera*'' (venereal plague) was used by French physician Jean Fernelius. The term ''syphilis'' was coined in 1530 by Italian poet and physician Girolamo Fracastoro in his work ''*Syphilis, sive Morbus Gallicus*'', in which the author presents a character named Syphilus, a shepherd who, resentful of the lack of rain, blames the god Apollo for the drought that ravages his flock and afflicts his people. As punishment for his insolence, Apollo curses him with a painful and disfiguring disease that ends up spreading to the entire population, the disease of Syphilus.[1,2]

Syphilis is a chronic infectious disease caused by *Treponema pallidum*, which is transmitted predominantly through sexual contact and can exhibit cutaneous and systemic manifestations. Congenital transmission occurs via the transplacental or hematogenous routes and, less frequently, transmission can also occur through blood transfusions, sharing of needles, or accidental inoculation. Humans are the only known reservoir.[3]

It is characterized by long latency periods and the ability to reach multiple organs, causing cutaneous, mucous, cardiovascular, and neurological lesions. In most cases, syphilis begins with an ulcerative lesion in the anogenital region. As with all sexually transmitted diseases, this ulceration is very important in the transmission of the human immunodeficiency virus (HIV) and hepatitis B and C. This situation is aggravated because syphilitic genital ulcers are densely infiltrated with lymphocytes (the main target cells for HIV infection) and, therefore, provide an important gateway for the acquisition of this virus.[3]

When it affects pregnant women, if left untreated, it can result in miscarriage, prematurity, neonatal death, or late manifestations of the conceptus, such as deafness, developmental deficit, and bone malformations, characterizing congenital syphilis.

There are three main theories to explain the origin of syphilis. The first, called the ''pre-Columbian theory'', states that ''*pinta*'' was the first treponematosis to appear in the Afro-Asian region, approximately in the year 15,000 BCE, with an animal as a reservoir. Mutations in the treponema are believed to have given rise to ''yaws'' in 10,000 BCE, ''endemic syphilis'' in 7,000 BCE, and ''sexually transmitted syphilis'' in 3,000 BCE in Southwestern Asia, from where it spread to Europe and the rest of the world.[1,2]

The ''unitary theory,'' considered by some authors to be a variation of the pre-Columbian hypothesis, argues that treponematoses have always had a global distribution. According to this theory, both syphilis and non-sexually transmitted treponematoses are geographic variants of the same original infection. The different clinical manifestations would be justified by adaptive responses of the treponema to the environment, cultural differences, and the miscegenation of people.[1,2]

Finally, the ''Colombian theory'', a very popular hypothesis accepted by many authors, states that the disease emerged in the Americas and was brought to Europe by the navigators of Christopher Columbus' fleet in 1493. This theory is supported mainly by the finding of skeletal lesions characteristic of the diagnosis of syphilis in multiple fossils, thousands of years old, found in several regions of the Americas. In Europe, the findings compatible with the presence of syphilitic alterations in human fossils are controversial and inconclusive.[1,2]

Epidemiology

In Brazil, acquired syphilis mainly affects adolescents and young adults between the ages of 15 and 25, but it can occur in any age group. The disease has no racial, gender, or socioeconomic class predilection; it is mainly associated with risky sexual behavior. It does not confer immunity, and reinfection and superinfection can occur.[3]

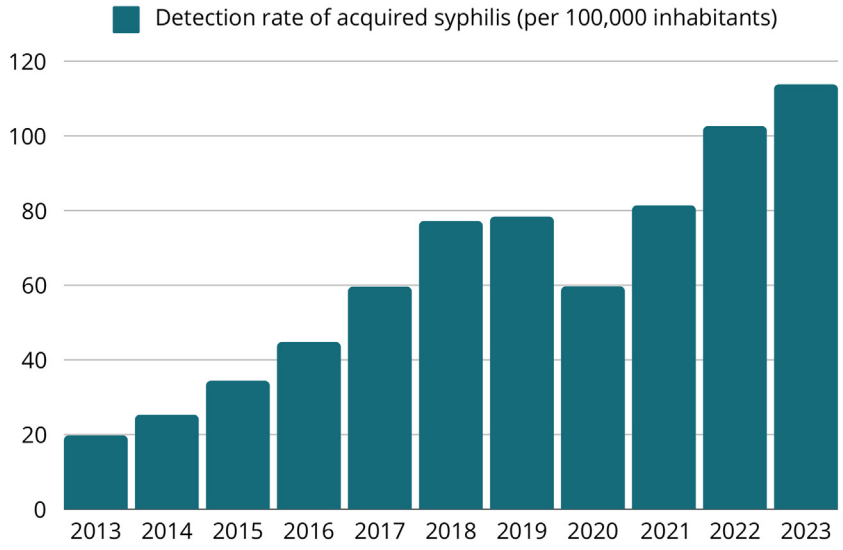
According to the Sexually Transmitted Diseases Bulletin of the Centers for Disease Control and Prevention (CDC) of the United States, the incidence of primary and secondary syphilis has been increasing since 2001. In 2022, 59,016 cases of primary and secondary syphilis were reported in the United States (17.7 cases per 100,000 inhabitants). From 2021 to 2022, the national rate of primary and secondary syphilis among women increased by 19.2%, with increases observed in 36 states and the District of Columbia. The increase in the number of cases among women is simultaneous to that observed among men who have sex only with women, reflecting the expanding epidemic of heterosexual syphilis in the United States. It should also be noted that men who have sex with men (MSM) account for almost half (45.1%) of all cases of primary and secondary syphilis in men in 2022.[4]

In Brazil, it became mandatory for acquired syphilis to be reported nationwide in 2010. In the period from 2012 to June 2023, 1,340,090 cases of acquired syphilis were reported in the Notifiable Diseases Information System (Sinan, *Sistema de Informação de Agravos de Notificação*). Of the total number of cases: 50.0% occurred in the southeastern region; 22.3% in the southern region; 14.2% in the northeastern region; 7.2% in the midwestern region and 6.3% in the northern region.[3]

In 2022, 213,129 cases were reported in Brazil, of which 101,909 (47.8%) were reported in the southeastern region, 46,291 (21.7%) in the southern region, 32,084 (15.0%) in the northeastern region, 16,327 (7.7%) in the northern region and 16,518 (7.8%) in the midwestern region.[3]

Between 2012 and 2018, the acquired syphilis detection rate showed an average annual growth of 35.4%. However, in 2019, this rate remained stable and declined by 23.4% in 2020, due to the COVID-2019 pandemic. From 2021 onwards, the detection rate increased again, to a level higher than the pre-pandemic period across the country, with an increase of 23.0% in the last year (Fig. 1). Between 2021 and 2022, the growth in the rate was 26.6% (from 76.3 to 96.6 cases per 100,000 inhabitants) in the midwestern region; 24.9% (from 90.4 to 112.9 cases per 100,000 inhabitants) in the southeastern region; 24.1% (from 121.8 to 151.2 cases per 100,000 inhabitants) in the southern region; 19.1% (from 72.5 to 86.3 cases per 100,000 inhabitants) in the northern region and 15.9% (from 47.8 to 55.4 cases per 100,000 inhabitants) in the northeastern region.[3]

In 2022, 61.3% of the total cases occurred in men and the detection rates reached 234.5 and 142.5 cases per 100,000 inhabitants in the age groups of 20 to 29 years and 30 to 39 years, respectively. The number of syphilis cases in female adolescents was higher than in male individuals, represent-



Source: Notifiable Diseases Information System (Sinan), updated on 06/30/2023.

Fig. 1 Longitudinal series of acquired syphilis incidence in Brazil since 2013, showing a progressive increase in case notifications with the exception of 2020, where there was an impact due to the COVID-19 pandemic.

ing a M:F ratio of 0.7 (seven men with syphilis for every ten women with syphilis) in 2022. On the other hand, in that same year, in the age groups of 20 to 29 years and 30 to 39 years, the M:F ratio was 1.8 (18 men with syphilis for every ten women) and 2.0 (20 men for every 10 women with syphilis), respectively.[3]

In the last 20 years, there has been a significant increase in the number of syphilis cases worldwide. This increase can be attributed to several factors, such as changes in sexual behavior and decreased fear of becoming infected with HIV. During this period, some studies identified an increase in the incidence of syphilis and other sexually transmitted infections (STIs) in individuals using HIV Pre-Exposure Prophylaxis (PREP).[5,6]

In patients living with HIV (PLHIV), the prevalence of syphilis is significantly higher than in the general population. In a Chinese study, the HIV/syphilis coinfection rate was 20%. Other studies carried out in Turkey and Brazil showed rates of 23% and 11%, respectively. In the subgroup analysis, the three studies showed a significantly increased prevalence of coinfection in the MSM group, when compared to the heterosexual group. In all three studies, the majority of patients had latent syphilis.[7–9]

Etiopathogenesis

Treponema pallidum, the etiological agent of syphilis, is a gram-negative, facultative anaerobic, and catalase-negative bacterium of the spirochete group. The treponema penetrates the host through small fissures in the skin or mucosa produced by sexual activity. Once inside the epithelium, it multiplies locally and invades the lymphatic vessels and bloodstream. During this invasion process, this extracellular bacterium avoids recognition and adaptation of the host's innate and adaptive immune responses due to the low expression of proteins in the plasma membrane, as well as the absence of lipopolysaccharides (highly pro-inflammatory glycolipids found in Gram-negative bacteria) and expression of lipoproteins capable of activating macrophages and dendritic cells.[10,11]

Although the scarcity of PAMPs (Pathogen-Associated Molecular Patterns, molecules recognized by the innate immune system as a sign of invasion by a group of pathogenic agents) in the outer membrane of *T. pallidum* allows the bacterium to replicate locally and disseminate, the detection of pathogens by the host is eventually triggered. The treponema is captured by dendritic cells that migrate to the lymph nodes and have treponemal antigens to B and T lymphocytes. Antibodies are produced that favor the degradation of spirochetes by phagocytes, releasing lipopeptides (cardiolipins) and other PAMPs that activate T cells, ending the cascade of cytokine production such as IFN-γ, tumor necrosis factor (TNF), and IL-6.[10,11]

Clinical aspects

An old Latin saying ''*Omnis syphiliticus mendax (est)*'' (''Every syphilitic is a liar'') is relevant even today: one cannot be certain that the case history reported by the patient with syphilis is in accordance with the facts, especially with regard to sexual history.[12–14] Thus, recognizing the clinical manifestations is essential for developing the clinical hypothesis and confirming the diagnosis with complementary exams. However, recognizing syphilis lesions is not always easy, since the disease is considered by most researchers to be a great imitator, given the diversity of clinical manifestations that resemble other diseases.[15,16]

The association between syphilis and HIV is well established, with syphilis increasing the risk of HIV transmission. HIV infection, in turn, can alter the natural history of syphilis, making it difficult to diagnose the disease caused by *T. pallidum*.[17,18] Along the descriptions of the clinical forms, the particularities of the patient who has co-infection with these two STIs will be highlighted.

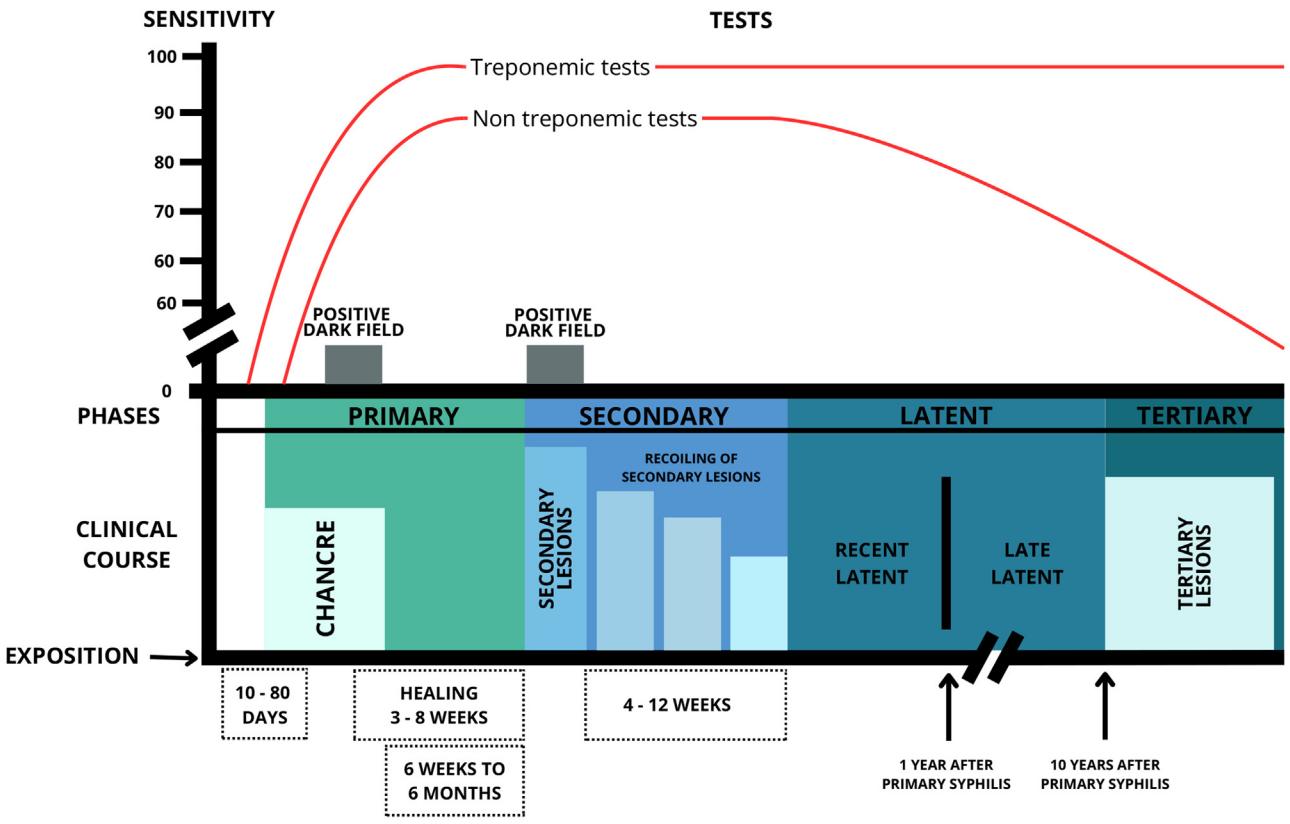


Fig. 2 Schematic diagram of the clinical and laboratory course of untreated acquired syphilis. Adapted from: Clinical Protocol and Therapeutical Guidelines for Comprehensive Care for People with Sexually Transmitted Infections (STIs), Ministry of Health, Brazil, 2021.

Syphilis can be classified into several forms, either by the time of disease progression (early, up to one year after infection, and late, after one year) or by stages of evolution (primary, secondary, latent and tertiary).[19] To facilitate the characterization of clinical aspects, the classification by stages of evolution was chosen in this paper (Fig. 2).

Primary syphilis

The classic lesion of primary syphilis is a painless chancre, which identifies the site of inoculation of the bacteria in the body. It occurs between three and 90 days after inoculation (mean 21 days) and develops from a macule to a papule and nodule, which loses its covering epithelium and then becomes an erosion. The loss of deeper tissue produces an ulcer, typically measuring 0.5 to 3 cm in diameter. The central surface of the chancre is clean, smooth, and mucoid and produces a slight serous exudate. The border is usually flat and well-demarcated. Chancres are hardened to the touch due to the surrounding edema and lymphocytic infiltration, giving rise to the name ''hard chancre'' for this lesion which is usually solitary. The occurrence of two or more lesions may be related to coinfection with the HIV virus (Fig. 3). It is important to note that protosyphiloma can often go unnoticed by the patient due to the painless nature of the lesion.[18,20–24]

When the chancre is located in an area with excess skin, such as the foreskin, the presence of the ''flag sign'' or ''button sign'', known in English as the ''dory flop sign'', is evidenced during a dynamic inspection, which depicts this infiltrate and solid lesion moving *en masse*.[22,24,25]

Chancre redux is an uncommon form of recurrent syphilis, in which a primary syphilis lesion, usually a hard chancre, reappears at the site of the original infection after the person has been inadequately treated or has not completed treatment for the disease. This recurrence occurs due to the persistence of the bacterium *Treponema pallidum* in the body. Chancre redux is a sign that the infection has not been completely eradicated and that treatment should be reassessed to ensure the complete elimination of syphilis. It is currently a less common manifestation since treatments with appropriate antibiotics are usually effective. It should not be confused with *pseudochancre redux*, a clinical manifestation of tertiary syphilis that presents a gummatous lesion at the site of the original chancre.[22,26]

Primary infection in the glans penis may present with multiple erosions of treponematous origin characterized by flat, whitish elevations that are easily confused with fungal or irritative etiology. This atypical presentation is named after its first descriptor, ''Follmann's syphilitic balanitis'', and may develop before or after the appearance of the primary chancre.[15,21,24,27–29]

Another manifestation that has been observed at this stage is the presence of painless, hardened ''cord-like'' lesions on palpation, located mainly in the balanopreputial sulcus (Fig. 3).[15]

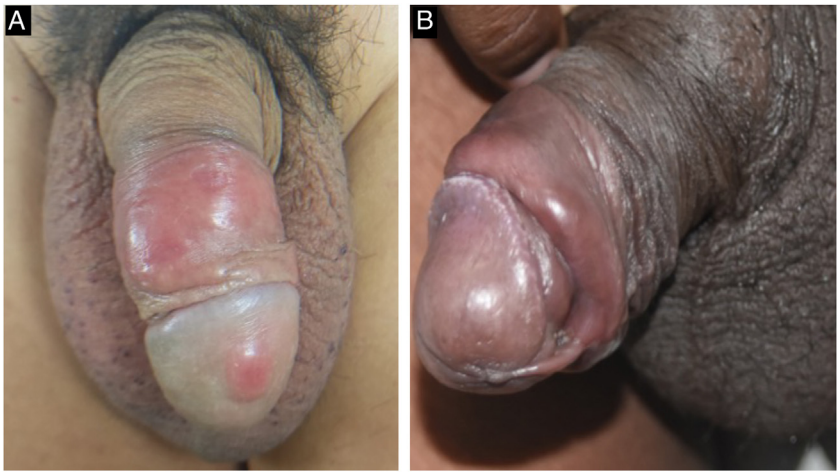


Fig. 3 Primary syphilis lesions on the penis. A- Patient with a hard chancre lesion on the glans and two on the foreskin. B- Note the presence of a ''cord-like'' lesion in the balanopreputial sulcus (which can also be seen in patient A).

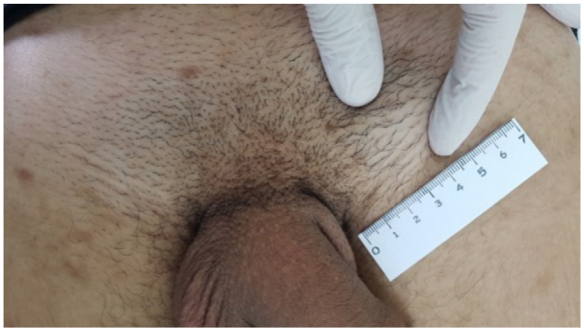


Fig. 4 Patient with primary syphilis showing left inguinal lymph node enlargement.

The inguinal lymphadenopathy seen at this stage has been highlighted by secular researchers. It follows the lymphatic drainage chain, preferably unilateral and inflammatory, but may be bilateral: lesions on the penis and vaginal labia tend to show inguinal lymphadenopathy; anal lesions, lymphadenopathy in the pelvic and abdominal cavity; oral and labial lesions, submandibular and cervical lymphadenopathy. The presence of regional lymph node enlargement is so frequent that Fournier stated that this manifestation ''follows the chancre as the shadow follows the body'', and it is also recognized as ''mayor lymph node'' (Fig. 4).[21,24]

Co-infection of *Treponema pallidum* and *Haemophilus ducreyi*, in the same ulcerated lesion, constitutes Rollet's mixed chancre (hard chancre associated with soft chancre). This situation is rarely described in the literature; perhaps not because of the rarity of the condition, but because of the syndromic approach to genital ulcers, with a low frequency of microbial investigation for both agents in the lesion.[30]

The primary form of syphilis can last between two and eight weeks and tends to disappear spontaneously, regardless of treatment, usually without leaving a scar.[21,22,24,31] The chancre is identified in about 15% of patients at the beginning of the secondary stage, and cases that exhibit this concomitant primary and secondary phase should be investigated for immunosuppression as co-infection with the HIV virus.[20,21,32]

Secondary syphilis

In untreated individuals, treponemas proliferate in the chancre and migrate via the lymphatic system to the bloodstream, from where they spread throughout the body. Signs and symptoms appear on average between six weeks and six months after infection and last on average between four and 12 weeks.[19,22,31]

Rarely, primary manifestations may be absent during the course of the infection, with the first signs of the disease represented by lesions in the secondary phase. This situation is known as ''decapitated syphilis'', due to the absence of the primary phase during the course of the disease, or ''*syphilis d'emblée*'', a French word that refers to the immediacy of the infection. It occurs when the treponema is inoculated directly into the bloodstream, such as untested blood transfusions or the sharing of needles.[33]

Thus, while primary syphilis represents the site of inoculation of the bacteria in the epithelium, secondary syphilis corresponds to the spread of the parasite throughout the host body. The most frequent clinical manifestations are mucocutaneous lesions (90%–97%), with or without systemic signs and symptoms, such as generalized lymphadenopathy (50%–85%), malaise (13%–20%), sore throat (15%–30%), body aches (6%–8%), and low-grade fever (5%–8%).[22,26,31,34] Involvement of internal organs such as the lungs, stomach, and intestine has been described, causing a variety of symptoms and clinical presentations.[35,36]

The cutaneous and mucous lesions of secondary syphilis are called syphilides, and the first cutaneous sign of this stage is a macular rash (''syphilitic roseola'') that is ephemeral, lasting a few days, with a pale erythema (''cupric erythema'' or ''sad erythema'') and a preference for the trunk and limbs. In melanodermic individuals, the roseola phase may go unnoticed, due to the difficulty in perceiving mild erythema on dark skin (Fig. 5).[22,26,31] Residual hypochromic macules (leukoderma) may follow the regression of the roseola stage and are more common in women

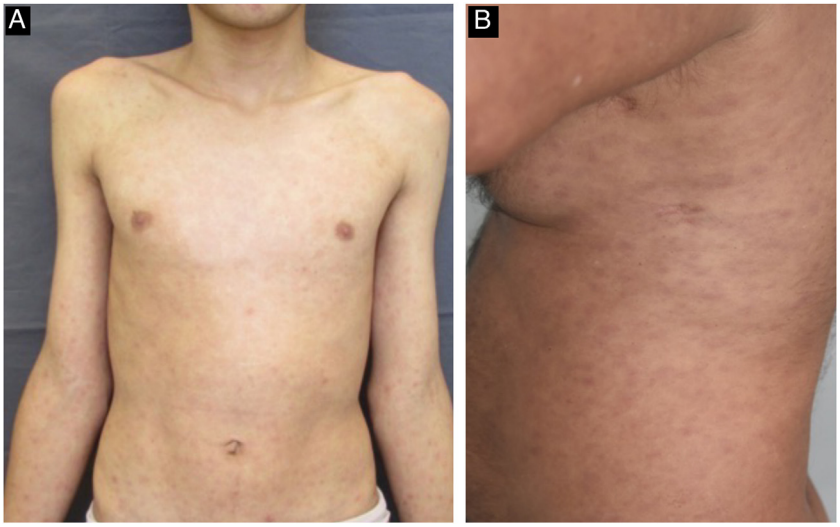


Fig. 5 Patients with secondary syphilis; A- Patient presenting with syphilitic roseola; B- Patient with maculopapular exanthema on the trunk.

with dark hair. Because it typically affects the neck and shoulders, it is known as the ''necklace of Venus'' and may be misdiagnosed as vitiligo.[26,34]

The initial macular stage develops into a symmetrical papular eruption including the palms and soles, usually desquamative, with peripheral desquamation called ''Biett collarette'' (Fig. 6), which may also be smooth, follicular or, rarely, pustular. In this phase, the erythema is more intense and evident (Fig. 5). Vesicles do not usually occur, although vesicopustular lesions are seen on rare occasions and are common on the palms and soles (Fig. 7).[22,26,31] Despite the extent of the lesions, pruritus is not a characteristic symptom of the disease. However, recent studies indicate that these eruptive lesions may be associated with this symptom, prominent eosinophilic infiltration on histopathology.[37,38]

With persistence of the skin lesions, regression occurs in the affected body area, localized in segments of the skin, while the elementary lesions increase to nodules and plaques and may acquire a corymbiform aspect (Fig. 8).[32,39,40] In skinfold areas, nodular and tumor lesions, called flat condylomas, appear (Fig. 9), which are extremely infectious and can be confused with condyloma acuminata caused by the human papillomavirus (HPV).[31,34,41,42] In

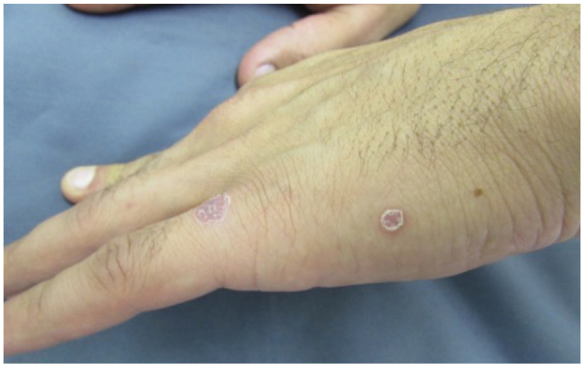


Fig. 6 Detail of a lesion in a patient with secondary syphilis, showing Biet's collarette.

melanodermic patients, facial lesions may acquire annular and circinate configurations, being called elegant or beautiful syphilides (Fig. 10).[26]

Mucosal lesions are also common and characteristic of secondary syphilis, occurring in 30% to 40% of patients. Mucosal patches are exudative, oval, well-demarcated

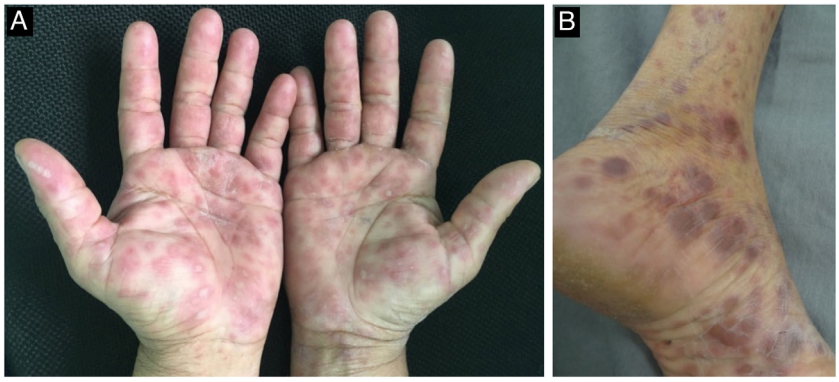


Fig. 7 Palmoplantar involvement of secondary syphilis. A- Erythematous papules and macules on the palmar region; B- Erythematous-violaceous papular lesions on the plantar region.

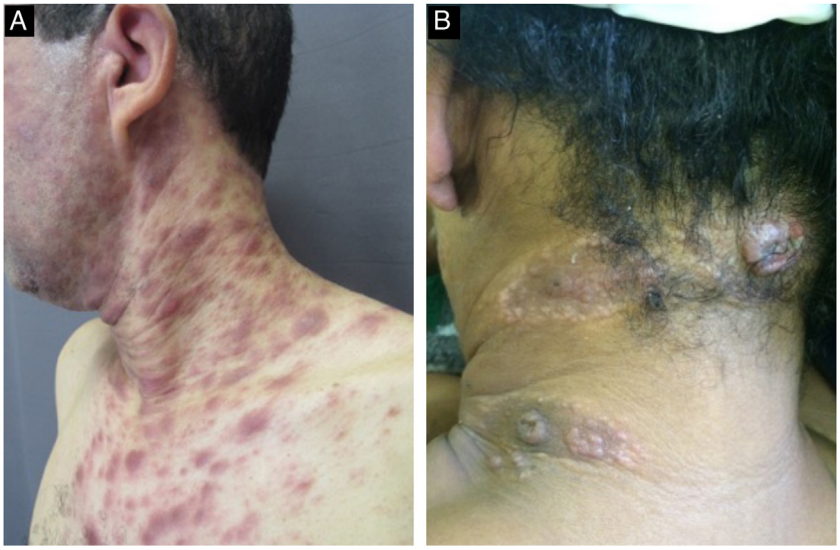


Fig. 8 A and B-Patients with secondary syphilis showing nodular lesions in the cervical region; B- Lesions in corymbiform arrangement.

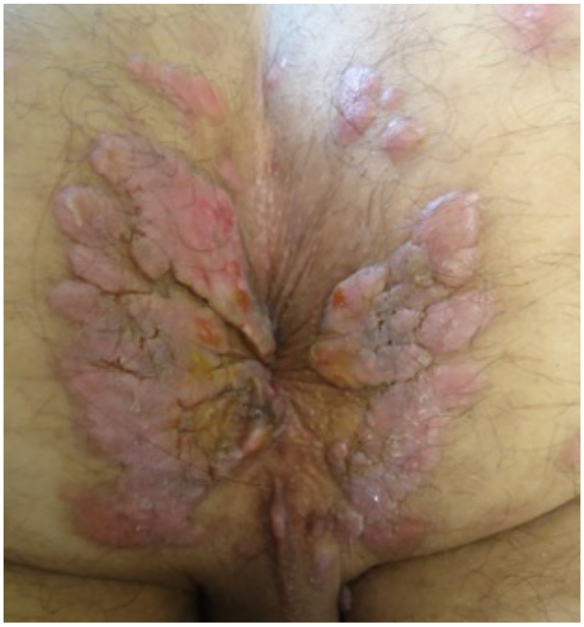


Fig. 9 Perianal flat condyloma, clinical manifestation of secondary syphilis that is a differential diagnosis for condyloma acuminata.

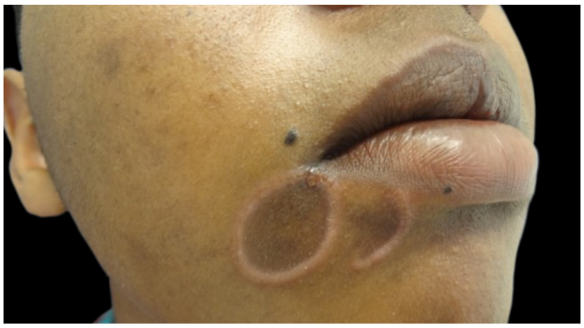


Fig. 10 Perioral elegant syphilides, clinical manifestation of secondary syphilis in an Afro-descendant patient.

erosions with erythematous borders, most commonly manifesting on the tongue and lips; like flat condyloma, these lesions are highly infectious. Occasionally, erosions can coalesce and take on a linear outline, and are called ''snail-track ulcers''. In the oral commissures, lesions may appear as papules with transverse erosions called ''split papules'' (Fig. 11).[22,34,43,44]

During the secondary stage, in addition to the involvement of the skin and mucous membranes, changes in the skin appendages may also occur, i.e., hair and nails. Hair loss is also called syphilitic alopecia (SA) which is classified as symptomatic (when lesions occur on the scalp associated with hair loss) and essential, when only hair loss occurs. The latter is subdivided into three patterns: patchy alopecia, diffuse alopecia, and mixed alopecia. Essential patchy SA is the most common and is characterized by the presence of multiple patches of non-cicatricial alopecia, without inflammation or desquamation; it is also called ''moth-eaten'' or ''in clearings'' (Fig. 12). It occurs mainly in the parieto-occipital region, but can also appear on the beard, eyelashes, armpits, pubis, trunk and legs. Diffuse essential SA is caused by telogen effluvium-like hair loss (Fig. 13), while mixed essential SA is characterized by small irregular patches that develop together with diffuse alopecia.[45,46] In addition to these clinical forms, some authors describe a fourth pattern of essential SA: the alopecia areata-like type (Fig. 13).[22]

Changes in the nail apparatus are rare. Changes in the nail plate result from the involvement of the matrix, causing fragility, splitting, fissures, corrosion, onycholysis, Beau's lines, onychomadesis (Fig. 14), and even loss of the nail. The onset of a periungual and/or subungual inflammatory leads to syphilitic paronychia, with erythema and edema in the periungual tissues.[22,47]

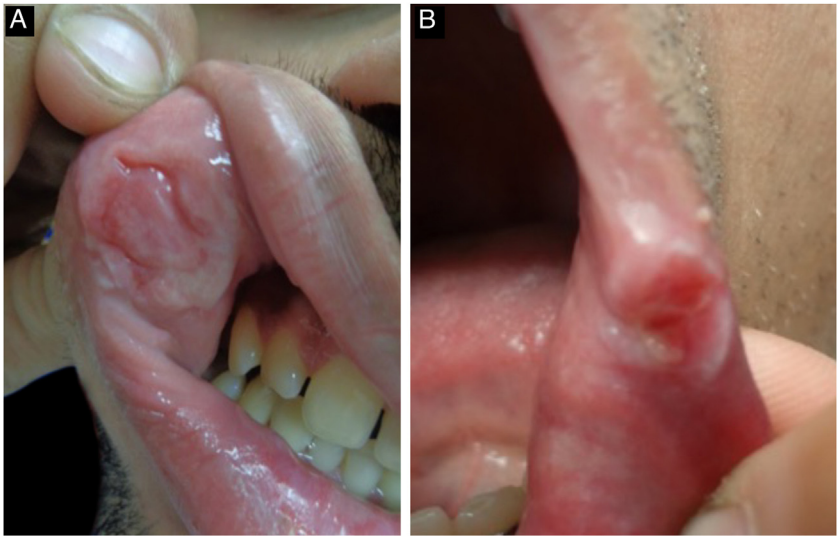


Fig. 11 Oral mucosal lesions of secondary syphilis. A- linear erosions on the labial mucosa (''snail track ulcers''); B Papules with transverse erosions on the labial commissure (''split papules'').

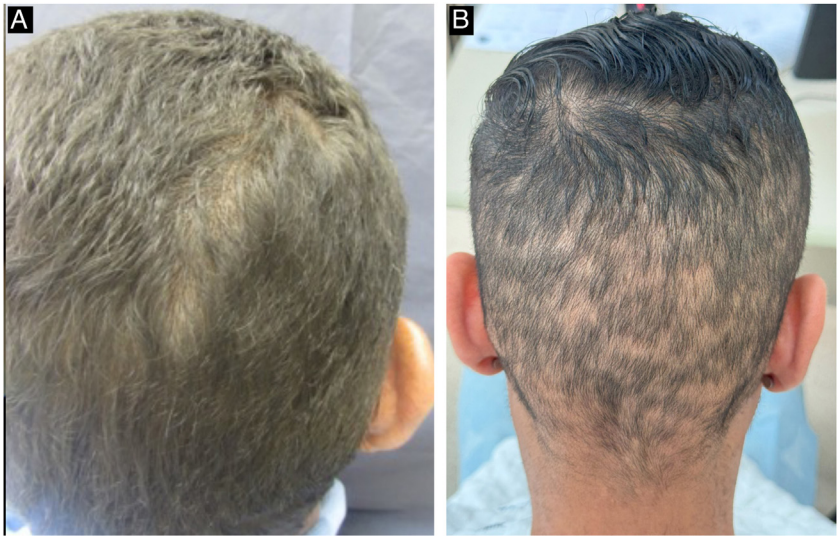


Fig. 12 Alopecia in secondary syphilis. A - ''moth-eaten'' pattern; B - ''clearing'' pattern.

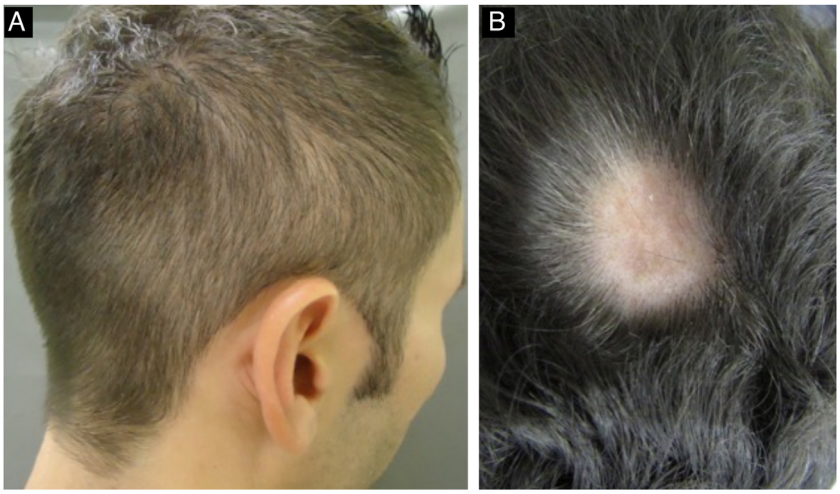


Fig. 13 Manifestations of alopecia in secondary syphilis. A - Diffuse essential alopecia; B- Alopecia areata-like lesion.

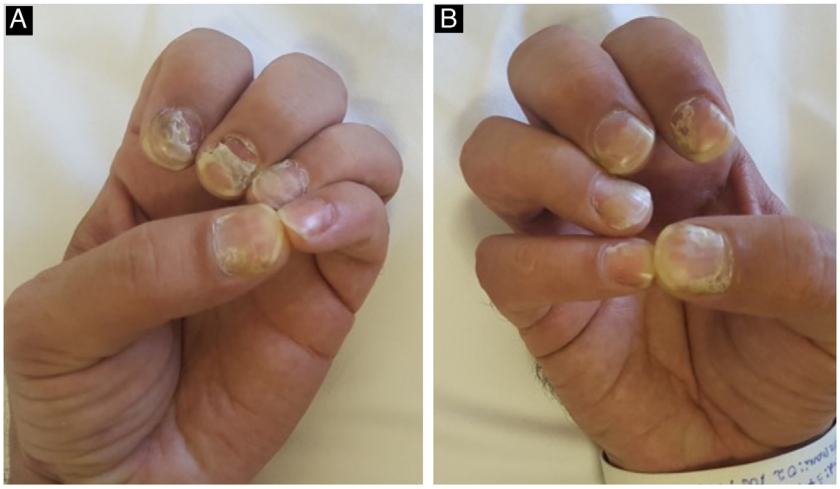


Fig. 14 A and B- Involvement of the nail apparatus in a patient with secondary syphilis, characterized by onychomadesis.

Malignant syphilis, or nodular-ulcerative syphilis, is typically characterized by the presence of asymmetric ulcers or round necrotic plaques with lamellar or rupioid crusts located on the scalp, face, trunk, and extremities. Oral ulcers may occur with systemic signs and symptoms; fever, headache, and lymphadenopathy are usually present. It is more common in patients with HIV infection and low CD4 + T lymphocyte counts, malnourished patients, MSM, patients with previous syphilis, diabetes mellitus, tuberculosis, and alcohol abuse.[14,18,20,22]

In addition to the skin manifestations caused directly by *Treponema pallidum* infection, there are reports of skin reactions secondary to the bacteria, considered reactive conditions, more common during secondary syphilis. The cases described are more common in patients with HIV coinfection and range from manifestations of Sweet's syndrome to erythema multiforme.[16,48,49] They are diagnosed by associating the clinical picture with positive serology for syphilis and a reactive pattern on histopathology, with no evidence of the bacteria by immunohistochemistry. Unlike the Jarisch-Herxheimer condition, where exacerbation of skin lesions occurs after the institution of treatment, these reactive conditions appear before and improve after treatment.

Secondary lesions tend to regress spontaneously after four to 12 weeks. Most lesions do not leave scars, but anetoderma may occur, most commonly reported in patients with positive HIV serology.[16,39]

Neurosyphilis and ocular syphilis

Neurosyphilis results from treponemal invasion of the CNS, with an increasing number of cases described in immunocompetent and heterosexual patients.[13] Invasion of the meninges by treponema occurs early, 12 to 18 months after infection, but disappears in 70% of the cases without treatment. When the infection persists, which occurs during any stage of the infection, neurosyphilis appears, which may be symptomatic or asymptomatic.[26]

In asymptomatic neurosyphilis, the patient does not have clinical manifestations, but there is evidence of CNS infection in the analysis of the cerebrospinal fluid (reactive VDRL, elevated protein or leukocyte count).[22]

In symptomatic neurosyphilis, the clinical picture is usually nonspecific and can develop at any time during the natural history of the disease. In patients with coinfection with the HIV virus, a more fulminant course usually occurs, while in immunocompetent individuals, the disease is more insidious, with nonspecific symptoms.[13,22]

The most common first symptoms of neurosyphilis are mild meningeal signs, such as headache and nausea. Cranial nerve palsies may occur, with unilateral or bilateral hearing loss, with or without tinnitus and nystagmus. Meningitis can cause fever, meningismus, and photophobia. In meningovascular syphilis, arteritis causes infarctions in the brain or spinal cord. The investigation of recent neurosyphilis should be performed in syphilitic patients with neurological or ocular signs, immunosuppression, or those who do not reduce VDRL levels after treatment.

Late symptomatic neurosyphilis, rare in the antibiotic era, most commonly causes general paresis (also called general paresis of the insane or paralytic dementia), which can manifest with dementia, seizures, and other psychiatric manifestations. Tabes dorsalis may also occur, which can manifest as fulminant pain, urinary incontinence, and erectile dysfunction, ataxia, Argyll-Robinson pupil (reacting to accommodation/focusing, but not to light), loss of reflexes, and impaired vibratory sensation.[22] In a review of 137 articles, reporting on 286 patients with neurosyphilis, only 10% had coinfection with HIV. The most relevant clinical presentations were general paresis (49% of cases), manifested by cognitive impairment and psychiatric changes, followed by syphilitic meningitis (22%), meningovascular syphilis (11.5%), tabes dorsalis (11.5%), parenchymal gummas (3.5%) and epilepsy (2%).[13]

Ocular syphilis is considered a type of neurosyphilis. While most cases of syphilitic meningitis are accompanied by ocular involvement, ocular syphilis is not always accompanied by syphilitic meningitis.[13,50] Therefore, ocular syphilis should be suspected in any case of unexplained ocular inflammation. The disease can occur up to six weeks after transmission and be the only presenting feature of systemic syphilis. The most common findings are panuveitis

and posterior uveitis, but ocular involvement can manifest in a variety of ways, affecting both the anterior segment of the eye (conjunctiva, cornea, and sclera) and the posterior segment (choroid and retina). These manifestations rarely occur in the primary stage, except as hard chancres located on the eyelid and conjunctiva. Keratitis, iris nodules, iridocyclitis, episcleritis, and scleritis may occur early in secondary syphilis, and chorioretinitis and vitritis may occur later in the secondary stage. However, ocular involvement is even more frequent in the late, latent, and tertiary stages of syphilis.[50,51]

Latent syphilis

Latent syphilis occurs when serological tests are positive but there is no clinical evidence of infection. The period of up to one year after contamination is classified as early latent syphilis, and from this date onwards, late latent syphilis begins.[51]

The diagnosis is generally based on situations in which tests are requested for patients without clinical symptoms, such as sexual partners or contacts of patients diagnosed with syphilis, routine or screening tests.

Based on studies that monitored the natural progression of syphilis, one-third of patients who had regression of secondary lesions achieve clinical and serological cure, one-third will develop no symptoms but will maintain positive non-treponemal serological tests, and the last third will have the disease progress to tertiary syphilis years to decades after the infection.[52,53]

Tertiary syphilis

Tertiary syphilis is rare and may manifest with mucocutaneous, cardiac, ophthalmological, neurological, skeletal, or gastric alterations.[54–57] The incidence of this phase of the disease decreased drastically with the use of penicillin in the treatment of the initial phases.[58]

The skin is the most affected organ. Cutaneous tertiary syphilis is classified as nodular and gummatous; the former shows dermo-epidermal involvement and the latter, hypodermal involvement.[54,57] The lesions of the nodular form are generally asymmetrical, chronic in appearance, painless, and slowly progressive in growth. The nodules are usually located on the face, interscapular areas, and extremities. These lesions may remain isolated, coalesce to form plaques or tumors, be distributed in an arciform pattern, or ulcerate.[54,58–61] The gummatous form presents as firm and painless subcutaneous nodules, usually solitary, which later develop ulcerations and drain solid necrotic material. These are destructive lesions that can invade deep into the tissue and bone, healing with deeply retracted scars. Due to the frequent involvement of the cardiovascular system, especially the ascending aorta, adequate cardiac investigation is recommended.[13,22,54,58,62,63]

Syphilis in patients living with HIV

It is known that syphilis can increase the risk of acquiring and transmitting HIV by two to ninefold, mainly due to genital ulcers; while HIV infection and antiretroviral therapy (ART) can, in additionally facilitate infection due to a decrease in the immune response mediated by T cells, and alter the natural history and clinical presentation of syphilis.[64,65]

In patients living with HIV, syphilis can present concomitant clinical manifestations of two different clinical stages, in addition to a greater predisposition to the formation of atypical, larger, and deeper lesions. Multiple primary chancres, a greater number of ulcerated lesions, and early malignant syphilis in the secondary form, systemic manifestations such as uveitis, aortitis, encephalitis, arthritis, gastric and hepatic involvement can be observed. The rate of neurological involvement is high, and this involvement is often early and asymptomatic.[66–68]

Diagnosis

The diagnosis of syphilis is clinical, laboratory based and can be confirmed by several methods, such as direct treponema detection and serological reactions (immunological tests), with the latter being the most commonly used. Direct treponema detection can be performed by dark-field microscopy (sensitivity of 74% to 86%), direct immunofluorescence, rapid tests, examination of stained material, and histopathological examination of tissue biopsies. These tests are called direct tests and are extremely important for confirmation of the diagnosis of syphilis.

Direct tests can be performed in symptomatic cases of syphilis, but in most cases, they are performed to investigate conditions with nonspecific skin lesions. Dark-field treponema testing, stained material examination, and histopathological examination of tissue biopsies are important for confirming the diagnosis of symptomatic phases of the disease. However, these tests are not always available in most health services. Immunological tests can be used in both the symptomatic and asymptomatic (latency) phases. The most commonly used immunological tests in clinical practice are treponemal and non-treponemal tests.

According to the Clinical Protocol and Therapeutic Guidelines for Comprehensive Care for People with Sexually Transmitted Infections (STIs) of the Brazilian Ministry of Health, asymptomatic individuals with a reactive non-treponemal test of any titer and a reactive treponemal test, with no record of previous treatment, should be considered as having acquired syphilis. This is an operational recommendation, since false-reactive tests can occur, and antimicrobial treatments for other diseases can also cure syphilis, in addition to the fact that there may be spontaneous resolution of untreated treponematosis. Likewise, individuals symptomatic for syphilis, with at least one reactive test, treponemal or not, are also considered cases of acquired syphilis.[19]

Whenever possible, it is recommended to start disease investigation with a treponemal test, preferably the rapid test (RT), and then associate a non-treponemal test to increase the positive predictive value of the initial test. It should be noted that rapid tests are not available in all health centers in the country.

Immunological tests

Treponemal tests

Treponemal tests detect specific antibodies produced during the initial immune response against *T. pallidum* antigens.

Therefore, they are the first to test positive and remain positive, in most cases, for the rest of the patient life, even after specific treatment. Individuals who have already been treated but who have a clinical epidemiological picture suggestive of syphilis should undergo a non-treponemal test for possible new treatment.

Hemagglutination and passive hemagglutination tests (PHAT), indirect immunofluorescence test (Fluorescent Treponemal Antibody – Absorption test – FTA-Abs), chemiluminescence, indirect immunoenzymatic assay, and rapid tests are treponemal tests. RT mainly uses the lateral flow immunochromatography or dual path platform (DPP) methodology and, according to the Brazilian Ministry of Health, is available in all health units of the Unified Health System (SUS, *Sistema Único de Saúde*).

Non-treponemal tests

Non-treponemal tests become positive after the host immune recognition of the treponema (action of anti-treponemal antibodies) when the bacteria degrade and release cardiolipin components from its cell structure. Thus, these tests detect non-specific anticardiolipin antibodies for *T. pallidum* antigens and are important both for diagnosis and for monitoring treatment response. The Venereal Disease Research Laboratory (VDRL), RPR (Rapid Test Reagin), and TRUST (Toluidine Red Unheated Serum Test) are examples of these tests.

Whenever a non-treponemal test is performed, it is important that the pure and diluted sample are employed, due to the prozone phenomenon.[69] In the case of test reactivity, the sample should be diluted, using a dilution factor of two, until the last dilution at which there is no more reactivity in the test. The final result of the reactive tests should be expressed in titers (1:2, 1:4, 1:8, etc.). Non-treponemal tests, although nonspecific, can be used in diagnosis (as a first test or complementary test) and also to monitor the response to treatment and control of cure. An adequate drop in titers is an indication of treatment success.

VDRL and RPR are useful and inexpensive tests, but non-specific; false-reactive results, although rare, can occur. Anticardiolipin antibodies may be present in lepromatous leprosy, Lyme disease, HTLV-1, malaria, tuberculosis, and other diseases in which lysis of cells containing cardiolipin in their structure occurs, such as occurs in several pathogens and the human cell itself (Table 1)[70]. In patients with a clinical picture suspicious for syphilis and nonspecific tests with low titers, treponemal tests with high specificity, such as RT, FTA-Abs, PHAT, MHA-TP or others, should be performed. If none of these tests are not available, it is advisable that the patient be treated as having syphilis.

The isolated analysis of a single non-treponemal test result can lead to diagnostic errors and inappropriate therapeutic decisions. High titers in adequately treated patients may be gradually decreasing and low titers can occur in three situations: recent infection, late stages of infection (late syphilis), individuals adequately treated but who have not yet tested negative or won't do so (serological scarring). The term serological scarring is used in situations in which an individual, proven to have been treated, shows a decrease in titer in two dilutions, but still shows reactivity in the tests. In these cases, treponemal tests tend to be reactive, and quantitative non-treponemal tests will show low titers ($\leq$ 1:4).

Table 1 Situations that can generate false-reactive results in non-treponemal tests.

Situations that may generate transient false-reactive results	Situations that can generate permanent false-reactive results
After immunizations	Injectable drug use
After myocardial infarction	Autoimmune diseases (antiphospholipid antibody syndrome and systemic lupus erythematosus, others)
Some febrile infectious diseases (malaria, hepatitis, varicella, measles, infectious mononucleosis, others)	HIV infection
Pregnancy	Leprosy
	Chronic hepatitis
	Advanced age

Source: Ministry of Health, 2021.[70]

Overall, immunological tests for syphilis in PLHIV do not show any changes when compared to those performed in non-coinfected individuals. However, in PLHIV, there may be a higher frequency of high dilutions, a longer time for tests to become negative, as well as false-negative results.

In patients not co-infected with HIV, the false-negative rate varies from 1% to 2%, while in co-infected patients, it can reach 10%. This may occur due to patients inability to develop an immune response with the production of antibodies against *T. pallidum*. Regarding non-treponemal tests (VDRL), there is also an increase in false negative results related to the prozone effect. This effect may be related to the anomalous function of B cells, leading to an increase in the production of antibodies against various antigens.[71]

According to the Clinical Protocol and Therapeutic Guidelines for the Management of HIV Infection in Adults, from the Ministry of Health, in the clinical follow-up of PLHIV, an immunological test should be performed every six months or after any risky sexual exposure.[72]

Dark-field treponema testing

Dark-field treponema testing is performed using samples obtained from primary or secondary syphilis lesions in adults or children. Collecting material from lesions in the oral cavity is not recommended due to the presence of other saprophytic spirochetes, which may result in false reactive tests. The test should be performed on fresh serous exudate from the lesion, avoiding erythrocytes, other organisms, and tissue debris. The collected sample should be immediately analysed on a microscope with a dark-field condenser to look for *T. pallidum*.

To identify *T. pallidum* using this technique, it is important to observe its morphology, size and typical movements. The spirochete consists of a thin organism (0.10 to 0.18 μm wide), 6 to 20 μm long, and with 8 to 14 regular spirals. *T.*

pallidum moves quickly, and it is possible to identify elongation and shortening movements; it rotates relatively slowly around its longitudinal axis, in addition to performing syncopated flexions and twists in its central region. In dark-field microscopy, the spirochetes appear as bright, white spiral bodies, illuminated against a black background.[70]

Examination of stained material

Sample collection for this examination should be performed in the same manner as is done for direct examination of fresh material. The available methods are:

- Fontana-Tribondeau method: the sample is smeared and allowed to dry on the slide and then stained with silver nitrate, which will impregnate the cell wall of the treponema, thus allowing the parasite to be seen under the microscope;
- Burri method: this technique is performed with Indian ink;
- Giemsa staining method: *T. pallidum* is stained faintly (palely), making it difficult to observe the spirochetes;
- Levaduti method: uses silver in histological sections.

The sensitivity of the examination of stained material is lower than that of dark-field treponema testing.[70]

CSF puncture

CSF puncture is indicated in cases of suspected neurosyphilis and is recommended in specific situations for syphilis diagnosis and patient follow-up after treatment has been implemented. It is worth emphasizing that the CSF analysis should include cytology, biochemical profile, and VDRL in the material.

Lumbar puncture is indicated for neurosyphilis screening in the following cases: presence of neurological or ophthalmological symptoms; in case of evidence of active tertiary syphilis and after clinical treatment failure without sexual re-exposure. For PLHIV, lumbar puncture is indicated after treatment failure, regardless of sexual history.

In the follow-up of a patient initially treated without neurosyphilis, the procedure is recommended when there is suspected treatment failure, that is, failure of the non-treponemal test to decrease in outpatient serological follow-up. The puncture is also indicated for patients diagnosed with neurosyphilis; the test should be performed every six months for laboratory monitoring of their infection. Treated patients who do not show the expected reduction in VDRL titers should be investigated through cerebrospinal fluid puncture for the possibility of neurosyphilis.

Although it is not considered a criterion by the Ministry of Health, some authors indicate the test for all patients coinfected with syphilis and HIV, regardless of the clinical stage, who meet at least one of the following criteria:[72]

- Neurological or ophthalmological signs or symptoms;
- Evidence of active tertiary syphilis (aortitis, syphilitic gummas, among others);
- After clinical treatment failure.

Treatment

Penicillin has been the mainstay of syphilis treatment since it became widely available in the late 1940s. *T. pallidum* resistance to penicillin has never been reported, and since this bacterium divides more slowly than others, it is necessary to maintain penicillin levels in the blood above the minimum inhibitory concentration for at least ten days, which is achieved by administering a single intramuscular injection of long-acting benzathine penicillin G.

Primary, secondary and recent latent syphilis

The first-line antibiotic is benzathine penicillin G, at a total dose of 2,400,000 IU, administered intramuscularly, in a single dose – 1,200,000 IU is administered in each buttock. Doxycycline, 100 mg, orally, twice a day for 15 days, can be used as an alternative drug (except for pregnant women).

Tertiary and late latent syphilis

Benzathine penicillin G is administered at a dose of 2,400,000 IU intramuscularly once a week for three weeks, totaling 7,200,000 IU. The alternative drug is doxycycline, 100 mg, orally, twice a day for 30 days (except for pregnant women). For pregnant women proven to be allergic to penicillin, desensitization is recommended in a tertiary service, according to existing protocols.

Individuals with a confirmed diagnosis of syphilis, whose disease duration cannot be determined, should be treated as having late latent syphilis.

Neurosyphilis and ocular syphilis

Since penicillin G benzathine is not able to cross the blood-brain barrier, treatment of neurosyphilis is hospital-based, carried out with crystalline penicillin, 18-24 million units per day, intravenously, administered in doses of 3-4 million IU, every four hours, for 14 days. Ceftriaxone, 2 g, administered intravenously, once a day, can be used as an alternative drug, for ten to 14 days.

Children

Recent phase: penicillin G benzathine, 50,000 IU/kg, intramuscularly, in a single dose.

Late phase: 50,000 IU/kg of body weight, intramuscularly, once a week, for three weeks.[73]

According to the Brazilian Ministry of Health, given the current epidemiological scenario, immediate treatment with benzathine benzylpenicillin is recommended, after only one reactive test for syphilis (treponemal or non-treponemal test) for the following situations (regardless of the presence of signs and symptoms of syphilis): pregnant women, victims of sexual violence, individuals with a chance of loss to follow-up, individuals with signs and/or symptoms of primary or secondary syphilis and individuals without a previous diagnosis of syphilis.

People living with HIV

In PLHIV, treatment should be carried out in a similar way to that of non-co-infected individuals. To date, in Brazil, there is no evidence of *T. pallidum* resistance to benzathine penicillin.

In PLHIV with early syphilis, there may be an increased risk of neurological complications and higher rates of inadequate serological response following the use of recommended regimens. Although data are limited, no syphilis treatment regimen has been shown to be more effective in preventing neurosyphilis in PLHIV than the syphilis regimens recommended for the general population.[74]

Careful follow-up after therapy is essential, and the use of antiretroviral therapy according to current HIV guidelines may improve clinical outcomes among people co-infected with HIV and syphilis. Differences in treatment response in HIV-syphilis co-infected patients may not apply to those with virological suppression of HIV.[74]

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction is characterized by the exacerbation of pre-existing skin lesions, associated with pain or pruritus, general malaise, fever, chills, headache, and arthralgia. This clinical picture is due to the massive destruction of treponemes by treatment, which causes an antigen storm in the host that induces an inflammatory response in the same proportions. Thus, it is more common in the treatment of secondary forms, mainly those with high titers in non-treponemal tests, and can occur during the 24 hours after the first dose of penicillin. This picture usually regresses spontaneously in 24 to 48 hours. If necessary, analgesics can be used.[75]

The main differential diagnosis is allergy to benzathine penicillin. However, this condition is rare and is usually characterized by the presence of urticarial lesions.

Monitoring after treatment

Non-treponemal tests are important in monitoring the cure of patients and should be performed three, six and 12 months after treatment.

An adequate immunological response to treatment is accepted when there is a decrease in the titer of two dilutions of non-treponemal tests within six months in individuals with recent syphilis, and two dilutions within twelve months in cases of late syphilis.[76] Seroreversion (non-reactive non-treponemal test) or progression to serological scarring may occur. Negative treponemal tests are not expected after the patient is cured.

Patients, including people living with HIV, should be monitored after completing treatment for syphilis using a non-treponemal test, preferably the same diagnostic method, every three months until the 12th month of patient follow-up, and every six months until the 24th month for patients whose tests were not negative. Pregnant women should be tested monthly.

Control actions

One of the pillars of the control actions for acquired syphilis is the continuous encouragement of educational activities for all STIs, encouraging their prevention through the use of condoms. Early diagnosis of the disease should be encouraged by expanding the supply of rapid tests in the public health system. It is also important that health professionals, especially those working in primary care, receive continous training for early diagnosis, correct treatment, adequate follow-up, and reporting of syphilis cases.[77]

Evaluation and treatment of sexual partners are crucial for interrupting the chain of syphilis transmission. For partners that report exposure to a person with syphilis, within 90 days, it is recommended that these sexual partners be offered presumptive treatment (regardless of the clinical stage or signs and symptoms), with a single dose of benzathine benzylpenicillin 2.4 million IU, IM (1.2 million IU in each buttock).

In addition to promoting safe sex based on condom use, other prevention measures are important and complementary to safe sexual practices, such as immunization for hepatitis B, C, and HPV; knowledge of the HIV serological status of the sexual partner(s); regular testing for HIV and other STIs; testing of all PLHIV; performing preventive exams for cervical cancer; performing pre-exposure prophylaxis (when indicated); access to contraception and conception and performing post-exposure prophylaxis (when indicated).[70]

It should be noted that, in the case of suspected syphilis or when unprotected sexual contact is referred, testing should be indicated, in endemic areas, not only for treponematosis but also for other detectable STIs such as HIV, hepatitis and HTLV.

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Authors' contributions

Carolina Talhari: Design and planning of the study; collection of data, or analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Kaique Arriel: Drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; critical review of the literature.

Marcio Soares Serra: Approval of the final version of the manuscript; drafting and editing of the manuscript or critical review of important intellectual content.

John Verrinder Veasey: Design and planning of the study; collection of data, or analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; effective participation in research

orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Clinical-histological characteristics and therapeutic management of primary cutaneous melanoma in elderly patients☆

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Abstract

Background: Life expectancy is rising in developed countries. The impact of age on melanoma characteristics is unclear, but it seems that melanomas in the elderly have distinct features affecting management and outcomes.

Objectives: To compare clinical and histopathological melanoma characteristics and management in elderly and younger patients.

Methods: A retrospective population-based study analyzed melanomas observed between 2007 and 2022 was made in the southern Seville health area (Spain). Patients were divided into two age groups: <65 and ≥65. Data were collected from clinical histories.

Results: Among 431 primary cutaneous melanomas, 33% were in patients ≥65-years. Elderly patients had more head and neck melanomas (37.8% vs. 14.9%; $p < 0.001$), larger lesions (1.3 vs. 0.9 cm; $p < 0.001$), more ulcerated melanomas (17.8% vs. 8.8%; $p < 0.012$), and higher Breslow thickness (1.03 vs. 0.65 mm; $p < 0.01$) than younger patients. No differences were found in the number of mitoses or histopathological invasions. Stage 0 and more advanced stages (II/III/IV) were observed more frequently in ≥65-years (29.3% vs. 23% and 27.1% vs. 15.7%, $p < 0.001$ respectively). Fewer wide excisions (28.4% vs. 5.6%, $p < 0.001$), sentinel lymph node biopsy (17.6% vs. 2.4%, $p < 0.001$), and adjuvant therapy (11.9% vs. 2.1%, $p < 0.001$) were performed in patients ≥65-years.

Study limitations: The study was retrospective, primarily covering the last 10-years, with older data missing. Key risk factors like the number of nevi and family history of melanoma were not collected.

☆ Study conducted at the Department of Dermatology of Hospital Universitario Virgen de Valme, Sevilla, Spain and Unit of Statistics and Research Methodology of Hospital Universitario Virgen de Valme, Sevilla, Spain.

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Conclusions: Melanomas in the elderly were diagnosed more frequently at initial and advanced stages despite having worse prognostic characteristics compared melanomas occurring in younger people.
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Introduction

As the population continues to age, the healthcare system will be faced with the prospect of caring for an increasing number of elderly individuals with diagnoses of cancer. In 2019, more than a fifth (20.3%) of the population of the European Union (EU) was 65-years of age or older. Projections indicate that the percentage of people aged 80 or over in the EU population will multiply by 2.5 between 2019 and 2100, from 5.8% to 14.6%.[1]

Although the incidence and mortality of cancer are generally higher in the older age groups, few studies have dealt primarily with elderly patients with melanoma. The incidence of melanoma and related mortality has been steadily increasing since 1970 in most developed countries.[2] In the United States, more than 40% of melanomas are diagnosed in patients older than 65-years.[3]

In Spain, incidence rates are estimated to be 16 per 100,000 in 2022. By age, the data indicates that the group that will have a higher incidence is that of ≥65-years, with 44% of the cases; followed by the group of 45- to 64-years, with 39%; and, finally, the one from 0 to 44-years old, with 17%.[4]

Although the number of melanoma cases among the elderly (>65-years) is expected to increase owing to the aging population, the influence of age on the characteristics of and outcome of melanoma is unclear. In the international literature, classical factors associated with a poorer prognosis in older patients are nodular subtype, tumors with a higher Breslow thickness, a higher mitotic index, and more advanced stages at diagnosis.[5–9]

Cancers in the elderly population, including melanoma, have features that distinguish them from cancers in younger cohorts and potentially affect the management and outcome of these patients. The present study evaluated to what extent clinical and histologic characteristics of primary cutaneous melanomas and their therapeutic management differed in older patients (≥65) compared with younger ones (<65).

Methods

Study population

The study was performed with the people belonging to Valme University Hospital, which provides health care to a population of about 500,000 inhabitants in the southern area of Seville (Spain). The study included patients over 18-years old who were diagnosed with primary cutaneous melanoma in the last 15-years and are still being followed up in the Oncological Dermatology unit of Valme Hospital. Patients under 18-years and patients with mucosal, ocular, lymph node melanoma or unknown primary melanoma were excluded.

Data collection

The study was approved by the ethics committee of Valme University Hospital in Seville (code 1765-N-22). Two groups were established in the study according to their age. Older patients were defined as individuals aged 65-years or older and were compared with those younger than 65-years (the younger group) for every study variable.

The following data were collected for each patient: age diagnosis of first/unique melanoma, sex, area of residence (urban vs. rural), sun exposition (occupational vs. recreational), sunburn (ever vs. never), use of UV cabins (ever vs. never) and phototype (I to VI).

The following data were collected for each melanoma: age diagnosis, anatomic location (head and neck, trunk, upper extremities, and lower extremities), lesion size (cm), histologic subtype (including superficial spreading melanoma [SSM], nodular melanoma, lentigo malignant melanoma [LMM], acral lentiginous melanoma, and other or unclassified subtypes), Breslow thickness (mm), ulceration (yes vs. no), mitosis (number), histological invasion (yes vs. no) and associated melanocytic lesion (yes vs. no).

Data of initial management was classified as excision biopsy (indicated done vs. indicated dismissed), definitive margin excision (indicated done vs. indicated dismissed), selective lymph node biopsy (SLNB) (indicated done vs indicated dismissed vs. no indicated), adjuvant therapies (indicated received vs. indicated dismissed vs no indicated). The initial stage was classified as 0, I, II and III/IV stages.

Statistical analysis

Quantitative variables were described as means and standard deviations or with medians and quartiles in the case of asymmetric distributions. Qualitative variables were described as numbers and percentages.

Different hypothesis contrasts were applied depending on the variables at play. Comparisons between the older and younger groups were performed using the χ^2 test, non-asymptotic Monte Carlo methods, Mann-Whitney *U*-test, Anova model, or the Kruskall-Wallis test, as appropriate; $p < 0.05$ was considered statistically significant. In cases of significance, 95% Confidence Intervals were calculated for the mean and prevalence estimates. Statistical analyses were performed using the statistical software IBM SPSS 28.0.

Results

A total of 399 patients with primary cutaneous melanoma were included in the study. A total of 431 primary cuta-

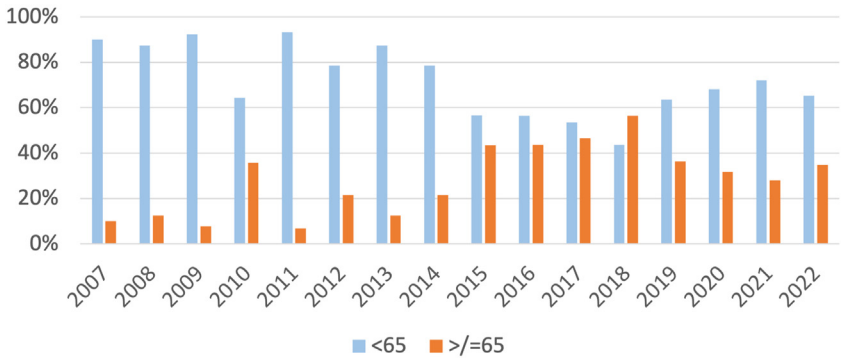

Fig. 1 Evolution of melanoma incidence between 2007–2022 in elderly people.

neous melanomas were analyzed. Between 2007–2022, 33% of patients with primary cutaneous melanoma were older than 65-years. The number of primary melanomas diagnosed in people over 65-years has been increasing from approximately 10% between 2007–2009 to an average of 35% in the last years (Fig. 1).

Patient characteristics

The median age of the first/unique primary melanoma in the older and younger groups was 74 (IQR = 69.75–78.25) and 48 (IQR = 37–55.5), respectively, with statistically significant differences ($p < 0.001$). Significant differences were also observed for sunburns (29.6% vs. 70.4% $p < 0.001$) and use of UV cabins (1% vs. 14.2% $p < 0.001$). No significant differences were observed for sex, area of residence, sun exposition and phototype (Table 1).

Melanoma characteristics

The median age of the melanoma diagnosed in the older and younger groups was 74 (IQR = 70–78) and 48 (IQR = 37.55–75). Melanomas located on the head and neck were more frequent in people over 65-years (37.8% vs. 14.9%; $p < 0.001$). Although the most frequent histological subtype was the SSM, its frequency decreased considerably with respect to those under 65-years (43.4% vs. 74.7% $p < 0001$). There was an increase of LMM (35% vs. 8.7%, $p < 0.001$) and nodular melanoma (14% vs. 9.4%, $p < 0.001$) in elderly patients. Those older than 65-years had larger melanomas (median 1.3 cm (IQR = 1–2) vs. median 0.9 cm (IQR = 0.6–1.3), $p < 0.001$), higher Breslow thickness (median of 1.03 mm (IQR = 0.5–3.1) vs. median of 0.65 (IQR = 0.48–1.3), $p < 0.01$ and more ulcerated melanomas (17.8% vs. 8.8%, $p < 0.012$). There were no differences in the number of mitoses or the presence of invasion (lymphatic, vascular, neural). On the other hand, melanomas in people over 65-years were less frequently associated with previous melanocytic lesions (21.3% vs. 35.5%, $p = 0.022$). Patients under 65-years doubled the risk of presenting a melanocytic lesion prior to melanoma (OR = 2.03 with 95% CI [1.1–3.7], $p < 0.005$), which could be multiplied by almost four (Table 2).

Initial tumor stage and initial management of primary cutaneous melanoma

Stage 0 and more advanced stages (II/III/IV) were observed more frequently in those over 65-years (29.3% vs. 23%, $p < 0.001$ and 27.1% vs. 15.7%, $p < 0.001$ respectively), while the I stage prevailed in those under 65 (61.3% vs. 43.6%, $p < 0.001$) (Table 3). Regarding therapeutic management, there were no differences in the type of primary melanoma resection (NS). However, fewer wide excisions (28.4% vs. 5.6%, $p < 0.001$) and fewer SLNB (17.6% vs. 2.4%, $p < 0.001$) were performed in those over 65-years of age although they were indicated. Furthermore, adjuvant therapy was started less frequently in older patients (11.9% vs. 2.1%, $p < 0.001$).

Discussion

The present results confirm and extend those of previous reports on the presentation and characteristics of melanoma in the elderly. In accordance with the previous series,[5,10,11] the authors observed that the head and neck were the most frequent location in older patients (37.8%). Previous authors have demonstrated that the head and neck location of melanoma increases with age and becomes the most common site after age 70-years.[12,13] It was suggested that this high incidence of head and neck melanoma might be attributable to cumulative photodamage, resulting notably in numerous LMM.

As in previous studies, the most relevant difference in terms of baseline prognostic characteristics between older and younger patients was a higher Breslow thickness in the older group.[5,10–13] Other classic poor prognostic characteristics such as larger clinical size and ulceration were also observed in the elderly group as in previous studies.[5,10–13]

While SSM is the most frequent histological subtype in younger age groups,[8] in the patients ≥65-years, there is disproportionately an excess of both lentigo malignant (35%) and nodular melanomas (14%), with fewer superficial spreading melanomas (43.4%). In most series, (NM ranks second in frequency[5,7]; However, in this study, the percentage of lentigo maligna/melanoma (LM/M) is in second position, which is likely significantly related to chronic sun exposure in the studied region. The excess of LMM seen in this study supports the association between LMM, advanced age and chronically sun-exposed skin.[14]

Table 1 Demographic characteristics of the patients at the time of diagnosis of their first melanoma.

Characteristic	Nº (%)			p
	Total	Age (years)		
	n = 399 (100%)	< 65 n = 265 (66.4%)	≥ 65 n = 134 (33.6%)	
Age (first/unique melanoma)				
Total	399 (100%)	265 (66.4%)	134 (33.6%)	< 0.001
Mean (± SD)	56 (±16.62)	75 (±6.35)	46 (±11.22)	
Median (RIQ)	56 (44–70)	48 (37–55.5)	74 (69.75–78.25)	
Sex				
Total	399 (100%)	265 (66.4%)	134 (33.6%)	NS
Male	199 (49.9%)	134 (50.6%)	65 (48.5%)	
Female	200 (50.1%)	131 (49.4%)	69 (51.5%)	
Area of residence				
Total	398 (99.7%)	265 (66.6%)	133 (33.4%)	NS
Rural	179 (45%)	119 (44.9%)	60 (45.1%)	
Urban	219 (55%)	146 (55.1%)	73 (54.9%)	
Sun exposition				
Total	358 (89.7%)	252 (70.4%)	106 (29.6%)	NS
Occupational/chronic	118 (33%)	76 (30.2%)	42 (39.6%)	
Recreational	240 (67%)	176 (69.8%)	64 (60.4%)	
Sun burns				
Total	358 (89.7%)	252 (70.4%)	106 (29.6%)	<0.001
Ever	224 (62.6%)	177 (70.2%)	47 (44.3%)	
Never	134 (37.4%)	75 (29.8%)	59 (55.7%)	
Use of UV cabins				
Total	348 (87.2%)	247 (71%)	101 (29%)	<0.001
Ever	36 (10.3%)	35 (14.2%)	1 (1.0%)	
Never	312 (89.7%)	212 (85.9%)	100 (99%)	
Phototype				
Total	368 (92.2%)	255 (69.3%)	113 (30.7%)	NS
I	1 (0.3%)	1 (0.4%)	0 (0.0%)	
II	168 (45.7%)	120 (47.1%)	48 (42.5%)	
III	157 (42.7%)	104 (40.8%)	53 (46.9%)	
IV	41 (11.1%)	30 (11.8%)	11 (9.7%)	
V	1 (0.3%)	0 (0.0%)	1 (0.9%)	
VI	0 (0.0%)	0 (0.0%)	0 (0.0%)	

NS, Not Significative.

Stage 0 and more advanced stages (II/III/IV) were observed more frequently in those over 65-years. Among factors that could explain this difference, the frequency of melanomas in situ and the nodular histologic subtype may play an important role. In the present study, melanoma in situ and nodular melanoma occurred 1.3 and 1.5, respectively, as frequently in the older group as in the younger one. The frequency of nodular melanomas, which are highly malignant, and progress rapidly may also explain the higher IV stage in older patients. In addition to nodular melanoma, poor prognosis in the older could be explained because of a delayed diagnosis as a consequence of location in scarcely visible areas (scalp and back), absence of a partner for home examination, poor vision, ignorance of clinical changes, and/or confusion between melanoma and seborrheic keratoses.[12]

Following initial diagnosis, the management of melanoma also appears to be a challenging issue. Chang et al.[15] emphasized that older patients should be treated according to the characteristics and prognostic factors of their tumors and not according to their more advanced age. In contrast to this statement, the authors observed that 28.4% of elderly people, compared with 5.6% of younger ones, had no wide excision.

Among patients typically eligible for SLNB, 17.3% of the older group vs. 2.4% of the younger one underwent this procedure just for the age or comorbidities. This may partly be the result of the limited practical value of SLNB in older patients for whom adjuvant therapies are not an option. However, the role of SLNB in older patients is contentious given their limited life expectancy and the presence of other competing causes of mortality; however, it is recommended that the decision to employ or go SLNB be evaluated on a case-by-case basis.[11]

Another major difference between older and younger patients was the rate of adjuvant therapy proposed and com-

Table 2 Initial clinical and histological characteristics of melanoma according to age.

Characteristic	No. (%)			p
	Total	Age (years)		
	n = 431 (100%)	< 65 n = 288 (66.8%)	≥ 65 n = 143 (33.2%)	
Age				
Total	431 (100%)	288 (66.8%)	143 (33.2%)	<0.001
Mean (±SD)	55.66 (±16.45)	46,31 (±11.13)	74.51 (±6.20)	
Median (RIQ)	55 (44–70)	48 (37–55.75)	74 (70–78)	
Location				
Total	431 (100%)	288 (66.8%)	143 (33.2%)	<0.001
Head and neck	97 (22.5%)	43 (14.9%)	54 (37.8%)	
Trunk	179 (41.5%)	140 (48.6%)	39 (27.3%)	
Uper limb	60 (13.9%)	39 (13.5%)	21 (14.7%)	
Lower limb	95 (22%)	66 (22.9%)	29 (20.3%)	
Size (cm)				
Total	383 (88.9%)	254 (66.3%)	129 (33.7%)	<0.001
Mean (±SD)	1.6 (2.54)	1.25 (±1.8)	2.53 (±3.5)	
Median (RIQ)	0.75 (0.5–1.6)	0.65 (0.48–1.3)	1.03 (0.5–3.1)	
Subtipo histológico				
Total	431 (100%)	288 (66.8%)	143 (33.2%)	<0.001
SSM	277 (64.3%)	215 (74.7%)	62 (43.4%)	
Nodular	47 (10.9%)	27 (9.4%)	20 (14%)	
LMM	75 (17.4%)	25 (8.7%)	50 (35%)	
ALM	19 (4.4%)	11 (3.85)	8 (5.6%)	
Other	13 (3%)	10 (3.5%)	3 (2.1%)	
Breslow thickness (mm)				
Total	429 (99.5%)	288 (67.1%)	141 (32.9%)	<0.01
Mean (±SD)	1.65 (±2.54)	1.25 (±1.83)	2.53 (±3.5)	
Median (RIQ)	0.75 (0.5–1.6)	0.65 (0.48–1.3)	1.03 (0.5–3.1)	
Ulceration				
Total	378 (87.7%)	249 (65.9%)	129 (34.1%)	0.012
Yes	45 (11.9%)	22 (8.8%)	23 (17.8%)	
No	333 (88.1%)	227 (91.2%)	106 (82.2%)	
Mitosis (number)				
Total	351 (81.4%)	227 (64.7%)	124 (35.3%)	NS
Mean (±SD)	1.82 (±4.03)	1.68 (±4.15)	2.07 (±3.81)	
Median (RIQ)	0 (0–2)	0 (0–1.)	1 (0–2.75)	
Histological invasion (lymphatic/perineural/vascular)				
Total	319 (74.0%)	208 (65.2%)	111 (34.8%)	NS
Yes	16 (5%)	7 (3.4%)	9 (8.1%)	
No	303 (95%)	201 (96.6%)	102 (91.9%)	
Associated melanocytic lesion				
Total	249 (57.8%)	155 (62.2%)	94 (37.8%)	0.022
Yes	75 (30.1%)	55 (35.5%)	20 (21.3%)	
No	174 (69.9%)	100 (64.5%)	74 (78.7%)	

NS, Not Significative; SSM, Superficial Spreading Melanoma; LMM, Lentigo Malignant Melanoma; ALM, Acral Lentiginous Melanoma.

pleted. The 11.9% of older patients compared with 2.1% of younger ones eligible for adjuvant therapy did not undergo the full course of therapy. Many older patients have poor health, making it difficult to prescribe adjuvant therapies. In addition, older patients may be reluctant to accept a treatment with significant adverse effects and little benefit.

There are some limitations to this study. It was a retrospective study and what the authors observed in the area may not be generalized to other territories. Most of the patients of this study have been collected in the last 10-years. Although many of the patients diagnosed before 2012 were discharged and the authors do not have their data, no significant differences were observed between these years for the characteristics of patients, melanomas and main features of management except for an increase in the number of primary cutaneous melanoma diagnosis in the last years. Other factors such as number of nevi, family history of melanoma, and history of nonmelanoma skin cancer or non-cutaneous cancer were not collected. Further studies are

Table 3 Stage and initial management of cutaneous melanoma according to age.

Characteristic	No. (%)			p
	Total	Age (years)		
	n = 431 (100%)	< 65 n = 288 (66.8%)	≥ 65 n = 143 (33.2%)	
Initial staging				
Total	427 (98.4%)	287 (67.2%)	140 (32.8%)	<0.001
0 (in situ)	107 (25.1%)	66 (23%)	41 (29.3%)	
I	237 (55.5%)	176 (61.3%)	61 (43.6%)	
II	43 (10.1%)	20 (7%)	23 (16.4%)	
III/IV	40 (9.3%)	25 (8.7%)	15 (10.7%)	
Excision				
Total	424 (98.4%)	281 (66.3%)	143 (33.7%)	NS
Indicated done	422 (99.5%)	281 (100%)	141 (98.6%)	
Complete	396 (93.4%)	268 (95.4%)	128 (89.5%)	
Incomplete	26 (6.1%)	13 (4.6%)	13 (9.09%)	
Indicated dismissed	2 (0.5%)	0 (0%)	2 (1.4%)	
Wide excision				
Total	429 (99.5%)	288 (67.1%)	141 (32.9%)	<0.001
Indicated done	373 (86.9%)	272 (94.4%)	101 (71.6%)	
Positive	15 (3.5%)	7 (2.4%)	8 (5.7%)	
Negative	358 (83.4%)	265 (92%)	93 (66%)	
Indicated dismissed	56 (13.1%)	16 (5.6%)	40 (28.4%)	
SLNB				
Total	430 (99.8%)	288 (67%)	142 (33%)	<0.001
Indicated done	134 (31.2%)	95 (33%)	39 (27.5%)	
Positive	32 (7.4%)	21 (7.3%)	11 (7.7%)	
Negative	102 (23.7%)	74 (25.7%)	28 (19.7%)	
Indicated dismissed	32 (7.4%)	7 (2.4%)	25 (17.6%)	
No indicated	264 (61.4%)	186 (64.6%)	78 (54.9%)	
Adjuvant therapy				
Total	431 (100%)	288 (66.8%)	143 (33.2%)	<0.001
Indicated	61 (14.1%)	33 (11.5%)	28 (19.6%)	
Received	38 (8.8%)	27 (9.4%)	11 (7.7%)	
Dismissed	23 (5.3%)	6 (2.1%)	17 (11.9%)	
No indicated	370 (85.8%)	255 (88.5%)	115 (80.4%)	

NS, Not Significative; SLNB, Selective Lymph Node Biopsy.

required to compare such risk factors and characteristics between older and patients younger.

Conclusions

In summary, the number of cases of melanoma in people over 65 has been increasing in the last decade. Compared with the younger group, older patients had primary cutaneous melanomas more frequent in the head and neck with higher Breslow thickness, larger clinical size, and ulceration. Melanomas were diagnosed more frequently in initial (in situ) and advanced (II, III, IV) stages and they have less association with previous lesions. In addition, more interventions and oncological treatments are ruled out solely because of the age despite the fact there are no contraindications.

Stage at diagnosis remains the most important difference between younger and older patients. Further public health campaigns regarding melanoma should focus on access of elderly people to early diagnosis and excision with appropriate margins. An assessment of the patient's comorbidities anticipated life expectancy, frailty, and ability to withstand the proposed treatment should be considered in planning the management of these patients.

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Authors' contributions

Juan-Manuel Morón-Ocaña: Preparation and writing of the manuscript; critical literature review.

Isabel-María Coronel-Pérez: Approval of the final version of the manuscript; manuscript critical review.

Ana- Isabel Lorente-Lavirgen: Approval of the final version of the manuscript; manuscript critical review,

Carmen-Victoria Almeida-González: Statistical analysis; study conception and planning.

Amalia pérez-gil: approval of the final version of the manuscript; manuscript critical review.

Conflicts of interest

None of the authors have any conflict of interests to declare.

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ORIGINAL ARTICLE

Efficacy and safety of dupilumab in patients with moderate-to-severe bullous pemphigoid: a systematic review and meta-analysis☆

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KEYWORDS
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Methylprednisolone;
Pemphigoid, bullous;
Pruritus

Abstract

Objective: Evaluate the safety and efficacy of dupilumab in treating moderate-to-severe bullous pemphigoid.

Methods: The authors performed a systematic review and meta-analysis of comparative studies of Dupilumab combined with corticosteroids and conventional corticosteroid therapy alone in patients with moderate-to-severe bullous pemphigoid. PubMed, Embase and Cochrane databases were searched for studies published up to December 2023. Data were extracted from published reports and quality assessment was performed according to Cochrane recommendations.

Results: A total of four studies involving 127 patients were included, of which 53 received Dupilumab combined with corticosteroids, while the other 74 were administered corticosteroids alone. Regarding efficacy, Dupilumab the time before new blister formation stopped (MD = −5.13 days; 95% CI −7.12 to −3.15; p < 0.0001) and demonstrated a greater reduction in Bullous Pemphigoid Disease Area Index (MD = −3.90; 95% CI −5.52 to −2.27; p < 0.0001) and Numeric Rating Scale for Pruritus (SMD = −1.37; 95% CI −2.02 to −0.72; p < 0.0001) compared with patients who received conventional therapy. However safety endpoints, adverse events (RR = 0.78; 95% CI 0.58 to 1.05; p = 0.10) and relapses (RR = 0.50; 95% CI 0.19 to 1.36; p = 0.17) showed no significance. The main limitations were retrospective studies with small samples and limited results in clinical practice and a moderate overall risk of bias.

☆ Study conducted at the Universidade da Região de Joinville, Joinville, SC, Brazil.

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Conclusion: Compared with conventional therapy, Dupilumab decreased the time before new blister formation stopped in 5.13 days, as well as Disease Area Index and Pruritus, without interfering with adverse events and relapse.
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Introduction

Bullous pemphigoid (BP) is the most common autoimmune blistering disease in elderly patients, presenting pruritus and tense bullae.[1,2] Commonly associated with cancer, drugs, and other autoimmune diseases such as systemic lupus erythematosus and scleroderma.[3] Conventional treatment for BP is based on systemic corticosteroids associated or not with immunosuppressants. This therapy is limited because of the adverse events due to the associated comorbidities and long-time use in elderly patients.[4,5]

Although the physiopathology is unclear, BP is mediated by antibodies that target hemidesmosomes proteins – BP180 and BP230. Studies identified that T-helper cells (Th2) responses produce cytokines such as Interleukin −4, −5, −9 and −13, which could induce IgE production in B-lymphocyte contributing to the loss of tolerance against BP180 and eosinophilia.[6,7]

Dupilumab (DP) is a recombinant humanized monoclonal antibody directly targeted Interleukin (IL)-4 receptor-alpha subunit which has been approved for moderate to severe atopic dermatitis. Moreover, DP blocks the downstream signal transduction of IL-4 and IL-13 fundamental cytokines in type-2 inflammation and pruritus genesis.[8]

Considering the correlation between bullous pemphigoid pathophysiology and DP pharmacokinetics, as well as its emergent role in the treatment of atopic dermatitis, further investigation is needed to evaluate the potential of DP as a novel therapy for autoimmune blistering diseases. The latest systematic review and meta-analysis on the subject evaluated several biological agents for BP, once there was limited data.[3] Since then, two recent studies have been published, increasing the population substantially.[9,10] Another systematic review analyzed rituximab, omalizumab, and Dupilumab, including only 36 patients treated with Dupilumab and with no control group for adequate comparison.[11] The scarcity of RCTs in this field highlights multiple challenges and implications, based on the longstanding use of corticosteroids as the primary treatment for BP.[4,5] Ethical concerns arise when designing trials comparing newer therapies such as Dupilumab to established standards, given the well-documented efficacy of corticosteroids and the rarity of BP. As well as significant financial and resource investments for such studies.

In light of this issue, the authors performed a systematic review and meta-analysis assessing the efficacy and safety of DP combined with corticosteroids and conventional corticosteroid therapy alone, exploring populations with moderate-to-severe BP.

Methods

Inclusion in this meta-analysis was restricted to studies that met all the following criteria, according to PICOS strategy, (1) Population: patients with moderate-to-severe BP, (2) Intervention: DP associated with methylprednisolone, (3) Comparative: corticosteroid alone, (4) Outcomes: any of the desired outcomes described below, (5) Study type: cohort studies or clinical trials written on English language. The authors excluded studies with no control group, overlapping populations, clinical trial register entry only, non-human studies and studies reported only as abstracts.

The authors systematically searched PubMed, Embase and Cochrane Central Register of Controlled Trials from inception to December 2023 with the following search strategy: ''Dupilumab'' AND ''bullous pemphigoid''. The references from all included studies were also searched manually for any additional studies. Two authors (J.O.N. and R.R.S.) independently extracted the data following predefined search criteria and quality assessment. The prospective meta-analysis protocol was registered on PROSPERO with registration number CRD42024498942.

Outcomes included: time to stop new blister formation (days), Bullous Pemphigoid Disease Area Index (BPDAI), Numeric Rating Scale (NRS) for itching/pruritus, time to taper methylprednisolone (days), cumulative and maintenance methylprednisolone dosage (milligrams), any adverse outcome and relapse.

The authors evaluated the risk of bias using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies – of Interventions).[12] Two independent authors completed the risk of bias assessment (R.R.S and J.O.N.S). Disagreements were resolved through a consensus after discussing reasons for discrepancies. Each study received an overall risk of bias of low, moderate, serious, critical, or no information according to 7 domains: confounding, selection, classification of intervention, deviation from intended intervention, missing data, measurement of outcomes, and selection of reported results.

Publication of bias assessment with funnel plots is not indicated for meta-analysis with fewer than ten studies included, according to Cochrane Collaboration guidelines. Therefore, the authors used a checklist, developed to facilitate GRADE certainty of evidence evaluation, including a questionnaire regarding publication bias.[13] This tool comprises a comprehensive search, grey literature evaluation, restriction in language basis in study selection, the indication of major industry influence, funnel plot asymmetry, and discrepancy with published trials.

The certainty of the evidence was classified according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) method and a summary of

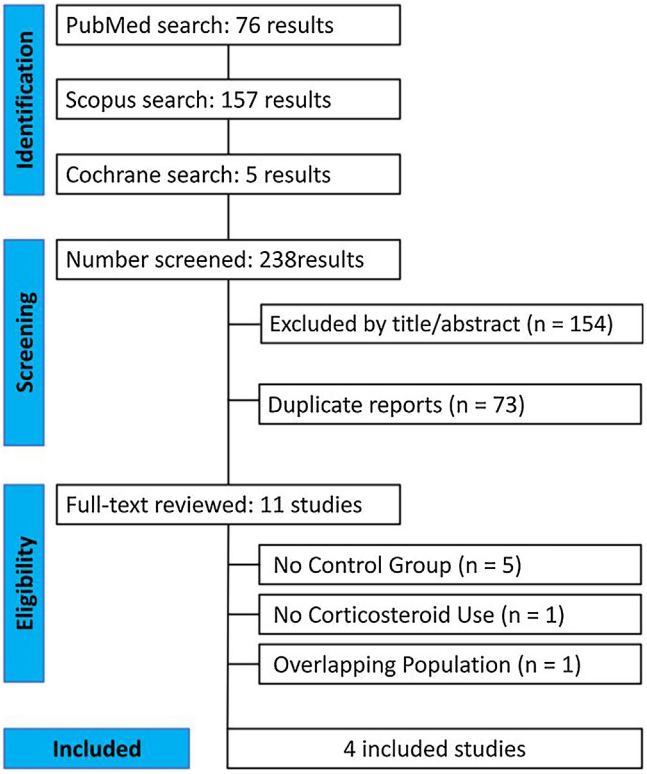

Fig. 1 PRISMA flow diagram of study screening and selection.

findings table generated by GRADEpro GDT. The systematic review and meta-analysis were performed and reported in accordance with the Cochrane Collaboration Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines.[14,15]

Review Manager 5.3 (Cochrane Center, The Cochrane Collaboration, Denmark) was used for statistical analysis. Risk-ratios (RR) with 95% Confidence Intervals were used to compare treatment effects for categorical endpoints. Continuous outcomes were compared with Mean Difference (MD) and Standardized Mean Difference (SMD). When the studies did not report standard deviation, p-value was used to infer the measure of dispersion, according to the Cochrane recommendations.[12] The authors assessed heterogeneity with I^2 statistics and Cochran Q test; p-values < 0.1 and I^2 > 25% were considered significant for heterogeneity. The authors used a fixed-effect model for outcomes with low heterogeneity (I^2 < 25%). Otherwise, a DerSimonian and Laird random-effects model was used. The authors also performed sensitivity analyses by excluding individual studies to evaluate the impact of a single study on each outcome.

Results

As detailed in Fig. 1, the initial search yielded 238 results. After the removal of duplicate records and studies with exclusion criterion based on title/abstract review, 11 studies remained and were fully reviewed for the inclusion and exclusion criteria, 5 studies were excluded due to lack of a control group.[16–20] Furthermore, 1 study was discarded due to the non-use of corticosteroids and 1 study had an overlapping population.[21,22] Ultimately, a total of 127 patients from 4 studies were included in this systematic review and meta-analysis. 53 were treated with DP combined with corticosteroids and 74 with conventional corticosteroid therapy.[1,7,9,10]

Within this cohort, the median age of the patient cohort across the included studies trended towards individuals in their 70 s (median age of 74 years in the intervention and 69 in the control). The baseline characteristics of the populations of each study are further presented in Table 1.

With regards to the efficacy, DP decreased time to stop new blister formation (MD = −5.13 days; 95% CI −7.12 to −3.15; p < 0.0001; I^2 = 0%; Fig. 2) and showed a greater reduction in BPDAI (MD = −3.90; 95% CI −5.52 to −2.27; p < 0.0001; I^2 = 46%; Fig. 3) and NRS pruritus score (SMD = −1.37; 95% CI −2.02 to −0.72; p < 0.0001; I^2 = 60%; Fig. 4) change from baseline compared with patients who received conventional therapy.

Moreover, time to taper methylprednisolone (MD = −25.78 days; 95% CI −36.42 to −15.13; p < 0.0001; I^2 = 0%; Fig. 5) and cumulative methylprednisolone dosage (MD = −533.88 mg; 95% CI −784.45 to −283.31; p < 0.0001, I^2 = 0%; Fig. 6) were lower in the DP group. Meanwhile maintenance dose (MD = −13.02 mg; 95% CI −30.39 to 4.34; p = 0.14; I^2 = 75%; Fig. 7) demonstrated no significance. Whereas, for the results reported in Figs. 5 and 7, only two studies participated in the analysis due to missing data.

As for the safety endpoints, any adverse event (RR = 0.78; 95% CI 0.58 to 1.05; p = 0.10; I^2 = 69%; Fig. 8) and relapse (RR = 0.50; 95% CI 0.19 to 1.36; p = 0.17; I^2 = 0%; Fig. 9) showed no significance. No serious adverse events or deaths were reported by the included studies.

Table 2 outlines the individual appraisal of each article included in the meta-analysis. Overall, all studies were deemed at moderate risk of bias. The main reasons were as follows: non-randomized trials leading to some concerns about confounding factors, two studies had retrospective analyses, treatment regimens not thoroughly exposed in the methods section, regularity of outcome measurement not clearly stated, and loss of follow-up. After using the checklist, publication bias was considered undetected. In the sensitivity analysis, there was no impact of single studies on any of the reported outcomes.

The evaluation of Certainty of Evidence according to the GRADE method revealed a low certainty for time to stop blister formation and BPDAI change from baseline, the remaining outcomes were considered very low certainty. The details are found in the Summary of Findings (Table 3).

Discussion

In this systematic review and meta-analysis of 4 studies and 127 patients, the authors compared DP combined with corticosteroids and conventional corticosteroid therapy alone in patients with moderate-to-severe BP. The main findings were as follows: (1) DP decreased time to stop new blister formation with a mean difference of −5.13-days. (2) There was a 3.90 greater reduction of BPDAI in the DP group. (3) DP significantly reduced NRS pruritus score with a standardized mean difference of −1.37, compared with conventional

Table 1 Baseline characteristics of included studies in the meta-analysis.

	Yang, 2022 (7)	Zhang, 2021 (1)	Qi, 2023 (10)	Huang, 2023 (9)
Population	Moderate to Severe BP	Moderate to Severe BP	Moderate to Severe BP	Severe BP
Intervention	D 600 mg + M < 0.4 mg/kg	D 600 mg + M 0.6 mg/kg + A 2 mg/kg	D 600 mg + M 40 mg	D 600 mg + M 0.4 mg/kg
Control	M 0.4–0.8 mg/kg	M 0.6 mg/kg + A 2 mg/kg	M 40 mg	M 0.4–0.8 mg/kg
Study design	Retrospective Cohort	Retrospective Cohort	Non-Randomized Trial	Prospective Cohort
Follow-up	12-weeks	32-weeks	3-months	12-months
Number of patients				
Intervention	20	8	9	16
Control	20	16	18	20
Total	40	34	27	36
Male sex				
Intervention	10	3	4	9
Control	8	6	12	13
Total	18	9	16	22
Age (Years)				
Intervention	72 (54–86)	64.5 (45.5–71.75)	72 (71–81.5)	74 ± 13
Control	72 (51–84)	64.5 (52.25–73.5)	71 (67.25–80.5)	69 ± 12
Disease duration (months)				
Intervention	5 (3–12)	2 (1.25–49.5)	4.5 (0.84–10)	4 (3–8)
Control	5 (2.5–7)	2.5 (1.0–8.75)	3.5 (1–9.75)	5 (3–9)
BPDAI baseline				
Intervention	37.5 ± 12.1	34.2	53.44 ± 13.22	51 (45–57)
Control	40.0 ± 9.9	36	55.50 ± 11.63	57 (46–62)
NRS itching baseline				
Intervention	19.0/30 ± 3.4	4–10/10 ± 7.9	5–9/10	9/10 (8–10)
Control	18.2/30 ± 3.1	4–10/10 ± 6.3	5–9/10	8/10 (8–10)
IgE count baseline				
Intervention	1507.9 ± 829.1	308–18,500	NA	550 (170–2143)
Control	1989.3 ± 955.6	215–6,550	NA	1589 (1309–1942)
EOS % baseline				
Intervention	NA	9.6%–24.8%	NA	10% (6–17)
Control	NA	5.4%–23.5%	NA	10% (7–12)

BP, Bullous Pemphigoid; D, Dupilumab; M, Methylprednisolone; A, Azathioprine; BPDAI, Bullous Pemphigoid Disease Area Index; NRS, Numeric Rating Scale; EOS, Eosinophilia; NA, Not Available.
*Absolute Number (Percentage) and Median (Standard Deviation).

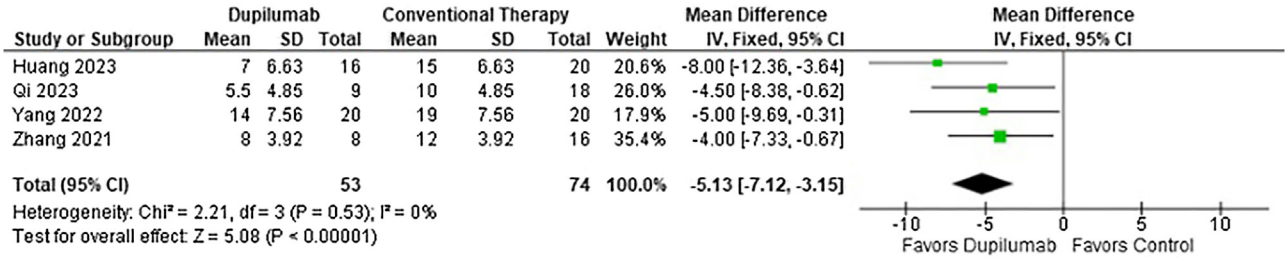

Fig. 2 Mean difference of time to stop new blister formation (days) for Dupilumab compared with conventional therapy.

therapy. (4) There was no difference in regard to adverse events and relapse.

High-potency topical corticosteroids are considered first-line treatment for BP, as demonstrated in a randomized controlled trial, which found similar efficacy with reduced side-effects and mortality rate when compared to systemic therapy.[23,24] Nevertheless, the difficulty for an older patient or caregiver to apply topical corticosteroids daily in extensive areas, might lead to the selection of an oral corticosteroid for initial therapy.[24,25] In this sense, systemic therapy poses a challenge once prolonged regimens cause serious adverse events.[23]

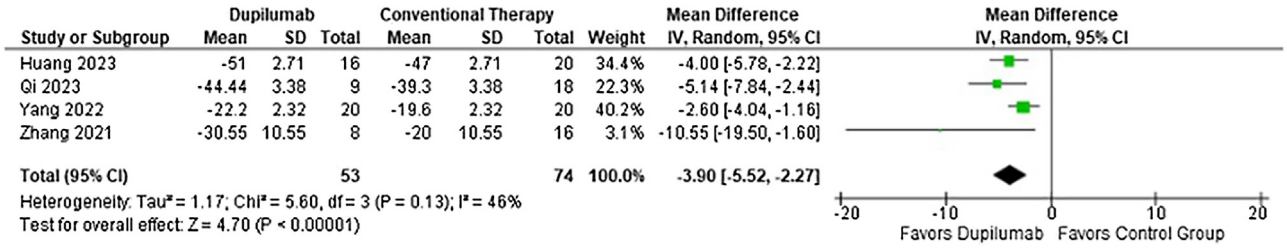

Fig. 3 Mean difference of Bullous Pemphigoid Disease Area Index (BPDAI) for Dupilumab compared with conventional therapy.

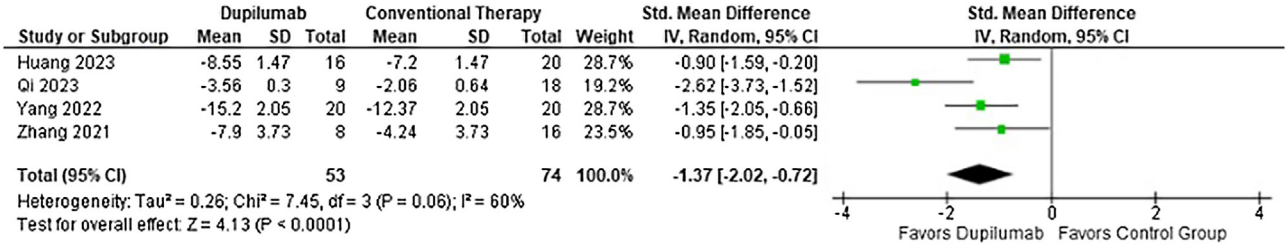

Fig. 4 Standardized mean difference of numeric rating scale for pruritus for Dupilumab compared with conventional therapy.

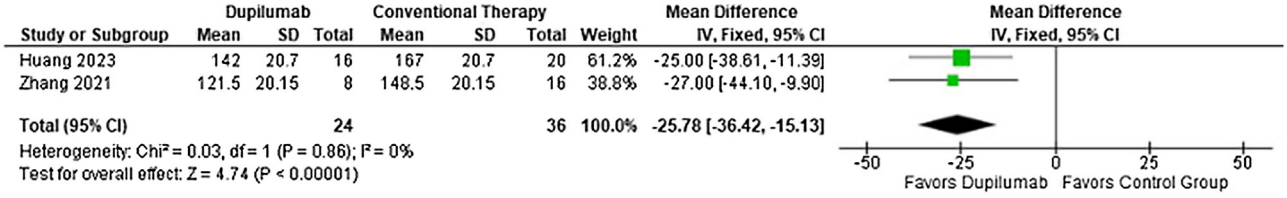

Fig. 5 Mean difference of time to taper methylprednisolone (days) for Dupilumab compared with conventional therapy.

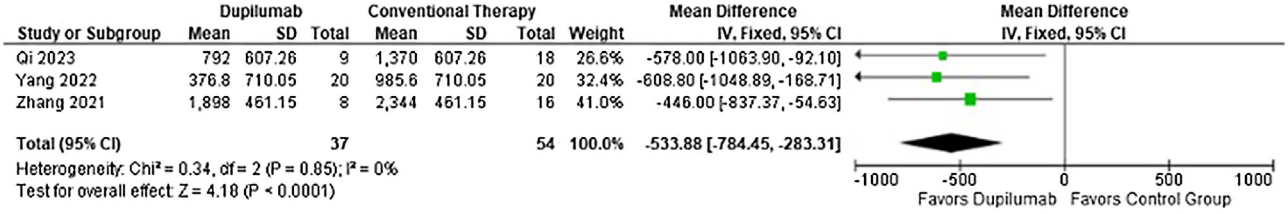

Fig. 6 Mean difference of cumulative methylprednisolone dosage (milligrams) for Dupilumab compared with conventional therapy.

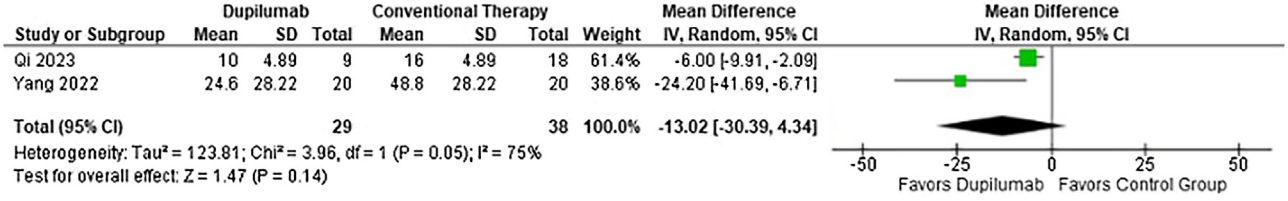

Fig. 7 Mean difference of maintenance methylprednisolone dosage (milligrams) for Dupilumab compared with conventional therapy.

Moreover, BP mortality ranged from 9.3% to 41%, with a significant association with systemic methylprednisolone, revealing the importance of developing corticosteroid-sparing therapy.[23,26,27] Immunosuppressants should be considered a second-line treatment in order to reduce corticosteroid dosage, depending on safety profile, physician experience and patient comorbidities. Azathioprine, doxycycline, and methotrexate were the most studied options, immunoglobulin has also been evaluated for refractory cases.[23,28–30] Wiliams et al. conducted a randomized controlled trial with 132 patients in order to analyze the efficacy of doxycycline compared to prednisolone in the

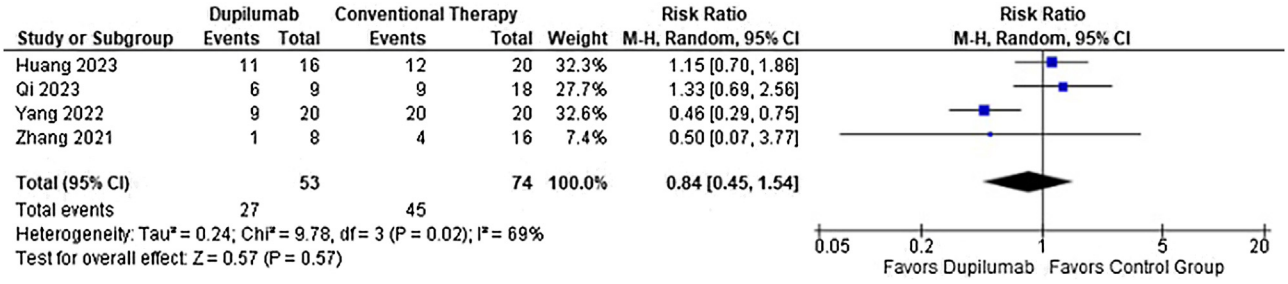

Fig. 8 Risk ratio of any adverse events for Dupilumab compared with conventional therapy.

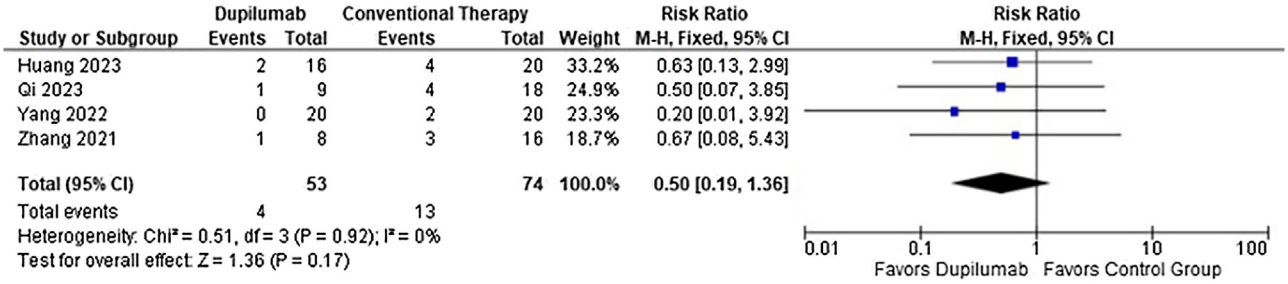

Fig. 9 Risk ratio of relapse for Dupilumab compared with conventional therapy.

Table 2 Risk of Bias Assessment of studies included in the meta-analysis.

Bias Domain	Yang, 2022	Zhang, 2021	Qi, 2023	Huang, 2023
Confounding	Moderate	Moderate	Moderate	Moderate
Selection	Moderate	Low	Low	Low
Classification of Interventions	Moderate	Moderate	Moderate	Moderate
Deviation from Intended Interventions	Moderate	Moderate	Moderate	Moderate
Missing Data	Moderate	Low	Low	Moderate
Measurement of Outcomes	Moderate	Moderate	Moderate	Moderate
Selection of Reported Result	Low	Low	Low	Low
Overall Risk of Bias	Moderate	Moderate	Moderate	Moderate

treatment of BP.[31] Doxycycline was not as effective as corticoid therapy, with an 18.6% lower rate in disease control at week 6, although presented with a reduction of 18.1% (p = 0.002) in severe, life-threatening, or fatal adverse events by 52 weeks.

There is no quality evidence pointing to an effective corticosteroid-sparing therapy without raising adverse events for BP, demonstrating the need to investigate novel drugs.[23] Considering the impact of anti-BP180 on disease control, mainly IgG4 and IgE antibodies, IL-4 inhibition might be a suitable option in BP treatment, for instance DP.[32]

A recently published Cochrane Review recommends topical corticosteroids for localized BP as an alternative to oral prednisolone regarding adverse events. Additionally, doxycycline can also be used as an initial approach for most patients with BP. However, there is no recommendation for Dupilumab probably due to lack of evidence. Other biologic agents failed to be superior to placebo, such as Mepolizumab.[33]

Regarding safety profile, a large clinical trial observed that the main adverse events associated with DP were soft tissue infections and eosinophilia, while conjunctivitis, facial erythema, psoriasis, and pneumonia were uncommon, related to older age and comorbidities.[32] Conversely, the meta-analysis found no significance in regard to adverse events, indicating DP as a viable treatment option.

An international panel of experts defined partial remission on minimal therapy as the presence of transient new lesions that heal within 1-week while the patient is receiving minimal therapy for at least 2-months. Furthermore, complete remission on minimal therapy is the absence of new or established lesions or pruritus while the patient is receiving minimal therapy for at least 2-months. Also, the experts classify relapse/flare as the appearance of 3 or more lessons

Table 3 Summary of findings and certainty of evidence according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE).

Certainty assessment						Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Inaccuracy	Other considerations	Dupilumab	Conventional Therapy	Relative (95% CI)	Absolute (95% CI)		
Time to stop new blister formation (follow-up: range 3 months to 12 months; assessed with: days)												
4	Observational study	Serious [a]	Do not serious	Do not serious	Serious[b]	None	53	74	–	MD **0–5.13** (7.12 minor to 3.15 minor)	⊕⊕◯◯ Download[a,b]	Critical
BPDAI (follow-up: variation 3 months to 12 months; assessed with: units)												
4	Observational study	Serious [a]	Do not serious	Do not serious	Serious[b]	None	53	74	–	MD **0–3.90** (5.52 minor to 2.27 minor)	⊕⊕◯◯ Download[a,b]	Important
NRS Pruritus Score (follow-up: change 3 months to 12 months; assessed with: units)												
4	Observational study	Serious [a]	Serious[c]	Do not serious	Serious[b]	None	53	74	–	MD **0–1.37** (2.02 lower to 0.72 lower)	⊕◯◯◯ Very low[a,b,c]	Important
Time to taper methylprednisolone (follow-up: range 8 months to 12 months; assessed with: days)												
2	Observational study	Serious [a]	Do not serious	Do not serious	Serious[b]	None	24	36	–	MD **0 −25.78** (36.42 lower to 15.13 lower)	⊕◯◯◯ Very low[a,b]	Important
Cumulative methylprednisolone dosage (follow-up: variation 3 months to 8 months; assessed with: mg)												
3	Observational study	Serious [a]	Do not serious	Do not serious	Serious[b]	None	37	54	–	MD **0 −533.88** (784.45 lower to 283.31 lower)	⊕◯◯◯ Very low[a,b]	Important

Table 3 (*Continued*)

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Inaccuracy	Other considerations	Dupilumab	Conventional Therapy	Relative (95% CI)	Absolute (95% CI)		
Maintenance methylprednisolone dosage (follow-up: average 3 months; assessed with: mg)												
2	Observational study	Serious [a]	Serious[c]	Do not serious	Serious[b]	None	29	38	–	MD **0 -13.02** (30.39 lowest to 4.34 highest)	⊕◯◯◯ Very low[a,b,c]	Important
Any adverse event (follow-up: range 3 months to 12 months; assessed with: events)												
4	Observational study	Serious [the]	Serious[c]	Do not serious	Serious[b]	None	27/53 (50.9%)	45/74 (60.8%)	**RR 0.84** (0.45 to 1.54)	**10 minus by 100** (from 33 minus to 33 plus)	⊕◯◯◯ Very low[a,b,c]	Important
Relapse (follow-up: variation 3 months to 12 months; evaluated with: events)												
4	Observational study	Serious [a]	Do not serious	Do not serious	Serious[b]	None	4/53 (7.5%)	13/74 (17.6%)	**RR 0.50** (0.19 to 1.36)	**9 minus for 100** (from 14 minus to 6 plus)	⊕◯◯◯ Very low[a,b]	Important

CI, Confidence Interval; MD, Mean Difference; RR, Risk Ratio.
Explanations:
[a] This systematic review included only non-randomized studies, with an overall moderate risk of bias.
[b] Downgraded due to low number of participants, as well as wide conference intervals.
[c] Outcomes with high heterogeneity.

in a month or one large (more than 10 cm) eczematous lesion that does not heal in 1-week, or extension of established lesions or daily pruritus in a patient who had achieved disease control.[34] Considering this time frame, the included studies follow-up was appropriate for the efficacy analysis, although longer periods could better evaluate relapse and other long-term adverse events.

Since BP causes self-limiting exacerbations, which last from several months to years, management involves improvement in quality of life with minimal adverse events.[23] In studies evaluating DP for atopic dermatitis, pruritus control showed an important increase in patient satisfaction, thus, similar findings might be expected for the treatment of BP.[35,36]

After treatment cessation, approximately half of the patients experience relapse, most commonly in the first 3-months.[23,37] Literature suggests discontinuation of initial therapy before 16-weeks leads to higher relapse rates, therefore, prolonged therapy might show superior results.[31] Hence, maintenance therapy plays an important role in BP, which consists of low-dose corticosteroids or topical clobetasol continued for up to 6 months after clinical remission.[23] Whereas, there was no difference in relapse rates between groups in the meta-analysis.

High heterogeneity demonstrated in the outcomes are due to different factors. For instance, NRS pruritus and adverse events might be affected by non-blinding of subjects and examiners. Meanwhile, Zhang et al. added azathioprine to both treatment regimens, which could have impacted the results for time to taper and cumulative dosage of methylprednisolone.[1]

In addition, outcomes regarding corticosteroid dosage and tapering were not reported by all included studies, limiting these findings due to missing data bias. The impossibility of collecting data from the studies concerning eosinophilia and IgE count did not impact the present results, as these were secondary outcomes and did not represent clinical endpoints.

Considering the meta-analysis included retrospective studies with small samples, the results have limited implications in clinical practice. Another limitation is that analysis of secondary outcomes, such as partial remission, and time to remission, was not feasible as sufficient data were not accessible. Furthermore, the overall risk of bias was deemed moderate for the four studies, which raises concerns about the validity of the evidence presented. This data may be important to guide posterior trials since there is only one ongoing randomized controlled trial registered in clinicaltrials.gov.[38]

Thus, DP demonstrated promising results, with a relevant reduction in time to stop new blister formation and clinical outcomes such as BPDAI and NRS pruritus, without increasing relapse or adverse events. Nevertheless, the quality of evidence is still low and randomized controlled trials must be conducted to attest to the real efficacy and security of DP for treating moderate-to-severe BP.

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Authors' contributions

Júlia Opolski Nunes da Silva: The conception and design of the study; drafting the article or critically reviewing it for important intellectual content; critical review of the literature; final approval of the final version of the manuscript.

Rodrigo Ribeiro e Silva: Data collection, or analysis and interpretation of data; statistical analysis; obtaining, analyzing, and interpreting data; final approval of the final version of the manuscript.

Paulo Victor Zattar Ribeiro: The conception and design of the study; drafting the article or critically reviewing it for important intellectual content; critical review of the literature; final approval of the final version of the manuscript.

Patrícia Silva Farah: The conception and design of the study; effective participation in research guidance; final approval of the final version of the manuscript.

Raquel Bissacotti Steglich: The conception and design of the study; effective participation in research guidance; final approval of the final version of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Hand dermatitis: a 6-year experience in a tertiary referral Brazilian hospital☆

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KEYWORDS
Dermatitis, allergic contact;
Dermatitis, irritant;
Dermatitis, occupational;
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Eczema, dyshidrotic;
Hand dermatoses

Abstract
Background: Hand dermatitis (HD) is a prevalent inflammatory skin disease with a significant socioeconomic impact.
Objectives: To characterize the population of HD patients followed up at the Department of Dermatology of a tertiary hospital.
Methods: A cross-sectional, retrospective and descriptive study was carried out through the analysis of medical records of HD patients assisted at the Allergy Clinic of the Department of Dermatology, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, between March 1, 2016 and August 31, 2022.
Results: Of the 175 patients, 73.3% were women, and the mean age at the onset of the condition was 41.7 years. There was a statistically significant association between occupation categories and the presence of occupational dermatitis. Cases were classified as irritant contact dermatitis (49.7%), allergic contact dermatitis (57.1%) and endogenous vesicular HD (3.4%). It was observed a statistically significant higher frequency of patch tests positivity for methylchloroisothiazolinone and methylisothiazolinone (MCI/MI) and nickel sulfate in women and for potassium bichromate and carba mix in men. DLQI was assessed in 77 patients, and the average score was 7.8 points.
Study limitations: As limitations, the authors point out data collection from medical records, which lacked some information. Furthermore, as this was a cross-sectional study, it was not possible to assess cause-and-effect relationships between the variables.
Conclusions: The present data reinforces the importance of patch tests in HD investigation and highlights the high sensitivity rates to MCI/MI and nickel sulfate in Brazilian women and to potassium bichromate and carba mix in Brazilian men patients.
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☆ Study conducted at the Department of Dermatology, Hospital das Clínicas, Faculty of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil.

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Introduction

Hand dermatitis is an inflammatory skin disease that usually begins in the third decade of life.[1] It presents a lifetime prevalence of 14.5% in the general population, and a pooled incidence rate of 7.3 cases/1000 person-years.[1] The condition is responsible for more than 80% of all occupational dermatitis.[2,3]

Subtypes of exogenous hand eczema include irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD).[3] The former consists of a nonspecific skin reaction to contact with a toxic or irritating chemical product, which may occur as early as the first exposure.[2–4] On the other hand, ACD is a delayed type IV immune reaction to contact with an allergen in a sensitized individual.[5] Its diagnosis is confirmed when there is a positive patch test reaction to the substance and a relevant exposure, documented or suspected, to the same.[3–5]

Endogenous vesicular hand dermatitis, formerly known as pompholyx or dyshidrotic eczema, is a form of endogenous disease that presents a poorly understood etiology.[3] It manifests with recurrent vesicular eruptions on the hands, usually symmetrical and pruritic, in the absence of relevant contact allergies or irritants that could cause hand dermatitis.[2,3,5]

As hand eczema tends to be multifactorial, it is generally not possible to identify and eliminate the causative factor in order to cure the condition.[4,6] In addition to behavioral measures, treatment involves topical and systemic options, depending on the severity of the disease.[7] It should be started as early as possible, once resistance to topical treatment is commonly seen in chronic disease.[4,6]

Overall, the prognosis for the condition is poor.[3] In a 15-year follow-up of hand eczema, 44% of the patients reported symptoms during the previous year, and 12% reported continuous symptoms during the entire follow-up period.[8] Regarding occupational disease, another investigation has found that only 19.3% of patients reported complete eczema remission after five years.[9]

Hand dermatitis is a highly prevalent disease with a negative physical, psychological, social, and economic impact.[6,10,11] It generates direct and indirect treatment costs due to working hours lost.[3,12]

The present study aimed to characterize the population of hand dermatitis assisted at the Department of Dermatology of a tertiary hospital in São Paulo, Brazil. The authors have collected epidemiological and clinical data from hand dermatitis patients and described their disease subtypes and patch test results.

Methods

Study design and subjects

A cross-sectional, retrospective, and descriptive study was carried out through the analysis of the medical records of hand dermatitis patients, followed up at the Allergy Clinic of the Department of Dermatology, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP). The local ethics committee approved the investigation (approval protocol number: CAAE 58151222.0.0000.0068).

Patients with hand dermatitis followed up between March 1st, 2016 and August 31th, 2022 were included in the analyses. The diagnosis of hand dermatitis was clinically established, excluding differential diagnoses, and supported by complementary exams if applicable. Exclusion criteria included patients who did not present hand dermatitis, patients with eczematous lesions on other locations than hands and feet, and those who did not perform the contact test or whose test showed inconclusive results, beyond the patients with incomplete medical records.

Medical records evaluations

Patients' medical records were evaluated to obtain the following data: age at the onset of hand dermatitis; age at the first visit at the outpatient clinic; sex; occupation; smoking habits; diagnosis of atopic dermatitis (AD) according to Hanifin and Rajka criteria[13]; other comorbidities; subtype of hand dermatitis and its characteristics at the dermatological examination; results of patch tests; and treatments prescribed during follow-up.

In addition, Dermatology Quality of Life Index (DLQI) scores were collected from the medical records, according to the questionnaire applied within 30 days of the patient's first visit to the outpatient clinic.[14] Hongbo and colleagues (2005) have proposed the following banding system for the DLQI score: 0–1 Indicates no effect on patient's Quality of Life (QOL); 2–5 Means a small effect; 6–10 A moderate effect; 11–20 A very large effect; and 21–30 Indicates an extremely large effect on patient's QOL.[15]

Occupational hand eczema is an inflammatory skin disease of the hands caused or aggravated by occupational exposure.[12] In this study, occupational allergic contact dermatitis was identified when the patient presented a positive patch test result for occupational exposure.[12] On the other hand, an occupational irritant contact dermatitis was defined when there were no positive patch test results for occupational exposure but there was relevant occupational exposure for irritants.[12]

Patch tests

Patch tests have followed the Brazilian Group for Studies on Contact Dermatitis' recommendations.[16] The 30 substances of Brazilian Standard Battery (supplied by Endo-Derme Formulas Magistrais Ltda, São Paulo, Brazil) were standardized and positioned in the containers and applied, preferably, in the upper dorsal region of the patient.[15] According to the exposure history, the Cosmetics Battery (supplied by Endo-Derme Formulas Magistrais Ltda, São Paulo, Brazil) was also applied.[16]

The tests were removed 48 hours after application for the first reading (D2). The second reading was performed 96 hours after the tests were applied (D4). Results were interpreted according to the clinical manifestation at the test site: negative (-); doubtful (?); mild reaction (+); strong reaction (++); and very strong reaction (+++).[17] The test was considered suggestive of sensitization by the substance when there was a result (++) or (+++) in D4.[17] However, in the case of positivity's intensity reduction between D2 and D4, the test was considered negative, suggestive of pri-

mary irritation.[16] A positive result was considered relevant when there was documented or suspected exposure to the substance.[3–5]

Statistical analysis

Qualitative and quantitative variables were analyzed through absolute and relative frequencies and by the mean, median, standard deviation, minimum and maximum values, 25th and 75th percentiles (quantitative variables). Data normality was assessed by the Kolmogorov-Smirnov test. Comparison between two independent groups was performed by Student's *t*-test (normal distribution data) and the Mann-Whitney test (data without normal distribution), while the comparison between three groups was evaluated by the Kruskal-Wallis test. Association between qualitative variables was performed by Pearson's Chi-Square test or Fisher's exact test. Data were analyzed using SPSS software for Windows v.25, adopting a 5% significance level.

Results

During the investigation time, 188 hand dermatitis patients were assisted at the Allergy Clinic of the Department of Dermatology of HC-FMUSP. After applying the exclusion criteria, 175 patients were included in the study.

Among the patients included, 129 (73.7%) were female. The mean age at onset of clinical manifestations was 41.7 years (range 2.9–74.2) and the mean age at the beginning of outpatient follow-up was 45.5 years (range 13.8–75.5). The mean time between the onset of symptoms and the beginning of outpatient follow-up was 46.0 months (range 0–360).

The declared occupations were grouped into categories. The most frequent occupational category was the one related to domestic care (Table 1). In the sample, 107 patients (61.1%) were classified as presenting an occupational disease.

There was a statistically significant association between occupation categories and hand dermatitis as occupational dermatitis ($p < 0.001$). As demonstrated in Table 1, the highest prevalence of occupational disease was observed in professionals with cleaning and tidying functions in non-domestic environments (n = 16, 94.1%), beauty professionals (n = 12, 92.3%), and occupations related to domestic care (n = 37, 86.0%).

Concerning smoking habits, 72% (n = 103; n total = 143) had never smoked, 13.3% had stopped the habit before starting follow-up at the outpatient clinic and 14.7% were active smokers.

In the sample, 12 patients (6.9%) had AD, 18 (10.3%) presented a diagnosis of psychiatric disorders (depression, anxiety and schizophrenia) and 21 (12.0%) had asthma or allergic rhinitis.

According to clinical manifestations, patients were divided into two groups: dyshidrosiform dermatitis (predominant presentation with vesicles) and non-dyshidrosiform dermatitis. In the first group, 74 patients (42.3%) were included, and in the other one, 101 participants (57.7%). Lesions on the palms and back of the hands were present in 75.4% (n = 132) and 43.1% (n = 75) of the patients, respectively, with 26.9% of the patients in the study (n = 47) presenting lesions in both locations. In addition, 36.0% (n = 63) of the patients manifested lesions on the feet.

Thirty-three hand dermatitis patients (18.9%) underwent anatomopathological examination, which results supported the diagnosis of eczema. One hundred and twenty-six patients (72.0%) had a positive patch test, of which 100 were considered relevant. Thus, 57.1% of the patients in the study had a positive and relevant patch test, while 14.9% presented a positive irrelevant result and 28.0% had a negative patch test.

Based on patch test results and clinical manifestations, patients were classified into ICD (n = 69, 39.4%), ACD (n = 82, 46.8%), ICD and ACD simultaneously (n = 18, 10.3%), and endogenous vesicular HD (n = 6, 3.4%). The antigens most frequently associated with relevant positive patch tests were nickel sulfate, methylchloroisothiazolinone, and methylisothiazolinone (MCI/MI – Kathon CG) and fragrance mix (25.7%, 24.0% and 14.3%, respectively) (Table 2).

Women had a higher positivity for MCI/MI (n = 36, 27.9%) and nickel sulfate (n = 39, 30.2%) compared to men (n = 6, 13.0%, for both antigens), and this association was statistically significant (Table 2). On the other hand, male patients presented higher positivity for potassium bichromate (n = 7, 15.2%) and carba mix (n = 5, 10.9%), compared to females (n = 5, 3.9 %, and n = 3, 2.3%, respectively), also with statistical significance (Table 2).

Patients with dyshidrosiform eczema had positive patch tests for MCI/MI in 37.8% of cases (n = 28), in comparison with positivity of 13.9% (n = 14) in patients without dishydrosiform eczema ($p < 0.001$). In addition, a higher percentage of patch test positivity for nickel sulfate and paraphenylenediamine was observed among patients with dyshidrosiform eczema compared with non-dyshidrosiform eczema: 35.1% (n = 26) vs. 18.9% (n = 19) and 8.1% (n = 6) vs. 1.0% (n = 1), with $p = 0.015$ and $p = 0.043$, respectively.

DLQI was assessed in 77 patients, and the average score was 7.8 points. No statistically significant differences were observed between DLQI scores and the patient's epidemiological, clinical, and treatment characteristics.

Regarding disease treatment, emollients were prescribed to all patients and topical corticosteroids to 174 (99.4%) of them. Topical tacrolimus was used in four patients (2.3%), while urea cream was administered in five cases (2.9%). Antibiotics were prescribed orally for 13 cases (7.4%) and topically for 17 patients (9.7%). Oral antihistamines were used in 140 cases (80%). Fifty-four patients (30.9%) have received cycles of oral prednisone to optimize clinical control. Methotrexate was administered to three patients to control recalcitrant disease. In the series, 43 (24.6%) patients were discharged from the outpatient clinic for regular control of clinical manifestations.

Among 87 patients with ICD, 62 were women (71.3%). The most frequent occupational category was domestic care (n = 21, 24.1%), followed by administrative functions (n = 18, 20.7%). Most of these cases (n = 68, 78.2%) presented clinically as non-dyshidrosiform eczema, compared to 37.5% (n = 33) of patients with other diagnoses – ACD and endogenous vesicular hand dermatitis ($p < 0.001$). Lesions were mostly located on the palms (n = 60, 69.0%), followed by the back of the hands (n = 34, 39.1%) and involvement of the feet were observed in 28 patients (32.2%). The frequency of

Table 1 Occupations of study's participants grouped into categories, Department of Dermatology of HC-FMUSP, March 2016 to August 2022.

Occupational category	Declared occupations	n = 174 ($n_{missing}$ = 1); n (%)	Occupational dermatitis	
			No (n = 67); n (%)	Yes (n = 107); n (%)
Occupations related to domestic care	Homemakers, elderly caregivers and domestic workers.	43 (24.7)	6 (14.0)	37 (86.0)
Beauty professionals	Hairdressers, barbers, beauticians, manicurists and massage therapists.	13 (7.5)	1 (7.7)	12 (92.3)
Healthcare professionals	Doctors, nurses, nursing assistants, orthopedic immobilization and orthoses technicians, community health agents, physiotherapists, dentists and surgical instrumentators.	17 (9.8)	5 (29.4)	12 (70.6)
Industry and mechanical metallurgy professionals	Chemical industry and metallurgist employees.	5 (2.9)	1 (20.0)	4 (80.0)
Construction-related occupations	Bricklayers, painters and plumbers.	16 (9.2)	4 (25.0)	12 (75.0)
Professionals with cleaning and tidying functions in non-domestic environments	Janitors and cleaners.	17 (9.8)	1 (5.9)	16 (94.1)
Professionals involved with food preparation and service in non-domestic environments	Cooks and butlers.	8 (4.6)	4 (50.0)	4 (50.0)
Professionals with administrative functions and/or who work in companies, commerce, telecommunications or transport services	Human resources professionals, sales supervisors, cashiers, logistics assistants, attendants, auditors, receptionists, sellers, administrative assistants, merchants, drivers, telecommunications installers, stockists, graphic designers and flyer distributors.	32 (18.4)	27 (84.4)	5 (15.6)
Rural professionals	Rural workers.	1 (0.6)	0	1 (100)
Artists	Craftsmen, printmakers, photographers, circus performers and dressmakers.	6 (3.4)	2 (33.3)	4 (66.7)
Occupations related to education	Teachers and students.	9 (5.2)	9 (100)	0
Retired and inactive professionals	Retirees, unemployed professionals and those temporarily away from work activities.	7 (4.0)	7 (100)	0

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lesions on the palms was lower in the group of ICD than in the group of other diagnoses (n = 72, 81.8%) and this association was statistically significant (p = 0.048). Twenty patients (23.0%) with ICD used oral prednisone, compared to 34 patients (38.6%) of the ones with other diagnosis (p = 0.025). Furthermore, among the patients who were discharged due to regular control of the condition, 65.1% (n = 28) had ICD, compared with 44.7% (n = 59), of those who were not discharged (p = 0.020).

One hundred patients were classified as ACD, 80% of which were women. Among ACD patients, the most frequent occupational category was domestic care (n = 27,

Table 2 Patch test results for patients with hand dermatitis followed up at the Department of Dermatology of HC-FMUSP, March 2016 to August 2022.

Tested substances		Relevant positive patch tests (n = 175); n (%)	Relevant positive patch tests by sex		p-value
			Male (n = 46); n (%)	Female (n = 129; n (%)	
Peru balsam	Yes	6 (3.4)	0	6 (4.7)	0.342[a]
	No	169 (96.6)	46 (100)	123 (95,3)	
PPD mix	Yes	5 (2.8)	0	5 (3.9)	0.328[a]
	No	170 (97.1)	46 (100)	124 (96.1)	
Hydroquinone	Yes	2 (1.1)	1 (2.2)	1 (0.8)	0.458[a]
	No	173 (98.8)	45 (97.8)	128 (99.2)	
Potassium bichromate	Yes	12 (6.8)	7 (15.2)	5 (3.9)	**0.015**[a]
	No	163 (93.1)	39 (84.8)	124 (96.1)	
Propylene glycol	Yes	1 (0.6)	1 (2.2)	0	0.263[a]
	No	174 (99.4)	45 (97.8)	129 (100)	
Neomycin	Yes	4 (2.3)	2 (4.3)	2 (1.6)	0.283[a]
	No	171 (97.7)	44 (95.7)	127 (98.4)	
MCI/MI	Yes	42 (24.0)	6 (13.0)	36 (27.9)	**0.043**[b]
	No	133 (76.0)	40 (87.0)	93 (72.1)	
Cobalt chloride	Yes	11 (6.3)	4 (8.7)	7 (5.4)	0.482[a]
	No	164 (93.7)	42 (91.3)	122 (94.6)	
Thiuram mix	Yes	8 (4.6)	3 (6.5)	5 (3.9)	0.435[a]
	No	167 (95.4)	43 (93.5)	124 (96.1)	
Ethylenediamine	Yes	1 (0.6)	0	1 (0.8)	0.999[a]
	No	174 (99.4)	46 (100)	128 (99.2)	
Fragrance mix	Yes	25 (14.3)	4 (8.7)	21 (16.3)	0.207[b]
	No	150 (85.7)	42 (91.3)	108 (83.7)	
MBT mix	Yes	1 (0.6)	1 (2.2)	0	0.263[a]
	No	174 (99.4)	45 (97.8)	129 (100)	
Quinoline mix	Yes	1 (0.6)	0	1 (0.8)	0.999[a]
	No	174 (99.4)	46 (100)	128 (99.2)	
Epoxy resin	Yes	1 (0.6)	1 (2.2)	0	0.263[a]
	No	174 (99.4)	45 (97.8)	129 (100)	
Thimerosal	Yes	17 (9.7)	5 (10.9)	12 (9.3)	0.775[b]
	No	158 (90.3)	41 (89.1)	117 (90.7)	
Turpentine	Yes	5 (2.9)	1 (2.2)	4 (3.1)	0.999[a]
	No	170 (97.1)	45 (97.8)	125 (96.9)	
Carba mix	Yes	8 (4.6)	5 (10.9)	3 (2.3)	**0.030**[a]
	No	167 (95.4)	41 (89.1)	126 (97.7)	
Promethazine	Yes	3 (1.7)	1 (2.2)	2 (1.6)	0.999[a]
	No	172 (98.3)	45 (97.8)	127 (98.4)	
Nickel sulfate	Yes	45 (25.7)	6 (13.0)	39 (30.2)	**0.022**[b]
	No	130 (74.3)	40 (87.0)	90 (69.8)	
Colophonium	Yes	8 (4.6)	3 (6.5)	5 (3.9)	0.435[a]
	No	167 (95.4)	43 (93.5)	124 (96.1)	
Paraphenylenediamine	Yes	7 (4.0)	0	7 (5.4)	0.192[a]
	No	168 (96.0)	46 (100)	122 (94.6)	
Formaldehyde	Yes	7 (4.0)	1 (2.2)	6 (4.7)	0.677[a]
	No	168 (96.0)	45 (97.8)	123 (95.3)	
Germall 115	Yes	1 (0.6)	1 (2.2)	0	0.263[a]
	No	174 (99.4)	45 (97.8)	129 (100)	
Tosylamide-formaldehyde resin	Yes	8 (4.6)	0	8 (6.2)	0.113[a]
	No	167 (95.4)	46 (100)	121 (93.8)	
Triethanolamine	Yes	12 (6.8)	2 (4.3)	10 (7.8)	0.734[a]
	No	163 (93.1)	44 (95.7)	119 (92.2)	
Bronopol	Yes	3 (1.7)	0	3 (2.3)	0.567[a]
	No	172 (98.3)	46 (100)	126 (97.7)	
Chlorhexidine	Yes	1 (0.6)	0	1 (0.8)	0.999[a]

Table 2 (*Continued*)

Tested substances		Relevant positive patch tests (n = 175); n (%)	Relevant positive patch tests by sex		p-value
			Male (n = 46); n (%)	Female (n = 129; n (%)	
	No	174 (99.4)	46 (100)	128 (99.2)	
Coconut fatty acid diethanolamide	Yes	2 (1.1)	1 (2.2)	1 (0.8)	0.458[a]
	No	173 (98.8)	45 (97.8)	128 (99.2)	

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p-value demonstrates the association between the variables sex and positivity in the patch test for each substance evaluated.
[a] Fisher's exact test.
[b] Pearson's Chi-Square test.

27.0%), followed by administrative functions (n = 19, 19.0%), and beauty professionals (n = 11, 11.0%). Most of the cases (n = 53, 53.0%) presented clinically as dyshidrosiform eczema, compared to only 28.0% (n = 21) of patients with other diagnoses (p = 0.001). Regarding the topography of the lesions, 81.0% (n = 81) of the patients manifested lesions on the palms (n = 81), 49.0% (n = 49) on the back of the hands and 37.0% (n = 37) also presented involvement of the feet. The frequency of injuries on the back of the hands was higher in this group (n = 49, 49.5%) compared to the ones with other diagnosis (n = 26, 34.7%) with statistical significance (p = 0.050). Oral prednisone was prescribed to 40.0% of these individuals during follow-up, compared to only 18.7% of patients with other diagnoses (p = 0.002). Among the patients who were discharged due to regular control of the condition, only 32.6% (n = 14) had ACD, compared with 65.2% (n = 86), of those who were not discharged (p < 0.001).

Six patients had endogenous vesicular hand dermatitis. Four of these patients (66.7%) were discharged due to regular control of the condition.

Discussion

The present study reveals the six-and-a-half-year experience with hand dermatitis at a dermatology-specialized clinic at a tertiary Brazilian hospital. In the sample, 73.3% of the patients were female, with a mean age of 42 years at the onset of clinical manifestations. Female sex has been considered a risk factor for hand eczema development, which is probably due to a higher exposure to triggers, as predominantly female occupations, related to aesthetics, cleanliness, and health, involve frequent hand contact with humidity and hygiene products.[1,18–20] It should also be considered that women probably most often seek medical care.[21] The gender distribution and the mean age at hand eczema onset were similar in the present study and in a recently published Brazilian investigation.[20]

Concerning the relatively long mean time (46-months) between the beginning of the condition and the beginning of outpatient follow-up, it possibly reflects patients' delay in seeking medical care for not considering hand dermatitis a disease or even because they are not aware of the treatment options.[3,22] It is also possible that the condition is not valued or accurately diagnosed by some healthy professionals.[3,22]

It was a statistically significant association between occupation categories and occupational dermatitis diagnosis, with the highest prevalence of occupational disease in professionals with cleaning and tidying functions in non-domestic environments (94.1%), beauty professionals (92.3%), occupations related to domestic care (86.0%), Industry and mechanical metallurgy professionals (80.0%), civil construction professionals (75.0%) and healthcare professionals (70.6%). These data are in agreement with the recent Brazilian literature.[20,21] An increase in hand dermatitis incidence is usually associated with wet work, possibly due to impairment of the skin barrier.[3,18,21,23] In addition, some occupations are frequently exposed to allergic and irritating triggers. A systematic review with meta-analysis demonstrated a significantly increased risk of contact dermatitis in healthcare professionals, hairdressers, factory workers, painters, metallurgists, and cleaners.[23]

The average DLQI score was 7.8 points, which means a moderate effect on patients' QOL, similar to previous studies' results.[15,22,24–26] It should be considered, however, that this tool may not be sufficient to analyze the magnitude of QOL impairment in hand dermatitis patients, since seriously impacted aspects, such as work capacity, are poorly represented, while other aspects less affected by the disease are valued.[17]

Only 6.9% patients in this sample had AD, which may have been underestimated due to the absence of the disease's clinical manifestations during the appointments and the lack of patients' accuracy to identify a previous condition. The exclusion of patients with eczematous lesions on other locations than hands and feet may also explain the lower frequency of AD patients. AD is considered an important risk factor for the development of hand dermatitis.[1,3,18–20,27,28] In the cohort study conducted by Koskelo et al. (2022), AD was confirmed in 72.4% of hand eczema patients, while in the meta-analysis by Quaade et al. (2021) the pooled proportion of adults with current or previous hand dermatitis and a history of AD was 34.4%.[1,19]

The authors have observed that women had a higher positivity frequency for MCI/MI and nickel sulfate in patch tests, while male patients presented higher positivity for potassium bichromate and carba mix. The main sensitizers found in the present study are in agreement with the literature.[20,21,29–36]

MCI/MI is used as a preservative in cosmetics, detergents, water-based paints, and industrial products. Therefore, sensitization occurs mainly in domestic occupations, cleaning workers, beauticians, painters and industrial workers; and some studies pointed to the female gender as a risk factor for this sensitization.[29–31] It is expected a reduction in the sensitivity rates to this preservative in Brazil since the National Health Surveillance Agency (ANVISA, Agência Nacional de

Vigilância Sanitária) issued a note stipulating the restriction of MCI/MI concentration at up to 15 ppm in personal products sold in the country, to be complied with before August 2024.[20,37]

Nickel is the main contact allergen in most industrialized countries, with a prevalence of approximately 8% to 19% in adults and a strong predominance in women compared to men (4–10 times).[32] Cutaneous exposure occurs from metallic items, detergents, and cosmetics, while systemic exposure occurs through food, water, surgical implants, and dental materials.[32]

Potassium bichromate is present in cement and leather products. It is considered the most common contact dermatitis trigger in civil construction workers and a statistically significant association between sensitization to this substance and male sex has been demonstrated.[33–35]

Carba mix is a mixture of rubber-accelerating substances, used in rubber industrial production for shoes, tires and gloves.[36] Warshaw et al. (2020) have demonstrated that patients sensitized to carba mix were more likely to be male and to have occupational dermatitis compared to individuals who did not react to this allergen.[36]

Concerning hand dermatitis treatment, emollients were prescribed to all patients in the study. These are considered a key component in hand dermatitis treatment, promoting the epidermal barrier recovery and helping to control symptoms.[7] Topical corticosteroids, which are considered a first-line pharmacological treatment for hand dermatitis, were used in almost all cases.[4] Topical calcineurin inhibitors can be considered in cases requiring long-term treatment.[5,7] In the present sample, 31.0% of patients received oral prednisone cycles to optimize clinical control, and oral antihistamines were used in 80.0% of cases, mainly to control pruritus. These findings are similar to what has already been previously described and recommended.[4,5,7]

Of the women studied, 62.0% presented ACD on the hands, while this diagnosis was confirmed in 43.5% of the male patients. The occupational category related to domestic care was the most frequent among patients with ICD and ACD, which coincides with the recent Brazilian literature.[20] Hand ICD manifested lesions on the palms in 69.0% of the cases. It has been described that irritating eczema is usually limited to exposure sites, generally the palms of the hands and the back of the fingers.[2,5] However, lesions on the palms, in the present sample, were more prevalent in cases of ACD. The authors emphasize, at this point, the limitation imposed by the data collection from medical records and the difficulty in establishing a relationship between the etiology and clinical findings of HD, which is a disease with a dynamic clinical course.[20] Lesions on the back of the hands were also more prevalent in cases of ACD, which is in line with the literature since it is pointed out that lesions in ACD are usually well demarcated at the site of exposure – mainly the back of the hands, fingers and wrists.[2,5]

Most of the patients who were discharged from the outpatient clinic after regular clinical control had a diagnosis of ICD. It can be justified by the possibility of controlling the irritant condition with behavioral changes, not depending on the exclusion of one or more specific triggers, as in the case of allergic conditions, which can be more difficult to perform. In fact, there are studies pointing to ACD as a risk factor for a poor long-term prognosis.[3]

In this sample, patients with dyshidrosiform eczema presented a higher percentage of patch test positivity for MCI/MI, nickel sulfate and paraphenylenediamine. The association between dyshidrosiform eczema and sensitization to nickel sulfate and paraphenylenediamine has already been described in the literature.[38–40] This aspect reinforces the importance of doing patch tests in patients with hand eczema.

As limitations, the authors point out the data collection from medical records, which in some cases lacked information, such as DLQI scores, smoking habits and lesions' precise topography. The frequency of patients with AD may have been underestimated. Furthermore, as this is a cross-sectional study, it was not possible to assess cause-and-effect relationships between the variables.

Conclusions

This Brazilian investigation of hand dermatitis presents epidemiological, clinical, diagnostic, and therapeutic aspects of the patients. The data reinforces the importance of patch tests in HD investigation and highlights the high sensitivity rates to MCI/MI and nickel sulfate in Brazilian women and to potassium bichromate and carba mix in Brazilian men patients.

Hand eczema is an important condition since its high prevalence and usually chronic course accounts for a significant portion of occupational diseases and compromises patients' QOL. It should be developed health education activities both to prevent the disease and to promote its control as early as possible.

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Authors' contributions

Larissa Relva da Fonte Gonçalves Endlich: Data curation; formal analysis; investigation; methodology; visualization, writing-original draft.

Luciana Paula Samorano: Conceptualization; investigation; methodology; project administration; supervision; validation; visualization; writing-review & editing.

Ricardo Spina Nunes: Formal analysis; investigation.

Vitor Manoel Silva dos Reis: Conceptualization; investigation; methodology; project administration; supervision; validation; visualization; writing-review & editing.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Histopathological analysis of the skin of renal transplant recipients submitted to three different immunosuppression regimens☆

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KEYWORDS
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Abstract

Background: Renal transplant recipients (RTRs) use a combination of immunosuppressive agents: a corticosteroid; a calcineurin inhibitor (cyclosporine or tacrolimus) and an antimetabolic agent (azathioprine [AZA] or a mycophenolic acid precursor [MPA] – Mycophenolate mofetil or sodium) or an mTOR inhibitor (mTORi) – sirolimus or everolimus. These treatments increase the incidence of various neoplasms, especially non-melanoma skin cancers (NMSCs).

Objectives: To evaluate the histopathological alterations in the skin of the RTRs under three different immunosuppressive regimens: one mTORi (sirolimus or everolimus); or one antimetabolic agent (MPA or AZA), comparing them by groups and with healthy controls.

Methods: This was a cross-sectional comparative study of 30 patients selected from the Renal Transplant Service and divided into three groups: mTORi (n = 10), MPA (n = 10), and AZA (n = 10). The control group consisted of 10 immunocompetent non-transplanted volunteers. All RTRs were using tacrolimus and prednisone. Each participant underwent two biopsies of intact skin: one in a sun-protected and another in a sun-exposed area. The specimens were analyzed without previous information on which group they belonged to.

Results: The most significant histopathological change was thinning of the epidermis in the mTORi group, both in photoexposed and photoprotected skin.

Study limitations: The study was conducted on a limited number of patients, which may influence the representativeness of the results.

☆ Study conducted at the Clinical Hospital, Faculty of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil.

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Conclusions: Only RTRs treated with mTORi presented interruption of epidermal proliferation. These findings help to understand the influence of these different types of immunosuppressive regimens and their subsequent potential effects on carcinogenesis.
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Introduction

Organ transplantation, particularly in renal transplant recipients (RTRs), has made extraordinary progress largely due to the optimization of immunosuppressive regimens, significantly contributing to reducing graft rejection rates and increasing survival, both for the organ and the patient. The strategies used to reduce immunogenicity involve the use of drugs that block the action of immune system cells.[1] In the maintenance phase, a combination of three therapeutic classes is used: a corticosteroid (prednisone) combined with a calcineurin inhibitor (CNI; tacrolimus [TAC] or cyclosporine [CsA]) and an antiproliferative agent: azathioprine (AZA) or a mycophenolic acid precursor (MPA) (mycophenolate mofetil [MMF] or mycophenolate sodium [MPS]). Alternatively, one of these agents can be replaced by a mammalian target of rapamycin inhibitors (mTORi), such as everolimus (EVE) or sirolimus (SRL, also called rapamycin). Subsequent changes, such as minimization and conversion, are only recommended when due to adverse events or related to efficacy or safety failures.[2]

The use of immunosuppressive drugs has several side effects, including cutaneous ones, particularly non-melanoma skin cancers (NMSCs), responsible for approximately 90% of all skin cancers in RTRs, which have different epidemiology and pathogenesis compared to the general population.[3–9] With a much higher incidence in RTRs, NMSCs generate substantial morbidity and mortality due to their common recurrence and higher metastatic potential. Among NMSCs, squamous cell carcinoma (SCC) is the most commonly found type, surpassing basal cell carcinoma (BCC).[10] The SCC/BCC ratio is 3-4:1, with the inverse being observed in the general population. The incidence rates of NMSCs increase steadily with time after transplantation. It is estimated at about 2.25% in one year to 4.95% in two years, 7.43% in three years, and then increases to 10%-27% and 40%-60% after 10 and 20 years of immunosuppression, respectively.[11] In large series, it is observed that RTRs show an estimated 65 to 250-fold increase in the incidence of SCC and a 10-fold increase in the incidence of BCC when compared to immunocompetent populations.[12–14] This epidemiological reversal increases with greater sun exposure and post-transplant time lapse.[15–19] RTRs have an increased risk of developing skin cancer in photoexposed skin areas, as well as immunocompetent individuals.

Different mechanisms by which drugs may contribute to the development of skin cancer include systemic immunosurveillance impairment and a direct oncogenic effect.[14,16,20] An aggravating factor is exposure to ultraviolet radiation (UVR), because, in addition to interacting with certain drugs by increasing skin photosensitivity, it causes gene mutations and exerts local or systemic immunosuppression.[21–23] Most tumors occur on photoexposed skin, in fair-skinned individuals, and in those with a history of chronic sun exposure and/or episodes of sunburn in childhood.[24–26] UVR causes genetic mutations in epidermal keratinocytes, which affect cell cycle regulation, suppress the immune response, inhibit the expression and activity of antigen-presenting cells, and compromises the antigen recognition of neoplastic cells in RTRs. The geographic location where transplant recipients reside is an aggravating factor, due to the degree of sun exposure. Patients living in countries with high sun exposure, such as Australia, have skin cancer risks of 45% and 70%, after kidney transplantation at 11 and 20 years, respectively, and those living in countries with limited sun exposure, such as the Netherlands, have post-transplant risks of 10% and 40% at 10 and 20 years, respectively.[13,27,28] Other factors that put the general population at risk for NMSCs are also associated with higher risk in RTRs. These include older age, mainly due to the cumulative rate of sun exposure; fair skin (low phototypes, Fitzpatrick I–III), history of prior skin cancer, and actinic keratoses. Additional risks include the immunosuppressive treatment duration, immunosuppression intensity, older age at the time of transplantation, depletion of CD4 cells in the blood, and human papillomavirus infection.[5,14,29–32]

Before the discovery of the skin immune defenses, the cutaneous interface was seen only as a passive barrier between the individual and the environment. In recent decades it has become evident that the mechanical aspects of epidermal defense are reinforced by a versatile and robust immune surveillance system.[33] The specific role of immunosuppressive drugs in the development of SCCs has been the subject of many studies in recent years. It is presumed that immunosurveillance impairment contributes greatly to the higher incidence of these neoplasms. The pro-oncogenic effects of AZA have been known since the early years of organ transplantation. The oncogenic effects of MPA precursors are not clearly defined.[34,35]

The action mechanisms of the three immunosuppressants assessed in this study are summarized below.[36]

AZA is a purine analog that is incorporated into cellular DNA, where it inhibits purine nucleotide synthesis and interferes with RNA synthesis and metabolism. AZA leads to the accumulation of its metabolite 6-thioguanine nucleotide in the DNA chain, transforming it into a chromophore that absorbs light in the UVR-A spectrum and thus is able to function as a source of oxidative photoproducts. A mechanism of indirect damage can also be identified through the inhibition of repair mechanisms in the keratinocytes of the epidermis and the consequent persistence of photoproducts from UVR type B (UVR-B).

MPA is a reversible, selective, non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), an enzyme important in the *de novo* synthesis of purine, which acts as a catalyst in the production of *de novo* guanosine triphosphate required for lymphocyte proliferation.

Blocking IMPDH inhibits many lymphocyte functions, without significantly affecting other cells. MMF is the semisynthetic 2-morpholinoethyl ester of MPA that has shown bioavailability, tolerability, and efficacy. Adverse effects on the gastrointestinal tract are frequent and to minimize them, a MPS formulation was developed, which has a gastroresistant coating, dissolving only in the intestine. The use of these drugs is associated with a significantly lower risk of developing malignancy compared with non-MPA-based immunosuppression regimens.

mTOR is a key kinase in the process of cell division. SRL and EVE have a similar action. They bind to a plasma immunophyllin, FKBP12 (FK binding protein), forming the rapa/FKBP12 complex that inhibits mTOR (hence they are called mTOR inhibitors: mTORi). This reduces the transduction of activation signals and proliferation of lymphocyte membrane receptors, especially those associated with the interleukin-2 receptor and the CD28 lymphocyte co-stimulation receptor.

The aim of this study was to comparatively analyze the histopathological alterations in the photoprotected and photoexposed skin of renal transplant recipients using three different immunosuppressive drug regimens (mTORi, MPA, and AZA), comparing them with non-transplanted immunocompetent individuals. At the same time, an analysis was performed on the same material on the immunohistochemical expression of B lymphocytes, total T lymphocytes, T-helper lymphocytes, cytotoxic T lymphocytes and Langerhans cells, which has already been published.[37]

Material and methods

This research was approved by the Ethics Committee for the Analysis of Research Projects of the Institution, under number 1.685.977, and is in accordance with the ethical standards of the national and international committees on experimentation on human beings (Declaration of Helsinki). Participants were selected from the population of kidney transplant recipients who were undergoing regular outpatient follow-up at the Renal Transplant Service (RTS) of the institution. Written informed consent was obtained from all subjects who agreed to participate in this study.

Inclusion and exclusion criteria

Renal transplant patients, of both genders, aged 18 years or older, who were undergoing stable immunosuppressive regimens containing mTORi or MPA or AZA, for a minimum of 12 months and a maximum of 72 months were included. All patients were also receiving tacrolimus and prednisone. Induction therapy was carried out with thymoglobulin (ATG) or basiliximab. Renal failure influences immunological factors and may act as a potential bias on the studied outcome. For this reason, the selected patients had stable renal function, with an estimated glomerular filtration rate (eGFR) equal to or greater than 45 mL/min/1.73/73 m^2, corresponding to stage $\leq$ G3a of the KDIGO (Kidney Disease: Improving Global Outcomes) classification and estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. The patients had phototypes II, III, IV or V, according to Fitzpatrick classification (1988). The patients were separated in three groups: group 1 or mTORi group: patients using mTOR inhibitors (EVE or SRL); group 2 or MPA group: using mycophenolic acid precursors (MMF or MPS); group 3 or AZA group: on azathioprine. Transplant recipients of any organ other than the kidney; skin phototypes I and VI, according to Fitzpatrick's classification (extreme phototypes could act as bias); those with previous and/or current neoplastic events; immunodeficiencies unrelated to kidney transplantation; and patients using immunosuppressants other than those indicated in this study were excluded. For comparison, healthy non-transplanted individuals (Control Group – CG) consisting of volunteers aged 18 years or older, of both genders and who had no history of skin disease, were included. Similarly, individuals with skin phototypes I and VI according to the Fitzpatrick classification, with a history of previous and/or current neoplastic events, and primary or secondary immunodeficiencies were excluded.

The following variables were investigated in all study individuals: gender, age (completed years), skin phototype, serum creatinine levels (in mg/dL) in the last three months, and corresponding eGFR. For transplant recipients, the following clinical variables were evaluated: type of induction therapy (ATG or basiliximab); type of maintenance immunosuppressant (EVE, SRL, MPS, MMF or AZA), and the duration of maintenance immunosuppression (in full months).

Two biopsies of intact skin were performed, both in patients and controls, one on the inner surface of the arm (area not exposed to solar radiation - photoprotected) and another on the dorsum of the ipsilateral hand (area exposed to sunlight - photoexposed). A 4-mm punch was used after infiltrative local anesthesia with 2% lidocaine, without vasoconstrictor. The samples were placed in 10% formaldehyde fixing solution buffered with phosphate salts at 7.4 pH. The specimens were processed by routine histological techniques and embedded in paraffin. Sequential histological sections of 4 μm thickness were made, mounted on glass slides and stained with hematoxylin-eosin.

The histopathological analysis was performed without prior knowledge of the group to which the specimens belonged. The evaluated variables were: (A) stratum corneum of the epidermis, classifying it according to the morphological type into three categories: basket weave, lamellar and compact. (B) Stratum granulosum of the epidermis, defined by the morphological aspect of the cutaneous sites of non-glabrous skin according to thickness in three categories: normal or usual thickness (presence of one to three cell layers), hypergranulosis, when there was thickening of this stratum (number of layers greater than three), and agranulosis, when this layer was absent. (C) The number of stratum spinosum cell layers in the epithelial cones (three cones/biopsy) and in the segments of the epidermis between epithelial cones (three segments/biopsy), with arithmetic means/biopsy being recorded. (D) Degree of solar elastosis, defined as the intensity of the pale or basophilic elastotic material present in the dermis as: mild (fibrillar); moderate (fibrillar and amorphous); intense (amorphous); absent (without the presence of this material in the dermis). (E) Lymphocytic inflammatory infiltrate, was categorized by the amount of cells present around superficial and/or deep vascular structures in the dermis as: mild; moderate; intense; or absent.

Table 1 Demographic, clinical, and laboratory data.

Variables	Control	mTORi	MPA	AZA	p
Sample size (n)	10	10	10	10	–
Age (mean, SD)	44.7 (14.6)	55.5 (19.2)	49.5 (11.9)	49.6 (17.07)	0.517[a]
Gender n (%)					0.971[b]
Female	5 (50.0)	4 (40.0)	5 (50.0)	6 (60.0)	
Male	5 (50.0)	6 (60.0)	5 (50.0)	4 (40.0)	
Phototype, n (%)					
II	2 (20.0)	3 (30.0)	2 (20.0)	2 (20.0)	0.999[b]
III	3 (30.0)	3 (30.0)	3 (30.0)	3 (30.0)	
IV	3 (30.0)	2 (20.0)	2 (20.0)	2 (20.0)	
V	2 (20.0)	2 (20.0)	3 (30.0)	3 (30.0)	
Immunosuppression time, mean (SD)	–	42.7 (13.26)	47.7 (9.34)	42.1 (14.18)	0.550[a]
Induction, n (%)	–				0.893[b]
ATG	–	3 (30.0)	5 (50.0)	4 (40.0)	
Basiliximab	–	7 (70.0)	5 (50.0)	6 (60.0)	
Creatinine mean (SD)[d]	0.86 (0.18)	1.39 (0.26)	1.06 (0.26)	1.25 (0.32)	<0.001[a]
eGFR, median (p.25; p.75)	106.8 (70.4; 111.65)	48.6 (46.98; 53.35)	71.9 (60.74; 81.87)	50.4 (57.29; 91.36)	<0.001[c]

The data are presented as n, absolute number with percentages (%), mean (standard deviation) and median (p.25; p.75: 25th and 75th percentiles, respectively). ATG, Antithymocyte Globulin; AZA, Azathioprine Group; SD, standard deviation; mTORi, mTOR Inhibitors Group; MPA, Mycophenolic Acid Group; n, Observed absolute frequency; p, Level of statistical significance; Conventional sign used: – No numerical data is applicable; eGFR, Estimated Glomerular Filtration Rate.

[a] ANOVA.

[b] Fisher's test.

[c] Dunn's test with Bonferroni correction.

[d] Only the mTORi, MPA, and AZA groups were included in the statistical analysis, since the individuals in the control group had both functionally normal native kidneys and were excluded from the analysis.

Sample size calculation and statistical analysis

To determine the number of participating individuals (n), the sample size was calculated, using a significance level of 5% and a power of 80%. The calculated sample consisted of ten individuals in each group.[37] Thus, 30 renal transplant patients and ten healthy volunteers were included. Absolute (n) and relative (%) frequencies were used for categorical variables, respectively. In these analyses, Fisher's exact test was used to compare the qualitative variables between the groups; Dunn's test with Bonferroni post-estimation for quantitative variables without normal distribution and ANOVA with Bonferroni correction for those with normal distribution. Means and standard deviations (SD) and medians and interquartile range (IQR) were used for quantitative variables. The program used was Stata® (StataCorp, LC) version 11.0.

Results

Demographic, clinical, and laboratory data

These data are summarized in Table 1.

Histopathological evaluation results

The results of the histopathological evaluation of photoprotected and photoexposed skin sections are depicted in Tables 2 and 3.

The photoprotected skin showed stratum corneum in basket weave (31/40; 77.5%) and lamellar (9/40; 22.5%) patterns. These findings were the same in the photoprotected skin of the four groups. On the other hand, the analysis of photoexposed skin fragments showed a thick and compact stratum corneum in 30 cases (30/40, 75%; Fig. 1).

The stratum granulosum of the epidermis was present with its usual thickness in the photoprotected skin of individuals in all groups (40/40; 100%; Table 2). On the other hand, the skin exposed to sunlight showed hyperplasia of the stratum granulosum of the epidermis (hypergranulosis) in 13 individuals, which corresponds to 32.5% of the individuals in this sample (13/40), six of them in the MPA group (6/10; 60%), four in the AZA group (4/10; 40%), two in the control group (2/10; 20%) and one in the mTORi group (1/10; 10%; Table 3).

Regarding dermal alterations, the most significant finding was solar elastosis of the photoexposed skin (Fig. 2). All skin specimens from photoexposed areas showed extensive solar elastosis in the superficial dermis. Intense elastotic alteration was observed in the photoexposed skin with the presence of abundant amorphous basophilic material in the superficial dermis of 28 individuals (28/40; 70%) and moderate elastotic alteration in 12 individuals, characterized by the presence of fibrillar basophilic material and some amorphous areas in the superficial dermis (12/40; 30%; Table 3). On the other hand, in photoprotected skin, mild elastotic alteration was observed with minimal fibrillar basophilia in the papillary dermis in 27 individuals (27/40; 67.5%) and absence of dermal elastosis in 13 (13/40; 32.5; Table 2).

Table 2 Distribution of histopathological data on photoprotected skin, according to groups.

Variables	TOTAL	Control	mTORi	MPA	AZA	p
Number of layers						
Between cones	5.3	5.10	4.40	6.30	5.40	<0.001[a]
(mean, 95% CI)	(5.02; 5.58)	(4.94; 5.26)	(4.15; 4.65)	(5.72; 6.88)	(4.98; 5.82)	
In the cones	7.64	7.37	5.97	8.97	8.27	<0.001[a]
(mean, 95% CI)	(7.22; 8.07)	(6.82; 7.91)	(5.55; 6.38)	(8.39; 9.54)	(7.75; 8.78)	
Stratum corneum n (%)						
Compact pattern	–	–	–	–	–	>0.999[b]
Basket weave pattern	31 (77.5)	8 (80.0)	8 (80.0)	8 (80.0)	7 (70.0)	
Lamellar pattern	9 (22.5)	2 (20.0)	2 (20.0)	2 (20.0)	3 (30.0)	
Granular layer n (%)						
Agranulosis	–	–	–	–	–	–
Usual thickness	40 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	
Hypergranulosis	–	–	–	–	–	
Elastosis n (%)						
Absent	13 (32.5)	4 (40.0)	3 (30.0)	3 (30.0)	3 (30.0)	>0.999[b]
Mild	27 (67.5)	6 (60.0)	7 (70.0)	7 (70.0)	7 (70.0)	
Moderate	–	–	–	–	–	
Intense	–	–	–	–	–	
Perivascular lymphocytic inflammatory infiltrate n (%)						
Absent	14 (35.0)	3 (30.0)	3 (30.0)	4 (40.0)	4 (40.0)	>0.999[b]
Mild	25 (62.5)	6 (60.0)	7 (70.0)	6 (60.0)	6 (60.0)	
Moderate	1 (2.5)	1 (10.0)	–	–	–	
Intense	–	–	–	–	–	

The data are presented as n, absolute number with percentages (%) and means. AZA, Azathioprine Group; SD, standard deviation; 95% CI, 95% Confidence Interval; mTORi, mTOR Inhibitors Group; MPA, Mycophenolic Acid Group; n, Observed absolute frequency; p, Level of statistical significance; Conventional sign used: – No numerical data is applicable.

[a] ANOVA.

[b] Fisher's test.

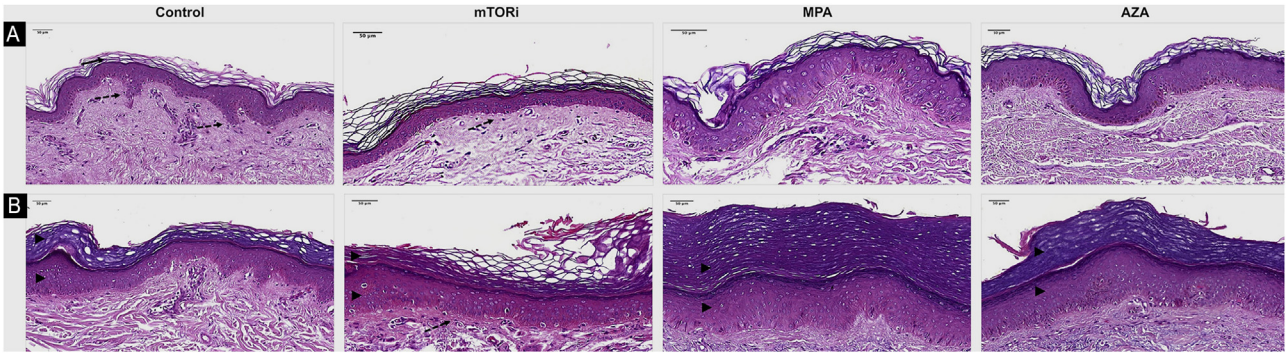

Figure 1 Histopathological differences related to the epidermal analysis of photoprotected (A) and photoexposed (B) skin of the control groups and renal transplant recipients submitted to immunosuppression regimens with mTOR inhibitors (mTORi), Mycophenolic Acid (MPA) and Azathioprine (AZA). The control group exhibits a basket weave pattern in the stratum corneum, typical of healthy non-acral photoprotected skin (arrow) and well-demarcated epithelial cones (discontinuous arrow). The mTORi group reveals a lamellar pattern in the stratum corneum, reduced number of epidermal cell layers, and rectification of the epithelial cones, both in photoprotected skin (discontinuous arrow; A) and in photoexposed skin (B). As a rule, photoexposed skin samples (B) exhibit thicker epidermis with hyperkeratosis and increased number of cell layers in the epithelial cones and in the epidermal segments between the cones, aspects which are more pronounced in the MPA (arrowheads) and AZA groups. (Hematoxylin & eosin, ×40; scale bar 50 m).

Table 3 Distribution of histopathological data on photoexposed skin, according to groups.

Variables	TOTAL	Control	mTORi	MPA	AZA	p
Number of layers						
Between cones	7.27	7.23	5.39	8.66	7.79	<0.001[a]
(mean, 95% CI)	(6.81; 7.74)	(6.64; 7.83)	(4.87; 5.92)	(8.10; 9.23)	(7.10; 8.50)	
In the cones	10.02	9.63	7.83	11.40	11.20	<0.001[a]
(mean, 95% CI)	(9.37; 10.66)	(8.30; 10.97)	(6.92; 8.74)	(10.97; 11.83)	(9.92; 12.48)	
Stratum corneum n (%)						
Compact pattern	30 (75.0)	8 (80.0)	6 (60.0)	9 (90.0)	7 (70.0)	0.720[b]
Basket weave pattern	3 (7.5)	–	2 (20.0)	–	1 (10.0)	
Lamellar pattern	7 (17.5)	2 (20.0)	2 (20.0)	1 (10.0)	2 (20.0)	
Granular layer n (%)						
Agranulosis	–	–	–	–	–	0.105[b]
Usual thickness	27 (67.5)	8 (80.0)	9 (90.0)	4 (40.0)	6 (60.0)	
Hypergranulosis	13 (32.5)	2 (20.0)	1 (10.0)	6 (60.0)	4 (40.0)	
Elastosis n (%)						
Absent	–	–	–	–	–	0.963[b]
Mild	–	–	–	–	–	
Moderate	12 (30.0)	3 (30.0)	3 (30.0)	4 (40.0)	2 (20.0)	
Intense	28 (70.0)	7 (70.0)	7 (70.0)	6 (60.0)	8 (80.0)	
Perivascular lymphocytic inflammatory infiltrate n (%)						
Absent	25 (62.5)	5 (50.0)	6 (60.0)	6 (60.0)	8 (80.0)	0.662[b]
Mild	15 (37.5)	5 (50.0)	4 (40.0)	4 (40.0)	2 (20.0)	
Moderate	–	–	–	–	–	
Intense	–	–	–	–	–	

The data are presented as mean and respective 95% Confidence Intervals. AZA, Azathioprine Group; SD, standard deviation; 95% CI, 95% Confidence Interval; mTORi, mTOR Inhibitors Group; MPA, Mycophenolic Acid Group; n, Observed absolute frequency; p, Level of statistical significance; Conventional sign used: – No numerical data is applicable.

[a] ANOVA.

[b] Fisher's test.

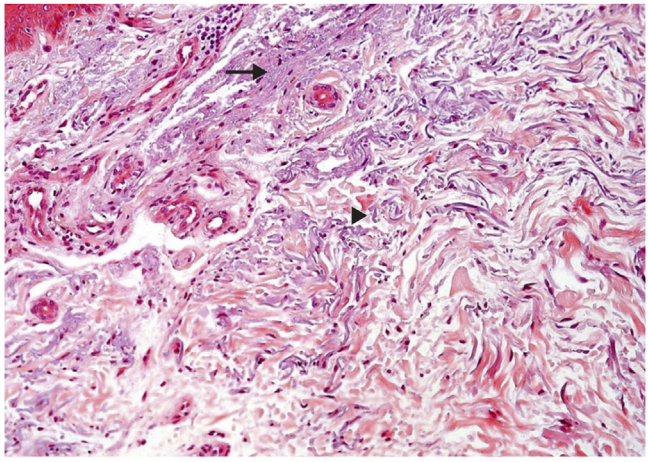

Figure 2 Histopathological characterization of dermal findings in photoexposed skin of a renal transplant recipient of the mTORi group. Solar elastosis is characterized by amorphous (arrow) and fibrillar (arrowhead) basophilic areas in the dermal connective tissue, where elastic fibers lose their usual characteristics. (Hematoxylin & eosin, ×200). mTORi, mTOR Inhibitors Group.

Regarding the inflammatory dermal infiltrate, the presence of perivascular lymphocytes was discrete, or even absent, both in photoexposed and photoprotected skin of transplant recipients and controls. The photoprotected skin revealed a lymphocytic infiltrate around the superficial dermal vessels of moderate intensity in one individual (1/40; 2.5%) of the control group and mild in 25 individuals (25/40; 62.5%). Of the latter, seven were in the mTORi group (7/10; 70%), six in the MPA group (6/10; 60%), six in the AZA group (6/10; 60%) and six in the control group (6/10; 60%; Table 2). On the other hand, in the skin exposed to sunlight, mild dermal superficial perivascular lymphocytic infiltrate was observed in 15 individuals (15/40; 37.5%). Of these, five were in the control group (5/10; 50%), four in the mTORi group (4/10; 40%), four in the MPA group (4/10; 40%), and two in the AZA group (2/10; 20%; Table 3).

There were differences in the mean number of cell layers in the epidermal cones ($p < 0.001$) and in the segments of the epidermis between the cones ($p < 0.001$) of photoprotected and sun-exposed skin among the four groups. It was observed that the highest mean values of the number of cell layers in the cones and in the epidermal segments between the cones were found in patients in the MPA and AZA groups. These findings were observed both in photoexposed skin and photoprotected skin of individuals in the MPA group.

Discussion

Regarding demographic data, the study groups were homogeneous, with no significant differences in gender, age, or skin phototype. From the point of view of clinical data, the characteristics related to the type of induction and duration of the immunosuppressive regimen were similar in patients of the three groups. No differences were found regarding the time of exposure to the three drugs. These data thus allowed a fair comparison between the groups. The comparative analysis of the renal function in the groups (performed only in the RTRs, since there is no comparison with healthy controls who have both native kidneys) indicated that the mean serum creatinine level was higher in the mTORi group than in the AZA and MPA groups, while the eGFR was higher in the MPA group than in the mTORi and AZA groups; however, it was not possible to provide a reliable explanation for these findings.

Some morphological findings were seen equally in the photoprotected skin of the four groups, revealing mild skin changes that do not seem to be linked to photoexposure or immunosuppressive therapy. On the other hand, epidermal thinning associated with mTORi therapy was the most remarkable histopathological alteration in this study, characterized by a decrease in the epidermal thickness due to the reduction in the number of stratum spinosum layers. This was seen in both the photoprotected and photoexposed skin of this group when compared to the epidermal thickness of the other groups. This reduction in epidermal proliferation may represent a lower risk of occurrence of carcinogenic mutations, configuring epidermal thinning in the mTORi group as a potential protective effect against carcinogenesis in RTRs. This finding of epidermal thinning of the skin in the mTORi group was corroborated by a study that showed a reduction in the proliferation of progenitor cells of the basal layer, leading to a thinned epidermis during embryonic development. Moreover, it should be considered that the mTOR pathway is also involved in the epidermal growth factor receptor action, which is a potent activator of many kinases, including serine/threonine kinase mTOR.[38] In the photoexposed skin specimens of all the study groups, when compared with photoprotected skin, epidermal hyperplasia was observed resulting from the greater proliferation of keratinocytes, which confirms that this type of pathological alteration in the skin is mediated by UVR-B. This alteration was more prominent in photoexposed skin of the MPA and AZA groups. These data related to the greater thickness of the stratum spinosum of the epidermis in an area of photoexposed skin is not an unusual finding, and this reactional effect to sun exposure has already been well described. One study showed that stimulation of the epidermis by UVR-B promotes hyperproliferation of basal layer cells in the cones and in the segments of the epidermis between the cones, with an increase in the number of cell layers.[39] The higher epidermal proliferation seen in the photoexposed skin of the MPA, AZA, and control groups, when compared to the mTORi group, does not exclude the role of UVR-activated mTOR pathway signaling in cell proliferation and of the pro-survival signaling cascades of epidermal keratinocytes from the skin of these patients.

Conclusions

The histopathological analyses performed comparatively on the skin of RTRs using the mTORi, MPA and AZA immunosuppression regimens, in comparison with a control group, showed that mTORi was superior in relation to the others, regarding the maintenance of some control mechanisms that may be linked to cutaneous carcinogenesis, since only mTORi presented epidermal proliferation. The most unique morphological alteration of this study was the skin epidermal thinning of RTRs treated with mTORi in both photoexposed and photoprotected skin of these patients.

Based on the data obtained in this study, it can be suggested that the use of mTORi therapy, when compared to the use of MPA and AZA may be recommended as the immunosuppressive regimen in patients who already have skin neoplasias or who are at increased risk for developing skin cancers related to photoexposure, such as NMSCs. However, there are not enough data to define whether it would be better to replace MPA or AZA with mTORi in patients with established skin cancer or whether it would be more advantageous to add the medication to the regimen being used. In the case of AZA, specifically, because it is recognized as carcinogenic, it is possible that it is better to suspend it and replace it by mTORi.

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Authors' contributions

Maria Victória Quaresma: Main Investigator.

Luiz Sergio Azevedo: Design and planning of the study; supervisor of the nephrological part and review of the manuscript.

Elias David-Neto: Coordinator of the service and review of the manuscript.

Mírian Nacagami Sotto: Design and planning of the study; advisor of the histological part and review of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Psoriasis and cardiovascular risk: associated and protective factors☆

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Abstract
Background: Psoriasis is an inflammatory skin disease associated with Metabolic Syndrome (MetS), Steatotic Liver Disease (SLD) and cardiovascular risk. However, the effect of anti-inflammatory therapy on cardiovascular risk is uncertain.
Objectives: To determine the relationship between anti-inflammatory therapy and subclinical atherosclerosis in individuals with psoriasis, using the gold standard carotid-femoral Pulse Wave Velocity (cf-PWV) measurement. Additionally, to evaluate the association between cf-PWV, steatosis and Advanced Fibrosis (AF) using Transient Elastography (TE) by Fibroscan®.
Methods: Cross-sectional study including psoriasis patients submitted to cf-PWV and TE. Steatosis was defined as a controlled attenuation parameter $\geq$ 275 dB/m, AF as liver stiffness measurement $\geq$ 10 kPa, and increased Aortic Stiffness (AoS) as cf-PWV $\geq$ 10 m/s. Significant cumulative methotrexate dose was $\geq$ 1500 mg (MTX1500). Logistic regression analysis evaluated the independent variables associated with increased AoS.
Results: Eighty patients were included (mean age 56.2 $\pm$ 11.5-years, 57.5% female, BMI 28.6 $\pm$ 5.3 kg/m^2). Prevalences of MetS, diabetes mellitus, dyslipidemia, systemic arterial hypertension, steatosis and AF were 57.5%, 40.0%, 67.5%, 70.0%, 50.0% and 16.3%, respectively. MTX1500 was present in 45%, immunobiological treatment in 33.8%, and cf-PWV $\geq$ 10 m/s

☆ Study conducted at the Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil, and Hospital Federal de Bonsucesso, Rio de Janeiro, RJ, Brazil.

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in 21.2%. On logistic regression analysis, age was independently related to cf-PWV ≥ 10 m/s (OR = 1.21; 95% CI 1.06–1.38; p = 0.003) and MTX1500 was a protective cardiovascular factor (OR = 0.18; 95% CI 0.038–0.87; p = 0.033). No association was observed between steatosis, AF or immunobiological therapy and cf-PWV ≥10 m/s.
Study limitations: Sample size.
Conclusion: In patients with psoriasis, increased AoS was associated with age, but not with steatosis or AF. A protective cardiovascular effect of MTX was found in a psoriasis population with a high prevalence of MetS and its components.
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Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease, which prevalence in Western countries is around 2%–4%,[1] and is associated with Metabolic Syndrome (MetS).[2] Psoriatic patients have a two-fold risk of Steatotic Liver Disease (SLD) compared to non-psoriatic controls,[3] and it increases the risk of Advanced Fibrosis (AF), cirrhosis, and cardiovascular disease.[4] Methotrexate (MTX) and Immunobiological (IB) therapy are effective anti-inflammatory strategies in psoriasis. On the last decades, liver fibrosis in psoriasis has been more associated with MetS and SLD than to the cumulative MTX dose.[5–7]

Long-term inflammatory status is associated with MetS and atherosclerosis.[8] Aortic Stiffness (AoS), assessed primarily by carotid-femoral Pulse Wave Velocity (cf-PWV), is an accurate marker for subclinical atherosclerosis.[9] Interestingly, it has been also described an association between increased arterial stiffness and advanced liver fibrosis, independent of other traditional cardiometabolic risk factors.[10] In type 2 Diabetes Mellitus (T2DM) patients with SLD, a high or increasing aortic stiffness predicted the development of advanced liver fibrosis on Transient Elastography (TE).[11]

Thereby, considering the potential association between psoriasis, cardiovascular risk and SLD, the aim of this study was to evaluate the prevalence of subclinical atherosclerosis assessed by AoS and relationships with MTX and IB therapy. Advanced liver fibrosis and steatosis, assessed respectively by transient elastography (FibroScan®) and Controlled Attenuation Parameter (CAP), were additionally evaluated regarding the possible independent association with cardiovascular risk in psoriasis.

Methods

Study design and patients

This was a cross-sectional study from 2020 to 2022 of outpatients with established psoriasis diagnosis (clinically and/or histologically), followed by the dermatology division at two tertiary centers, Hospital Federal de Bonsucesso and Hospital Universitário Clementino Fraga Filho, with at least 18-years-old, regardless of the type of psoriasis specific treatment.

Exclusion criteria were: HIV, hepatitis B and hepatitis C infected patients, as well as those with other etiologies for chronic liver diseases, except Metabolic-Associated Steatotic Liver Disease (MASLD); use of hepatotoxic drugs in the last six months; use of steatogenic drugs (except MTX), like systemic corticosteroids, amiodarone, valproic acid and tamoxifen in the last two years or systemic chemotherapy in the last five years; daily alcohol intake greater than 20 g for women and 30 g for man in the last five years; conditions that could interfere with liver stiffness analysis (liver congestion, ascites, serum aminotransferase values greater than 5 times the upper normal limit, cholestasis and pregnancy). The Local Ethic Committee of both hospitals approved the study and all patients have signed an informed consent form.

Study procedures

Individuals included in the study were submitted to anthropometric, clinical and laboratory evaluation, measurement of cf-PWV and liver stiffness /CAP measurements using TE. Blood sample collection for metabolic evaluation, Liver Stiffness Measurements (LSM), and the measurement of cf-PWV were performed on the same day.

Demographic, clinical and laboratorial variables

Demographic (sex, age), anthropometric (Body Mass Index [BMI], abdominal circumference) and clinical (diagnosis of T2DM, systemic arterial hypertension, dyslipidemia, MetS according to ATPIII criteria)[12] data were collected. Data regarding clinical psoriasis characteristics were time since psoriasis onset (time since the first cutaneous lesion onset, reminded by the patient), use of IB therapy (anytime) and cumulative MTX dose. Cumulative MTX doses ≥1500 mg were considered at risk for liver fibrosis.[5] Laboratorial data included Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gammaglutamyl Transferase (GGT), total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glycated haemoglobin and platelet count. Liver enzymes (AST, ALT and GGT), were analyzed as absolute values and as indexes (absolute value/upper normal limit).

Liver stiffness and controlled attenuation parameter measures

Liver stiffness measurement was performed with at least 3 hours of fasting by a single experienced operator using Fibroscan® TOUCH 502 (Echosens, France) with M and XL probes designed for this device. The used technique was previously described.[13] Only results with 10 valid shots, success

rate >60% and an Interquartile Interval (IQR)/median liver stiffness ratio <30% were included in the analysis. The results were expressed in kilopascals (kPa). CAP was simultaneously evaluated within valid LSM and was expressed in decibels per meter (dB/m). The XL probe, designed to evaluate measurements between 35 mm and 75 mm in depth (against 25–65 mm in the M probe), was used in those patients who failed to obtain valid measurements with the M probe. A cut-off of 10 kPa was used to rule out advanced fibrosis[14] and CAP results equal or greater than 275 dB/m defined the presence of steatosis.[15]

Measurement of carotid-femoral pulse wave velocity (cf-PWV)

The cf-PWV was measured by the validated Complior SP device and software (Arthech Medical, Paris, France), by a single experienced operator. Carotid and femoral waveforms were recorded simultaneously using mechanotransducers applied directly to the skin, positioned in correspondence to the right carotid internal artery and right femoral artery. The software measured the difference in time (in milliseconds) elapsed between the beginning of the carotid and femoral pulse waves. The distance between the two points, the carotid-femoral distance (in centimeters), was measured directly and multiplied by 0.8.[16] Two measurements were obtained from each patient, the result was the mean of the two measurements. If the difference between the two measurements was more than 0.5 m/s, a third measurement was taken. Cf-PVW was considered increased if $\geq$ 10 m/s.[16]

Statistical analysis

Data was recorded in case report forms and entered in SPSS 21.0 software (IBM Corp, Armonk, New York). Categorical and continuous variables were analyzed and expressed as frequencies for categorical variables, means with standard deviations, and medians with interquartile intervals for continuous variables. Univariate analysis was performed using the Chi-Square or Fisher test for categorical variables, and Student's *t*-test or Mann-Whitney test for continuous variables, as appropriate. For the identification of variables independently associated with the presence of cf-PWV $\geq$ 10 m/s, binary logistic regression analysis was performed. The variables included in the model were those with clinical plausibility or p-values <0.20 on the univariate analysis. The level of significance adopted was 5%, with descriptive levels (p) below this value being considered statistically significant.

Results

From 2020 to 2022, eighty patients were included (mean age 56.2 $\pm$ 11.5 years, 57.5% females, BMI 28.6 $\pm$ 5.3 kg/m^2). The median duration of illness was 252-months (86–383 months). All patients had successful cf-PWV and LSM measurements, as well as blood sample collection. Demographic, anthropometric, and clinical data are shown in Table 1. In univariate analysis, only age, T2DM, systemic arterial hypertension and cumulative MTX dose $\geq$ 1500 mg were associated with cf-PWV $\geq$10 m/s (the latter inversely associated) (Table 2). MetS, steatosis and advanced liver fibrosis were not associated with increased aortic stiffness. Variables included on logistic regression were age, sex, T2DM, systemic arterial hypertension, LSM (kPa) and cumulative MTX dose $\geq$ 1500 mg.

Beyond MTX use, age was the only other independent factor associated with cf-PWV $\geq$ 10 m/s. Cumulative MTX dose $\geq$1500 mg, presented in 45% of the population, represented a cardiovascular protective factor, but not IB use (Table 3).

Table 1 Clinical-demographic and laboratorial data of patients with psoriasis.

Variables	n = 80
Clinical-demographic characteristics	
Female gender (%)	57.5
Age (years)	56.2 $\pm$ 11.5
BMI (Kg/m^2)	28.6 $\pm$ 5.3
Abdominal circumference (cm)	101.7 $\pm$ 12.6
Type 2 Diabetes (%)	40.0
Arterial Hypertension (%)	70.0
Dyslipidemia (%)	67.5
Metabolic Syndrome (%)	57.5
Time since psoriasis onset (months)	252.0 (85.8–383.3)
Cumulative MTX dose $\geq$ 1500 mg (%)	45.0
Immunobiological treatment (%)	33.8
Laboratory	
ALT index	0.47 (0.34–0.67)
AST index	0.51 (0.44–0.74)
GGT index	0.54 (0.37–0.79)
LDL (mg/dL)	121.0 $\pm$ 37.0
HDL (mg/dL)	46.0 (37.5–55.0)
Triglycerides (mg/dL)	133.5 (85.0–182.5)
Platelet count ($\times$10^3)	256.5 $\pm$ 76.1
Liver Transient Elastography	
LSM (kPa)	5.6 (4.4–8.7)
LSM (kPa) $\geq$ 10 (%)	16.3
CAP (dBm)	273.5 $\pm$ 51.9
CAP (dB/m) $\geq$ 275 (%)	50.0
Carotid-femoral pulse wave velocity	
cf-PWV (m/s)	8.8 $\pm$ 2.0
cf-PWV $\geq$ 10 m/s (%)	21.2

Values are proportions for categorical data, mean (SD) for normally distributed data and medians (interquartile intervals) for non-parametric data. BMI, Body Mass Index; ALT index, Absolute ALT value/upper normal limit; AST index, Absolute AST value/upper normal limit; GGT index, Absolute GGT value/upper normal limit; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; LSM, Liver Stiffness Measurement; CAP, Controlled Attenuation Parameter; cf-PWV, Carotid-femoral Pulse Wave Velocity.

Discussion

This study, conducted on psoriasis patients with a high prevalence of MetS and its components such as T2DM, dyslipidemia, and systemic arterial hypertension, demonstrated a protective cardiovascular effect of cumulative MTX dose $\geq$1500 mg on subclinical atherosclerosis, using cf-PWV

Table 2 Comparative analysis between patients with psoriasis with and without increased aortic stiffness (cf-PWV ≥ 10 m/s).

	cf-PWV < 10 m/s (n = 63)	cf-PWV ≥ 10 m/s (n = 17)	p-value
Age (years)	53.7 ± 11.2	65.7 ± 6.7	<0.001
Female gender (%)	58.7	52.9	0.66
BMI (Kg/m^2)	28.9 ± 5.5	27.6 ± 4.6	0.18
Type 2 Diabetes (%)	31.7	70.6	0.004
Arterial Hypertension (%)	63.5	94.1	0.014
Dyslipidemia (%)	63.5	82.4	0.14
Metabolic Syndrome (%)	54	70.6	0.21
CAP (dB/m)	274.7 ± 49.6	269.1 ± 61.1	0.34
CAP ≥ 275 dB/m (%)	50.8	47.1	0.78
LSM (kPa)	5.4 (3.6)	7.1 (3.7)	0.20
LSM ≥ 10 kPa (%)	17.5	11.8	0.57
Time since psoriasis onset (months)	252.0 (299.4)	240 (289.5)	0.98
Cumulative MTX dose ≥ 1500 mg (%)	50.8	23.5	0.04
Immunobiological treatment (%)	36.5	23.5	0.31

Values are proportions for categorical data, means (SD) for normally distributed data and medians (interquartile ranges) for non-parametric data. Univariate analysis was performed using the Chi-Square or Fisher test for categorical variables, and Student's *t*-test or Mann-Whitney test for continuous variables. BMI, Body Mass Index; ALT index, Absolute ALT value/upper normal limit; AST index, Absolute AST value/upper normal limit; GGT index, Absolute GGT value/upper normal limit; N/A, Not Applicable; CAP, Controlled Attenuation Parameter; cf-PWV, Carotid-femoral Pulse Wave Velocity.

Table 3 Final regression model for independently associated variables with the presence of increased aortic stiffness (cf-PWV ≥ 10 m/s).

Covariates[a]	Odds Ratio	p	95% CI
Age	1.21	0.003	1.06–1.38
Cumulative MTX dose ≥ 1500 mg	0.18	0.033	0.038–0.87

CI, Confidence Interval.
[a] Adjusted for age and sex.

measurement for AoS. Although a high prevalence of SLD was found in this population, increased AoS was not associated with steatosis or AF.

Individuals with psoriasis have well-established increased arterial stiffness when compared to controls,[9,17,18] and in most of the studies, it is independent of the effect of traditional risk factors, like smoking status, systemic arterial hypertension, and BMI. It suggests that psoriasis itself confers increased cardiovascular risk, probably due to chronic inflammation. The medium cf-PWV measurement in our study was 8.8 ± 2.0 m/s, and it was similar to most of the studies using cf-PWV for comparative analysis.[9,19] All previous studies in psoriasis were case-control, and none of them used the established recommendations for the measurement of cf-PWV, defined by a standard cut-off value of 10 m/s for the prediction of cardiovascular events.[16] Therefore, our study was the first to report the prevalence of increased AoS using a standard value of cf-PVW ≥10 m/s on a population of psoriasis patients.

Our prevalence of PWV ≥ 10 m/s was 21.2%, similar to the 25% prevalence found on 477 patients with type 2 diabetes from the study nested within the Rio de Janeiro Type 2 Diabetes Cohort Study,[20] also a population with high cardiovascular risk. Of note, increased AoS was not independently associated with MetS and its components in our study, and this corroborates with the hypothesis that psoriasis itself could increase cardiovascular risk.

As MASLD is itself a risk factor for atherosclerosis,[10,21] evaluation of aortic stiffness may be useful to predict both cardiovascular and liver fibrosis risk in this population. Increased aortic stiffness could be the ''hallmark'' to link the multiple inflammatory and cytokine-mediated mechanisms from the Hepato-Dermal Axis hypothesis,[22,23] as it reflects the long-term effects of established and unknown risk factors[18] for cardiovascular and hepatic complications. Our study is the first to evaluate the association between arterial stiffness with SLD in psoriasis. Unfortunately, we could not show this link between liver fibrosis and early atherosclerosis, probably due to a rather small sample size. Hence, studies with larger sample sizes are necessary to better clarify this potential relation.

The independent association between age and increased AoS reflects the pathophysiological processes caused by aging on arterial walls extracellular matrix composition.[18,24] Curiously, the duration of disease in our study had no association with increased AoS, although it has been previously reported in a case-control study,[25] which confirmed this association even after adjustment for confounders (age, weight, height, heart rate and central mean pressure). We could hypothesize that, in our study, patients using MTX had a benefit in cardiovascular risk, minimizing the effect of disease duration.

The protective effect of MTX on subclinical atherosclerosis in psoriasis found in our study is scarce in the

literature. Using carotid or brachial intima-media thickness and endothelial function measurements, results with MTX and IB are divergent.[21,26] In our study, we evaluated subclinical cardiovascular risk (not cardiovascular events) with the gold standard method and could demonstrate the anti-inflammatory effect of MTX on cardiovascular risk, despite the high prevalence of cardiovascular co-morbidities like arterial hypertension, dyslipidemia and MetS itself in more than 50% of patients. This data highlights the role of inflammation in atherosclerosis regardless of the metabolic phenotype.[27,28] We could not demonstrate the same protective effect with IB therapy, probably due to the smaller number of patients using IB and/or the fact that it is a more recent therapy for psoriasis.

When analyzing cardiovascular events, three meta-analyses with patients presenting systemic inflammation (mainly rheumatoid arthritis),[29–31] MTX treatment was associated with reduced incidence of cardiovascular events. On Horreau et al.[29] systematic review, exclusively in psoriasis patients, two large retrospective studies found a protective effect of MTX on major cardiovascular events incidence. In one of them, treatment with MTX and biological agents was also associated with reduced risk of death and cardiovascular disease events in patients with severe psoriasis in a subsequent real-world analysis.[32]

There are some limitations in our study. The cross-sectional design does not allow causality to be proven. Disease severity was not measured, and associations were not performed regarding this variable. Sample size could have compromised the potential associations between liver fibrosis and early atherosclerosis, as well as a potential protective effect of IB on cardiovascular risk. Nevertheless, most of the case-control studies that established significantly higher AoS in psoriasis patients involved samples ranging from 20 to 73 patients.[18]

Conclusion

A protective cardiovascular effect of MTX on subclinical atherosclerosis was found in a psoriasis population with a high prevalence of MetS and its components.

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Authors' contributions

Luciana Agoglia: Critical literature review; data collection, analysis and interpretation; preparation and writing of the manuscript; statistical analysis; study conception and planning.

Helena Peixoto: Data collection, analysis and interpretation.

Ana Carolina Cardoso: Intellectual participation in propaedeutic and/or therapeutic management of studied cases; approval of the final version of the manuscript.

Lívia Barbosa: Intellectual participation in propaedeutic and/or therapeutic management of studied cases; aproval of the final version of the manuscript.

Cecília S.X.L. Victer: Intellectual participation in propaedeutic and/or therapeutic management of studied cases; approval of the final version of the manuscript.

Sueli Carneiro: Intellectual participation in propaedeutic and/or therapeutic management of studied cases; approval of the final version of the manuscript.

Gil F. Salles: Manuscript critical review; approval of the final version of the manuscript.

Cristiane A. Villela-Nogueira: effective participation in research orientation; manuscript critical review; preparation and writing of the manuscript; statistical analysis; study conception and planning.

Maria Chiara Chindamo: Effective participation in research orientation; manuscript critical review; preparation and writing of the manuscript; statistical analysis; study conception and planning.

Conflicts of interest

None declared.

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Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.abd.2024.07.013.

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ORIGINAL ARTICLE

Pyoderma gangrenosum: a 22-year follow-up of patients in a tertiary reference hospital in Brazil☆

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KEYWORDS
Pyoderma gangrenosum;
Sweet syndrome;
Skin ulcer

Abstract
Background: Pyoderma gangrenosum (PG) is a rare dermatosis often associated with systemic diseases. There are autoinflammatory mechanisms with neutrophilic infiltrate and necrosis. Due to the high morbidity, variable response to therapy and lack of treatment standardization, PG constitutes a highly burdensome condition.
Objectives: To evaluate the epidemiological, clinical and laboratory features and response to therapy of patients with PG followed at HCFMUSP.
Methods: This retrospective and descriptive study included patients with confirmed PG under follow-up at HCFMUSP from January 2000 to August 2021. Data were retrieved from medical records.
Results: Fifty patients were included. The mean time from the onset of symptoms to diagnosis was 26.5 months. Lesions predominated on the lower extremity in 72% (n = 36/50), and the ulcerative type was the most common (n = 43/50; 86%). Local pain was mentioned in 39/50 (78%) and 12/50 (24%) presented pathergy. The most frequently associated diseases were inflammatory bowel disease (n = 10/20; 20%) and hidradenitis suppurativa (n = 10/20; 20%). High-dose systemic corticosteroid was mostly the first therapy (88%), either alone (n = 7/50; 14%) or in association with classic immunosuppressants or immunobiologicals (n = 37; 74%). Most patients (n = 32/50; 64%) had at least one hospitalization. Disease control was achieved in 44/50 (88%), with recurrences in 48% (n = 24/50) and total healing without medication in 24% (n = 12). Sixteen patients (32%) were treated with at least 1 immunobiological agent in addition to classic drugs.
Study limitations: Retrospective, descriptive design and number of patients.
Conclusions: There was delay in diagnosis, association with systemic and cutaneous conditions, and the need for prolonged immunomodulatory or immunosuppressive therapy (classic agents and also biologic agents) to control PG.
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☆ Study conducted at the Clinical Hospital, Faculty of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil.

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Introduction

Pyoderma gangrenosum (PG) is an uncommon dermatosis, characterized by the accumulation of neutrophils in the dermis, hypodermis, and, rarely, in internal organs.[1] PG affects 3–10 people per million per year,[1] especially adult women, but can occur at any age.[2] PG lesions are considered an autoinflammatory manifestation resulting from dysregulation of innate immunity and overproduction of inflammatory mediators (such as interleukins 1 and 17, tumor necrosis factor-alpha) that promote tissue neutrophilic infiltration.[1,3]

Clinical presentation of PG is polymorphous and includes the ulcerative (or classic), pustular, vegetative, and bullous (or atypical) variants. The ulcerative form is the most common, evolving from papules or pustules into painful ulcers with well-defined violaceous border and undermined edge. It mainly affects the lower limbs and is often associated with inflammatory bowel disease (IBD), inflammatory arthropathies, IgA gammopathy and neoplasms. The pustular variety, also associated with IBD, is characterized by pustules on the trunk and lower limbs that regress without scarring or may progress into classic PG. The vegetative form presents as a slow-growing single violaceous plaque or abscess, usually on the trunk, which heals with a cribriform pattern. Bullous PG is characterized by rapidly progressing blisters usually on the face and upper limbs, that progress to necrosis. It is frequently associated with hematologic diseases such as myeloid leukemia, lymphoma, monoclonal gammopathy, and myelodysplastic syndrome. Chronic PG that affects the oral and labial mucosa is called pyostomatitis vegetans. PG may also develop in other organs including lungs, kidneys, bones and eyes.[4]

PG may also be associated with HIV and hepatitis C infections, systemic lupus erythematosus, diabetes mellitus and psoriasis.[5,6] It may also be induced by drugs such as cocaine, propylthiouracil and antipsychotics. It may also occur in the context of autoinflammatory syndromes, such as PAPA (pyogenic arthritis, PG and acne), SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) and PASH (PG, acne and hidradenitis suppurativa). Traumas, including surgical procedures, may worsen or trigger lesions, a phenomenon called pathergy. Postoperative pyoderma gangrenosum has been documented after orthopedic, cardiothoracic, general, plastic, and gynecological surgery. The challenge in diagnosis arises from its lack of recognition, its tendency to mimic wound infections and exacerbation after debridement (a standard practice for treating wound infections) due to pathergy.[6–26]

Once PG is suspected, a comprehensive evaluation is recommended including cutaneous biopsies for histopathological examination and cultures to rule out infectious, neoplastic, and autoimmune etiologies. The histopathology of PG is not specific showing mixed inflammatory infiltrate. Systemic workup includes the investigation of frequently associated diseases.[8–12]

Therapy varies according to PG severity, extension, associated diseases and patient tolerance, with the aim of reducing inflammatory activity, promoting wound healing, pain control and management of associated conditions. In addition, traumas such as surgical debridement and grafting should be carefully indicated, as they may worsen or trigger new lesions.[1,10] Systemic corticosteroids and cyclosporine are considered first-line therapy. Other immunosuppressants and immunobiological agents are often required due to the refractoriness of PG lesions.[8,12,27]

PG portends a high impact on patient's quality of life either because of the painful and disfiguring lesions or due to the associated comorbidities.[4] The delay in diagnosis due to the rarity of the disease and the inexperience of health professionals, the socioeconomic burden related to the time spent with medical care, adverse drug effects and hospital admissions further contribute to increased PG morbidity.[1,3,9]

The objective of this study is to outline the clinical, epidemiological, laboratory and therapeutic profile of patients with PG under follow-up at Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (University of São Paulo Medical School Hospital) from January 2000 to August 2021.

Methods

After ethics committee approval (CAAE: 57067622.0.0000.0068), this retrospective and descriptive study included all patients with PG under follow-up at the Dermatology Department of HCFMUSP from January 2000 to August 2021. The diagnosis of PG was based on (1) clinical features, (2) compatible histopathological findings and (3) exclusion of other differential diagnoses.

Clinical records of patients were analyzed to obtain the following data: sociodemographic variables, previous diagnostic hypotheses, onset of symptoms, number and location of lesions, clinical subtypes, associated symptoms, comorbidities, laboratory and histopathological exams, medications, hospitalizations, time to achieve disease control and recurrences.

Categorical variables were expressed as frequencies and percentages. Means, standard deviation, median and minimum and maximum values were calculated for quantitative variables. The association between categorical variables was assessed using Pearson's Chi-Square test. The significance level adopted was 5%. Analyzes were performed using SPSS for Windows v.25 statistical software.

Results

Sociodemographic data

From January 2000 to August 2021, 50 patients were diagnosed with PG. There was a female predominance (n = 29/50; 58%). The mean age at the onset of symptoms was 33.7 years (3 to 65 years); 87.8% declared themselves white. Other sociodemographic characteristics are presented in Table 1.

Clinical features and comorbidities

PG was the single diagnostic hypothesis in 24 out of 50 (48%) cases. Mean age at diagnosis was 36.2 years (5 to 65-years), with a mean duration of symptoms of 26.5 months (0.25 to 480-months).

Multiple lesions (> 2) occurred in 19 out of 50 (38%) patients. The most frequent region was the lower extremity

Table 1 Gender, age at onset and skincolor of patients.

Aspects	n = 50		n (%)	$n_{missing}$
Gender	Female		29 (58.0)	
	Male		21 (42.0)	
Age at onset (years)	Means (SD)	33.7 (16.0)		
	Median (min-max)	30 (3-65)		
skin color (self-declared)	White		43 (87.8)	1
	Black		4 (8.2)	
	Brown		2 (4.1)	

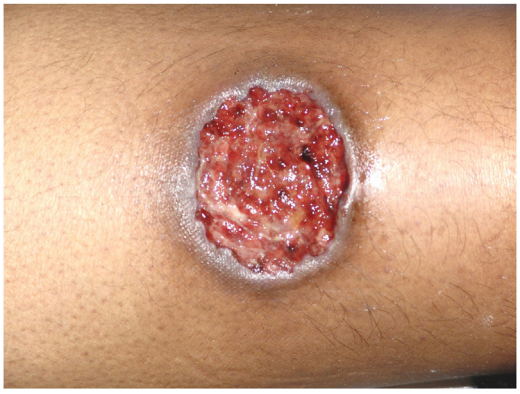

Figure 1 Clinical subtype of pyoderma gangrenosum – ulcerative.

Table 2 Number, location and subtype of lesions.

Aspects	n = 50	n (%)
Number of lesions at onset	1 lesion	18 (36.0)
	2 lesions	13 (26.0)
	>2 lesions	19 (38.0)
Location		
Lower limbs		36 (72.0)
Upper limbs		15 (30.0)
Head and Neck		12 (24.0)
Trunk		13 (26.0)
Oral		2 (4.0)
Other location	Breast; Genital	2 (4.0)
Clinical subtype		
Ulcerative		43 (86.0)
Pustular		1 (2.0)
Bullous		1 (2.0)
Vegetative		7 (14.0)
Pyostomatitis vegetans		2 (4.0)
Systemic Involvement	Pulmonar	1 (2.0)

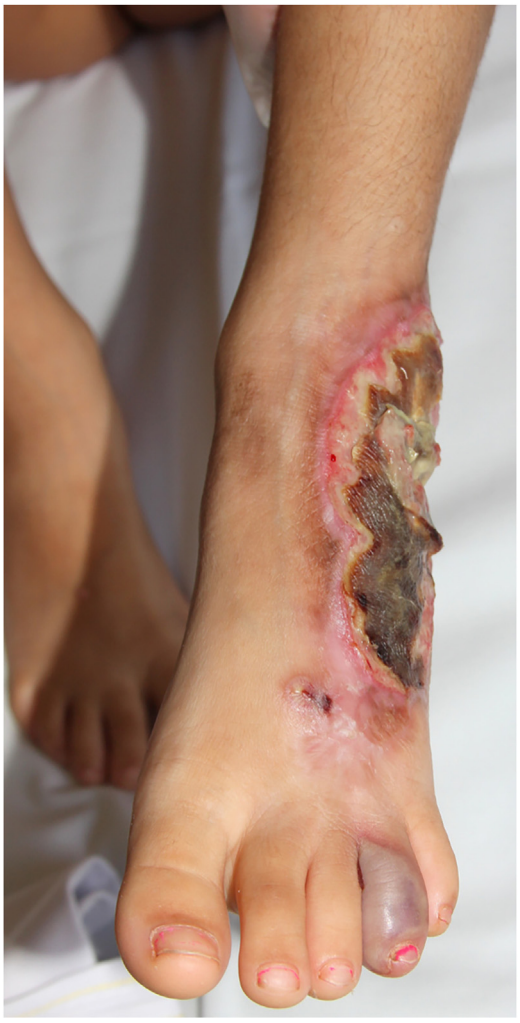

Figure 2 Clinical subtype of pyoderma gangrenosum – bullous.

(n = 36/50; 72%), followed by the upper extremity (n = 15/50; 30%), trunk (n = 13/50; 26%) and head and neck (n = 12/50; 24%). The ulcerative subtype (Fig. 1) was the most common (n = 43/50; 86%) (Table 2). Two patients had oral involvement and one had systemic involvement (lungs). Twenty patients (40%) had lesions in more than one location, and the association of lower and upper limbs was the most frequent one (n = 7/20; 35%). When multiple lesions were presented, the ulcerative subtype was the most found (n = 17/20; 85%). Bullous and vegetative subtypes are illustrated in Figs. 2 and 3.

Local pain, usually of extreme intensity was present in 39 (58% of the cases). Systemic symptoms were present in 40 (80%) cases: fever in 12 (24%), joint pain in 11 (22%) and weight loss in 7 (14.9%).

The associated comorbidities are detailed in Table 3.

Pathergy was noted in 14 (28%) cases; in 3 cases after medical procedures (breast biopsy, hepatectomy and grafting), the remaining following minor injuries.

Table 3 Associated conditions.

Aspects	n = 50 (%)
Associated conditions	40 (80.0)
Inflammatory bowel disease	10 (20.0)
Crohn's disease	3 (6.0)
Ulcerative colitis	7 (14.0)
Solid organ neoplasm	2 (4.0)
Prostate	1
Liver	1
Hematological disease	5 (10.0)
Monoclonal gammopathy	1
Policlonal gammopathy	1
Myelofibrosis	1
Myelodysplastic syndrome	2
Arthritis	6 (12.0)
Lupus arthritis	1
Psoriatic arthritis	1
Rheumatoid arthritis	3
Pyogenic arthritis	1
Hidradenitis suppurativa	10 (20.0)
PASH	2
PAPASH	2
PAPA	1
Undefined autoinflammatory disease	1
Triggered by medication	2 (4.0)
Isotretinoin	1
Tocilizumab	1
Infectious diseases	3 (6.0)
Hepatitis C	2
HIV	1
Other dermatosis except HS	7 (34.0)
Acne conglobata	1
Erythema annulare centrifugum	1
Lupus erythematosus	1
Psoriasis	1
Subcorneal pustulosis	1
Sweet's syndrome	1
Vitiligo	1
Pyoderma activity associated with comorbidity activity (n = 40)	**6 (15.4)**
Pathergy	14
Grafting	1
Hepatectomy	1
Breast biopsy	1
Minor injury[a]	11
Family history of associated diseases	3 (6.0)
Crohn disease	2
Ulcerative colitis	1
Treatment-related comorbidities	
Arterial hypertension	11 (22.0)
Sepsis	7 (14.0)
Diabetes	5 (10.0)
Substance use	
Tobacco	14 (28)
Cocaine	2
Crack	1

[a] Dog Scratch, insect bite, hair removal, laceration, blunt trauma, piercing.

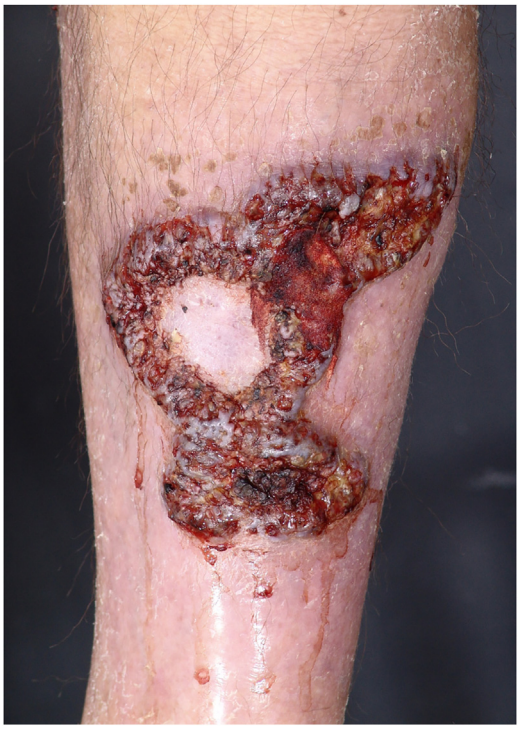

Figure 3 Clinical subtype of pyoderma gangrenosum – vegetative.

Laboratory and histopathological tests

Laboratory data are shown in Table 4.

Histopathological examination was available in 47 of the 50 cases, with a predominance of mixed inflammatory infiltrate (n = 27/47; 57.4%) followed by neutrophilic infiltrate (n = 16/47; 34%), granulomatous infiltrate (n = 13/47; 37.7%) and lymphohistiocytic infiltrate (n = 4/47; 8.5%). Detailed histopathological analysis is summarized in Table 4.

Treatment

Prednisone was used in 44 out of 50 cases (88%), as the sole medication (n = 7/50; 14%) or in association (n = 37/50; 74%). The second most used drug was dapsone (n = 36/50; 72%). Of note, dapsone alone resulted in complete disease control in 2 cases. Fourteen patients (28%) used cyclosporine in addition to other medications and sixteen patients (32%) used at least one immunobiological agent (Table 5). Among these 16 patients using immunobiologicals, 5 achieved complete healing making it possible to gradually taper down and eventually suspend prednisone and other agents. In ten cases, disease control was achieved using immunobiologicals in association with other classical immunosuppressants (Table 6). Control was not achieved in one PG + HS patient despite the association of high doses of prednisone, cyclosporine, and two different immunobiologicals (adalimumab and ustekinumab).

Of note, for 7 patients the main indication of immunobiological was PG; for 7 patients the main indication was IBD (5UC and 2CD); for one patient, psoriatic arthritis and

Table 4 Laboratorial and Histopathological aspects.

Aspects		n = 50 (%)	$n_{missing}$
Hemogram			
Anemia		34 (68.0)	0
Hemoglobin value	Means (SD)	11.6 (2.2)	0
	Median (min–max)	12 (6.3–16)	
Leukocytosis		25 (50.0)	0
Leukocytes value	Means (SD)	12289.8 (6345.0)	
	Median (min–max)	10815 (1108–34200)	
Inflammatory markers			
High C-reactive protein		32 (78.0)	9
C-reactive protein value	Means (SD)	64.7 (86.6)	
	Median (min–max)	22.8 (0.3–354.3)	
Ferritin	Low	4 (10.8)	13
	Normal	19 (51.4)	
	High	14 (37.8)	
Ferritin value	Means (SD)	290.1 (387.7)	13
	Median (min–max)	141 (7.4–1944)	
Hypogammaglobulinemia		5 (13.5)	13
Gammaglobulinemia value	Means (SD)	1.30 (0.60)	13
	Median (min–max)	1.20 (0.60–3.60)	
Histopathological		n = 47 (%)	
Inflammatory infiltrate	Lymphohistiocytic	4 (8.5)	3
subtype	Neutrophilic	16 (34.0)	
	Mixed	27 (57.4)	
Granulomatous infiltrate associated		13 (27.7)	3
Local of the inflammatory	Intraepidermal	14 (29.8)	3
infiltrate	Dermal	46 (97.9)	3
	Hipodermal	18 (38.3)	3
	Anexial	7 (14.9)	3

SD, Standard Deviation; min, minimum value; max, maximum value.

Table 5 Medication (isolated).

Aspects	n = 50 (%)	$n_{missing}$
Prednisone	44 (88.0)	
Cyclosporine	14 (28.0)	
Dapsone	36 (72.0)	
Doxycycline	5 (10.0)	
Colchicine	2 (4.0)	
Methotrexate	9 (18.0)	
Mycophenolate mofetil	5 (10.0)	
Azathioprine	13 (26.0)	
Immunobiologicals	16 (32.0)	
Infliximab	10 (62.5)	
Adalimumab	7 (43.8)	
Ustekinumab	4 (25.0)	
Secukinumab	2 (12.5)	
Belimumab	1 (6.3)	
Topical corticosteroid	14 (28.6)	1
Clobetasol	6	
Betamethasone	3	
Triamcinolone	2	
Clobetasol + triamcinolone	2	
Topical tacrolimus	9 (18.4)	1

for one patient, lupus arthritis (belimumab). Details about drugs, associations and outcome are described at Table 6.

Hospitalization and progression

Hospitalization was required in 32 out of 50 cases (64%) in order to control either PG, pain or infection.

Disease control (healing of ulcers, enabling dose tapering of the main medication, usually prednisone) was achieved in 44 out of 50 (88%) patients after an average of 3.56 months (median 1–34).

PG recurrence was observed in 49% of the cases, in most cases (70.8%) involving the same location of the initial lesion.

Complete disease remission occurred in 12 patients (24%), that are off therapy. Five patients required immunobiologicals to maintain disease control after total tapering of classic immunosuppressants. The median disease-free time was 37-months (12 to 192 months).

Patients using immunobiologicals were disease-free in 31.3% of cases, while patients not using immunobiologicals were disease-free in 35.3% of cases.

Discussion

PG may occur at any age, especially between 20 and 50 years, and predominate in females.[1] In this series, the mean age at diagnosis was 33.7 years and 58% of the patients were women, in accordance with the literature.[1–3] Eight (16%) patients were younger than 18 at the time of disease onset.

Table 6 Drugs and associations.

Drugs and associations	Total healing	Disease control	No disease control	Total
Dapsone	0	2	1	3 (6.0)
Prednisone	5	2	0	7 (14.0)
Prednisone + dapsone	6	10	2	18 (36.0)
Prednisone + dapsone + cyclosporine	1	3	2	6 (12.0)
Immunobiologicals	2	1	0	3 (6.0)
Prednisone + immunobiologicals	1	2	0	3 (6.0)
Prednisone + dapsone + immunobiologicals	1	1	0	2 (4.0)
Prednisone + cyclosporine + immunobiologicals	0	0	1	1 (2.0)
Prednisone + dapsone + cyclosporine + immunobiologicals	1	6	0	7 (14.0)
Total	17 (34.0)	27 (54.0)	6 (12.0)	50 (100.0)

In most cases (52%), PG was not the initial hypothesis, thus leading to a mean time from symptom onset to diagnosis of 26.5-months. These data demonstrate that PG still represents a diagnostic challenge possibly related to the rarity of the disease and multiplicity of differential diagnoses and being regarded as an exclusion diagnosis, despite its characteristic presentation.

Among the clinical subtypes, the ulcerative form is the most common[1,3–6] and was also the most frequent in this analysis (86%). Lesions predominantly affected the lower limbs, corroborating with previous studies.[1,4,5,8–10]

One of these cases had pulmonary involvement, which had been previously described in 42 case reports.[7–9] Pathergy is described in 25% to 50% of the cases,[3,5,11] and occurred in 24% of the studied patients.

The postoperative form of PG shows a lesser association with systemic diseases compared to other types of PG, with hematologic disorders being the most prevalent. The breast and abdomen are the most commonly affected areas in postoperative cases. On average, it develops around seven days after surgery. As it is often misdiagnosed as a wound infection, debridement can worsen the progression of the lesions. PG should be included in the differential diagnosis of postoperative wound dehiscence.[26]

Local pain, which is usually disproportionate to the size of the lesion, occurred in 78% of the present cases and 24% of the patients had a fever.[6] Binus et al. observed pain in 62.1% of the cases in a retrospective study including 103 PG patients.[6]

Systemic diseases, mainly IBD, inflammatory arthropathies, and hematological disorders[6,12,13] may precede, coexist, or follow the diagnosis of PG. Most of the patients (80%) had at least one associated condition. In this series, the most common non-dermatological condition was IBD (20%). PG may also occur in the context of a paraneoplastic syndrome. According to Shah et al., paraneoplastic PG usually presents as an ulcerative lesion on the extremities and is related to a breast tumor.[15] Two of the patients had a history of solid neoplasia (liver and prostate).

One patient developed Sweet's syndrome and 10 (20%) had HS. Six (12%) of the patients had associated autoinflammatory syndromes (PASH, PAPASH, PAPA and undefined autoinflammatory disease). The coexistence of PG and Sweet's syndrome has been reported.[19,20,28–33] Other dermatoses observed among the patients included: acne conglobata, lupus erythematosus (with lupus arthritis), psoriasis (with psoriatic arthritis), vitiligo, subcorneal pustulosis, and erythema annulare centrifugum.

In this series, 17 patients reported the use of tobacco (n = 14), cocaine (n = 1) and crack (n = 1). Keith et al. reported the association between PG and cocaine adulterated with levamisole. Cocaine has a toxic effect on endothelial cells and levamisole promotes vasculopathy, which are likely pathophysiological mechanisms in the development of PG.[21–23] One patient developed PG after acne treatment with isotretinoin and 1 patient after anti-IL6 therapy (tocilizumab) for rheumatoid arthritis. Drug-induced cases are uncommon and may be related to an abnormal migration and functionality of neutrophils, triggering a dysregulated inflammatory response and apoptosis of keratinocytes.[19,21,22]

Anemia occurred in most of the patients (68%) due to several factors including associated diseases (IBD, hematological disorders), PG chronicity, bleeding from the lesions, dapsone-induced hemolysis. The authors also observed leukocytosis and increased CRP, which may be attributed to the PG pro-inflammatory status, the frequent association with secondary infection, and peripheral neutrophilia induced by systemic corticosteroids.[11,23]

Intense neutrophilic infiltration was present in 34% of these cases, also affecting adnexa in 14.9%, and four of these cases (8.5%) had lymphohistiocytic infiltrate. Granulomatous infiltrate may also occur[1] and it was observed in 27.7% of these cases. Few studies have evaluated the histopathological features of PG. Chakiri et al. reported that among 14 patients with PG, a dense neutrophilic infiltrate occurred in all cases, with vasculitis in 4 cases and lymphoplasmacytic infiltrate in 5 cases.[1] The histopathologic findings of PG are not specific and vary according to the stage of the lesion. Initial lesions may show deep suppuration, often folliculocentric, with dense neutrophilic infiltrates.[1,11] After ulceration, there may be necrosis and hemorrhage, thrombosis of dermal or hypodermic blood vessels, with a lymphocytic infiltrate.[11]

PG treatment aims to reduce inflammatory activity and pain, promote wound healing, and control associated diseases.[2,11,24,25] It still poses a challenge as no specific therapy is currently available and there is no consensus on which treatment is most effective. Systemic corticosteroids are generally effective and considered the first-line treatment at a dose equivalent to 0.5–1 mg/kg/day of prednisone.

More resistant lesions require longer therapy (>3-months), increased doses, or association with other immunomodulatory agents. In the present study, most cases were treated with prednisone 0.25–1.5 mg/kg/day (88%) as primary line therapy.[1,2,4–6,11,24] Cyclosporine is also considered a first-line therapy often in association with prednisone in recalcitrant cases and was required in 28% of these cases at some point in the follow-up.[27]

Other immunosuppressants and immunomodulators may be indicated, such as dapsone, azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate. Immunobiological agents including infliximab, adalimumab, ustekinumab and canakinumab have also been utilized.[1,2,4–6,11,24] The second most used drug in our series was dapsone (72%) and two out of three patients achieved disease control with dapsone in monotherapy. Azathioprine was also used in 13 of our patients for the treatment of IBD, however, it showed no improvement in PG lesions.[1,2,4–6,11,24]

Immunobiologicals are promising therapeutic options due to their activity on inflammatory cytokines involved in the pathogenesis of PG, such as TNF-α, IL-1, IL-17.[2,4,24,27,28] Sixteen of our patients (32%) used at least 1 immunobiological agent once PG lesions were refractory to corticosteroid therapy (n = 9) or for the management of a comorbidity (n = 7). It has been demonstrated that some IBD patients have an adequate response only with immunobiologicals, suggesting that they should be considered as first-line therapy for the treatment of PG.[8,11,12]

Most patients required hospitalization at least once (32 cases, 64%), similar to the rate reported by Platzer et al. in a review of 36 cases (69.4%).[4] Seven (14%) of our patients developed sepsis during immunosuppressive therapy in at least one of the disease recurrences. Among these seven patients, 3 used prednisone + dapsone + cyclosporine + immunobiologicals; 1 used prednisone + dapsone + immunobiologicals; 1 used prednisone + immunobiologicals; and 2 used only prednisone. Infections are among the main causes of death in PG studies.[4,13] Two of our patients presented severe cataracts as a complication of prolonged use of prednisone. One patient developed irreversible nephropathy and demyelinating disease after prednisone and cyclosporine. These data may suggest the benefits of early introduction of immunobiologicals.

Disease control was achieved in 44 out of 50 patients (88%) after an average of 3.56 months, in agreement with the remission rates described.[3] PG recurrence occurred in 49% of our patients, mostly in the previous location (70.8%). Variable recurrence rates were reported in the literature (17%–61%) and were also more common in the primary lesion site.[3,4]

At the end of our follow-up, among 17 patients (34%) that were disease-free, five patients remained using immunobiologicals while 12 patients were off any maintenance therapy. All 5 patients who achieved complete disease remission with immunobiological had IBD (3UC and 2CD) and 3 also had HS. None of the 5 had a recurrence of lesions. These data provide additional evidence that patients with comorbidities may benefit from the early use of immunobiologicals.[8,11,12] Of note, 20 of 32 (62.5%) patients with idiopathic PG or HS-associated or syndromic PG controlled with classic immunosuppressants, and 6 (18.75%) of them only achieved disease control with immunobiologicals.

The main limitations of the present study are its retrospective nature, the descriptive design, and the number of patients. Therefore, although it seems like a small sample compared to more common diseases, PG is a rare disease, and this is one of the largest series ever published including Latin America and patients and with a long follow-up.

Conclusion

The present study confirms that PG is a rare disease, often difficult to diagnose and associated with systemic diseases, and autoinflammatory syndromes. Although systemic corticosteroids remain a first-line therapy, this data suggests that expanding the use of immunobiologicals early in the management of PG may represent a promising therapeutic tool to avoid disease recurrences and frequent hospitalizations.

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Authors' contributions

Livia Maria Oliveira Salviano: Approval of the final version of the manuscript; critical literature review; data collection, analysis and interpretation; effective participation in research orientation; intellectual participation in propaedeutic and/or therapeutic management of studied cases; manuscript critical review; preparation and writing of the manuscript; statistical analysis; study conception and planning.

Denise Miyamoto: Approval of the final version of the manuscript; effective participation in research orientation; intellectual participation in propaedeutic and/or therapeutic management of studied cases; manuscript critical review; study conception and planning.

Claudia Giuli Santi: Approval of the final version of the manuscript; effective participation in research orientation; intellectual participation in propaedeutic and/or therapeutic management of studied cases; manuscript critical review; study conception and planning.

Tatiana Mina Yendo: Approval of the final version of the manuscript; effective participation in research orientation; intellectual participation in propaedeutic and/or therapeutic management of studied cases; manuscript critical review; study conception and planning.

Maria Cecilia Rivitti-Machado: Approval of the final version of the manuscript; effective participation in research orientation; intellectual participation in propaedeutic and/or therapeutic management of studied cases; manuscript critical review; study conception and planning.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

The real-world burden of atopic dermatitis: MEASURE-AD results from Brazil, Mexico, and Argentina☆

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☆ Study conducted at the 14 study sites in Argentina, Brazil, and Mexico.

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KEYWORDS
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Abstract:
Background: Atopic dermatitis (AD) burden increases with disease severity.
Objective: Characterize the real-world burden of AD in Brazil, Mexico, and Argentina.
Methods: MEASURE-AD enrolled patients (≥12-years old) with moderate to severe AD receiving or candidates for systemic therapy between December 2019-December 2020. Patient characteristics, treatments, and outcomes were recorded during one office visit. Primary outcome measures included worst itch/past 24 hours (Worst Pruritus Numerical Rating Scale [WP-NRS]), quality of life (QoL, Dermatology Life Quality Index [DLQI] and Children's DLQI [CDLQI]).
Results: Of 180 patients (adults, n = 157; adolescents, n = 23), 52.2% were male, the mean (SD) age was 33.8 (17.0) years, and all were receiving AD treatment (65.6% systemic therapy). Severe pruritus (WP-NRS ≥ 7) was reported by 54.4% (adults, 57.3%; adolescents, 34.8%). A very/extremely large effect on QoL (DLQI/CDLQI ≥ 11) was reported among 50.0% of patients ≥ 16 years old and 42.9% of patients 12–15 years old. The mean Eczema Area Severity Index (EASI) was 17.0 (adults, 17.7; adolescents, 12.4); 3.9% of patients had clear skin (EASI 0) and 26.7% had severe AD (EASI 23–72). Over the previous 6 months, 0, 1–2, 3–4, 5–6, and > 6 flares were reported by 8.3%, 27.2%, 31.1%, 11.7%, and 15.6% of patients, respectively. On average, flares lasted 15.2 days (adults, 15.9 days; adolescents, 11.1 days).
Study limitations: Patient self-reported information and recall during one office visit.
Conclusions: Despite treatment, disease severity and impact on QoL were high, suggesting that AD is not adequately controlled in all patients, highlighting a considerable unmet need for effective treatments to reduce AD burden.
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Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, relapsing, inflammatory skin disease that often has a negative physical, psychological, and socioeconomic effect on patients' lives.[1,2] The burden of AD increases with disease severity and with the repeated occurrence of disease flares, adversely affecting patient Quality of Life (QoL).[2–4]

The management of AD aims to reduce symptoms (e.g., itch, pain, sleep disturbance), and inflammation, induce skin clearance, improve QoL, and control the disease over the long term.[1] Treatment strategy varies by disease severity, patient age, and country and can be influenced by treatment accessibility and local recommendations as well as differences in healthcare resources across countries and geographic regions.[5–9]

Few studies have reported AD disease severity and treatment patterns in Latin America. The overall prevalence of AD among children and adolescents from Latin America has been reported to range from 2.8% to 24.6% across countries,[10,11] whereas, generally, a lower prevalence has been reported among adults (Argentina, 3%–5%;[12,13] Brazil, Mexico, and Colombia, 2%–10%).[13,14] In three studies conducted in Brazil and Colombia, approximately two-thirds of patients were reported to have moderate to severe disease (65%–87% across studies and assessment methods).[15–17] In the same studies, the most common treatments included topical corticosteroids and oral antihistamines followed by systemic corticosteroids.[15–17] The use of biologic therapies remained low (approximately 10% of patients).[16,17] A negative impact on QoL, work productivity, and direct and indirect costs has also been reported.[15,16,18,19] However, gaps remain in the authors' understanding of the effect of AD on the lives of patients with moderate to severe disease in Latin America.

The objective of this analysis of the MEASURE-AD study was to assess the physical, psychological, and socioeconomic

burden of disease, treatment patterns, and Healthcare Resource Utilization (HCRU) in adolescent and adult patients with moderate to severe AD in Latin America who were receiving or were candidates for systemic therapy.

Methods

Study design and participants

MEASURE-AD was a cross-sectional, multicounty, observational cohort study conducted in 28 countries across Western Europe/Canada, Asia/Australasia, Eastern Europe/Middle East, and Latin America.[20] Reported here are results for patients enrolled in MEASURE-AD in three Latin American countries (Brazil, Mexico, and Argentina).

The study design has been reported previously.[20] Briefly, MEASURE-AD enrolled adults (≥18 years-old) and adolescents (12–17 years-old) with AD during a routine dermatology clinic or office visit between December 2019 and December 2020. Patients who had a physician-confirmed diagnosis of AD, had physician-assessed moderate to severe disease, and were either current candidates for systemic therapy for AD according to the healthcare professional, or were currently receiving systemic therapy for AD were included in the study. Additionally, 6 months of medication history was required. Patients needed to provide a patient authorization form or disclose personal health information and give informed consent (with parental support as required). Notifications/submissions to the responsible ethics committees, health institutions, and/or competent authorities were performed as required by applicable local laws and regulations. Patients were excluded if they were currently participating in an interventional clinical trial (participation in another non-interventional study or registry was not an exclusion criterion).

Endpoints

The primary endpoints were the worst itch within the past 24 hours assessed using Worst Pruritus Numeric Rating Scale (WP-NRS; score range 0–10) and QoL using Dermatology Life Quality Index (DLQI; assessed in patients aged ≥ 16 years; score range 0–30) or Children's DLQI (CDLQI; assessed in patients aged 12–15 years; score range 0–30); higher score indicates greater itch or lower QoL.

In addition, the following secondary endpoints were assessed: Patient Oriented Eczema Measurement (POEM; score range 0–28), patient-assessed disease control (using the Inadequately Controlled AD Questionnaire based on the statement, ''I feel my current treatments are effective in controlling my atopic dermatitis'', on a 5-point scale ranging from ''completely disagree'' to ''completely agree''), SCORing Atopic Dermatitis (SCORAD; score range 0–103), Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD; score range 0–4), body surface area involvement (score range 0%–100%), and Eczema Area and Severity Index (EASI; score range 0–72). Frequency and duration of disease flares within the last 6 months were evaluated based on patient self-report (flare was defined as a sudden worsening of AD with a need for treatment escalation or a need to visit a healthcare provider because of AD worsening). The effect of AD on sleep was also evaluated (during the past week: hours of sleep per night, minutes until falling asleep, and sleep interfering with daily function).

Other patient-reported endpoints included 5D-Pruritus (score range 5–25), Atopic Dermatitis Impact Scale (ADerm-IS), Atopic Dermatitis Symptom Scale (ADerm-SS), Hospital Anxiety and Depression Scale (HADS), including HADS anxiety (HADS-A; score range 0–21) and HADS depression (HADS-D; score range 0–21) subscales, and Short Form-12 Health Survey (SF-12; score range 0–100) for adults and Short Form-10 Health Survey (SF-10; score range 0–100) for adolescents. In addition, Work Productivity and Activity Impairment due to AD (WPAI-AD) and HCRU (number of healthcare visits and the number of acute care visits in the last 6 months due to AD and out-of-pocket expenses for specified healthcare aspects for AD) were assessed.

Statistical analyses

Data were collected during a single visit. In addition, retrospective data previously collected from healthcare providers were reported. All analyses were based on observed data. Continuous data were descriptively characterized using mean, Standard Deviation (SD) and median, Interquartile Range (IQR). Categorical data were characterized descriptively using frequency distributions (i.e., number and percentage of patients).

Subgroup analyses by EASI disease severity levels (clear, 0; mild, 0.1–5.9; moderate, 6.0–22.9; and severe, 23.0–72.0),[21] systemic therapy use (yes/no), dupilumab use (yes/other systemic), DLQI effect levels (no effect, 0–1; small, 2–5; moderate, 6–10; very large, 11–20; and extremely large, 21–30), POEM disease severity levels (clear or almost clear, 0–2; mild, 3–7; moderate, 8–16; severe, 17–24; and very severe, 25–28),[22] and AD Symptom Scale Total Symptom Score–7 (ADerm-SS TSS-7) score category (< 28 vs. ≥ 28) were conducted.

Differences among subgroups were statistically compared; a Kruskal-Wallis test was used for continuous variables and a Chi-Square test for categorical variables. All statistical analyses were carried out by means of the SAS® package version 9.4 (SAS, Cary, NC, USA).

Results

The MEASURE-AD Latin American population (Brazil, Mexico, Argentina) consisted of 180 patients (adults, n = 157; adolescents, n = 23). Mean (SD) age was 33.8 (17.0) years, and 52.2% of patients were male (Table 1). At the time of the study visit, patients had a history of AD averaging 16.5 years (adults, 17.2 years; adolescents, 11.6 years).

All patients were receiving AD treatment, including 74.4% receiving topical therapy alone or in combination (6.1% topical therapy alone). Although all patients were eligible for systemic treatment, only 65.6% were receiving systemic therapy alone or in combination and 12.2% were receiving systemic therapy alone; 18.9% of patients had continuous systemic therapy over the last 12 months (Table 1).

Table 1 Baseline patient demographics and characteristics among patients from Brazil, Mexico, and Argentina.

	Total population (n = 180)	Adults (n = 157)	Adolescents (n = 23)
Age, mean (SD)/median (IQR), y	33.8 (17.0) 28.0 (21.0–43.0)	36.6 (16.4) 32.0 (23.0–46.0)	14.8 (1.6) 15.0 (13.0–16.0)
Male sex, n (%)	94 (52.2)	82 (52.2)	12 (52.2)
BMI, mean (SD)/median (IQR), kg/m^2	25.9 (4.7) 25.2 (22.9–28.6)	26.3 (4.5) 25.4 (23.3–28.8)	22.9 (5.0) 21.9 (19.6–25.8)
Duration of AD, mean (SD)/median (IQR), y	16.5 (12.1) 15.1 (6.5–23.7)	17.2 (12.7) 16.7 (6.1–24.6)	11.6 (4.1) 12.7 (9.4–14.4)
Inadequately controlled AD, n (%)	45 (25.0)	42 (26.8)	3 (13.0)
Time from AD diagnosis to first therapy, mean (SD)/median (IQR), y	9.1 (10.8) 5.1 (0.3–16.1) n = 52	9.3 (11.5) 5.0 (0.0–16.3) n = 45	7.2 (3.6) 7.7 (4.0–9.7) n = 7
Time from AD diagnosis to first systemic therapy, mean (SD)/median (IQR), y	10.3 (10.6) 8.4 (1.2–17.0) n = 143	10.8 (11.1) 8.2 (1.0–18.4) n = 124	7.3 (5.1) 8.9 (2.4–12.5) n = 19
Continuous systemic therapy over previous 12 mo, n (%)	34 (18.9)	29 (18.5)	5 (21.7)
Current therapy, n (%)	180 (100.0)	157 (100.0)	23 (100.0)
Systemic therapy, alone or in combination	118 (65.6)	101 (64.3)	17 (73.9)
Systemic corticosteroids	41 (34.7)	38 (37.6)	3 (17.6)
Methotrexate	39 (33.1)	32 (31.7)	7 (41.2)
Dupilumab	29 (24.6)	24 (23.8)	5 (29.4)
Cyclosporine	20 (16.9)	19 (18.8)	1 (5.9)
Azathioprine	2 (1.7)	1 (1.0)	1 (5.9)
Systemic therapy alone	22 (12.2)	20 (12.7)	2 (8.7)
Systemic corticosteroids	41 (22.8)	38 (24.2)	3 (13.0)
Methotrexate	39 (21.7)	32 (20.4)	7 (30.4)
Dupilumab	29 (16.1)	24 (15.3)	5 (21.7)
Cyclosporine	20 (11.1)	19 (12.1)	1 (4.3)
Azathioprine	2 (1.1)	1 (0.6)	1 (4.3)
Topical therapy, alone or in combination	134 (74.4)	117 (74.5)	17 (73.9)
Topical therapy, alone	11 (6.1)	10 (6.4)	1 (4.3)
TCS or TCI alone	6 (3.3)	6 (3.8)	0 (0.0)
Previous systemic therapy, n (%)	166 (92.2)	145 (92.4)	21 (91.3)
Systemic therapy, alone or in combination	92 (51.1)	85 (54.1)	7 (30.4)
Systemic therapy alone	21 (11.7)	19 (12.1)	2 (8.7)
Dupilumab, alone or in combination	2 (1.1)	1 (0.6)	1 (4.3)
Dupilumab alone	0	0	0

AD, Atopic Dermatitis; BMI, Body Mass Index; IQR, Interquartile Range; SD, Standard Deviation; TCI, Topical Calcineurin Inhibitor; TCS, Topical Corticosteroid.

Among the 118 patients receiving systemic therapies, the most common were systemic corticosteroids (34.7%), methotrexate (33.1%), dupilumab (24.6%), and cyclosporine (16.9%); among all 180 patients, the usage was 22.8% for systemic corticosteroids, 21.7% for methotrexate, 16.1% for dupilumab (15.3% among adults), and 11.1% for cyclosporine. The mean (SD) time between AD diagnosis and until first administration of systemic treatment was 10.3 (10.6) years (adults, 10.8 [11.1] years; adolescents, 7.3 [5.1] years). Approximately one-quarter of patients overall (26.8% in the adult population and 13.0% of the adolescent population) reported that they had inadequately controlled disease.

Primary endpoints: Itch and QoL

The mean WP-NRS score was 6.1, and median score was 7 (adults, 6.3 and 7, respectively; adolescents, 4.7 and 5) (Fig. 1A). Severe pruritus (WP-NRS $\geq$7) was reported by 54.4% of patients (adults, 57.3%; adolescents, 34.8%) (Fig. 1B). The mean DLQI was 11.4, and the mean CDLQI was 8.1 (Fig. 2A). A very or extremely large effect on QoL (DLQI or CDLQI $\geq$ 11) was reported by 50.0% of patients $\geq$ 16 years old and 42.9% of patients 12 to 15 years old (Fig. 2B).

Secondary endpoints

Secondary endpoints showed a similar burden of disease for both the adult and adolescent populations (Table 2).

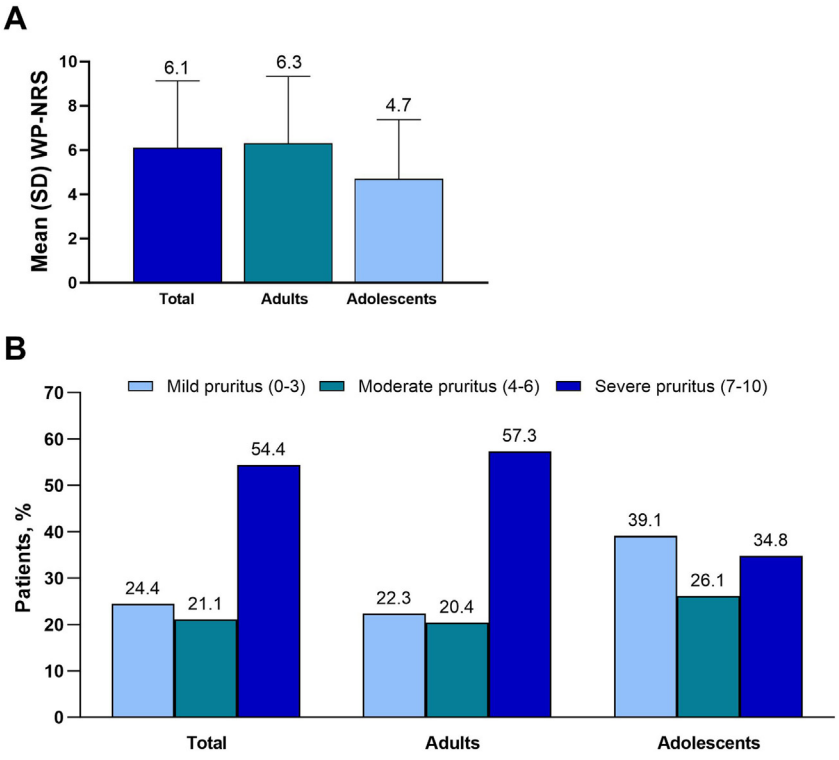

Fig. 1 Primary endpoint (A) mean (SD) WP-NRS and (B) proportion of patients in WP-NRS categories. WP-NRS, Worst Pruritus Numeric Rating Scale.

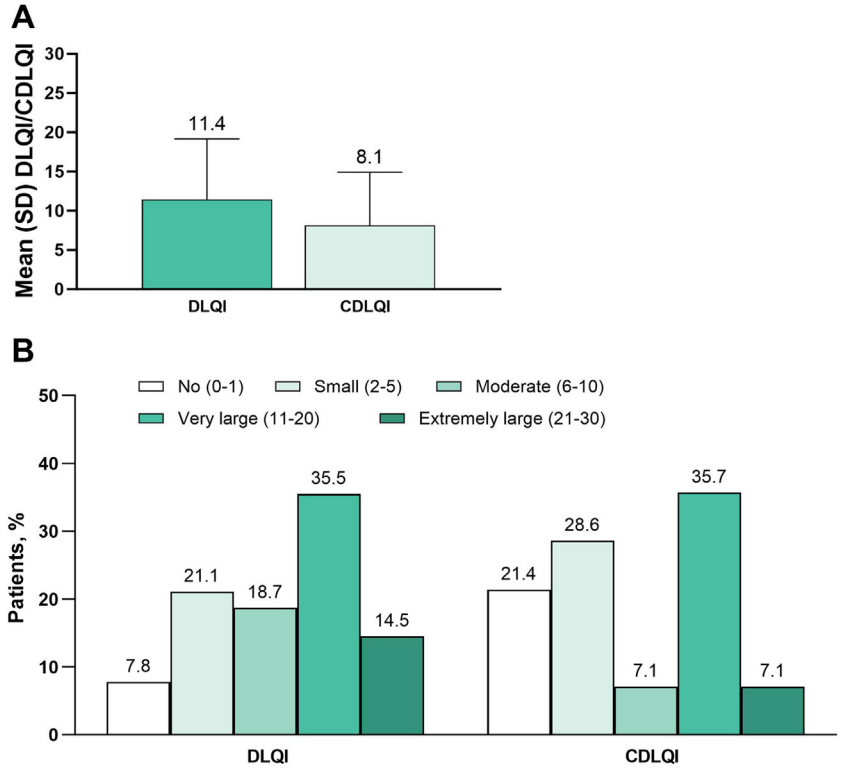

Fig. 2 Primary endpoint (A) mean (SD) DLQI/CDLQI and (B) proportion of patients in DLQI/CDLQI categories. CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index.

Table 2 Clinical Burden of AD.

	Total population (n = 180)	Adults (n = 157)	Adolescents (n = 23)
POEM, mean (SD)/median (IQR)	15.7 (7.4) 17.0 (10.0–21.0)	16.3 (7.3) 17.0 (11.0–22.0)	11.4 (7.0) 11.0 (6.0–11.0)
Average hours of sleep per night in the past week, mean (SD)/median (IQR)	6.1 (1.9) 6.0 (5.0–8.0)	5.9 (1.9) 6.0 (5.0–7.0)	7.4 (1.4) 8.0 (6.0–8.0)
Average minutes needed to fall asleep per night in the past week, mean (SD)/median (IQR)	43.2 (50.3) 30.0 (17.5–60.0)	43.5 (49.1) 30.0 (20.0–60.0)	41.4 (58.8) 20.0 (10.0–60.0)
Sleep problems interfered with daily function over the past week, n (%)			
I do not have sleep problems	14 (7.8)	11 (7.0)	3 (13.0)
Not at all	48 (26.7)	37 (23.6)	11 (47.8)
A little	31 (17.2)	26 (16.6)	5 (21.7)
Somewhat	28 (15.6)	28 (17.8)	0 (0.0)
Much	31 (17.2)	30 (19.1)	1 (4.3)
Very much	28 (15.6)	25 (15.9)	3 (13.0)
SCORAD, mean (SD)/median (IQR)	52.5 (20.7) 55.3 (40.5–67.1) n = 179	54.3 (19.9) 55.9 (43.2–68.8) n = 156	40.8 (22.5) 44.0 (30.8–60.9)
SCORAD categories, n (%)			
Mild (<25.0)	17 (9.4)	12 (7.6)	5 (21.7)
Moderate (25.0–50.0)	57 (31.7)	49 (31.2)	8 (34.8)
Severe (>50.0)	105 (58.3)	95 (60.5)	10 (43.5)
vIGA-AD, mean (SD)/median (IQR)	2.9 (1.0) 3.0 (3.0–4.0)	3.0 (0.9) 3.0 (3.0–4.0)	2.5 (1.3) 3.0 (1.0–3.0)
vIGA-AD categories, n (%)			
Clear (0)	6 (3.3)	4 (2.5)	2 (8.7)
Almost clear (1)	12 (6.7)	8 (5.1)	4 (17.4)
Mild (2)	17 (9.4)	15 (9.6)	2 (8.7)
Moderate (3)	98 (54.4)	88 (56.1)	10 (43.5)
Severe (4)	47 (26.1)	42 (26.8)	5 (21.7)
Body surface area, mean (SD)/median (IQR), %	26.5 (21.3) 21.5 (10.0–40.0)	27.2 (21.5) 22.0 (10.0–40.0)	21.4 (19.0) 20.0 (6.0–35.0)
EASI, mean (SD)/median (IQR)	17.0 (11.5) 15.0 (8.9–23.6)	17.7 (11.4) 15.9 (9.2–24.6)	12.4 (10.7) 9.8 (4.4–18.0)
EASI categories, n (%)			
Clear (0)	7 (3.9)	4 (2.5)	3 (13.0)
Mild (0.1–5.9)	18 (10.0)	14 (8.9)	4 (17.4)
Moderate (6.0–22.9)	107 (59.4)	95 (60.5)	12 (52.2)
Severe (23.0–72.0)	48 (26.7)	44 (28.0)	4 (17.4)
Number of flares in the past 6-months, mean (range)/median (IQR)	5.0 (0–50) 3.0 (2.0–6.0) n = 169	4.9 (0–50) 3.0 (2.0–6.0) n = 148	5.8 (0–30) 3.0 (2.0–4.0) n = 21
Number of flares in past 6-months, n (%)			
0	15 (8.3)	12 (7.6)	3 (13.0)
1–2	49 (27.2)	44 (28.0)	5 (21.7)
3–4	56 (31.1)	48 (30.6)	8 (34.8)
5–6	21 (11.7)	20 (12.7)	1 (4.3)
> 6	28 (15.6)	24 (15.3)	4 (17.4)
Missing	11 (6.1)	9 (5.7)	2 (8.7)
Average duration of flares in past 6-months, mean (range)/median (IQR), d	15.2 (0–180) 7.0 (4.0–15.0) n = 172	15.9 (0–180) 10.0 (5.0–15.0) n = 149	11.1 (0–90) 7.0 (3.0–8.0)
Average duration of flares in past 6-months, n (%), d			
≤ 2	28 (15.6)	23 (14.6)	5 (21.7)
3–7	60 (33.3)	48 (30.6)	12 (52.2)
8–14	26 (14.4)	24 (15.3)	2 (8.7)
≥ 15	58 (32.2)	54 (34.4)	4 (17.4)
Missing	8 (4.4)	8 (5.1)	0

Table 2 (*Continued*)

	Total population (n = 180)	Adults (n = 157)	Adolescents (n = 23)
5D-Pruritus score, mean (SD)/median (IQR)	16.2 (4.5) 17.0 (13.0–20.0) n = 176	16.5 (4.3) 17.0 (13.0–20.0) n = 154	13.9 (4.6) 12.5 (11.0–15.0) n = 22
Total ADerm-IS, mean (SD)/median (IQR)	42.3 (30.7) 40.0 (13.0–69.0) n = 177	45.0 (30.4) 43.0 (18.0–71.0) n = 155	23.5 (26.7) 11.0 (6.0–34.0) n = 22
ADerm-IS Sleep Domain, mean (SD)/median (IQR)	13.5 (10.6) 13.0 (2.0–24.0) n = 179	14.3 (10.6) 15.0 (4.0–24.0)	8.0 (9.3) 3.0 (0.0–15.0) n = 22
ADerm-SS TSS-7, mean (SD)/median (IQR)	34.2 (21.1) 31.0 (17.5–53.0)	36.2 (20.7) 35.0 (20.0–54.0)	20.3 (18.9) 14.0 (6.0–26.0)
ADerm-SS TSS-11, mean (SD)/median (IQR)	49.2 (31.6) 44.0 (24.0–76.0) n = 177	51.8 (31.1) 49.0 (29.0–77.0) n = 154	31.3 (29.3) 26.0 (9.0–44.0)
ADerm-SS Skin pain, mean (SD)/median (IQR)	4.4 (3.7) 4.0 (1.0–8.0)	4.6 (3.8) 5.0 (1.0–8.0)	2.9 (3.1) 2.0 (0.0–5.0)
SF-12 PCS, mean (SD)/median (IQR)	NA	48.6 (9.0) 50.4 (42.9–55.1) n = 154	NA
SF-10 PHS, mean (SD)/median (IQR)	NA	NA	38.0 (14.5) 42.0 (32.5–48.4)

ADerm-IS, Atopic Dermatitis Impact Scale; ADerm-SS, Atopic Dermatitis Symptom Scale; ADerm-SS TSS-7, Atopic Dermatitis Symptom Scale Total Symptom Score-7; EASI, Eczema Area and Severity Index; IQR, Interquartile Range; POEM, Patient Oriented Eczema Measurement; SCORAD, SCORing Atopic Dermatitis; SF-12 PCS, 12-item Short-Form Health Survey Physical Component Summary (adults); SF-10 PHS, 10-item Short-Form Health Survey Physical Health Score (adolescents); vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

The mean POEM was 15.7 (adults, 16.3; adolescents, 11.4). The total population reported a mean of 6.1 hours slept per night. Overall, 48.3% of patients reported sleep problems that interfered with daily function over the past week as occurring ''somewhat to very much''. The mean SCORAD score was 52.5 and was higher among adults (54.3) compared with adolescents (40.8). A total of 9.4% of patients had mild AD (SCORAD < 25), 31.7% moderate AD (SCORAD 25–50), and 58.3% severe AD (SCORAD > 50).

The mean vIGA-AD was 2.9 (adults, 3.0; adolescents, 2.5) and the mean EASI score was 17.0 (adults, 17.7; adolescents, 12.4). Overall, 3.9% of patients had clear skin (EASI = 0) and 26.7% had severe AD (EASI 23–72).

The mean ADerm-SS Skin Pain was 4.4, indicating moderate disease (Table 2). The mean ADerm-SS TSS-7 and TSS-11 scores (34.2 and 49.2, respectively) showed similarly moderate symptom burden (Table 2).

A total of 169 patients reported a frequency of flares. Over the previous 6 months, 0, 1 to 2, 3 to 4, 5 to 6, and > 6 flares were reported by 8.3%, 27.2%, 31.1%, 11.7%, and 15.6% of patients, respectively. On average, flares lasted 15.2 days (adults, 15.9 days; adolescents, 11.1 days).

Borderline abnormal to abnormal anxiety (HADS-A $\geq$ 8) and depression (HADS-D $\geq$8) were reported by 55.0% and 33.3% of patients in the total population; a slightly higher rate of anxiety was reported among adolescents (65.2%) versus adults (53.5%; Table 3). The mean SF-12 mental component summary score was 41.8 for adults and the mean SF-10 psychosocial component summary score was 44.6 for adolescents (Table 3). A mean work productivity loss of 35.9% was observed among employed adults (Table 3). Similar effects of AD were reflected in the ADerm-IS Emotional State scores (mean, 14.3) and ADerm-IS Daily Activities scores (mean, 14.6), indicating moderate disease (Table 3). The mean number of healthcare or acute care visits during the previous 6 months was 7.6; this was similar for adults (7.7) and adolescents (7.1) (Table 3). Mean monthly healthcare-related expenses and costs of everyday necessities related to AD (converted to 2021 US Dollars [USD]) were 103.3 USD in the total population (adults, 101.8 USD; adolescents 113.4 USD).

Subgroup analyses

In a subgroup analysis by current systemic therapy use (yes, n = 118; no, n = 62), no significant differences in primary or secondary endpoints were observed between groups (Table 4). The only exceptions were a slightly higher mean SF-12 mental component summary score (worse mental health) and a greater proportion of patients with EASI $\geq$ 16.0 among systemic therapy users versus non-systemic therapy users (Table 4). Substantial disease burden was observed among patients who were and who were not currently receiving systemic therapy, as based on mean WP-NRS (6.1 and 6.1), mean DLQI (11.8 and 10.7), mean EASI (18.1 and 14.7), mean SCORAD (53.2 and 51.3), and mean number of flares in the past 6 months (4.8 and 5.3, respectively) (Table 4).

Table 3 Psychosocial-economic burden of AD.

	Total population (n = 180)	Adults (n = 157)	Adolescents (n = 23)
HADS Anxiety subscale, mean (SD)/median (IQR)	8.4 (4.7) 8.0 (5.0–12.0)	8.3 (4.7) 8.0 (5.0–12.0)	9.0 (4.4) 10.0 (6.0–12.0)
HADS Anxiety subscale ≥8, n (%)	99 (55.0)	84 (53.5)	15 (65.2)
HADS Depression subscale, mean (SD)/median (IQR)	6.0 (3.8) 6.0 (3.0–8.0)	5.9 (3.9) 6.0 (3.0–8.0)	6.1 (3.5) 6.0 (3.0–8.0)
HADS Depression subscale ≥8, n (%)	60 (33.3)	52 (33.1)	8 (34.8)
SF-12 MCS, mean (SD)/median (IQR)	NA	41.8 (11.1) 40.4 (33.9–51.0) n = 154	NA
SF-10 PSS, mean (SD)/median (IQR)	NA	NA	44.6 (9.2) 45.3 (36.4–51.6)
ADerm-IS Daily Activities, mean (SD)/median (IQR)	14.6 (12.5) 11.0 (3.0–24.0) n = 178	15.6 (12.5) 14.0 (4.0–25.0) n = 155	8.0 (10.5) 3.0 (2.0–14.0)
ADerm-IS Emotional State, mean (SD)/median (IQR)	14.3 (10.9) 15.0 (3.0–25.0)	15.3 (10.8) 18.0 (4.0–25.0)	7.1 (9.3) 3.0 (0.0–12.0)
WPAI-AD employed, n (%)	83 (46.1)	79 (50.3)	4 (17.4)
Absenteeism, mean (SD)/median (IQR), %	12.1 (21.9) 0.0 (0.0–16.7) n = 75	12.0 (22.2) 0.0 (0.0–16.7) n = 71	14.2 (18.9) 8.3 (0.0–28.3) n = 4
Presenteeism, mean (SD)/median (IQR), %	31.2 (28.0) 25.0 (10.0–50.0) n = 78	32.0 (28.0) 30.0 (10.0–50.0) n = 74	15.0 (23.8) 5.0 (0.0–30.0) n = 4
Overall work productivity impairment, mean (SD)/median (IQR), %	35.3 (28.7) 32.3 (10.0–58.3) n = 73	35.9 (28.8) 32.3 (10.0–58.3) n = 69	26.1 (30.5) 23.0 (0.0–52.2) n = 4
Hours missed from work, mean (SD)/median (IQR)	7.0 (22.2) 0.0 (0.0–4.0) n = 78	7.3 (22.8) 0.0 (0.0–4.0) n = 74	1.3 (1.5) 1.0 (0.0–2.5) n = 4
Activity impairment, mean (SD)/median (IQR), %	39.8 (34.8) 30.0 (10.0–70.0)	42.2 (35.2) 30.0 (10.0–70.0)	23.9 (23 (26.9) 20.0 (0.0–40.0)
Healthcare resource utilization			
Number of healthcare or acute care visits in previous 6-months, mean (SD)	7.6 (9.4) n = 123	7.7 (9.7) n = 108	7.1 (7.1) n = 15
Out-of-pocket expenses			
Total monthly healthcare-related expenses and costs of everyday necessities related to AD, mean (SD), USD	103.3 (132.1) n = 168	101.8 (137.8) n = 146	113.4 (87.5) n = 22

AD, Atopic Dermatitis; ADerm-IS, Atopic Dermatitis Impact Scale; ADerm-SS, Atopic Dermatitis Symptom Scale; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile Range; SD, Standard Deviation; SF-12 MCS, 12-item Short-Form Health Survey Mental Component Summary (adults); SF-10 PSS, 10-item Short-Form Health Survey Psychosocial Summary Score (adolescents); USD, US Dollars; WPAI-AD, Work Productivity and Activity Impairment-Atopic Dermatitis.

For comparison of dupilumab (monotherapy or combination, n = 29) versus other systemic therapy (n = 89), patients receiving dupilumab generally had lower disease severity and activity impairment, but differences were only significant for mean EASI ($p = 0.002$), mean WP-NRS ($p < 0.001$), and activity impairment ($p = 0.032$) and for proportions of patients with EASI ≥ 7.1 ($p = 0.029$), EASI ≥ 16.0 ($p = 0.025$), WP-NRS 0–1 ($p < 0.001$) and WP-NRS ≥ 4 ($p = 0.002$; Table 4). Substantial disease burden was still observed among patients receiving dupilumab based on mean WP-NRS (4.2), mean DLQI (9.6), mean EASI (12.2), and mean number of flares in the last 6 months (4.3) (Table 4).

In a subgroup analysis by EASI severity, overall work productivity impairment, activity impairment, and overall number of acute care visits were significantly associated with increasing disease severity (Table 5). Similarly, higher DLQI (Fig. 3), more severe POEM (Fig. 4), and greater ADerm-SS TSS-7 (Fig. 5) were associated with significantly greater disease severity, itch severity, and impairments in work productivity and activity.

Table 4 Clinical, psychosocial, and economic burden of AD by systemic therapy use.

	Current Use of Systemic Therapy					
	Yes			No	p-value	
	Any systemic (n = 118)	Dupilumab (n = 29)	Systemic other than dupilumab (n = 89)	No systemic therapy (n = 62)	Systemic vs. no systemic	Dupilumab vs. other systemic
Primary endpoints						
WP-NRS, mean (SD)/median (IQR)	6.1 (.1) 7.0 (4.0–8.0)	4.2 (3.3) 4.0 (1.0–7.0)	6.7 (2.7) 7.0 (5.0–9.0)	6.1 (3.0) 7.0 (3.0–8.0)	0.987	**<0.001**
WP-NRS 0–1, n (%)	14 (11.9)	9 (31.0)	5 (5.6)	7 (11.3)	0.909	**<0.001**
WP-NRS ≥ 4, n (%)	90 (76.3)	16 (55.2)	74 (83.1)	46 (74.2)	0.758	**0.002**
DLQI, mean (SD)/median (IQR)	11.8 (8.0) 11.0 (5.0–18.0) n = 104	9.6 (8.6) 8.0 (2.0–15.0) n = 26	12.6 (7.6) 12.0 (5.0–19.0) n = 78	10.7 (7.3) 9.0 (4.0–15.0) n = 58	0.451	0.055
CDLQI, mean (SD)/median (IQR)	8.3 (7.3) 7.0 (2.0–14.0) n = 10	5.3 (8.4) 1.0 (0.0–15.0) n = 3	9.6 (7.1) 9.0 (3.0–14.0) n = 7	7.8 (6.2) 8.0 (3.0–13.0) n = 4	0.943	0.305
Clinical outcomes						
EASI, mean (SD)/median (IQR)	18.2 (12.6) 17.0 (8.6–26.4)	12.2 (10.7) 10.7 (1.9–17.2)	20.1 (12.7) 18.3 (11.0–26.8)	14.7 (8.4) 13.2 (9.0–20.4)	0.131	**0.002**
EASI ≥ 7.1, n (%)	94 (79.7)	19 (65.5)	75 (84.3)	55 (88.7)	0.127	**0.029**
EASI ≥ 16.0, n (%)	62 (52.5)	10 (34.5)	52 (58.4)	23 (37.1)	**0.049**	**0.025**
SCORAD, mean (SD)/median (IQR)	53.2 (23.1) 57.6 (40.4–70.6) n = 117	–	–	51.3 (15.0) 52.0 (41.0–61.7) n = 62	0.236	–
SCORAD ≥ 25, n (%)	103 (88.0)	–	–	59 (95.2)	0.122	–
vIGA-AD categories, n (%)					0.055	–
Clear (0)	5 (4.2)	–	–	1 (1.6)		
Almost clear (1)	7 (5.9)	–	–	5 (8.1)		
Mild (2)	12 (10.2)	–	–	5 (8.1)		
Moderate (3)	56 (47.5)	–	–	42 (67.7)		
Severe (4)	38 (32.2)	–	–	9 (14.5)		
Body surface area, %, mean (SD)/median (IQR)	28.1 (22.8) 25.0 (10.0–40.0)	–	–	23.4 (17.8) 20.0 (8.0–38.0)	0.283	–
Number of flares in the past 6 months, mean (SD)/median (IQR)	4.8 (6.8) 3.0 (2.0–6.0) n = 110	4.3 (5.8) 3.0 (1.0–4.0) n = 28	5.0 (7.1) 3.0 (2.0–6.0) n = 82	5.3 (7.5) 4.0 (2.0–6.0) n = 59	0.433	0.167
Number of flares categories, n (%)					0.358	0.253
0	9 (8.2)	4 (14.3)	5 (6.1)	6 (10.2)		
1–2	35 (31.8)	9 (32.1)	26 (31.7)	14 (23.7)		
3–4	36 (32.7)	9 (32.1)	27 (32.9)	20 (33.9)		
5–6	10 (9.1)	0	10 (12.2)	11 (18.6)		
> 6	20 (18.2)	6 (21.4)	14 (17.1)	8 (13.6)		
Inadequately controlled AD, n (%)	33 (28.0)	–	–	12 (19.4)	0.205	–

Table 4 (*Continued*)

	Current Use of Systemic Therapy					
	Yes			No	p-value	
	Any systemic (n = 118)	Dupilumab (n = 29)	Systemic other than dupilumab (n = 89)	No systemic therapy (n = 62)	Systemic vs. no systemic	Dupilumab vs. other systemic
Average hours of sleep per night in the past week, mean (SD)/median (IQR)	6.1 (1.9) 6.0 (5.0–8.0)	–	–	6.1 (1.9) 6.0 (5.0–7.0)	0.899	–
Psychosocial outcomes						
HADS Anxiety subscale ≥8, n (%)	66 (55.9)	–	–	33 (53.2)	0.729	–
HADS Depression subscale ≥8, n (%)	41 (34.7)	–	–	19 (30.6)	0.579	–
SF-12 MCS, mean (SD)/median (IQR)	40.4 (10.9) 38.7 (33.2–49.4) n = 98	–	–	44.2 (11.2) 45.2 (35.7–53.4) n = 56	**0.046**	–
Work Productivity and Activity Impairment						
Absenteeism, mean (SD)/median (IQR), %	11.9 (22.4) 0.0 (0.0–16.7) n = 48	14.6 (21.8) 6.2 (0.0–19.1) n = 10	11.2 (22.8) 0.0 (0.0–16.7) n = 38	12.3 (21.4) 4.8 (0.0–16.7) n = 27	0.519	0.171
Presenteeism, mean (SD)/median (IQR), %	30.6 (27.1) 20.0 (10.0–50.0) n = 49	41.0 (32.5) 30.0 (10.0–60.0) n = 10	27.9 (25.4) 20.0 (0.0–50.0) n = 39	32.1 (29.8) 30.0 (0.0–50.0) n = 29	0.963	0.215
Overall work productivity impairment, mean (SD)/median (IQR), %	35.8 (28.3) 32.3 (10.0–55.0) n = 47	45.1 (32.3) 42.9 (12.5–67.7) n = 10	33.2 (27.0) 31.2 (10.0–50.0) n = 37	34.5 (30.1) 29.2 (4.8–58.5) n = 26	0.876	0.246
Activity impairment, mean (SD)/median (IQR), %	41.2 (36.5) 30.0 (10.0–70.0)	30.0 (37.8) 10.0 (0.0–60.0)	44.8 (35.6) 40.0 (10.0–70.0)	37.3 (31.2) 30.0 (10.0–60.0)	0.679	**0.032**
Hours missed from work, mean (SD)/median (IQR)	7.4 (25.4) 0.0 (0.0–3.0) n = 50	5.5 (9.2) 2.0 (0.0–7.0) n = 11	7.9 (28.4) 0.0 (0.0–2.0) n = 39	6.2 (15.4) 2.0 (0.0–5.0) n = 28	0.262	0.152
Healthcare resource utilization						
Number of acute care visits in the previous 6-months, mean (SD)/median (IQR)	0.4 (2.8) 0.0 (0.0–0.0) n = 84	–	–	0 0.0 (0.0–0.0) n = 37	0.053	–
Number of healthcare visits in the previous 6-months, mean (SD)/median (IQR)	7.1 (7.6) 4.0 (2.0–8.0) n = 87	6.5 (5.7) 6.0 (3.0–8.0) n = 21	7.3 (8.2) 4.0 (2.0–8.0) n = 66	7.8 (12.2) 4.5 (2.0–8.0) n = 36	0.987	0.622
Monthly healthcare-related expenses and costs due to AD, mean (SD)/median (IQR), USD	108.4 (146.2) 64.5 (33.4–120.0) n = 110	113.2 (134.9) 74.4 (41.1–109.2) n = 28	106.8 (150.7) 60.0 (33.0–126.0) n = 82	93.6 (100.6) 59.5 (33.6–117.0) n = 58	0.778	0.471

AD, Atopic Dermatitis; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile Range; SCORAD, SCORing Atopic Dermatitis; SF-12 MCS, 12-item Short-Form Health Survey Mental Component Summary; USD, US Dollars; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS, Worst Pruritus Numeric Rating Scale.

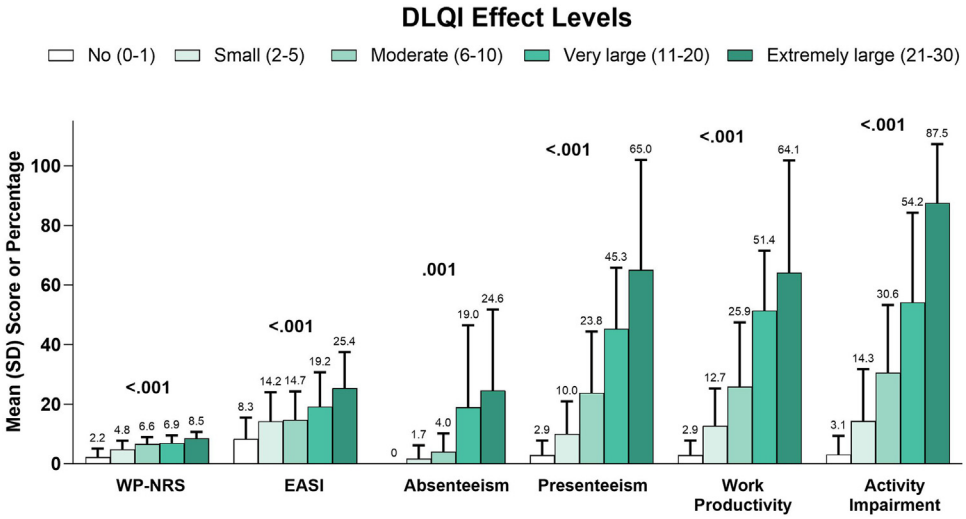

Fig. 3 Clinical outcomes and economic burden of AD by DLQI. AD, Atopic Dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; WP-NRS, Worst Pruritus Numeric Rating Scale.

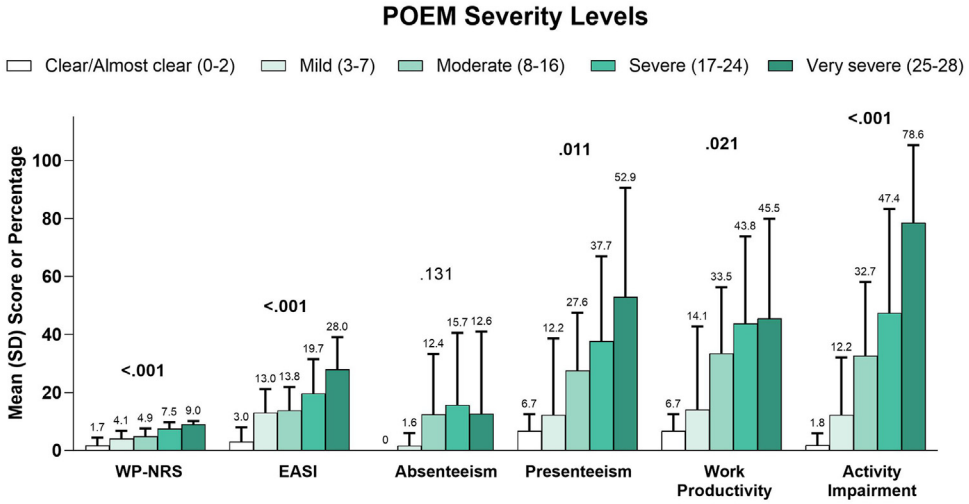

Fig. 4 Clinical outcomes and economic burden of AD by POEM. AD, Atopic Dermatitis; EASI, Eczema Area and Severity Index; POEM, Patient Oriented Eczema Measurement; WP-NRS, Worst Pruritus Numeric Rating Scale.

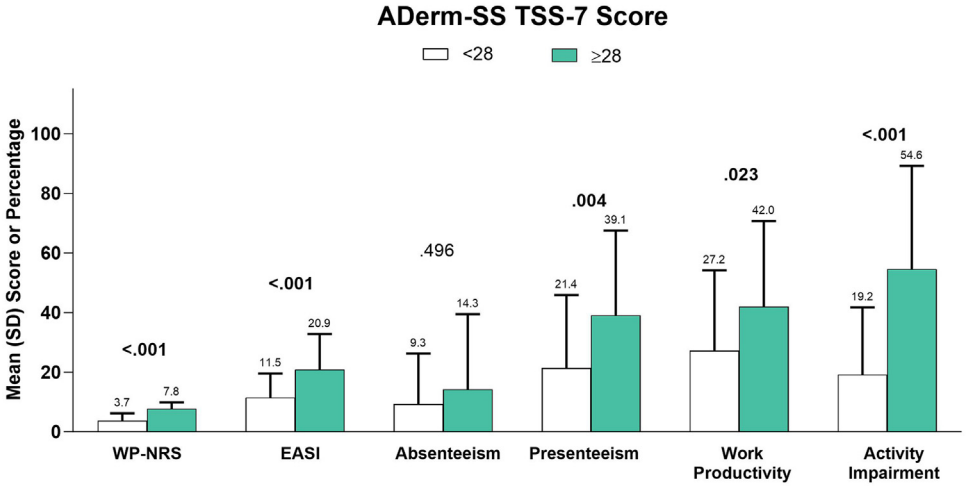

Fig. 5 Clinical outcomes and economic burden of AD by ADerm-SS TSS-7. AD, Atopic Dermatitis; ADerm-SS TSS-7, Atopic Dermatitis Symptom Scale Total Symptom Score-7; EASI, Eczema Area and Severity Index; WP-NRS, Worst Pruritus Numeric Rating Scale.

Table 5 Psychosocial and economic burden of AD by EASI disease severity level.

	EASI Severity Levels				
	Clear (n = 7)	Mild (n = 18)	Moderate (n = 107)	Severe (n = 48)	p-value
Psychosocial outcomes					
HADS Anxiety subscale ≥ 8, n (%)	4 (57.1)	7 (38.9)	57 (53.3)	31 (64.6)	0.298
HADS Depression subscale ≥ 8, n (%)	2 (28.6)	6 (33.3)	28 (26.2)	24 (50.0)	0.059
SF-12 MCS, mean (SD)/median (IQR)	42.3 (15.3) 43.4 (29.7–54.9) n = 4	44.3 (10.0) 41.6 (37.6–49.5) n = 14	43.0 (10.3) 43.4 (34.7–51.4) n = 94	38.1 (12.3) 35.7 (29.7–50.1) n = 42	0.072
Work Productivity and Activity Impairment					
Absenteeism, mean (SD)/median (IQR), %	12.5 (NA) 12.5 (12.5–12.5) n = 1	1.3 (2.3) 0.0 (0.0–2.4) n = 8	11.0 (20.7) 0.0 (0.0–12.7) n = 50	20.9 (28.6) 10.8 (0.0–28.8) n = 16	0.127
Presenteeism, mean (SD)/median (IQR), %	50.0 (NA) 50.0 (50.0–50.0) n = 1	18.9 (19.7) 20.0 (0.0–20.0) n = 9	29.2 (27.9) 20.0 (5.0–45.0) n = 52	43.1 (29.8) 45.0 (20.0–60.0) n = 16	0.121
Overall work productivity impairment, mean (SD)/median (IQR), %	56.3 (NA) 56.3 (56.3–56.3) n = 1	16.0 (17.3) 15.0 (0.0–24.0) n = 8	32.9 (28.8) 30.0 (10.0–55.0) n = 49	52.1 (26.1) 50.0 (31.2–70.0) n = 15	**0.029**
Activity impairment, mean (SD)/median (IQR), %	12.9 (26.3) 0.0 (0.0–20.0)	16.1 (18.5) 10.0 (0.0–30.0)	34.1 (31.4) 30.0 (10.0–60.0)	65.4 (33.2) 75.0 (35.0–100.0)	**<0.001**
Hours missed from work, mean (SD)/median (IQR)	6.0 (NA) 6.0 (6.0–6.0) n = 1	0.4 (0.9)0.0 (0.0–0.0) n = 9	7.3 (25.6) 0.0 (0.0–4.0) n = 52	9.6 (16.4) 2.0 (0.0–12.0) n = 16	0.119
Healthcare resource utilization					
Number of acute care visits in the previous 6-months, mean (SD)/median (IQR)	0 0.0 (0.0–0.0) n = 5	0 0.0 (0.0–0.0) n = 14	0 (0.17) 0.0 (0.0–0.0) n = 71	1.1 (4.5) 0.0 (0.0–0.0) n = 31	**0.037**
Number of healthcare visits in the previous 6 months, mean (SD)/median (IQR)	6.5 (7.8) 6.5 (1.0–12.0) n = 2	13.6 (12.1) 9.0 (3.0–27.0) n = 9	7.1 (9.9) 4.0 (2.0–7.0) n = 75	6.4 (5.9) 4.0 (3.0–8.0) n = 37	0.574
Monthly healthcare-related expenses and costs due to AD, mean (SD)/median (IQR), USD	94.0 (80.1) 72.0 (48.0–90.0)	99.4 (63.6) 66.0 (49.5–144.0) n = 17	89.7 (106.6) 54.5 (31.2–110.4) n = 98	135.0 (191.3) 67.5 (30.2–144.0) n = 46	0.288

AD, Atopic Dermatitis; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile Range; SD, Standard Deviation; SF-12 MCS, 12-item Short-Form Health Survey Mental Component Summary; USD, US Dollars.

Discussion

This analysis of 180 adults and adolescents with AD from 3 Latin American countries demonstrated considerable clinical, psychosocial, and economic burden of disease. More than half of the adult patients (57%) and 35% of adolescent patients reported severe itch. A very large or extremely large effect on QoL was reported by 50% of adults and 43% of adolescents. In addition, anxiety, depression, and sleep problems were prevalent, with 54% of adults reporting HADS-A ≥ 8 (65% of adolescents), 33% reporting HADS-D ≥ 8 (35% of adolescents), and 53% reporting sleep problems occurring somewhat to very much (17% of adolescents).

Although all patients received treatment and two-thirds received systemic therapies, moderate to severe disease was reported by 90% and 86% of patients based on SCORAD and EASI scores, respectively, suggesting inadequately controlled disease. In a subgroup analysis by systemic therapy use, no difference in disease burden was observed between patients receiving systemic therapy versus patients not receiving systemic therapy; disease burden (including number of flares, QoL impact, and economic burden) remained high in both groups. However, among patients receiving the biologic therapy dupilumab, a trend for lower disease severity, better QoL, and lower activity impairment was observed compared with patients receiving other conventional systemic therapies or patients not receiving systemic therapy.

Nevertheless, a substantial disease burden was still observed among patients receiving dupilumab, indicating a remaining unmet need for effective AD therapies.

Overall, the results in the Latin American population from MEASURE-AD indicated that a considerable disease burden still exists among patients with AD, regardless of current treatment, including systemic therapy.

These results are also in line with previous studies from Latin America. In a retrospective, registry-based study conducted in Brazil between 2016 and 2017, 87% (85/98) of patients had moderate to severe disease as assessed by SCORAD and 75% (24/32) as assessed by EASI.[17] The use of oral corticosteroids (33% [61/187]) was slightly higher in that population than in the MEASURE-AD Latin America population (23% [41/180]).[17] In another observational study from Colombia enrolling patients between 2019 and 2020, 76% (SCORAD) and 61% (EASI) of patients had moderate to severe disease with 63% (133/212) using oral corticosteroids and 7% (14/212) using dupilumab (vs. 23% [41/180] and 16% [29/180], respectively, in MEASURE-AD Latin America).[16] Similar results have been demonstrated in other studies from Latin America.[15,23] Furthermore, psychological, social-functioning, and economic effects are also relevant among patients from Latin America.[15,18] In a web-based survey involving 1650 adult and pediatric patients with AD in Argentina, 86.5% of patients reported a negative impact on QoL, with frustration, anger, mood alternations, stress, sleep and routine alterations, pain, and economic impact being among the highest ranked domains.[18] Topical treatments were frequently used, including by 60% of patients receiving topical corticosteroids; however, 21.7% of patients reported treatment satisfaction as moderate, and 40.5% were dissatisfied with their treatment regimen. Another important finding from the study was a delay in diagnosis, which was more evident in the provinces away from Buenos Aires, and a lack of knowledge about the diagnosis of the disease among specialists.[18]

Results from studies in children and adolescents with AD also show a high impact of disease. In the international PEDISTAD study of 732 children (with 23% from Latin America), a significant impact of moderate to severe AD on itch, sleep, QoL, and family was demonstrated in children and their caregivers. This might have been explained by the low use of systemic therapies (23%).[24] Similarly, a study of 50 children and adolescents with AD from Brazil demonstrated a moderate to high negative effect of AD on QoL in 72% of patients and 74% of families.[25] These results are consistent with the findings of the MEASURE-AD study, which demonstrated considerable disease burden (including itch) and sleep and QoL impairment among Latin American adolescents, of whom only 22% used systemic treatment continuously over the previous 12 months.

A slightly higher disease burden was reported in the Latin American population versus the global MEASURE-AD population, in which severe itch was reported by 42% of patients, a very large or extremely large effect on QoL was reported by 46% of adults and 32% of adolescents, and moderate to severe disease was reported by 69% (EASI $\geq$ 6) and 76% (SCORAD $\geq$ 25) of patients.[20]

Interestingly, the time to first systemic therapy was longer in the MEASURE-AD global (17 years) versus Latin American (10 years) population, which may indicate that the Latin American patients with AD sought treatment later in the disease course and escalated to systemic therapy more rapidly than the global population. Although the use of systemic therapies was slightly higher in the Latin American versus global population (66% vs. 56%), the use of biologic therapy (dupilumab) among systemic therapy users was considerably lower in Latin America (25% vs. 56%, respectively), which could explain the higher disease burden. In contrast, the use of systemic corticosteroids (35% vs. 18%) and methotrexate (33% vs. 16%) among systemic therapy users was higher in the Latin American versus the global population. Among all adult patients enrolled in MEASURE-AD (n = 1434), the use of biologic therapy (dupilumab) was much lower in Latin America (15% [24/157]) compared with other geographic regions, such as Saudi Arabia, Kuwait, and United Arab Emirates (62% [26/42]), Italy (57% [67/118]), Germany (46% [96/210]), Canada (44% [88/200]), Switzerland and Austria (46% [43/94]), and Spain (42% [38/91]). In Latin America, the cost of systemic medication affects treatment choices in addition to access to treatment. Both methotrexate and oral corticosteroids are less expensive and easier to administer, which may explain their high use versus dupilumab. Of note, the COVID-19 pandemic was ongoing at the time of the study, which could have affected access to dupilumab and lowered its use. Overall, these findings may be explained by market access differences across countries and indicate that not all patients from Latin America have access to systemic medications and remain undertreated.[26]

Of note, dupilumab was the only biological therapy approved for AD at the time of MEASURE-AD study. The number of treatment options for AD has since increased with the approval of Janus kinase inhibitors (baricitinib, upadacitinib, and abrocitinib) and biologics (such as tralokinumab) in some countries. Thus, future studies are needed to assess the effect of the approval of these therapies on AD disease burden.

The strengths of this study included the reporting of a wide variety of both physician- and patient-reported outcomes, including QoL. Furthermore, this was the largest study assessing the multidimensional burden of AD (clinical, psychological, socioeconomic) and the impact of available systemic treatments on disease burden in Latin America. Limitations of this study included relying on patient self-reported measures and recall during a single office visit and that only patients who were receiving or were candidates for systemic therapy were included. Furthermore, dupilumab was the only approved biological therapy at the time of the study, which was conducted before Janus kinase inhibitors were available. In addition, local regulatory approval status and market access/reimbursement policies varied across countries and some patients had limited access to innovative treatments.

Conclusion

Patients with moderate to severe AD in Brazil, Mexico, and Argentina continue to experience substantial multidimensional disease burden and uncontrolled disease. Although

most patients used topical treatments, two-thirds were receiving systemic treatments (mainly corticosteroids or methotrexate) either alone or in combination. Future studies need to look at the effect of newer and more effective therapies on the burden of disease. Overall, a significant unmet need remains for effective treatments to improve patients' psychosocial and clinical outcomes and reduce the economic burden of AD.

Study conducted at the 14 study sites in Argentina, Brazil, and México

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Brazil

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México

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Authors' contributions

Catalina Rincón Pérez: Approval of the final version of the manuscript; critical literature review; data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic management of studied cases; effective participation in research orientation; analysis and interpretation of data; manuscript critical review; preparation and writing of the manuscript.

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Conflicts of interest

Catalina Rincón Pérez has been an investigator, speaker, and/or advisor for AbbVie and a speaker and/or advisor for Janssen, Leo, Lilly, Novartis, Pfizer, and Sanofi Genzyme.

Valeria Aoki has received research grants as an investigator from Lilly and Sanofi Laboratories (the funds were administered by her institution) and served as an advisor/speaker for AbbVie, LEO Pharma, and Pfizer.

Roberta F. Criado has served as an advisor and/or speaker for AbbVie, Mantecorp, Novartis, and Sanofi.

Martti Antila has served as a speaker/consultant for Abbott, AbbVie, Aché, AstraZeneca, Chiesi, Eurofarma, IPI ASAC, and Sanofi and received research support from AbbVie, AstraZeneca, EMS, Eurofarma, GSK, Humanigen, Janssen, Novartis, Sanofi, and Veru.

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Delfina Guadalupe Villanueva Quintero has served as a speaker, advisor, and principal investigator for AbbVie, Amgen, BI, BMS, Janssen, Lilly, Novartis, Sanofi, and Teva.

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Adriana López Tello-Santillán has served as a speaker, investigator, and advisor for AbbVie, Janssen, LEO, Lilly, Novartis, Pfizer, and UCB.

Magda Weber has been an investigator, speaker, and/or advisor for AbbVie and has received funds from ISCMPA.

Daniel Lorenzini has been an investigator, speaker, and/or advisor for AbbVie, Galderma, LEO, Lilly, Pfizer, and Sanofi-Genzyme.

Caio Cesar Silva de Castro has served as a speaker or consultant for AbbVie, Aché, Janssen, Knight, LEO, Novartis, Sanofi, and Sun Pharma.

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REVIEW

Chronic pruritus: a narrative review☆

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Pruritus

Abstract Chronic pruritus encompasses a manifestation of several cutaneous, allergic, infectious, neurological, psychological, and systemic conditions, whose etiological investigation and therapeutic strategy can be challenging. This comprehensive review aims to enhance the understanding of pruritus by highlighting important elements in its pathogenesis, including keratinocytes, Merkel cells and mast cells, nerve fibers, histaminergic and nonhistaminergic pathways, and the interaction of itch signals with the central nervous system. Diagnostic evaluation of chronic pruritus may require a meticulous approach, guided by the identification of skin lesions or signs/symptoms of underlying systemic diseases. A comprehensive evaluation, including a detailed medical history, thorough physical examination, and appropriate laboratory and imaging tests, often supplemented by skin biopsy and direct immunofluorescence, is essential. Treatment strategies for chronic pruritus should be individualized based on the etiology identified. General measures, such as emollients, serve as initial interventions, followed by targeted approaches. Topical corticosteroids, calcineurin inhibitors, phototherapy, and systemic immunosuppressants address cutaneous inflammation. Antihistamines, antidepressants, and immunosuppressants may be employed based on the specific etiology. Emerging therapies, including biologic drugs and JAK inhibitors, have potential in refractory cases.
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Introduction

Pruritus (itching) is the most frequently reported symptom among patients who see dermatologists.[1] It was defined by the German physician Samuel Hafenreffer more than 350 years ago as an ''unpleasant sensation that provokes the urge or reflex to scratch''.[2,3]

Chronic Pruritus (CP), i.e., pruritus that lasts more than 6 weeks,[1] has an estimated prevalence ranging from 8% to 25% and can be localized or generalized.[4–6] The prevalence of CP in children aged 6 to 10 years is estimated at 15%[7] and in older people (≥65-years), it is 25%.[8]

Patients suffering from CP often experience a significant impact on psychosocial well-being, including sleep disturbances, shame, or even body dysmorphic disorders due to visible injuries caused by scratching.[9–11] Patients with severe itching have a lower quality of life and suffer more from depressed mood and anxiety. Suicidal ideations were reported in 18.5% of patients with CP.[12]

The International Forum for the Study of Itch (IFSI) has classified chronic pruritus into three categories: (i) Chronic Pruritus on primarily Lesional (altered) skin (CPL), where an underlying skin disorder is present; (ii) Chronic Pruritus on Primarily Non-Lesional (unchanged) skin (CPNL), where there are no initial skin lesions (formerly known as pruritus sine materia); and (iii) Chronic pruritus with severe scratching lesions (e.g., chronic prurigo, lichen simplex), which prevents classification into the first or second category.[13] This classification is crucial for guiding both diagnosis and treatment, as the underlying mechanisms and therapeutic strategies may vary significantly depending on the type of pruritus.

The primary aim of this review is to explore the pathogenesis of CP, its origins in the skin/mucosa or Central Nervous System (CNS), with particular attention to these different distinctions of pruritus and the causes related to underlying dermatological conditions, internal diseases, or when classified as Chronic Pruritus of Unknown Origin (CPUO), along with current recommendations for investigation and treatment.

Pathogenesis of chronic pruritus

Histamine was the first mediator identified in association with pruritus. However, antihistamine therapy has proven effective only in treating a few conditions, such as hives, allergic drug reactions, and insect bite reactions. Pruritus is a symptom resulting from a complex interaction of inflammatory mediators, immune cells, skin cells, and neuronal networks, involving both the peripheral and central nervous systems to produce the characteristic scratching response. The process begins in the epidermis and dermal-epidermal junction, where a pruritogen – originating from immune cell products, exogenous compounds, or keratinocytes – activates pruritic receptors on unmyelinated C-nerve fibers.[14] These fibers can be classified as histaminergic or non-histaminergic based on receptor expression.[15] Histaminergic nerve fibers are typically involved in the transition from acute itch to histamine-activated pruritus, whereas Chronic Pruritus (CP) is associated with non-histaminergic fibers, which are activated by pruritogens other than histamine.[16]

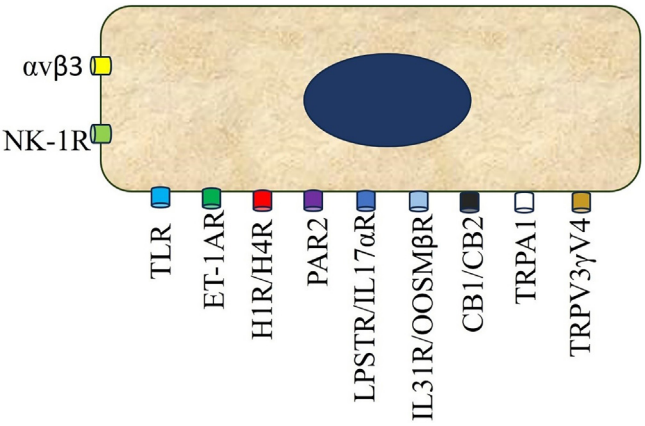

Fig. 1 Keratinocyte receptors enrolled in pruritus.

Dysregulated communications between sensory nerve endings, immune cells, keratinocytes, skin-resident cells, as well as the CNS trigger CP chronification. After triggering cutaneous stimuli, itching signals are sent to the peripheral nerve from cutaneous nerve endings, which originate from the Dorsal Root Ganglion (DRG), ascend to the somatosensory thalamus, and are then projected into the cerebral cortex (Figs. 1 and 2).[17]

Itchy skin involves the main components: (i) Skin-resident cells; (ii) Itching nerve fibers (PNS); (iii) Itch receptors; (iv) Histaminergic and nonhistaminergic itch pathways; (v) Transmission of itching in the spinal cord; (vi) Itching in the brain (CNS).[18]

(i) Resident cells in the skin

Keratinocytes

They are considered to be on the front line of the nervous system, given their high bioactivity and ability to secrete pruritogens.[19] They express Protease-Activated Receptor (PAR2), Toll Receptor 3 (TRL3), Histamine Receptors (HR1-HR4), Endothelin A (ETA) and B (ETB), serotonin (5-HTR), Oncostatin M β receptor (OSMRβ), integrin αvβ3, Thymic Stromal Lymphopoietin Receptor (TSLPR), Neuropeptide Y receptors (NPY), including TRPV3 and V4 (Fig. 1).

The indirect pathway of itch induction involves the disruption of the epidermal barrier, leading to an increased inflammatory gradient and transepidermal water loss. This disruption is typically accompanied by the production of pro-inflammatory cytokines (e.g., IL-6) and various chemokines (e.g., CXCL-8, CCL17/TARC, CCL19/MIP-3β, CCL22/MDC, CCL23/MIP-3, CCL4/MIP-1β, and CXCL1/GRO1α), as well as Nerve Growth Factor (NGF) by keratinocytes. The main pruritic mediators released by keratinocytes that can directly activate pruritic nerve endings include TSLP, periostin, ET-1, IL-33, and BNP.[19,20]

TSLP and other Th2 cytokines may induce periostin secretion, which in turn can stimulate further TSLP release, potentially establishing a pruritic positive feedback loop. One of the most potent pruritic mediators derived from keratinocytes is ET-1, whose production can be triggered by

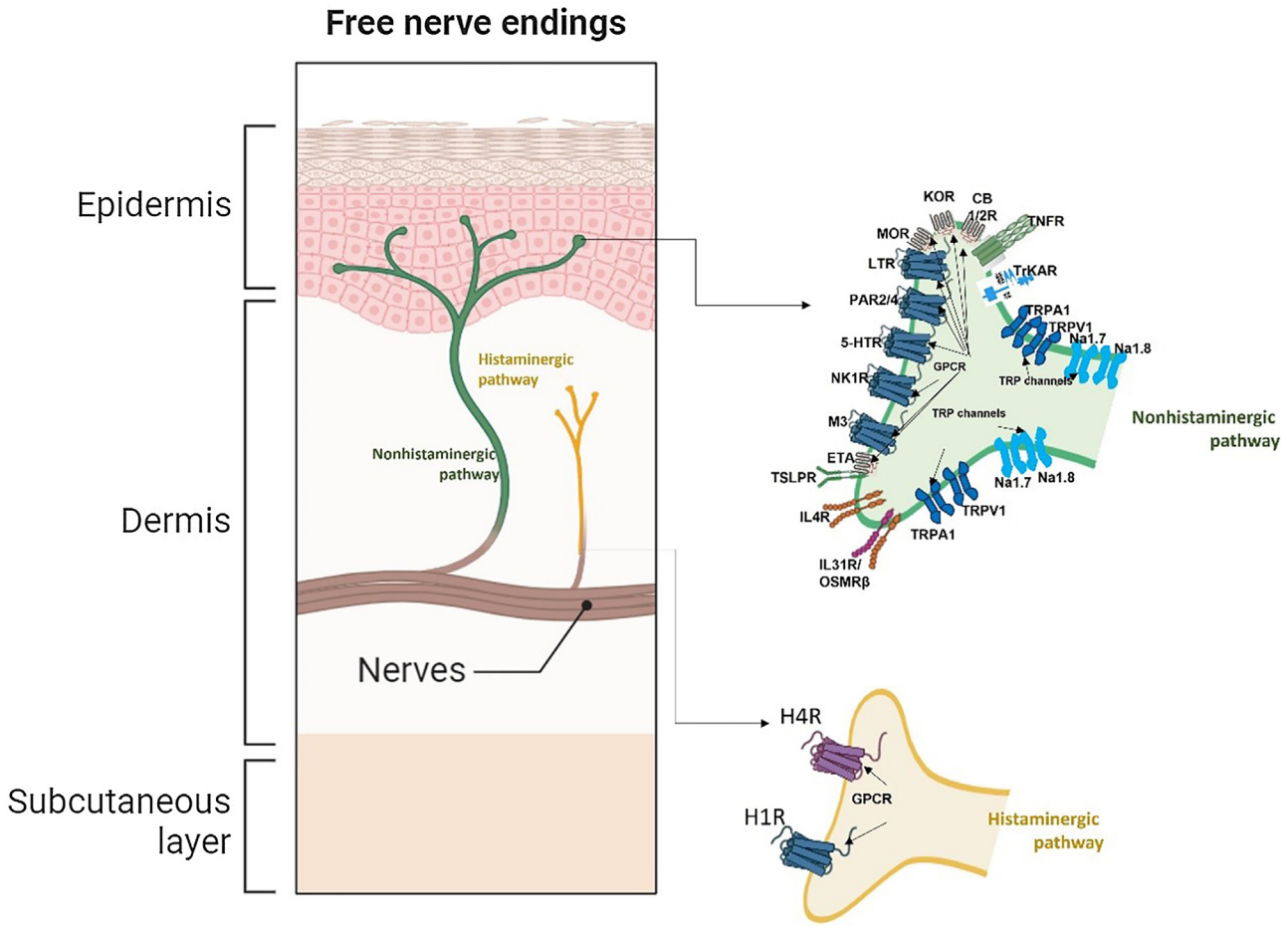

Fig. 2 Pruritus receptors (PNS) in the epidermis and dermis. There are at least 3 subsets of pruriceptors expressing dedicated pruritogen receptors. These neurons are generally subdivided into NP1, NP2, and NP3 neurons based on their expression patterns. Cation channels transient receptor potential vanilloid subtype 1 and/or transient receptor potential ankyrin1 and NaV1.7 and NaV1.8, respectively, are required for downstream signaling of the itch receptors and are consistently expressed across subsets of these neurons (nonhistaminergic pathway). Histaminergic itch results from the direct action of the pruritogen histamine on its receptor (H1R) and (H4R) on sensory nerves to transmit itch signals. Although the H1R is coexpressed with other pruritogen receptors on pruriceptors, its utility as an itch therapeutic target is limited to certain inflammatory itch diseases as such as urticaria. Abbreviations: 5-HTR, serotonin receptor; CB1/2, cannabinoid receptor type 1 and 2; ETA, endothelin A receptor; H1/4R, histamine receptor type 1 and 4; IL31R, interleukin 31 receptor; IL4R, interleukin 4 receptor; KOR, kappa opioid receptor; LTR, leukotrienes receptor; M3, muscarinic acetylcholine receptor 3; MOR, mu opioid receptor; Nav1.7/1.8,voltage-gated sodium channel; NK1R, neurokinin 1 receptor; OSMRβ, oncostatin M receptor beta; P, phosphate; PAR2/4, protease-activated receptor type 2 and 4; TNFR, tumor necrosis factor receptor; TrkA, tropomyosin receptor kinase A; TRPA1, transient receptor ankyrin 1; TRPV1, transient receptor potential vanilloid 1;TSLPR, thymic stromal lymphopoietin receptor. Image partially created using BioRender®.

the activation of PAR2, TLR3, TRPV3, and TRPV4. IL-33, a member of the IL-1 family of inflammatory cytokines, is constitutively expressed in the nucleus of keratinocytes and acts as an alarmin, released in response to inflammation or cell damage.[20]

Initially, IL-33 was shown to act on cells of both the innate and adaptive immune systems, specifically mast cells, Innate Lymphoid Cells type-2 (ILC2), basophils, and type-2 helper T-cells. However, its receptor, ST2, is also expressed on sensory nerve endings in the skin, and its activation leads to an itch response in mice. Additionally, IL-33 is upregulated in Atopic Dermatitis (AD) lesions, potentially contributing to the pruritic phenotype associated with this condition.[20]

Merkel cells

These cells trigger the pruritus-scratch cycle after stimulation by the Piezzo receptor-2.[19] The complex formed by Merkel cells and pruriceptive MRGPRA3+ endings (C fibers) in cases of xerosis and prurigo nodularis may be functionally impaired. Merkel cells express TRPM8.[19]

Mast cells

These innate immune cells are located in the papillary dermis, near nerve fibers, around the pilosebaceous unit, around dermal blood vessels, and are loaded with pru-

ritogens, capable of activating both histaminergic and non-histaminergic pathways.[19]

(ii) Itch nerve fibers

The cell bodies of the myelinated Alpha-Delta (Aδ) fibers (mechanical itch), unmyelinated C-fibers (CM and CMH), both non-histaminergic, and the unmyelinated C-fibers (CMi/histaminergic) reside in the Dorsal Root Ganglia (DRG) with axons innervating the skin (epidermis and dermis), and dendrites synapsing in the dorsal horn of the spinal cord.[18] Pruritus is initiated when endogenous and exogenous pruritogens bind to their receptors on these sensory nerve endings.[18]

(iii) Itch receptors and channels[18,21]

There are 3 major classes of *itch receptors*: G Protein-coupled Receptors (GRPs), Toll-Like Receptors (TLRs) and cytokine receptors (for example, interleukin-31, thymic stromal lymphopoietin, interleukin-4, interleukin-13, interleukin-33, Omcostatin-M [OSM]).[18,21] The members of the Mas-related GPCR (MRGPR) involved on itch are represented by MRGPRX1 and MRGPRX4 in humans, and as an example, chloroquine elicits itching through MRGPRA3 stimulation in rodents and MRGPRX1 in humans.[21] One class of channels broadly associated with pruritus is the Transient Receptor Potential (TRP) channels. This group includes TRP Vanilloid-1 (TRPV1) and TRP Ankyrin-1 (TRPA1), which activate the Nav1.7 and Nav1.8 sodium channels, thereby propagating the action potential of the itch signal. Both histaminergic and non-histaminergic itch pathways rely on TRP signaling. Table 1 provides a summary of the distinct itch receptors, their activating compounds, and the associated pathways or diseases.[22,23]

There are several chemical stimuli that trigger itch at different stages, including neuropeptides, amines, cytokines, chemokines, proteases, lipids, and opioids and their respective receptors, as demonstrated in Table 2.[24] Mediator related itch implies that pruritus is associated with mediators including histamine, 5-hydroxy tryptamine, proteases, opioid peptides, peptides, and eicosanoids.[24]

(iv) Histaminergic and nonhistaminergic pathways

Histaminergic and nonhistaminergic sensory nerves constitute the two major pathways of pruritus.[18] The histaminergic pathway transmits acute and chronic itch, as in cases of acute or chronic spontaneous urticaria, and is mediated by histamine secreted primarily by mast cells, basophils, and keratinocytes.[18] Once released, histamine binds to H1 and H4 receptors on histaminergic nerves, activating TRPV1.[18] Nonhistaminergic itch is elicited by nerves that express several receptors, activated by pruritogens other than histamine.[18] These pruritogens are released by a variety of effector cells, including mast cells, granulocytes, macrophages, lymphocytes, Innate Lymphoid Cells type-2 (ILC2), keratinocytes, and neurons.[18] Recent evidence also suggests that basophils can promote itch mediated by Immunoglobulin E (IgE), independent of mast cells.[18]

(v) Pruritus in the spinal cord

The itch signal is transmitted through the neuron cell bodies in the DRG to the dorsal horn of the spinal cord (Fig. 3).[18] The activated sensory neurons release Gastrin-Releasing Peptide (GRP) which binds to GRP Receptor (GRPR)-positive intermediate neurons (interneurons) in the spinal cord.[18] Structural abnormalities of the spinal cord can also modulate the itch signaling pathway, causing localized neuropathic pruritus.[18] Specific populations of inhibitory interneurons were involved in the control of itch, and their dysfunction could lead to enhanced itch perception.[25] Radiculopathy of cervical nerves a contribute to brachioradial pruritus, whereas in notalgia paresthetica the dorsal rami of intercostal nerves are involved.[18]

(vi) Itch in the brain (CNS)

After transmission through the spinal cord, itch signals running along the spinothalamic tract and reach the thalamus and parabrachial nucleus, followed by brain.[18]

Pruritus perception involves the primary and secondary somatosensory cortex, insula, and anterior cingulate cortex.[18]

Histaminergic and nonhistaminergic pruritus also activate distinct areas of the brain and can resemble pain perception. It is very important to remember that brain activation upon pruritic stimulation is different in patients with chronic itch compared to healthy volunteers. This has been shown in functional Magnetic Resonance Imaging (fRMI) studies for instance with atopic dermatitis patients, where the frontostriatal circuit is relevant for the itch. There are top-down inhibitory pathways from the brain stem modulating the itch signal at the spinal level.[18] These pathways seem to be affected in patients with chronic itch.[26]

(vii) Efferent pathway of itch: motor action of scratching

In the CNS (brain), the main neurotransmitters are Noradrenaline (NA) and serotonin (5-HT).[19]

The population of NA + neurons is located in the *locus coeruleus*, while their $\alpha 1$ adrenergic receptors are found in inhibitory interneurons of the spinal cord. The 5-HT1A receptor, expressed in GRPR + interneurons, also plays a direct role in the efferent (descending) signaling of itch. The Periaqueductal Gray Matter (PAG) receives input from both the amygdala and the parabrachial nucleus, actively contributing to the central processing of the emotional component of itch.[27] A subpopulation of Tachykinin-1-expressing glutamatergic neurons (TAC1+) promotes stimuli that sustain the itch-scratch vicious cycle. The anterior cingulate cortex forms part of a circuit with the anterolateral thalamic nucleus and dorsomedial striatum, modulating histaminergic itch via a spinal circuit dependent on Bhlhb5+ interneurons.[19]

Table 1 Itch channels, receptors, their activating compounds and associated pathways, conditions or diseases.[20–25].

Channels / Receptors	Type	Activating Compounds	Associated Pathways/Diseases	
Transient receptor potential (TRP) channels	TRPA1 (TRP Ankyrin 1)	Allicin (found in garlic), allyl isothiocyanate (alkaloid found in mustard oil, wasabi, and horseradish), arachidonic acid, BAM8-22, bile acids, bradykinin, carvacol, chroloquine, cowhage, cinnamaldeyde (found in cinnamon oil), endothelin-1, hydrogen peroxide, IL-33, IL-31, LPA, LTB4, prostaglandins, t-BHP, TSLP, 5-HT (serotonin), periostin	*MRGPR-associated nonhistaminergic pruritus and PAR-mediated nonhistaminergic pruritus*; conditions as AD, allergic contact dermatitis, cholestatic pruritus, psoriasis	
	TRPV1 (TRP Vanilloid 1)	Capsaicin, histamine, ATP, lipoxygenase products, prostaglandins, imiquimod, periostin, IL31, IL-33	*Histaminergic pruritus and PAR-mediated nonhistaminergic pruritus, IL-31 and IL-33 mediated itch pathways*; conditions: AD, psoriasis, prurigo nodularis.	
	TRPV2 (TRP Vanilloid 2)	Increased temperature, physical stimuli	Mast cell degranulation, PKA-mediated inflammatory cascade	
	TRPV3 (TRP Vanilloid 3)	Plant-derived compounds, arachidonic acid, farnesyl pyrophosphate (FPP)	*PAR-mediated nonhistaminergic pruritus*, IL-31-mediated BNP synthesis; Conditions: Olmsted syndrome (missense mutation with gain-of-function of the gene codifying TRPV3), AD, psoriasis	
	TRPV4 (TRP Vanilloid 4)	Histamine, endothelin-1, 5-HT, lysophosphatidylcholine (LPC)	*Histaminergic pruritus*; dry skin pruritus, allergic contact dermatitis, psoriasis, chronic idiopathic pruritus	
	TRPM8 (TRP Melastatin 8)	Menthol, icilin	*Histaminergic and nonhistaminergic pruritus*; B5-1 neuron-associated spinal interneuron circuit; dry skin pruritus, AD, urticaria, scalp pruritus	
	TRPC3 (TRP Cannonical 3)	Chloroquine, beta-alanine	*Nonhistaminergic pruritus*; contact dermatitis	
	TRPC4 (TRP Cannonical 4)	Sertraline	Sertraline receptor HT2B-associated pruritus	
G protein-coupled receptors (GRPs)	Receptors (human and murine)		Ligand endogen	Ligand exogen
	MRGPX2 (human ortholog), MrgprB2 (murine ortholog)		Substance P, platelet factor-4, AC-30/SC, β-defensin, cathelicidin, LL-37, BAM (8–22; 13–22; 22), catestatin, cortistatin, hemokinin-1	Ciprofloxacin, Levofloxacin, moxifloxacin, ofloxacin, atracurium, rocuronium, tubocurarine, angiopeptin, cetrorelix, hexarelin, icatibant, leuprolide, octreotide, sermorelin, compound 48/80, mastoparan, CSP-CSP1-CSP-2, entf, streptin-1

Table 1 (*Continued*)

Channels / Receptors	Type	Activating Compounds	Associated Pathways/Diseases	
	MRGPRX1 (human ortholog), Mrgprc11 (murine ortholog)		BAMB98-220, β-defensin, SLIGL [Tyr^6] γ2-MSH96-12), neuropeptide FF	IPDef1; IRDef2
	MRGPRX1 (human ortholog), Mrgpra3 (murine ortholog)		β-defensin	Chroroquine
	MRGPRX1 (human ortholog), Mrgpd (murine ortholog)		β-alanina, alamandine, 5-oxoETE, angiotensin (1–7), GABA	ND
	MRGPRX4 (human ortholog), Mrgpra1 (murine ortholog)		Bilirubin, Salusin β, Arg-Phe-amide containing neuropeptides (FLRF-amide, FMRF-amide and NPFF)	ND
	Mrgpra4		Neuropeptide FF, ACTH	ND
Toll-like receptors (TLRs) [22,23]	TLRs function as innate sensors in the immune system.[22] They may have a similar role in the nervous system, but this possibility has not been demonstrated conclusively.[22] Chronic itch after skin injury also requires TRPA1. Several types of nociceptor-expressed TLRs, such as TLR2, TLR3, TLR4, and TLR7, have been implicated in itch modulation via functional coupling to TRPA1 or/and TRPV1.[23]		TLR3, TLR7, and potentially TLR4 are expressed on small-sized primary sensory neurons. TLR3, TLR7, and potentially TLR4 are expressed in a subtype of pruriceptive/nociceptive neurons in the dorsal root and trigeminal ganglion providing a direct link between TLR activation and itch.[22] Activation of neuronal TLRs can initiate itch sensation by coupling with ion channels.[22] Furthermore, TLRs are expressed in skin cells and glial cells in the spinal cord to regulate inflammation and neuroinflammation in chronic itch.[22]	

Table 1 (*Continued*)

Channels / Receptors	Type	Activating Compounds	Associated Pathways/Diseases
Cytokine Receptors [24]	TSLP and its receptor complex IL7Rα/TSLPR[24,25] The intracellular signalization of these interleukin receptors is mediated by TRPA1.		Expressed by a small subset of itch-sensing DRG neurons.[24] High TSLP skin expression is a hallmark feature of AD, and TSLP is released by KCs in response to a broad range of stimuli, including in allergy and proteolytic PAR2 activation.[24]
	IL-33 and their receptor complex ST2/IL1RAP[24,25] The intracellular signalization of these interleukin receptors is mediated by the channels TRPA1/TRPV1.		Expressed by a subset of histamine-sensitive DRG neurons.[24] However, the exact involvement of IL-33 in itch is less clear.[24] Although this cytokine is important for the development of chronic itch conditions such as ACD and xerosis.[24] IL-33 has been reported to stimulate enkephalin production in group 2 innate lymphoid cells.[24] The derivative of proenkephalin A-bovine adrenal medulla 8–22 is a potent MRGPR agonist.[24]
	Type-2 immune cell-derived Interleukins (ILs)- IL-4, IL-13, IL-31 and their receptors[24,25] The intracellular signalization of IL-13Rα1 and IL-4Rα are mediated by JAK1/STAT pathway.		These type-2 cytokines lay a major role in AD-associated itch.[24] The involvement of these cytokines in AD skin disease had already been known, but these cytokines have recently also been implicated in the direct modulation of itch neurons.[24] In mice, the IL-4 and IL-13 receptor complex IL-4Rα/IL-13Rα1 is broadly expressed by itch-sensing DRG neurons, and the IL-31 receptor complex IL-31Rα/OSMRβ is further expressed by some 5-HT – sensitive fractions of these neurons.[24] The expression of these receptors has also been detected in human DRGs.[24] These cytokines broadly enhance itch neuronal excitability, thereby potentiating both histaminergic and nonhistaminergic itch pathways.[24]

ACTH, Adrenocorticotropic Hormone; AD, Atopic Dermatitis; BAM, Bovine Adrenal Medulla; BAM, Bovine Adrenal Medulla; BNP, B-type Natriuretic Peptide; CSP, Competence-Stimulating Peptide-1; GABA, Gamma Aminobutyric Acid, IL, Interleukin; IPDef1 (IP defensin-1) and IRDef2 (IR defensin-2), both are tick salivary peptides; JAK/STAT, Janus Kinase/Signal-Transducer and Activator of Transcription; LTB4, Leukotriene B4; LPA, Lysophosphatidic Acid; 5-HT, 5-Hydroxyptamine (serotonin); oxoETE, 5-Oxieicosatetraenoic acid; LPA, ND, Not Determined; MSH, Melanocyte-Stimulating Hormone; NPFF, Neuropeptide FF; PAMAP, Proadrenomedullin Peptide, PACAP, Pituitary Adenylate Cyclase Activating Polypeptide; PAR, Protease Activated Receptor; PKA, Protein Kinase-A; VIP, Vasointestinal Peptide, TSLP, Thymic Stromal Lymphopoietin.

Table 2 Distinct mediators and receptors involved on chronic pruritus.[20,25–27]

Classes of mediators and/or targets involved on pathogenesis of itch	Mediators	Cells involved, actions and disorders associated
Neuropeptides (critical in the transmission of itch sensation from the peripheral nervous system to the spinal nervous system and to brain)	*Calcitonin gene-related peptide (CGRP)*	Vasodilator agent expressed in the sensory neurons, motor neurons, monocytes, macrophages, Langerhans Cells (LCs) and keratinocytes. CGPRα is expressed in the CNS and Peripheral NervousS (PNS), whereas CGRPβ is less found in PNS, but is the only form found in keratinocytes.[20] The CGRP is released after activation of *transient receptor potential cation channel subfamily V member 1* (TRPV1, also known as the capsaicin receptor and the vanilloid receptor-1) on membrane of sensory neurons.[20] CGRP act on several immune cells, including-T and B-cells, Dendritic Cells (DC), mast cells, macrophages, LCs, causing neuro-inflammation, neurogenic vasodilatation, and immune response. $CGRP^+$ interneurons (in DRG) may mediate spinal itch transmission, but not pain signals.[20]
	Substance P (SP)	SP is an important transmitter of the afferent neurons in the PNS and CNS.[25] SP acts in distinct immune cells, such as eosinophils, mast cells, T-cells and promotes skin inflammation. *Neurokinin-1 receptor* (NK-1R) is traditionally regarded as the main SP receptor, however on mast cells, *mas-related G-protein-coupled receptor member B2* (MrgprB2/MrgprX2) may be the critical receptor for SP-mediated mast cell activation. SP actives mast cells to release histamine, Leukotriene B4 (LTB4), Prostaglandin D2 (PGD2), and Tumor Necrosis Factor alpha (TNF-α).[25] These mediators reach sensory nerve endings in epidermis and dermis where induce SP release and exacerbate itch, in a vicious cycle of positive feedback for itch.[25] SP released from the sensory nerve endings, especially from C-fibers, can increase histamine and TNFα release from mast cells, IL-1, IL-6 and IL-8 production in keratinocytes, or IL-8 production in dermal microvascular endothelial cells, all contributing to local inflammation.[25]
	Neuropeptide Y (NPY)	Spinal inhibitory interneurons express receptors for this molecule which form synapses with afferent fibers stimulated by secretion of natriuretic peptide B.[27]
	Neurotrophin	Neurotrophin is a large family of physiological activators promoting the growth, differentiation, and maintenance of neurons.[26] It primarily contains Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurotrophic Factors-3 (NT-3), and Neurotrophic Factors-4 (NT-4).[26] NGF levels in the itchy lesions of AD and psoriasis significantly increased and correlated with the severity of diseases;[26] NGF, at the same time, upregulated the expression of sensory neuropeptides, which may induce the release of TRPV1, elicit the degranulation of mast cells, and result in pruritus.[26]

Table 2 (*Continued*)

Classes of mediators and/or targets involved on pathogenesis of itch	Mediators	Cells involved, actions and disorders associated
	B-type natriuretic peptide (BNP)	BNP is a central itch mediator.[5] Release and synthesis of BNP is upregulated by Interleukin-31 (IL-31) in sensory Dorsal Root Ganglionic Neurons (DRGs).[20] IL-31 receptors (IL-31RA and OSMR) are co-enriched with the BNP gene (Nppb) in DRG.[20] BNP and receptor expression is increased in the pathogenic skin of AD patients.[20] In the human skin cells, the pro-inflammatory and itch-promoting phenotypes are promoted by BNP.[20] In the skin, BNP was found to sensitize Transient Receptor Potential Vanilloid-3 (TRPV3), resulting in enhanced Serpin E1 release, an itch-specific mediator with transcription levels positively correlated with the severity of human AD skin.[20]
	Gastrin-releasing peptide (GRP)	GRP is a spinal itch-selective transmitter known to be highly expressed in a population of spinal cord Dorsal Horn (DH) interneurons and may serve as a ''leaky gate'' for nociceptive signals.[20] GRP neurons receive direct input from MrgprA3+ pruritoceptors.[20] GRP level is also increased in AD patient skin and GRP seems to promote Thymic Stromal Lymphopoietin (TSLP) release from keratinocytes.[20]
	Somatostatin (SST)	SST originates from the DRGs and spinal dorsal horn neurons and is an important endocrine hormone and a neuropeptide in the nervous system, including the PNS and CNS.[20]
	Opioid peptides	Opioid peptides have peripheral and central itchy effects. They effectively work by activation of μ-Receptor (MOR) and inhibition of κ-Receptor (KOR) in the central nervous system. MOR is the major functional receptor for itching production, but KOR does the opposite. At the periphery, on the other side, morphine induces pruritus generation by eliciting the degranulation of mast cells.[26] All of these opioid peptides could cause itching after intrathecal administration.[26] Endogenous endorphins demonstrate affinity for MOR expressed in C and A fibers.[27] These form synapses with GRPR + excitatory interneurons in the posterior horn, where signaling is pruritogenic.[27] Th e KOR bind to dynorphin, whose activity is antipruritogenic.[27] At physiological level there is a homeostasis between MOR and KOR activation, controlled mainly by excretion of dynorphin.[27] In the spinal cord, there is a subpopulation of dynorphin + inhibitor interneurons.[27] Loss of function of these interneurons are implicated in central signaling of pruritus and alloknesis.[27]

Table 2 (*Continued*)

Classes of mediators and/or targets involved on pathogenesis of itch	Mediators	Cells involved, actions and disorders associated
Amines	*Histamine*[27]	Histamine is a chemical medium mainly stored in the basophilic leukocyte and mast cells.[26] When these cells are activated by immune and nonimmune factors, histamine is induced to release.[26] Its receptors belong to the members of the G Protein-Coupled Receptors (GPCR), in which H1 and H4 Receptors (H1R and H4R) play important roles in the appearance of pruritus.[26] Previously, it was considered that histamine dominated the development of pruritus via binding to H1R and activating phospholipase Cβ3 (PLCβ3) and Phospholipase A2 (PLA2).[26] HR-4 is present in keratinocytes and in C fibers (histaminergic).[27] Histamine could increase the calcium influx in the axon terminals of the spinal cord neurons by activating Transient Receptor Vanilloid-1 (TRPV1) receptor and then promote a series of intracellular signal activation and ultimately lead to itching generation.[26] Nowadays, histamine is the main mediator in some conditions as acute and chronic urticaria, a few drugs adverse reactions and insect bites. Spinal cord H4R-mediated itch can be persistent, and antagonists for H4R attenuated itch in AD patients whereas antagonists for H1R and H2R are largely ineffective in AD and psoriasis.[20]
Proteases	Proteases perform as any enzyme about proteolysis, which are involved in diverse physiological reactions. It is believed proteases are extremely important substances in causing histamine-independent pruritus.[27] Recent studies have demonstrated that proteases play a crucial role in itching attack by combining to GPCR called Proteases Activated Receptors (PARs), especially PAR2 and PAR4.[26]	
Other Peptides	*Bradykinin*	Bradykinin belongs to an active peptide of the kinin group of proteins. It is a potent inflammatory mediator and endothelium-dependent vasodilator, which contribute to the production of inflammatory reaction and the dilation of blood vessels.[26] The receptors of Bradykinin comprise Receptor B1 (B1R) and Receptor B2 (B2R) belonging to the members of GPCR family.[26] By combining with its receptors, bradykinin initiates and induces a variety of physiological and pathological reaction.[26]

Table 2 (*Continued*)

Classes of mediators and/or targets involved on pathogenesis of itch	Mediators	Cells involved, actions and disorders associated
Phospholipids metabolites	*Cannabioides*	Cannabinoids (CB) belong to the derivatives of arachidonic acid, the receptors of which contain CB1 receptor and CB2 receptor. CB1 receptor is distributed in the central nervous system, while CB2 receptor is distributed in the peripheral tissues.[27] CBs, by binding to their receptors, could induce the release of 13-endorphins, further, to relieve pain and alleviate histamine induced pruritus.[27] These results indicate that CB may be involved in the regulation of pain and pruritus.[26] In mice, both receptors have been detected in sensory neurons, whereas in humans, only CB2R has been so localized.[15] Activation of CBR in sensory neurons may decrease neuronal activity and modulate the axon-flare response.[15] Tetrahydrocannabinol, a bioactive component of marijuana, blocked scratching behavior elicited by compound 48/80.[15]
	Eicosanoids	There are multiple subfamilies of eicosanoids, consisting of Leukotrienes (LTs), prostaglandins, resolvins, lipoxins, eoxins, and thromboxanes.[26] LTs, most prominently, are important regulators in the modulation of pruritus, and LTB4 levels are significantly elevated in AD and psoriatic lesions, which were usually accompanied with pruritus.[26]
	Platelet-Activating Factor (PAF)	PAF has a variety of physiological and pathophysiological effects, which acts as an important mediator and activator in anaphylaxis, inflammation, platelet aggregation and degranulation, and leukocyte chemotaxis.[26] Normally, PAF is produced in low quantities by various cells (e.g., platelets, neutrophils, macrophages, endothelial cells, and monocytes), but it emerges in larger quantities from inflammatory cells in response to specific stimulator.[26]

Table 2 (*Continued*)

Classes of mediators and/or targets involved on pathogenesis of itch	Mediators	Cells involved, actions and disorders associated
Cytokine and Chemotactic Factor Induced Itch	The cytokines build ''a bridge of communication'' between the immune system and the nervous system. AD-related skin lesions and itch are aggravated under the mutual interaction of neural–epidermal immune signal pathways.[20] Pruritus is caused by a variety of pruritus-derived cytokines, including TSLP, Interleukin-2 (IL-2), Interleukin-4 (IL-4), Interleukin-13 (IL-13), IL-31, Interleukin-33 (IL-33), etc., and by the imbalance of the neuro-immune circuit between the receptors IL-4R, IL-13R, IL-31RA, OSMR, Mrgprs, and itching peptides (SP, BNP, CGRP, GRP and protease, etc.).[20] As the quantity of TH2 cells is increased, the inflammation related to specific cytokines and the generation of eosinophilia and Immunoglobulin E (IgE) are promoted, whilst the generation of epidermal barrier proteins and antibacterial peptides is inhibited. IL-4 and IL-13 are typical type-2 cytokines and have been proven to directly stimulate the sensory neurons via the Janus Kinase-1 (JAK1) signals and promote itch sensation.[20]	
	IL-13	IL-13 levels are increased in skin and serum from AD patients, and IL-13 participates in the initiation of AD and itching. Together with IL-4, it aggravates epidermal barrier dysfunction by downregulation of the Filaggrin (FLG) and Involucrin (IVL) expression in the keratinocytes.[20] The sensory neurons and keratinocytes express heterodimer receptor IL-4, receptor alpha/IL-13, receptor alpha-1 (IL-4Rα/IL-13Rα1), and IL-13 receptor alpha-2 (IL-13Rα2).[20] IL-13 binds with IL-13Rα1 with low affinity, and when the heterodimer receptor consisting of IL-13Rα1 and IL-4Rα is formed, with high efficiency, the latter is a type-II receptor.[20] IL-13 and TLR2 heterodimer agonists can upregulate the transcription of IL-13Rα2 in keratinocytes and sensory neurons, respectively, thereby promoting neurogenic inflammation and exacerbating AD and itch.[20]
	IL-31	IL-31 plays an important role in the induction of itch and inflammation in AD and chronic contact dermatitis in mice and humans.[20] IL-31 stimulates itch-related neuronal subset NP3, a subpopulation also responsive to mast-cell-released 5-HT, Leukotriene C4 (LTC4), and S1p, and release BNP and SST. Moreover, IL-31 binds to its receptors on epidermal keratinocytes and immune cells (i.e., eosinophils) to induce skin barrier dysfunction and cutaneous inflammation.[20]

Table 2 (*Continued*)

Classes of mediators and/or targets involved on pathogenesis of itch	Mediators	Cells involved, actions and disorders associated
	IL-33	IL-33 is an effective amplifier of type-2 immune reaction and is an important target for dry skin pruritus and chronic pruritus of unknown origin (CPUO).[20] IL-33 receptor ST2 (also named IL-33R) is expressed in DRGs, keratinocytes, immune cells, fibroblasts, and mast cells.[20] Binding of IL-33 to keratinocytes contributes to the impeded filaggrin and claudin-1 protein expressions and functional damages to the skin barrier, and facilitation of immune regulation.[20] IL-33 stimulates diverse cells including ILC2 (innate lymphoid cell type-2) and generates type-2 cytokines including IL-5 and IL-13.[20]
	TSLP	TSLP is a pro-allergic cytokine that is mainly released from keratinocytes and is the prime target in AD. TSLP drives TH2-mediated inflammation and enhances periostin release from keratinocytes, thereby promoting itch signaling, and this effect is susceptible to JAK2 inhibitor SD1008 and the STAT3 inhibitor niclosamide. Upon release from keratinocytes, TSLP activates various immune cells such as T-cells, dendritic cells, mast cells, and sensory neurons directly to evoke itch behaviors.[20] The biological functions of TSLP require heterodimer formation between the TSLP Receptor (TSLPR) and interleukin-7 Receptor-alpha (IL-7Ra).[20] TSLPR activation of primary afferent sensory neurons requires TRPA1 but not TRPV1.[20] TSLP is also important for promoting wound-induced hair growth and regeneration in mice, which may be an issue that should be considered to use TSLP antagonists for pruritus accompanied by hair loss.[20]
	Periostin	Periostin plays critical roles in pathogenesis of skin fibrosis, lesional AD, psoriasis, allergic skin inflammation, and prurigo nodularis.[20] Periostin is released from dermal keratinocytes and fibroblasts upon stimulation by TH2 cytokines IL-13 and IL-4, then activates integrin aVβ3 on a fraction of SST+/NPPB + sensory itch fibers.[20] Meanwhile, periostin stimulates keratinocytes and immune cells to release various cytokines, including TH2 cytokines such as IL-31.[20] MC903 and house dust mites promote periostin release via a JAK/STAT-mediated mechanism.[20] Periostin also induces TSLP release in a periostinTSLP-TH2 cytokine–periostin feedback loop.[20]
	Lipocalin-2 (LCN2)	LCN2 is a central modulator of chronic itch via a STAT3-dependent mechanism in the spinal astrocytes.[20] It is also released by neutrophils and keratinocytes.[20] The serum level of LCN2 is associated with the severity of itch in patients with psoriasis.[20]
	IL-2	IL-2 is an itch inducer as well as an autocrine cytokine, and its single intradermal injection induces a long-time low-intensity local skin itch that lasts 48–72 h, as well as erythema in human AD patients and healthy subjects.[20] IL-2 is released from keratinocytes and various immune cells, then activates histaminergic neurons. Moreover, it induces erythema and dermal T-cell infiltration.[20]

Table 2 (*Continued*)

Classes of mediators and/or targets involved on pathogenesis of itch	Mediators	Cells involved, actions and disorders associated
	IL-6	IL-6 is predominantly expressed in dendritic cells, keratinocytes, macrophages, and neurons.[20] The dendritic-cell-derived IL-6 level is linked to AD. IL-6 facilitates production of IL-4 expression by CD4+ T-cells and their differentiation to TH2 cells.[20]
	Oncostatin M (OSM)	OSM is released by dermal T cells, macrophages, dendritic cells, neutrophils, and monocytes. Its receptor OSMR resides in sensory neurons expressing BNP; however, OSM does not activate sensory neuronal calcium entry, thus it is different from other pruritogens.[20] OSM also potentiates histamine- and leukotriene-evoked itch behaviors.[20]

Table 3 Classification of chronic pruritus into groups and categories.[4,28]

Clinical groups in chronic pruritus	Etiological categories
IFSI I: *chronic pruritus on primarily lesions (altered) skin (CPL)*: in the presence of a skin disorder (previously: pruritus cum materia). This type is related mainly in conditions related as category I IFSI II: *chronic pruritus on primarily non-lesional (unaltered) skin (CPNL)*: without the initial presence of a skin lesions (previously: pruritus sine materia). Usually, the clinical aspect is a normal skin, and have as etiology related to mainly category II, III, IV. Some conditions classified in this class include: pruritic skin disease before skin eruptions, disorders of iron metabolism, uremia, hepatic disease (especially cholestasis), internal malignancy, hematological disorders, infections, endocrine disorder, neurological disorder, heart failure, somatoform conditions, adverse drug reactions, pregnancy, pruritus of elderly skin and pruritus of unknown origin (CPUO) IFSI III: *chronic pruritus with severe scratch lesions*: predominance of chronic scratch lesions (for example, chronic prurigo, lichen simplex) precluding the classification into the first or second group. The clinical picture is related to chronic secondary scratch lesions like prurigo nodularis, and the etiology may relate to categories I-IV	Category I: dermatological origin of chronic pruritus (related to inflammatory dermatoses, infectious dermatoses, autoimmune dermatoses, genodermatoses, dermatoses of pregnancy, neoplasms, etc.) Category II: Systemic origin of chronic pruritus (related to endocrinological and metabolic disorders, infectious diseases, hematological and lymphoproliferative disorders, visceral neoplasms, pregnancy, drug-induced pruritus, etc.) Category III: neurogenic origin or neuropathic diseases. a) Neurogenic origin (without neuronal damage): few clinical examples yet, potentially hepatic itch with increased μ-opioids (dis-inhibition of itch) b) Neuropathic diseases (neuronal damage causes itch): multiple sclerosis, neoplasms, abscesses, cerebral or spinal infarcts, brachioradial pruritus, notalgia paresthetica, meralgia paresthetica, post-herpetic neuralgia, vulvodynia, small fibre neuropathy Category IV: somatoform pruritus (psychiatric/psychosomatic diseases, depression, anxiety disorders, obsessive-compulsive disorders, schizophrenia, tactile hallucinoses, fatigue Category V: mixed (chronic pruritus as result of more than one conditions classified on distinct categories; overlapping and coexistence of several diseases) Category VI: chronic pruritus of undetermined/unknown origin (CPUO)

Pruritus classification and investigation according to the presence or absence of primary skin lesions

CP may continue apart of its cause and can acquire an independent disease status, with neuroimmune inflammatory behavior, in several condition.[13] In Table 3, the current classification of chronic pruritus according to the International Forum for the Study of Itch (IFSI) is adapted and presented on their respective groups and categories.[28]

Also, for the comprehension of pruritus, some important terminologies are important, such as: allodynia, which refers to pain or itching caused by stimuli that are typically non-painful or non-pruritic, and is associated with central sensitization; alloknesis, the triggering of itch from stimuli that usually do not provoke pruritus; atmoknesis, which is itch that occurs when the skin is exposed to air, such as when clothing is removed; central sensitization, describing the increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold stimuli, often linked to peripheral injury or inflammation, resul-

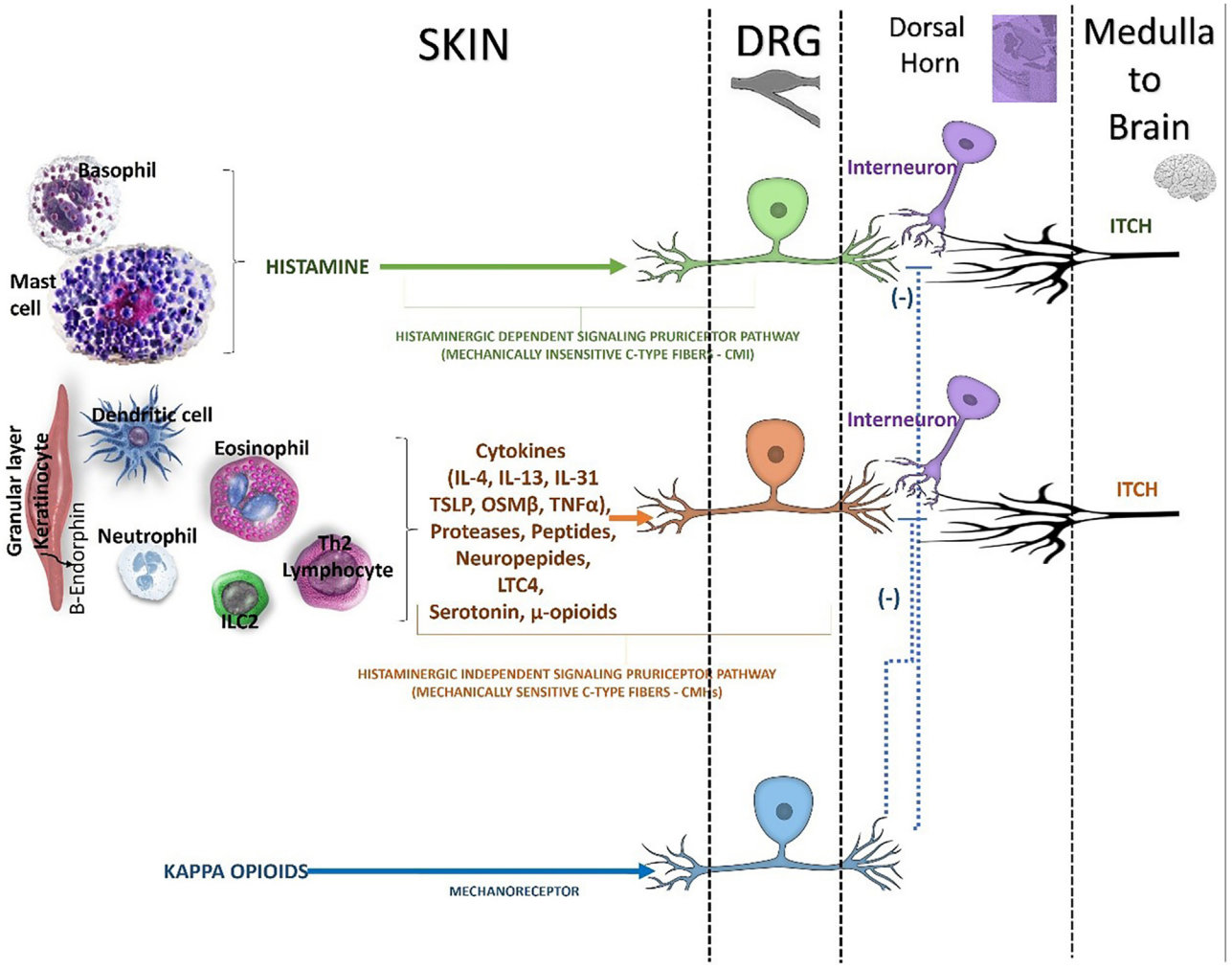

Fig. 3 Pathways inducing and inhibiting the itch in spinal cord. Beside inflammatory mediators, it has long been appreciated that mu opioids (e.g, morphine) can trigger pruritus. Although it is well appreciated that mu opioids trigger itch, in part, within the central nervous system (CNS), mu opioid receptor (MOR) is abundantly expressed on pruriceptors fibers in the skin. Mu opioids act as direct pruritogens. The peripheral itch neurocircuitry have unveiled abroad array of nonhistaminergic pathways within the skin (epidermis and dermis), that can trigger various forms of itch. There are endogenous pathways dedicated to suppressing itch both in the periphery and the CNS. It is well known that mechanical stimuli (e.g., scratching) and pain may suppress the itch. This is likely due, in part, to inhibitory pathways being triggered within the spinal cord. In addition, endogenous kappa opioids, distinct from mu opioids, have been shown to suppress itch by their ability act on sensory neurons, the spinal cord (dorsal horn), and the brain. The activation of kappa opioid receptor (KOR) counterbalances the pruritogenic effect of MOR activation. However, KOR activation in the periphery is predominantly expressed on mechanosensory neurons (mechanoreceptors), rather than on pruriceptors.
DRG, dorsal root ganglion; ILC2, innate lymphoid cell type 2; IL, interleukin, TSLP, thymic stromal lymphopoietin; OSMβ, oncostatin beta, LTC4, leukotriene C4; μ-opioids, mu-opioids; (-), inhibitory effect.

ting in heightened excitability of central pathways, reduced inhibitory activity, and the development of chronic pain or itch; dysesthesia, an abnormal sensation that may include burning, itching, pain, or tingling, often associated with the scalp; and neurogenic inflammation, which is related to the release of mediators, such as substance P (SP) or calcitonin gene-related peptide (CGRP), from peripheral afferent neurons, impacting the immune system.[29]

Outcome measures in pruritus were created to help clinicians and researchers evaluate the severity of pruritus in a standardized and quantifiable manner, reported by the patients. The main outcome measures include:

a) Visual Analog Scale (VAS): patients rate the intensity of pruritus on a continuous line, ranging from 0 (no itching) to 10 (worst imaginable itch);[30]
b) Numerical Rating Scale (NRS): similar to VAS, NRS involves patients assigning a numerical value (e.g., 0–10) indicating the severity of pruritus. It provides a quick and straightforward assessment of itching;
c) Dermatology Life Quality Index (DLQI): represents the impact of pruritus on a patientś quality of life, including questions from different domains, such as symptoms, daily activities and emotional well-being, providing

a comprehensive view of how itching affects various aspects of life;[31]
d) Itch Numeric Rating Scale (Itch NRS): This is a specific numerical rating scale designed for assessing the severity of itch, ranginf from a value of 0–10;[32]
e) Patient-Oriented Eczema Measure (POEM): Originally designed for eczema, this questionnaire evaluates the impact of pruritus on symptoms and its effect on daily activities.[33]

Diagnostic workup in chronic itch

An essential step in addressing CP involves a meticulous recording of the patient's medical history and a thorough clinical examination (Table 4). Additionally, an interdisciplinary diagnostic workup, incorporating laboratory tests and imaging studies, is imperative for the diagnosis.[13]

i Chronic pruritus related to dermatological conditions

When a primary dermatosis is present, the differential diagnosis can be defined through a careful consideration of the clinical history and dermatologic examination.[34] Unfortunately, CP has been globally misdiagnosed, primarily attributed to the incorrect diagnosis and treatment of patients with chronic scabies, especially in atypical presentations (Fig. 4). Therefore, dermoscopy examination and direct microscopic examination become critical for dermatologists.[35,36]

Biopsy of skin dermatoses, including Hematoxyllin-Eosin stain (HE), immuno-histochemistry (especially in cases where cutaneous lymphoma is a differential diagnosis), and direct immunofluorescence (to rule out autoimmune dermatoses) may be extraordinarily helpful in this scenario if the etiology is not readily evident from history and physical exam alone.[34] Some relevant laboratory exams (e.g. IgE serum levels, eosinophils count in peripheral blood, indirect immunofluorescence) are very useful for etiological diagnosis in chronic pruritus.[37–39]

ii Chronic pruritus secondary to internal or systemic diseases

Iron deficiency and pruritus

Normally, it is present as generalized pruritus without a skin primary cutaneous lesion.[2] The most attributable cause of generalized pruritus in patients with underlying systemic disease was found to be iron deficiency anemia, which responded to iron replacement.[2] In all cases of Generalized Pruritus Without Rash (GPWOR), especially where iron loss is suspected, it is important to enquire about diet (vegetarian or vegan), potential sources of blood loss, previous bariatric surgery, and gastrointestinal symptoms. Iron replacement leads in some patients to complete cessation of pruritus very shortly after to introduction of iron therapy.[2]

When iron deficiency is suspected but ferritin levels appear to be within the 'normal' range, it may be necessary to check serum iron and total iron-binding capacity as well. A trial of iron replacement should be considered if ferritin levels are below the lower limit of the reference range (15 to 25 μg/L), or if there is anemia or microcytosis not attributable to other causes (e.g., gastrointestinal blood loss, urinary loss, thalassemia trait, or polycythemia). Individuals with unexplained iron deficiency should also be tested for Tissue Transglutaminase (TTG) antibodies, particularly anti-transglutaminase-2 antibodies, provided they have not been excluding gluten from their diet for at least six weeks. If the TTG test results are abnormal, referral to a gastroenterologist for consideration of endoscopy and small bowel biopsy is recommended. A biopsy may be indicated even with a negative TTG result, as IgA deficiency, which is relatively common, can lead to a falsely negative TTG measurement.[2]

Iron overload

It may also be associated with generalized itch, either in association with hemochromatosis or hiperferritinemia in the absence of hemochromatosis.[2]

Hematological and other malignant neoplastic causes related to chronic pruritus

A retrospective population level cohort study included 327,502 eligible patients diagnosed with unspecified itch with matched controls. Comprised 68.1% females, 59.3% white race, 22.2% black race, and a mean age of 42.2 ± 22-years. Pruritus patients had increased 1-year risk of Hodgkin's lymphoma (RR = 4.42, 95% CI 2.83–6.88), myeloid leukemia (RR = 2.56, 95% CI 1.79–3.67), multiple myeloma (RR = 2.38, 95% CI 1.66–3.42) non-Hodgkin's lymphoma (RR = 2.35, 95% CI 1.96–2.82), monoclonal gammopathy (RR = 1.90, 95% CI 1.55–2.32), myelodysplastic syndrome (RR = 1.74, 95% CI 1.14–2.64), and lymphocytic leukemia (RR = 1.47, 95% CI 1.07–2.02).[40] The authors concluded that undifferentiated pruritus is highest in the first 12-months, and LDH (Lactate Dehydrogenase) has limited diagnostic utility in these patients. Providers should screen patients with undifferentiated pruritus for hematologic malignancies as clinically indicated.[40] In patients with chronic pruritus without concomitant dermatologic diagnoses, older age, male sex, liver disease, and tobacco abuse increase the odds of an underlying malignancy.[41]

Itch can be a prodrome of malignancy, often appearing before other signs and symptoms. It is particularly common in hematologic malignancies, with prevalence estimates of up to 30% in patients with Hodgkin lymphoma, 15% in those with non-Hodgkin lymphoma, and 67% in patients with polycythemia vera. Lymphoproliferative disorders likely involve the expression of Th2-related cytokines, including IL-3 and TSLP.[39]

Patients with polycythemia vera often experience aquagenic pruritus, triggered by contact with water of any temperature, typically within minutes of exposure, and often more severe with hot water. Other hematologic conditions can also present with generalized pruritus, which may be accompanied by eczematous, urticarial, or lichenified skin findings, such as in hypereosinophilic syndrome. Among solid tumors, there is a notable association between pruritus and cancers of the hepatobiliary system. Although solid malignant tumors are a relatively rare cause of pruri-

Table 4 Relevant medical data of in anamnesis of patients suffering from chronic pruritus.[28]

Characteristics of the itch		-date of the onset, duration -anatomical distribution: localization (onset, spread or localized) -quality (typification: pure pruritus, neuropathic characteristics) -intensity: (severity on numeric rating scale) -course: diurnal fluctuations, continuous/attack-like or paroxysmic course, spontaneous improvement/aggravation, nocturnal aggravation -provocation factors (example, aquagenic, physical exercise), alleviation factors (example, cold, skin covered by clothes) -scratching behavior -temporal association with pre-existing diseases, surgeries, intake of medications, other events -previous therapies with/without success -patientś perception of the itch cause -factors of psychosocial burden -impairment of health-related quality of life, mental distress, sleep disturbances
General information		-pre-existing diseases, including dermatoses -previous surgeries -travel history -pregnancy -atopic conditions associated -allergies: type I and type IV -intake of medications, infusions, blood transfusions -living on endemic area of infestations
Screening questions related to anxiety and depression disorders		• Screening of depression: • In the last month, did you often feel low, melancholic, or hopeless? • In the last month, did you often have little interest or enjoyment in your activities? If both questions are answered in the negative, major depression can be excluded with a high sensitivity of 96%. • Screening of anxiety disorders: •During the last 4-weeks, did you feel significantly impaired by: nervous tension, anxiety, feeling to have lost your mental balance? Did you worry about all kinds of things? •During the last 4-weeks, did you have an anxiety attack (sudden feeling of anxiety or panic?) The anxiety screening has a sensitivity of 86% and a specificity of 83%.
Particular characteristics of medical history	Several family members are affected	Scabies or other parasitic diseases
	Pruritus after contact with water	• Aquagenic pruritus associated with lymphoproliferative diseases (example, polycythemia vera); • Pruritus during contact with water (showering, bathing) irrespective of the temperature or during cooling of the skin after bathing
	Pruritus during/after physical exercise	Cholinergic pruritus
	Pruritus and icterus	• Pancreatic cancer • Cholestatic hepatitis • Intrahepatic cholestasis of pregnancy
	Pruritus in winter	• Xerosis • Asteatotic eczema

Table 4 (*Continued*)

	Pruritus with B symptoms (weight loss, drenching night sweats, fever, and generalized pruritus)	• Internal neoplasms • Lymphomas (such as Hodgkiṅs disease, chronic lymphocytic leukemia)

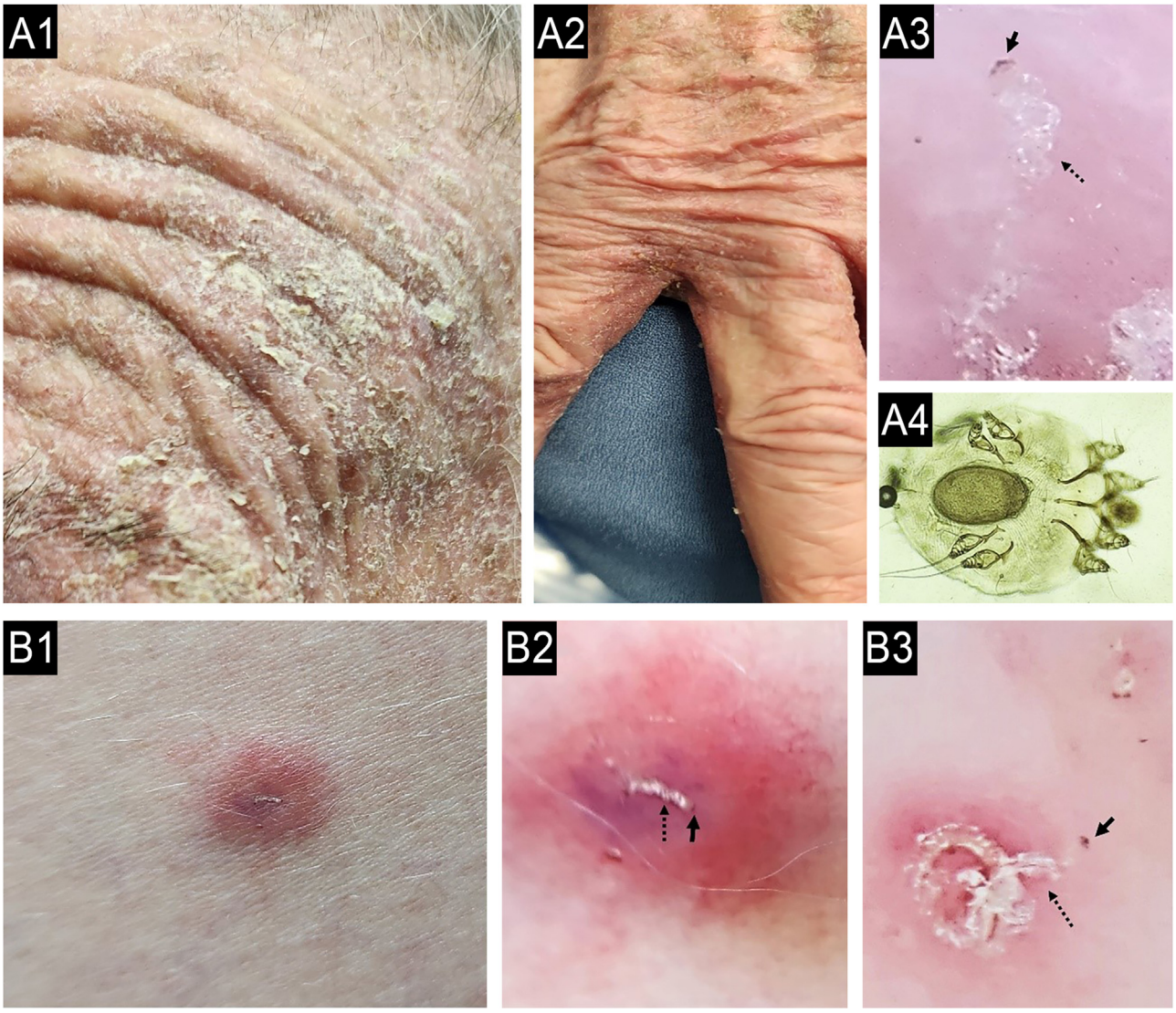

Fig. 4 (A) Case of chronic pruritus misdiagnosed as drug adverse reactions (case A1-4) and other (B) as atopic dermatitis (case B1-3) presenting as scabies surrepticious, diagnosed by dermoscopy and direct scrapping of the skin guided by dermoscopy. A: A 87-years-old female patient suffering with chronic pruritus during 7 months noticed a history of 15 days of hospitalization due to a clinical hypothesis of drug adverse reaction; A1: erythematous = scaling lesions on face; A2:erythamtosus-descamative interdigital lesions on hands; A3: Dermoscopy of interdigital area showing ''jet with contrail'' (burrowś acari) (dotted black arrow) and the ''delta wingś sign'' (full black arrow) (30x magnification); A4: optical microscopy (KOH staining, 800x magnification) of the scales collect of the skin oriented by Dermoscopy examination, a female adult *Sarcoptes scabei var. hominis* showing an egg in the her body). (B) A female patient suffering due to chronic pruritus and scattered papules on trunk during the last 6 months, misdiagnosed as adult atopic dermatitis, treated with first three months with upadacitinib 30 mg/day, and after due to intractable itching, the physician associated dupilumab to treatment; B1: erythematous papules in lateral thigh; B2: dermoscopy showing the ''jet with contrail'' (dotted black arrow) and full black arrow demonstrating the ''delta wingś sign'', 10x magnification; B3: dermoscopy of plantar lesions showing ''jet with contrail'' (burrowś acari) (dotted black arrow) and the ''delta wingś sign'' (full black arrow) (400x magnification).

Table 5 Clinical characteristics (symptoms and signs) of some cancer associated with chronic pruritus.

Malignant neoplasms associated with chronic pruritus	Symptoms (1) and Signs (2)
All types of cancers (including hematological neoplasms)	(1) Loss of appetite, lethargy (2) Weight loss, lymphadenopathy, fever
Breast cancer	(1) Breast or axillary lump, change in breast shape, bloodstained nipple discharge (2) Breast or axillary lump, change in breast shape, bloodstained nipple discharge
Cholangiocarcinoma	(1) Nonspecific upper abdominal discomfort (2) Jaundice, pale stools, dark urine
Colorectal cancer	(1) Persistent change in bowel habit, diarrhea, abdominal pain, discomfort or bloating brought on by eating (2) Blood in the motions, in the absence of hemorrhoids on examination
Gastric cancer	(1) Persistent nausea, reflux symptoms, dysphagia or vomiting (2) Melaena, jaundice; very rarely, cutaneous stigmata of acanthosis nigricans and/or tripe palms
Gastric carcinoid tumour	(1) Abdominal pain, diarrhea, intermittent facial and/or trunk flushing (2) Very rarely, cardiac valve murmurs, cutaneous stigmata of neurofibromatosis type 1 or tuberous sclerosis
Insulinoma	(1) Intermittent double vision or blurred vision, confusion, anxiety and irritability, dizziness, mood swings, weakness, sweating and hunger (2) Symptoms correlate with episodic hypoglycemia
Lung cancer	(1) Persistent cough and breathlessness, persistent chest or shoulder pain (2) Persistent chest infections and wheeze, facial swelling, hoarse voice, finger clubbing. Very rarely, cutaneous stigmata of acanthosis nigricans and/or tripe palms, or dermatomyositis
Testicular cancer	(1) Intermittent dull ache or sharp pain in the testicle or scrotum (2) Clinical difference between one testicle and the other in texture or firmness.
Thymoma	(1) Persistent cough, shortness of breath, pain or pressure in the chest, diplopia, dysphagia (2) Anemia, frequent infections, muscle weakness, ptosis, arm or facial swelling. Very rarely, cutaneous stigmata of paraneoplastic pemphigus or pemphigus vulgaris/foliaceous

tus, Table 5 highlights malignant neoplasms associated with CP and their clinical characteristics.[39]

Generalized pruritus in malignancy is usually multifactorial.[2] It can be a true paraneoplastic symptom, a feature of paraneoplastic dermatoses, secondary to paraneoplastic neuropathy, a consequence of secondary skin involvement by cutaneous or noncutaneous primary tumors, or a side-effect of cancer treatment.[2] Paraneoplastic itch is defined as an itch that arises early in the course of malignancy or even precedes its clinical diagnosis. It is not caused by the invasion or compression of the neoplastic mass and typically resolves after the tumor is removed.[42] Paraneoplastic skin diseases associated with itch of varying intensity can be classified into two groups: (i) Paraneoplastic syndromes, which include erythroderma, Bazex syndrome, Grover's disease, the sign of Lesser-Trélat, generalized granuloma annulare, dermatomyositis, and malignant acanthosis nigricans, and (ii) Associated malignancies, which encompass hematological malignancies, and cancers of the head and neck, upper airway, digestive tract, colon, breast, ovaries, and nasopharynx.[43] Although pruritus is thought to be an uncommon symptom in other solid malignancies, there have been case reports of itch occurring in patients with non-small-cell lung carcinoma, insulinoma, gastric carcinoid tumors, and other solid malignancies.[39] Itching and burning sensation is reported among patients with glucagonoma syndrome. Patients with chronic unexplained pruritus that favors a possibility of underlying malignancy include older age, male sex, possible liver disease, and chronic tobacco usage.[2] Also, several cancer treatments, including radiotherapy, can lead to pruritus by a variety of mechanisms.[2]

Paraneoplastic pruritus should be especially considered when chronic pruritus lasts less than 12-months.[2] Many cancer treatments, including radiotherapy, can lead to pruritus by a variety of mechanisms. Treating the underlying malignancy can often alleviate pruritus. When cancer-drug-induced pruritus occurs, it may require modifying or discontinuing the offending medication. And biological therapies are now commonly used in oncology.[2] A recent meta-analysis of 33 RCTs concluded that pruritus was a significant side-effect of cancer treatment with this class of agent.[44] Pruritus is a common side effect of epidermal growth factor inhibitors, which have either biological or intracellular mechanisms of action.[2] Oncology patients receiving biological therapies or chemotherapy (can cause

Table 6 Workup directed for patient suffering with chronic pruritus of unknown origin (CPUO).[28]

Laboratory tests for all patients	Complementary tests in case of primary or secondary skin lesions, if necessary	Pruritus during pregnancy	Other possible exams/tests	Imaging technique (Even if medical history, physical examination, and laboratory tests do not result in a specific clinical suspicion, a chest X-Ray and an abdominal ultrasound may be performed to look for evidence of a potential malignancy)	Interdisciplinary cooperations
Erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP)	Bacteriological/ mycological swabs	In case of prominent skin findings: dermatological examination to rule out polymorphic eruption of pregnancy (PEP), gestational pemphigoid-	***In case of anal pruritus***: parasites, worm eggs, digital rectal examination, PSA	Chest X-Ray	Neurological and/or psychiatric findings
Complete blood count with differential, ferritin	Skin biopsy (histology, direct immunofluores- cence, electron microscopy)		***In case of aquagenic and genital pruritus, pruritus of unknown origin:*** lactose/sorbitol intolerance test	Abdominal ultrasound (including retroperitoneal lymph nodes)	
Bilirubin, transaminases (GPT [ALT], GOT [AST]), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase,	Detection of scabies mites	In the absence of prominent skin findings: basic laboratory tests (see above) plus bile acids (fasting)	***In case of blood count abnormalities (example, bicitopenia)/suspected lymphoproliferative diseases***: vitamin B12, folic acid, protein electrophoresis, immunofixation, peripheral blood immunophenotyping (proliferative panel), JAK2 status, bone marrow biopsy (if necessary) with (immuno-)cytology and histology	Lymph node ultrasound (cervical, supraclavicular, axillary, inguinal), punc- ture/extirpation (if necessary) Thyroid ultrasound Gastroscopy (with biopsy and Helicobacter pylor*i* test, if necessary), colonoscopy (with biopsy, if necessary)	Cooperation with other physicians and specialists: general medicine, allergology, dermatology, internal medicine, (gastroenterology, hepatology, endocrinology, hematology, and medical oncology), urology, gynecology, and others
Creatinine, urea, estimated glomerular filtration rate (egfr), K+, urinalysis (test strip)					
Blood glucose level (fasting)			***In case of iron deficiency/stool irregularities***: stool guaiac test	CT, MRI, MRCP, scintigraphy (if necessary), ERCP (if necessary), liver biopsy (if necessary)	
Lactate Dehydrogenase (LDH)			***In case of suspected hepatobiliary disease***: hepatitis serology (anti-HAV, HBsAg, anti-HBc, anti-HCV), bile Acids, Antimitochondrial Antibodies (AMA), Perinuclear Antineutrophil Cytoplasmic Antibodies (pANCA), Antinuclear Antibodies		

Table 6 (*Continued*)

Laboratory tests for all patients	Complementary tests in case of primary or secondary skin lesions, if necessary	Pruritus during pregnancy	Other possible exams/tests	Imaging technique (Even if medical history, physical examination, and laboratory tests do not result in a specific clinical suspicion, a chest X-Ray and an abdominal ultrasound may be performed to look for evidence of a potential malignancy)	Interdisciplinary cooperations
Thyroid-Stimulating Hormone (TSH) Complete blood count with differential, ferritin			(ANA), Anti-Smooth Muscle Antibodies (SMA), anti-Soluble Liver Antigen Antibodies (SLA), anti-Liver-Kidney Microsomal Antibodies (LKM), anti-tissue transglutaminase antibodies, alpha-fetoprotein (in case of live cirrhosis/hepatic mass) ***In case of abnormal fasting glucose levels***: HbA1c, glucose-tolerance test ***In case of primary or secondary skin changes***: direct and indirect immunofluorescence, autoantibodies against dermal proteins (BP180, BP230, desmoglein) ***In case of suspected allergy***: total IgE, specific IgE (if necessary), prick testing, patch testing ***In case of suspected endocrine disorders***: parathyroid hormone, phosphate, Ca2+, fT3, fT4, 25-OH cholecalciferol, anti-TSH receptor antibodies (TRAb), anti-thyroid peroxidase antibodies (TPO-Ab) In case of suspected HIV: HIV serology, syphilis serology (if necessary) In case of suspected mastocytosis: tryptase levels - In case of suspected neuroendocrine tumors: chromogranin A - 24 h urine collection: porphyrins (porphyria), 5-hydroxyindoleacetic acid (neuroendocrine tumors), methylimidazole acetic acid (mastocytosis)		

itch by distinct mechanisms, for instance by inducing a small-fibre neuropathy) should be asked about pruritus on review.[2]

Chronic pruritus related to renal disorders

Pruritus is a common symptom in advanced chronic kidney disease, affecting 40%–90% of hemodialysis patients. The itch associated with chronic kidney disease is linked to uremic xerosis and/or neuropathy, systemic inflammation, and an imbalance in the opioid receptor system, characterized by increased μ-opioid receptor activity and decreased κ-opioid receptor activity. Secondary hyperparathyroidism due to chronic kidney disease has also been suggested as a potential cause of generalized pruritus, although the mechanism remains unclear. This hypothesis is supported by small cohort studies that observed an improvement in itch following parathyroidectomy.[19,39]

Chronic pruritus related to endocrine disorders

Itch is more prevalent in diabetic patients than in healthy controls, with rates of 26% compared to 15%. Pruritus in Diabetes Mellitus (DM) may result from the harmful effects of elevated glucose levels on cutaneous nerve fibers, often manifesting as a consequence of diabetic polyneuropathy, particularly small-fiber neuropathy. Other endocrine disorders that can trigger pruritus include hyperthyroidism and hypothyroidism.[39]

Chronic pruritus related to hepatobiliary disorders

Cholestasis from hepatobiliary conditions is a common cause of pruritus. These conditions include both primary and secondary causes of biliary obstruction, such as primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, intrahepatic cholestasis of pregnancy, viral hepatitis, and cirrhosis. Cholestatic itch arises from a complex interplay of factors, including bile acids, lysophosphatidic acid, bilirubin, and increased μ-opioid receptor activity.[39] Cholestatic pruritus is often characterized by itch that initially affects the palms and soles, becoming more generalized as the disease progresses. The mechanisms behind HCV-associated pruritus are believed to involve HCV-induced cholestasis and the induction of interferon-stimulated genes due to viral overload.[20]

In the pediatric population, there are some distinct etiologies associated to chronic itch: primary sclerosing cholangitis (itch in 30% of these patients), biliary atresia, Alagille syndrome (45% of patients have itch), progressive familial intrahepatic cholestasis (itch in 76%–100%) and benign recurrent intrahepatic cholestasis.[39]

Other systemic etiologies for chronic pruritus including infestations and infections

Although their exact pathophysiology remains to be fully elucidated, other potential etiologies of itch may include exposure to heavy metals, vitamin deficiencies, HIV, and other viral infections. Elevated blood levels of heavy metals, such as cadmium and lead, have been associated with chronic itch. Additionally, low levels of vitamin D have been observed in patients with chronic pruritic skin conditions, including atopic dermatitis, psoriasis, and chronic urticaria. Low levels of vitamin B12 have been noted in patients with generalized itch from various systemic causes.[39]

Pruritus is commonly reported in patients with viral infections, particularly those living with HIV, where it correlates directly with viral load and can be associated with eosinophilia and eosinophilic folliculitis. Chronic itch is a significant comorbidity among HIV-positive patients, affecting 13%–45% of this population.[39] Many HIV-positive patients also experience concurrent pruritic disorders, including lichen simplex chronicus, prurigo nodularis, scabies, seborrheic dermatitis, mycosis fungoides, and psoriasis. Additionally, itch in these patients may be caused by xerosis, drug therapies, and photosensitivity.[2]

Eosinophilia and generalized pruritus are features of parasitic infections, notably helminths such as *Strongyloides stercoralis*, but also onchocerciasis, cercariae dermatitis (due to skin penetration by cercariae of schistosomes or *Trichobilharzia* spp. in Western Europe).[2] In tropical areas, pruritus may be a feature of arboviruses such as dengue, zika and less frequently, chikungunya infection.[2,45]

A French prospective study followed 95 patients with pruritus *sine materia* over a period of five years (1996–2001). In 40% of cases (38 patients), a systemic cause was identified. The main conditions included toxocariasis (8 cases), hematologic diseases (7 cases), chronic renal failure (6 cases), hypothyroidism (5 cases), and iron deficiency (5 cases). Neoplasms were found in eight cases (8.42%): seven involved hematologic malignancies (3 myeloma, 2 Hodgkin's disease, 2 myeloproliferative syndromes) and one involved a solid tumor (pulmonary adenocarcinoma). Toxocariasis, an often-underestimated disease, was the most frequently identified condition.[46]

Human toxocariasis is a parasitic disease characterized by the presence of larvae of the genus *Toxocara* in human tissues.[47] *T. canis* and *T. cati*, found in dog and cat intestines, respectively, are the most common causative agents of the disease.[47] Toxocaral larvae usually cause two severe syndromes: visceral larva migrans and ocular larva migrans, depending on the location of the larvae.[47]

iii Chronic pruritus related to neurogenic, neuropathic or central nervous system conditions

Neuropathic pruritus

Neuropathic pruritic conditions may originate from the peripheral nervous system or central nervous system.[21]

The conditions originating from the peripheral nervous system are:[21]

a) Small fiber neuropathy: metabolic, drug-induced, infectious, or genetic origin (itch starts usually distally and may generalize);
b) Scars and burns: iatrogenic or traumatic (itch on lesional skin);

c) Radiculopathies: compression of a peripheral nerve by degenerative alterations or space-occupying lesions (itch and dysesthesias at the affected dermatome);
d) Postherpetic neuralgia: damage of peripheral nerve by the varicella-zoster virus (itch and dysesthesias at the affected dermatome);
e) Trigeminal trophic syndrome: injury of the sensory fibers of the trigeminal nerve (unilateral dysesthesia and hypoesthesia of the central face. Self-induced ulceration of the nasal ala, cheek, and upper lip).

The conditions originating from the central nervous system are:[21]

a) Space-occupying lesions: tumors, abscesses, vascular lesions, syringomyelia (clinical features according to affected neural structures);
b) Stroke: Ischemic or hemorrhagic (generalized or unilateral itch);
c) Multiple sclerosis: demyelinating disease (generalized itch or localized at the head and upper back);
d) Neuromyelitis optica: demyelinating disease (depending on injured spinal level);
e) Infectious diseases: meningitis, encephalitis, prion disease;
f) Traumatic brain or spinal cord lesions: accidents or iatrogenic lesions.

Generally, includes brachioradial pruritus, notalgia paresthetica, meralgia paresthetica, scalp pruritus (excluding dermatological diseases), gonalgia paresthetica (saphenous nerve damage), anogenital pruritus, and other conditions.[48] The latter is caused by direct damage to the nerve itself.[48] Although specific itch conditions have predominant contributors to their pathogenesis, it is most likely that there are multiple etiologies.[48]

Neuropathic pruritus refers to a group of disorders characterized by chronic itching caused by dysfunction or damage to pruriceptors.[48] In these conditions, pruritus is not triggered by external stimuli, such as irritants or allergens, but rather emerges spontaneously.[20] The neuropathic itch can occur owing to nerve damage that may be caused by mechanical, metabolic, inflammatory, or cytopathic injury.[48]

Pruritus neural hypersensitivity is exhibited in the following common neuropathic itch conditions.[20] Brachioradial pruritus is characterized by itching on the arms bilaterally. It is often associated with compression or irritation of the nerves of the cervical spine.[20] Notalgia paresthetica is a common chronic itch condition characterized by localized itching or burning sensation in the subscapular region and it may be caused by thoracic nerve damage or irritation in the affected area.[20] Postherpetic pruritus is a complication of herpes zoster due to nerve damage caused by viral cytopathic changes.[20] Finally, scalp pruritus is neuropathic when it occurs independently of any observable cutaneous eruption (e.g., seborrheic dermatitis).[20] The damage to the occipital nerves from the cervical spine causes scalp pruritus.[20]

Painless self-injury from neuropathic itch is far more common on the face than anywhere else on the body.[49] For example, itch is far more common after zoster affecting the face than the torso.[49] The face is also unclothed and readily accessible to the fingers.[49]

Nerve fiber compression can cause pruritus in the corresponding dermatome, and nerve fiber degeneration (such as small fibre neuropathy) can cause localized or generalized pruritus.[4] Small fiber neuropathy can occur in systemic diseases such as diabetes mellitus, Guillain-Barre syndrome, sarcoidosis, neurofibromatosis type 1 and HIV.[2] Diabetic neuropathy can lead to a regional pruritus affecting the trunk.[2] Small fiber neuropathy may be too small to produce clinical or electrophysiological changes, and the only investigation that may reveal anything is a skin biopsy with immunohistochemical staining of cutaneous nerve fibers.[2]

Central nervous system, pruritus and delusional infestation

Central nervous system lesions affecting sensory pathways, such as strokes, multiple sclerosis, and cavernous hemangiomas, can lead to central itch. Damage to itch-transducing, conducting, or processing neurons can result in neuropathic pruritus. There are reports of patients developing new self-inflicted injuries decades after strokes or trigeminal surgery, often exacerbated by dementia, which causes uncontrolled scratching. Less common causes of central itch include multiple sclerosis, brain tumors, abscesses, and Sjögren's syndrome. Rare cases have also been linked to anterior circulation strokes, particularly those affecting the thalamus.[49]

Neurogenic pruritus

Neurogenic is a more general term that encompasses a pathologic process arising from the nerve.[20] In other words, tumors of the nerve or other pathologies that have nothing to do with sensation or afferent transmission can still be referred to as neurogenic.[20]

Sensory nerves can contribute to neuroinflammation by releasing neuropeptides, which inflame tissues through efferent pathways. There are two primary ways in which sensory neurons can cause pruritus: (i) Neuropathic itch, where neuropathology leads to excessive afferent itch transmission to the CNS, and (ii) Neuroinflammatory processes, where sensory neurons activate immune cells or other intermediaries to trigger itch. A clear example of this is the release of substance P by sensory neurons, which binds to Mas-related G-protein-coupled receptor member X2 on mast cells, leading to the release of pruritogenic factors such as histamine and LTC4 from mast cells.[20]

A prime example of the neurogenic itch is Chronic Inducible Urticaria (CIndU). In this condition, various neurologic triggers, including thermal stimuli (heat, cold), mechanical stimuli (friction, pressure, vibration), and autonomic stimuli (acetylcholine), lead to the formation of hives and associated itch. CIndU exemplifies neurogenic itch, where itch is initiated by the nervous system in the absence of clinically defined neuropathic itch, likely through the activation of intermediate mast cells. Additionally, it is widely believed that Prurigo Nodularis (PN) also involves underlying

Table 7 Drugs that may induce chronic pruritus.[34]

Antibiotics	Amoxicillin, ampicillin, cefotaxime, ceftazidime, clindamycin, ciprofloxacin, erythromycin, minocycline, metronidazole, penicillin G, rifampicin, tetracyclines, trimethoprim/sulfamethoxazole, vancomycin, antifungals, antimalarials
Antiuricosuric agents	Allopurinol, colchicine, probenecid, tiopronin
Cardiovascular agents	Amlodipine, amiodarone, candesartan, captopril, clonidine, diltiazem, enalapril, flecainide, irbesartan, lisinopril, methyldopa, verapamil
Hormones	Oral contraceptives, corticosteroids, clomiphene, danazol, estrogen, progesterone, testosterone, tamoxifen
Glucose-lowering agents	Metformin, glimepiride, gliclazide, gliptins, tolbutamide
Lipid-lowering agents	Clofibrate, fenofibrate, fluvastatin, lovastatin, pravastatin, simvastatin
Immunosuppressants	Cyclosporin, cyclophosphamide, metronidazole, mofetil mycophenolate, thalidomide, tacrolimus
Oncologic and biological agents	Adalimumab, 5-fluoracyl, cetuximab, chlorambucil, erlotinib, gefitinib, gemcitabine, infliximab, ipilimumab, nilotinib, panitumumab, paclitaxel, rituximab, temsirolimus, tamoxifen, vemurafenib
Opioids and analgesics	Acetylsalicylic acid, codeine, celecoxib, diclofenac, fentanyl, ketoprofen, morphine, naproxen, oxycodone, piroxicam
Neuroleptics, antiepileptics and antipsychotics agents	Amitriptyline, citalopram, chlorpromazine, carbamazepine, haloperidol, fluoxetine, paroxetine, phenytoin, risperidone, sertraline, topiramate
Miscellaneous	Antithyroid agents, iodine contrast, enoxaparin, interleukin-2, hydroxyethyl starch (HES), pentoxifylline, ticlopidine

neurogenic itch processes that trigger the development of cutaneous nodules.[20]

iv Chronic pruritus secondary to somatoform (psychiatric/psychosomathic) disorders

Chronic generalized pruritus is commonly associated with various psychiatric disorders, including depression, anxiety disorders, obsessive-compulsive disorder, substance abuse, and delusional infestation. Somatoform pruritus is characterized by itch where psychological, psychiatric, and psychosomatic factors play a crucial role in the onset, intensity, exacerbation, or persistence of the condition.[50]

v Chronic pruritus of undetermined/unknown origin (CPUO)

Once both underlying pruritic skin disease and other secondary causes of pruritus have been excluded, an individual may be considered to have CPUO.[2] The prevalence of pruritus of unknown cause in individuals with generalized pruritus ranges from 3.6% to 44.5%, with the highest prevalence among the elderly.[13,51]

The initial clinical approach includes a detailed medical history and full physical examination (including total body skin examination, lymph nodes palpation, liver and spleen examination, lung and heart auscultation, abdomen and pelvis palpation).[51] Initial investigation should not only blood samples, but also urinalysis, stool routine, and occult blood, as well as X-Ray chest (radiologist to report), ultrasonography abdomen, and skin biopsy for direct immunofluorescence.[52] On Table 6, described the main laboratory exams and complementary diagnostic approaches for patients with chronic pruritus of unknown origin.

However, in some cases, the underlying cause remains unclear, and is Called Pruritus of Unknown Cause (CPUO).[51] As CPUO is a diagnosis of exclusion, patients suffering from it are re-examined periodically.[51]

CPUO may affect younger patients but is highly prevalent in those aged over 65 years.[2] Although many factors are thought to underlie CPUO, physiologic changes associated with aging likely contribute, including epidermal barrier dysfunction, sensory neuropathy, immunosenescence, and aging are characterized by a proinflammatory state with enhanced type-2 immune responses and reduced type-1 immunity.[53] In the elderly, besides the possibility of internal malignancy and cutaneous lymphoma, there are two chronic itchy conditions that should be remembered: atypical forms of bullous pemphigoid[54,55] and eosinophilic dermatoses with hematological malignancy (Fig. 5)(Table 8).[56]

vi Drug-induced chronic pruritus

Approximately 5% of cases of pruritus are caused by drugs. Drug-induced chronic pruritus may occur with or without a rash.[2] Proposed mechanisms of drug-induced pruritus

Table 8 Special conditions associated with itch in the elderly patients.[46–48]

Skin condition	Distinct characteristics
Atypical bullous pemphigoid (ABP)	Up to 20% of the BP cases the onset is characterized by a non-bullous phase.[47] Atypical manifestations of BP as described as:[47] Non-bullous BP, annular-like; erythema multiformis-like; pemphigoid nodularis; lichen planus pemphigoids; exfoliative erythrodermic; vegetans BP; pretibial BP, and drug-induced or post-irradiation (PUVA, narrow band UVB therapy, photodynamic therapy or radiotherapy) BP. Nevertheless, all cases of atypical BP have the same immunopathological features of the classic form.[46] The histological and Direct Immunofluorescence (DIF) findings and the detection of circulating autoantibodies, by Indirect Immunofluorescence (IIF), Enzyme-Linked Immunosorbent Assay (ELISA) or immunoblotting are the key elements to the correct diagnosis.[46,47] DIF of perilesional skin shows a continuous linear deposition of IgG (70%–90% of patients), or C3 (90%–100% of patients), or both, along the Basement Membrane Zone (BMZ).[47] Indirect Immunofluorescence (IIF) studies can demonstrate in 60%–80% of patients the presence of circulating IgG autoantibodies that typically bind to the epidermal side of salt-split normal human skin.[47] Circulating autoantibodies can be detected by Enzyme-Linked Immunosorbent Assay (ELISA), with sensitivity up to 100% when various ELISAs using the NC16A domain and other extracellular portions of BP180 or of BP230 are used together. Nowadays, ELISA has mostly replaced immunoblot and immunoprecipitation techniques, which are valid techniques but not very easy for routine testing. Cozzani et al. suggested diagnostic criteria for atypical bullous pemphigoid: *Major criteria*: a) DIG of perilesional skin showing a continuous linear deposition of IgG, C3 or both; b) Detection of circulating antibodies against BP 180 and/or 230 by ELISA and/or IIF on salt plit skin (with deposition og IgG and C3 at the roof). *Minor criteria*: c) Pruritus (itch) d) Histopathological findings: Early phases: subepidermal clefts, eosinophilic spongiosis, and/or an infiltrate of eosinophils in the upper dermis lining the dermal-epidermal junction are detectable. Established lesions: subepidermal bullae, absence of acantholysis, superficial dermal infiltrate of eosinophils. Polymorphic clinical aspects: widespread large, tense serous or hemorrhagic bullae on pruritic erythematous, urticarial or apparently normal skin; erythematous or urticarial plaques; polycyclic, annular, figurate lesions; hyperkeratotic excoriated nodules; plane, purple, polygonal, pruritic papules; small vesicles; erythroderma; vegetative, crusted purulent lesions. *The definitive BP diagnosis requires*: 2 major criteria or 1 major criteria plus 2 minor criteria.
Eosinophilic dermatosis of hematologic malignancy (EDHM)	Skin lesions composed by tissue eosinophilia arising in the context of hematologic disease is known as eosinophilic dermatosis of hematologic malignancy. The most associated malignancy is Chronic Lymphocytic Leukemia (CLL), although it has also been reported in association with other B-cell hematologic malignancies (mantle cell lymphoma, acute lymphoblastic leukemia, large cell lymphoma, multiple myeloma), and with acute monocytic leukemia, myelofibrosis, and nonmalignant processes, such as HIV infection and congenital agammaglobulinemia. EDMH is a rare condition with a wide variety of clinical presentations, ranging from papules, erythematous nodules, or blisters that simulate arthropod bites, to the formation of true plaques of differing sizes. The clinical presentation takes the form of pruritic papules or urticarial-like nodules reminiscent of arthropod bites. Cases have also been reported involving true plaques of variable size and occasionally vesiculobullous lesions. Lesions usually affect exposed and unexposed areas of the skin and occur predominantly on the limbs. Skin symptoms recur in situations in which insect bites would be unlikely. Histopathological skin exam reveals the presence of abundant eosinophils the presence of an eosinophil-rich, perivascular and periadnexal, interstitial inflammatory lymphocytic infiltrate, which occasionally extends into the subcutaneous tissue. The lymphocytic infiltrate is predominantly composed of T-cells (CD3+, CD43+, CD45RO+); when B-cells are present, they form polyclonal aggregates. Usually, no leukemic cells are observed. The diagnostic criteria for EDHM includes: a) Pruritic papules, nodules and/or vesiculobullous eruption refractory to standard treatment (as antihistamines, topical corticosteroids for itching). b) Eosinophil-rich lymphohistiocytic infiltrate in the upper and deep dermis. c) Exclusion of other causes of tissue eosinophilia d) Prior or subsequent diagnosis of hematological malignancy

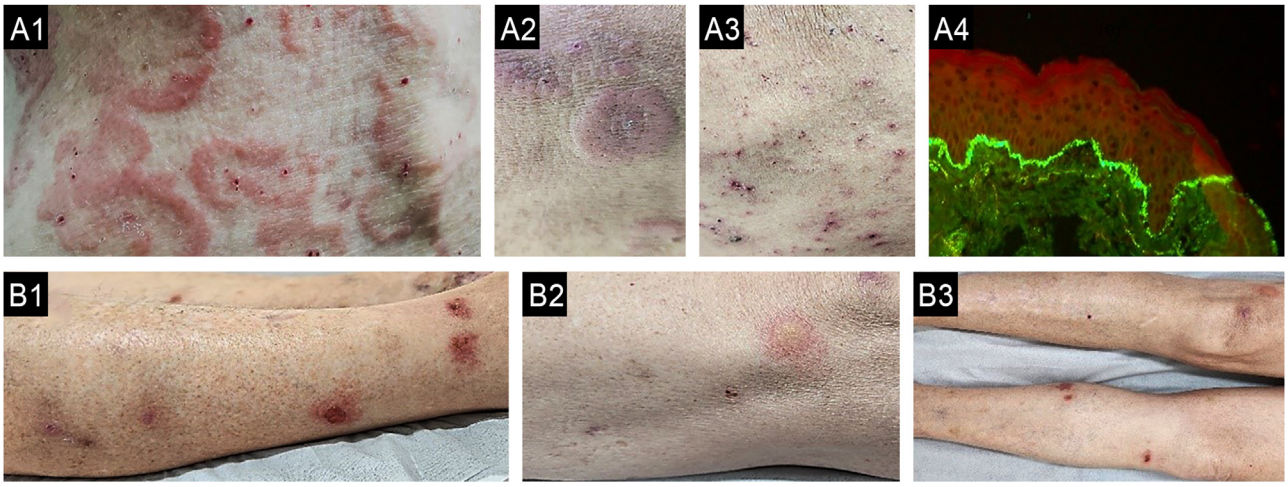

Fig. 5 Unusual chronic pruritic conditions found on elderly patients: atypical bullous pemphigoid (ABP) (A) and eosinophilic dermatoses with hematological malignancy (B). Atypical lesions of bullous pemphigoid. A1: annular urticarial-like lesions with excoriated hematic crusted lesions; A2: urticarial plaques resembling urticarial vasculitis; A3: erythematous eczematous crusted lesions, with excoriated papules with hematic crusts and hyperchromic residual lesions; A4: direct immunofluorescence positive to IgG in a granular pattern on basal zone membrane of the skin, obtained from normal appearance skin of a 69-years-old female with 2 years complain of chronic itch. Eosinophilic dermatoses of hematological malignancy: image of a patient suffering from chronic itch for 2 years after covid-19, with progressive elevated count of lymphocytes on total blood count and a diagnosis of chronic lymphocytic leukemia. B1: showing erythematous excoriated and exulcerated lesions on ankles; B2: urticarial-like lesion resembling insect bites, and B3: several excoriated lesions on legs due to intense chronic itching.

include cholestasis, direct drug or metabolite deposition, alteration of neural signaling, photodermatoses, xerosis or cell stimulation (for example, codeine), however, most cases are idiopathic.[2,19] Opioid-induced pruritus is common and affects 2%–10% of patients receiving oral, 10%–50% intravenous and 20%–100% epidural and intrathecal opioids.[2] The common culprits of drug-induced pruritus include immune checkpoint inhibitors;[39] agents targeting epidermal growth factor receptor, B-Raf proto-oncogene, cytotoxic T-lymphocyte-associated protein-4, and Programmed cell Death protein-1/Programmed cell Death-Ligand-1 (PD-1/PD-1L).[39] Table 7 displays the most frequent drugs that may induce chronic pruritus.[19]

Treatment

The therapy of CP is quite complex and should be directed to their cause when it is found. There are, in most of the patients, especially in the elderly, several possible causes in the same patient, complicating the identification of the origin of CP.[57] A temporal relationship between a certain cause and the onset of the pruritus may provide important hints about its origin.[57]

Therapeutic options may be restricted in certain populations, such as children, pregnant women, and breastfeeding or in elderly patients due to eventual concomitant stage of life, comorbidities and co-medication.[57] In elderly patients, particularly, *xerosis cutis* is present in most patients and can be effectively treated with emollients.[57] Systemic therapies should be used with caution, especially in very young patients or elderly patients after weighing risks and benefits.[57] Additionally, polypharmacy often observed in elderly patients can hamper the choice of available therapeutic options due to possible interactions with antipruritic drugs.[57]

Supportive care for itching patients

The main attitudes include prescribing continuous use of moisturization agents, especially adequate for patients with atopic dermatitis and/or sensitive skin (Table 9).[58]

For all modalities of approach to treat CP, the experience has shown that it takes a long time before patients respond to treatment (up to 12-weeks); in case of cessation of itch, treatment should not be discontinued too quickly (gradual tapering over at least four weeks).[13] The advent of Janus Kinase (JAK) inhibitors has ushered in a transformative paradigm shift, affording quick alleviation of pruritus.[59]

Causal treatment

The range of causal treatments for pruritus includes addressing the underlying dermatosis, avoiding contact allergens, discontinuing medications, and employing specific systemic, neurological, and psychiatric therapies, as well as surgical interventions for tumors. In rare cases, treating or curing the underlying disease may lead to resolution of chronic pruritus. However, exceptions exist, such as short-term pruritus associated with Hodgkin's disease and early chemotherapy, where the itch may not fully resolve even with treatment of the underlying condition.[13]

Topical treatment

In CP basic therapy with emollients alone or in combination with specific topical, systemic agents and/or UV photother-

Table 9 General measures and topical treatments for pruritus.

General measures[50]		
-reducing exposition to high temperatures and low relative air humidity; -trimming the nails to prevent excoriations; -avoid long baths; -avoid sauna for patients with itch triggering by these factors; -alleviating measures (e.g., wearing light or non-synthetic fibre clothes); -avoid smoking, alcohol, caffein and other stimulants, spices, and stress; -showering is better than taking a bath, with warm water, for 10 minutes at most; -shower with detergent-free soap (Syndet), shower oils, or cleansing cream; -avoid perfumed products and irritative substances such as sodium lauryl sulfate; -avoid bathing using antibacterial/antiseptic soaps; -emollient creams or hypoallergenic, free of fragrances and preservatives; -soft and loose-fitting cotton clothing.		
Topical Treatments		
Drugs	Mode of use	Observations
Hydrocortisone 1%[28]	1% 2×/day	Face and folds, or patients with thin skin
Betamethasone valerate 0.1%[28]	Topical or occlusive 1×/day	Extension areas
Tacrolimus 0.03%–0.1%[28]	2×/day	Sensorial itching or a local burning sensation may present during the first applications and can be reduced with oral acetylsalicylic acid 500 mg, initially, and by avoiding alcohol consumption[34]
Pimecrolimus[28]	2×/day	
Capsaicin 0.025% to 0.1% cream[34]	4 to 6×/day	Induces TRPV1 activation with subsequent SP depletion, desensitizing the nerve fibers
Corticosteroids [19,34]	Occlusive or intralesional	Caution should be used due to the risks of skin atrophy and hypopigmentation.
Menthol 1% lotion[34]	3–4×/day	Acts via TRPM8 pathway
Topical anesthetics:[34]		
-Polidocanol 2%–10%		Application to localized (<10% of the body surface area, BSA
-Formulation: lidocaine 2.5%–5% + amitriptyline 5% + ketamine 5%–10% o/w cream	Transdermal application (3×/day)	Never more than 30% of the BSA)
-Pramoxine 1% lotion, cream, foam, gels	3–4×/day	Cooling potentiates itch relief in neuropathic pruritus, via activaction of thermoreceptive type Aδ snd C nerve fiber[19]
-Lidocaine 2%–5%	2–4×/day	Take care with the occurrence of metahemoglobinemia if high doses of EMLA® (lidocaine + prilocaine) are applied in pediatric patients.
Doxepine 5% cream[34]	4×/day 4/4h	There are risks of contact dermatitis, local sensation of itching/burning and anticholinergic effects (applied on <10% of the body surface area, BSA)
Botulinum neurotoxin	Intralesional 2–10μ	Inhibits release of pruritogens, such as SP, CGRP, and acetycholine.[19] Small studies have treated itch in lichen simplex chronicus and neuropathic etiologies of itch.[19]
Gabapentin 6%–10%[19]	2–4×/day	6% for uremic pruritus and 10% for scalp pruritus No drug-related adverse effects
Crisaborole1 [19,49]	2×/day	A phosphodiesterase 4 inhibitor that reduces AD associated itch

Table 9 (*Continued*)

Other alternatives	
Phototherapy UVA or UVB[49]	Efficacy in atopic dermatitis, cutaneous T-cell lymphoma and in CP arising from systemic diseases (e.g. end-stage renal disease, cholestasis). It may also be a viable treatment method for pruritus of unknown origin.

apy is recommended.[13] The first choice of topical treatment in lesional skin is topical corticosteroids, such as hydrocortisone (on the face or intertriginous areas),[60] betamethasone valerate, or calcineurin inhibitors (do not combine with UV phototherapy).[13] Calcineurin inhibitors may have a particular use in thin and sensitive skin areas, and prolonged use compared to topical corticosteroids.[61]

Another possible topical agent with antipruritic effect published only in case series or case reports is capsaicin which is indicated in neuropathic pruritus (notalgia paresthetica, brachioradial pruritus, postherpetic pruritus), aquagenic or uremic pruritus.[19] In case of residual single nodules the use of intralesional corticosteroid intradermal injection is a possible alternative.[18,19]

Localized CP may be treated with other agents, but the level of recommendation is based on case studies non-placebo controlled, such as menthol 1% lotion and topical anesthetics.topical antidepressive/histamine.[19] intralesional botulinum neurotoxin, gabapentin 6%–10%, phosphodiesterase inhibitors (crisaborole, difamilast, roflumilast).[18,57]

Phototherapy for chronic pruritus

Ultraviolet phototherapy [e.g., Narrow Band (NB) UVB 311 nm] constitutes an interesting option for all patients, including the elderly population as it is well tolerated, with few side effects and drug interactions.[19,57] Long treatment cycles lead to skin aging and can increase the risk of epithelial skin cancer.[54]

Excimer lamps also decrease the density of intraepithelial nerve fibers.[19] UVA1 (340–400 nm) decreases the levels of IL-4, IL-13, IL-17 and IL-23.[19] Repeated exposure to suberythematogenic doses of both ofUVA1 and NB-UVB decrease IL-31 concentration, whereas high doses have the opposite effect, especially with UVB.[19]

Systemic treatments

a Antihistamines

Second-generation anti-H1 medications such as cetirizine, desloratadine, bilastine, rupatadine, fexofenadine, and levocetirizine are indicated in chronic urticaria. They cause less sleepiness than first-generation antihistamines and also interact with fewer medications. For the treatment of CPUO, the German Guideline for CP indicates as first line recommendation the second-generation H1 antihistamines (up to fourfold dosage).[13] Most conditions involving CP have nonhistaminergic pathway involvement, then anti-H1 drugs have suboptimum effects or no effects to treat chronic pruritus.[13]

Oral first-generation H1 antihistamines, such as diphenhydramine and hydroxyzine, are commonly used as first-line options for CP, except in chronic urticaria, in children with milder cases, mostly due to their sedative properties.[58] Side effects such as sedation and confusion from dialysis.[58] The standard dosage for children is 5 mg/kg/d of oral diphenhydramine HCl or 2 mg/kg/d of hydroxyzine given at nighttime for sedation.[58]

b Antidepressants agents[19]

These types of medications are indicated for uremic, cholestatic or paraneoplastic pruritus. The peak of the effect is reached after 4–6-weeks. Adverse effects limit their use, particularly in the case of Selective Serotonin Receptor Inhibitors (SSRIs) and mirtazapine.[19] These agents are less useful than gabapentin or pregabalin in neuropathic itch.[19]

Antidepressants should be used with caution in elderly patients due to reported severe side effects, mainly those of a cardiac nature.[57] Serotonin reuptake inhibitors (e.g., paroxetine, fluvoxamine) can be used in somatoform, paraneoplastic, and aquagenic pruritus arising from hematological proliferative conditions.[57] Sertraline has proven effective for the treatment of cholestatic pruritus.[57] Tetracyclic antidepressants, namely, mirtazapine, amitriptyline, doxepin have also shown antipruritic effects on CP of various origins and beneficial effect on patients with impaired sleep quality due to CP (mirtazapine).[57]

Table 10 displays the main antidepressant medications used in distinct types of CP.

c Gabapentinoids[19]

Gabapentinoids, especially gabapentin and pregabalin, are indicated for the treatment of neuropathic pain and can be also used to treat forms of neuropathy with both localized (e.g., brachioradial pruritus, notalgia/meralgia/gonalgia paresthetica, postherpetic neuralgia) and generalized (e.g., small fiber neuropathy due to diabetes) pruritus.[19] Gabapentinoids have also shown efficacy in systemic diseases such as renal insufficiency and aquagenic pruritus.[19] Depending on renal function, for adult patients gabapentin's recommended dose is until 900 mg/day (however, higher doses as 3600 mg/day may be necessary) and pregabalin 75–225 mg/day.[13] In order to reduce the occurrence of side effects, it is important that the dose be slowly increased until therapeutic doses are reached.[19] Additionally, the dose should be reduced in senior patients and those with

Table 10 Antidepressants used to treat chronic pruritus.

Antidepressant	Uses in distinct types of chronic pruritus	Adult dose	Children dose
Amitriptyline	Brachioradial pruritus, lichen amyloidosis, uremic pruritus, notalgia paresthetica, post-stroke pruritus, mycosis fungoides, HIV	25 mg/day	Not indicated
Doxepin	Uremic pruritus, pruritus of unknown origin	10–20 mg/day	Starting dose 1 mg/day for infants, and maintenance doses range form 3 mg in an 8 kg baby with developmental delays to 10 mg in all children.[51] The dose is escalated by 2 mg every 3-days to an average effective maintenance dose of 9 mg.[51] Adverse effects in the form of behavioral side effects (aggression) and enuresis.[51]
Fluoxetine (SSRI)	Aquagenic pruritus	20 mg/day	Not reported
Fluvoxamine	Chronic pruritus, in patients with AD, lymphomas, paraneoplastic pruritus, psychiatric patients	25–100 mg/day	Not reported
Paroxetine	Pruritus of unknown origin, psychogenic pruritus, paraneoplastic pruritus	20 mg/day	Not reported
Nortriptyline	Vulvar pruritus of unknown origin	74 mg/day	Not reported
Mirtazapine	Psychogenic pruritus, pruritus of unknown origin, paraneoplastic pruritus, nighttime pruritus of unknown origin	15–30 mg/day (at night)	Children >10y-up to 15 mg orally; preferably at nighttime
Sertraline			1 mg/kg/day-4 mg/kg/day orally until maximum 100 mg/day

Withdrawal symptoms have been described with antidepressants as SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-neuroepinephrine reuptake inhibitors) in children, adolescents, and adults over the past several decades and generally emerge when antidepressants are discontinued abruptly, although withdrawal symptoms can occur with missed doses and, in some patients, following significant dose reductions.[52] These symptoms can include gastrointestinal (vomiting, diarrhea) and flu-like symptoms, dysesthesias, dyssomnia, increasing anxiety, agitation, or irritability and must be distinguished from recrudescence of symptoms associated with the disorder being treated.[52]

The general approach to managing antidepressant withdrawal is ensuring (i) adherence and (ii) slow discontinuation when stopping an antidepressant is necessary. For tapering in pediatric patients, using a typical taper, a patient taking sertraline 100 mg, then reduced to 50 mg, and then to 25 mg (i.e., 50% dose reduction at each titration point), every month.[52]

impaired renal function.[19] Common side effects include tiredness, dizziness, and weight gain.[19] Gabapentinoids have few interactions with other drugs and thus constitute an appealing treatment option for older patients. The dosage of gabapentin in the elderly be initiated at 100–300 mg (pregabalin 25–75 mg) at night and slowly titrated up.[62]

d Opioids

The Mu Opioid Receptor (MOR) antagonists and the Kappa Opioid Receptor (KOR) agonists have been shown to be very useful given their role as central pruritus regulators.[19] These medications are classified as: (i) KOR agonists *difelikefalin* for parenteral use in cases of uremic pruritus in patients on hemodialysis; *nalfurafin* for parental use in patients with cholestatic pruritus, and *nalmefene* for oral use in cholestatic itch); (ii) KOR agonists/MOR antagonists: *nalbufin* for parenteral use in patients with uremic pruritus and prurigo nodularis; *butorphanol* for intranasal use and applied in intractable cholestatic itch; (iii) MOR antagonists: *naloxone* for parenteral use (reversal of side effects of opioids or intoxication) indicated for the drug-induced itch, brachioradial pruritus and cholestatic itch,[19] and systemic administration of intravenous naloxone (0.002–0.02 μg/kg body weight/min) provides rapid management of pruritus along with a low quantity of side effects;[62] *naltrexone* for

oral use (50–150 mg/day), indicated for drug-induced itch, cholestatic itch, Hailey-Hailey disease, lichen planus pilaris, psoriasis, Darierś disease.[19] Low-dose naltrexone administered at 2 mg daily also has antipruritic effects and can be used in patients who cannot tolerate standard doses.[18] MOR antagonist receptors, such as naloxone, naltrexone, or nalmefene, have been demonstrated to be effective in reducing itch in chronic urticaria, AD, PN as well as cholestatic and uremic itch.[62] In contrast, activation of KORs inhibits pruritus.[57] Butorphanol, a kappa-opioid agonist with some mu-opioid antagonist properties, has been shown in case series to effectively reduce itch due to PN, cholestasis, uremic itch, and idiopathic pruritus in elderly patients.[62]

The most common side effects of opioid modulators include gastrointestinal distress (such as diarrhea and vomiting), drowsiness, fatigue, dizziness, and insomnia. Additionally, there is a risk of liver injury at high doses, which necessitates caution when prescribing these medications to elderly patients.[18,62] Patients taking opioid agonists should avoid concurrent use of opioid antagonists, as this can trigger rapid withdrawal symptoms. Long-term use of agonists like butorphanol can also increase the risk of dependence. It is important to note that difelikefalin – a selective kappa-opioid receptor agonist – is FDA-approved only as an injection for the treatment of moderate-to-severe itching associated with chronic kidney disease in adults undergoing hemodialysis. Most other opioid medications used for chronic itch are used off-label.[18]

e Bile acids resins and rifampicin

Cholestyramine is a bile acid resin that alleviates itch by sequestering pruritogenic bile acids. Rifampin, an antibiotic, helps reduce itch by promoting the conversion of bile acids to less pruritogenic forms. However, due to its hepatotoxic and nephrotoxic side effects, rifampin is not suitable for long-term use but can be an effective second-line treatment when cholestyramine is insufficient.[18]

f Thalidomide

Thalidomide is a nonspecific immunomodulator that may disrupt the degeneration of type C unmyelinated nerve fibers.[65] It can be effective in treating uremic pruritus and Prurigo Nodularis (PN). However, notable side effects include sedation, bowel obstruction, and peripheral neuropathy, which typically reverses upon discontinuation of the drug. Thalidomide is classified as a pregnancy category X drug due to its severe teratogenic effects, necessitating strict adherence to the Risk Evaluation and Mitigation Strategies (REMS) program. Thalidomide dosage is recommended in tablets of 50–200 mg/day.[18]

g Immunosuppressive drugs

Systemic immunosuppressive drugs are well-established in the treatment of inflammatory dermatoses, such as atopic dermatitis, psoriasis vulgaris, or cutaneous T-cell lymphoma.[57] They should be considered following an unsuccessful treatment with topical or physical alternatives and after the exclusion of contraindications.[57] Cyclosporine (2.5–5 mg/kg/day), methotrexate (7.5–20 mg weekly), mycophenolate (1–2 g/day) and azathioprine (1–3 mg/kg/day, often 50–100 mg/day) are the most widely used substances.[18,57] Due to the complex interactions and undesirable side effect profiles of these drugs, they should be recommended with caution, particularly for older individuals. For instance, increases in retention parameters, liver enzymes, and hypertension are commonly observed. Therefore, a risk-benefit analysis should be conducted before initiating systemic immunosuppressive therapy, and patients should be thoroughly informed about the potential risks and side effects.[57]

h Biologic therapies and oral small molecules

Dupilumab (600 mg initial, 300 mg Q2W), a monoclonal antibody targeting the receptor for IL-4, has been shown in large RCTs to reduce symptoms and improve quality of life in those with moderate to severe AD.[18] The average age of participants in these trials was under 50, providing little evidence of efficacy in the elderly population.[18] We have gained clinical experience using this drug in older patients with success, including an 87-year-old with itch and PN refractory to other treatments.[63]

Adverse effects have not been specifically detailed for the elderly, but in the general adult population, they include conjunctivitis, headache, and injection site reactions. There is no demonstrated increased risk of secondary infections, such as herpes viral infections or urinary tract infections, that would be of particular concern when prescribing to older patients.[18] Several additional biologic therapies including targets of IL-31RA (nemolizumab for PN and AD), rocatinlimab (anti-OX40, in clinical trial for AD and PN), amlitelimab (anti-OX40 L, in clinical trial for AD) and lebrikizumab/tralokinumab (anti-IL-13, for AD) anti-OSMRβ (vixarelimab for PN) may control CP.[64]

Oral JAK inhibitors show promise in early phase trials for their antipruritic properties particularly, several itching dermatoses, including AD, PN, and chronic idiopathic pruritus).[18,59,63] Baricitinib (JAK1/2-1), abrocitinib (JAK-1) and upadacitinib (JAK-1) are already approved for AD in several countries. JAK inhibitors such as tofacitinib (5–10 mg/day) have adverse effects that should be strongly considered when used in the elderly including increased risk of herpes and other infections.[18,65,66] A phase II clinical trial (NCT05038982) evaluating the efficacy of abrocitinib 200 mg during 12-weeks for reducing pruritus in adults with CPUO and prurigo nodularis was recently completed and is awaiting the publication of the results.[66,67]

Based on the identification that JAK1 is expressed in neurons coupled with evidence of type 2 immune responses in CPUO, severe and refractory CPUO patients maybe could have benefits in the use of oral JAK inhibitors (not indicated to patients > 65-year-old in the atopic dermatitis setting).[53] Dupilumab is currently being investigated in RTCs enrolling patients with CPUO.[68,69]

Conclusions

In conclusion, understanding the distinct categories of chronic pruritus, particularly the differentiation between

pruritus with and without dermatological lesions is crucial for effective management. Pruritus without any dermatological lesions, often underdiagnosed or misdiagnosed, requires careful consideration and reevaluation. Recognizing these different forms of pruritus allows for a more targeted approach to treatment, addressing the specific pathophysiological mechanisms involved. Future research should continue to refine our understanding of these categories, potentially leading to more effective and personalized therapeutic strategies for patients suffering from chronic pruritus of various origins.

Ongoing research and development bring promise to the future of drugs targeting pruritus. Emerging pathways include compounds modulating neuroreceptors like Transient Receptor Potential (TRP) channels and opioid receptors.[70] Advances in understanding molecular pathways open opportunities for developing targeted biologics and small molecules. JAK inhibitors, currently in use, might see refinement and broader application for pruritic conditions.

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Authors' contributions

Paulo Ricardo Criado: Design and planning of the study, drafting and editing of the manuscript and approval of the final version of the manuscript.

Roberta Fachini Jardim Criado: Design and planning of the study, drafting and editing of the manuscript and approval of the final version of the manuscript.

Mayra Ianhez: Design and planning of the study, drafting and editing of the manuscript and approval of the final version of the manuscript.

Hélio Amante Miot: Design and planning of the study, drafting and editing of the manuscript and approval of the final version of the manuscript.

Conflicts of interest

Dr. Paulo Criado: *Advisory board* - Pfizer, Galderma, Takeda, Hypera, Novartis, Sanofi; *Pesquisa clínica* - Pfizer, Novartis, Sanofi, Amgen e Lilly; *Palestrantre:* Pfizer, Abbvie, Sanofi-Genzyme, Hypera, Takeda, Novartis.

Dra. Roberta Fachini Jardim Criado: *Advisory board* – Pfizer, Takeda, Hypera, Novartis, Sanofi; *Pesquisa clínica* – Pfizer, Novartis, Sanofi, e Lilly; *Palestrantre:* Pfizer, Abbvie, Sanofi-Genzyme, Hypera, Takeda, Novartis.

Dra. Mayra Ianhez: *Advisory Board* – Galderma, Sanofi, Pfizer, Novartis, Abbvie, Janssen, UCB-Biopharma, Boehringer-Ingelheim; *Palestrante* – Galderma, Sanofi, Pfizer, Theraskin, Novartis, Abbvie, Janssen, Leopharma, FQM.

Dr. Hélio Miot: *Advisory Board* – Johnson & Johnson, L'Oréal, Theraskin, Sanofi e Pfizer; P*esquisa clínica* – Abbvie, Galderma e Merz.

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REVIEW

New insights into pyroptosis in pemphigus: from cellular structure to therapeutic targeting☆

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Abstract

Background: Pemphigus is an autoimmune blistering disease where autoantibodies target desmoglein (Dsg) antigens on keratinocytes, triggering the p38 MAPK pathway, Dsg internalization, desmosomal dissolution, and keratinocyte apoptosis, are essential for blister formation. Recent research indicates keratinocyte pyroptosis may exacerbate acantholysis and delay wound healing. Current treatments, including corticosteroids and immunosuppressants, are effective but have significant side effects, such as prolonged wound healing and increased infection risk. Understanding these inflammatory processes is crucial for developing effective treatments for pemphigus.

Methods: The authors conducted a comprehensive review of the literature, analyzing recent findings regarding the upregulation of pyroptosis-related proteins in pemphigus.

Results: The present findings highlight a significant upregulation of pyroptosis-related proteins, which play a crucial role in the inflammatory response and blister formation characteristic of pemphigus. Key proteins such as cytokines IL-1β, IL-18, High Mobility Group Box-1 (HMGB1), and Parkin, along with NOD-like receptors and P2 × 7 receptors, were identified as pivotal in facilitating pyroptosis. The study also discusses potential therapeutic approaches targeting these proteins to modulate the disease pathway effectively.

Study limitations: This study aimed to investigate the role of pyroptosis in the pathogenesis of pemphigus, focusing on its potential as a novel therapeutic target.

Conclusions: Pyroptosis significantly contributes to the pathogenesis of pemphigus and presents a promising target for therapy. Targeting specific molecules involved in the pyroptosis pathway offers the potential for developing more precise and less toxic treatments, allowing the shift from traditional therapies towards targeted therapeutic strategies.

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Introduction

Pyroptosis is a kind of programmed cell death that occurs in a highly inflammatory environment. It is characterized by cell lysis, swelling, the creation of pores in the cell membrane, and the release of cell contents and pro-inflammatory mediators, all of which lead to cell death. Pyroptosis differs fundamentally from apoptosis and necrosis in cell form and mechanism, and it is involved in a variety of biological processes including immunological defense, inflammatory response, and disease progression. The role of the acantholysis pathway in pemphigus has recently attracted a lot of research interest.

Pemphigus is an autoimmune bullous skin condition characterized by a lack of attachment of the epidermis's Kerationcyte (KC) to the mucosa, resulting in blister formation. Pathogenic autoantibodies of the Desmoglein (Dsg) antigen activate various signaling pathways, which contribute to the illness. The pathogenesis of pemphigus is now based on four theories: the Dsg Compensation Hypothesis,[1] the steric hindrance hypothesis,[2] the multipathogenic theory/multiple hit theory, and the apoptotic lysis theory.[3] Autoantibodies specifically target adhesion molecules between epidermal and mucosal KC, such as Dsg1 and Dsg3, causing cell disjunction and blistering. In addition to antibody-mediated effects, pemphigus causes alterations in intracellular signal transduction, such as endoplasmic reticulum stress response,[4] cytoskeletal recombination,[5] inflammatory mediator release,[6] and apoptosis,[7] and pyroptosis pathways.[8]

Understanding the clinical implications of pyroptosis in pemphigus is essential. Clinically, patients with pemphigus exhibit erosive lesions that are more difficult to heal compared to normal skin, and these erosions are prone to bacterial or viral infections. Investigating whether pyroptosis plays a significant role in these clinical manifestations is crucial. Pyroptosis, through its release of pro-inflammatory mediators, might exacerbate the inflammatory environment, leading to delayed healing and increased susceptibility to infections in pemphigus patients. Understanding the contribution of pyroptosis to these clinical outcomes could help in developing targeted therapies that improve wound healing and reduce infection rates, thereby enhancing the overall management of pemphigus. This study summarizes the scientific developments on pyroptosis in pemphigus.

Activation mode of pyroptosis

Pyroptosis is caused by the activation of inflammasomes via two major pathways: classical and non-classical.[9,10] Toll-Like Receptors (TLR) or Nod-Like Receptors (NLR) on the cell surface recognize pathogenic or injury-related molecular patterns, which activate the pyroptotic cascade in the classical pathway. As a result, the inflammasome is generated, which is a protein complex that activates the pro-Caspase-1 precursor when it recognizes the presence of a pathogen or cell damage. Caspase-1 activation causes the cleavage of the Gasdermin-D (GSDMD) protein, resulting in the formation of GSDMD-N. GSDMD-N then causes pores in the cell membrane, resulting in changes in osmotic pressure, cell swelling, and, ultimately, membrane rupture.[11] Caspase-1 promotes the production and release of inflammatory cytokines IL-1β and IL-18, triggering an inflammatory response.

Bacterial components such as Lipopolysaccharides (LPS) can activate Caspase-4/5/11 via a non-traditional method.[12] Caspases 4, 5, and 11 activate the Pannexin-1 channel, which allows the cell to release ATP into the extracellular space. This activates the P2 × 7 channel on the cellular membrane, causing membrane pores to develop and the pyroptosis process to commence. Activated Pannexin-1 activates the NLRP3 inflammasome by releasing potassium ions, resulting in the creation and release of IL-1β and IL-18. This technique completes the release of inflammatory factors, accelerating the advancement of inflammation.[13]

Expression of pyroptosis-related protein in pemphigus

Secretory protein: Cytokine

The IL-1 family's pro-inflammatory molecules, IL-1β and IL-18, play a crucial role in pyroptosis (Shown in the left part of Fig. 1). Research indicates that untreated patients with active pemphigus have high levels of IL-1β in their serum and tissues,[14–16] but patients in remission have low levels. The increased expression of IL-1β may directly contribute to the inflammation and damage process in pemphigus. Tear IL-1β levels in patients with pemphigus were substantially elevated compared to those of healthy controls, as determined by Feng J et al. from pemphigus patients' tears.[17] Huang et al. used microarray technology, GO enrichment, and KEGG pathway analysis to show that monocyte infiltration-related genes were highly expressed in pemphigus patients' skin lesions, with dense neutrophil infiltration, high expression of the IL-17 signaling pathway in skin lesions and peripheral blood monocytes, and peripheral blood monocytes responded abundantly to IL-1.[18] IL-1 is a potent inducer of IL-17, which in turn recruits bone marrow cells that secrete IL-1,[19] implying that there may be a positive feedback loop in pemphigus, with IL-1 amplifying pemphigus inflammation via IL-17-related signaling pathways. Hebert et al. discovered significantly elevated expression of IL-1β, IL-23p19, and IL-12p35 proinflammatory cytokine coding genes in autoreactive B-cells of pemphigus patients using quantitative polymerase chain reaction.[20] In a study by Narbutt et al., pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) were found to be more expressed in cells incubated with pemphigus antibodies from active, remission, and healthy patients.[21] Feliciani et al. created a mouse IL-1 gene knockout model and injected pemphigus antibodies. They discovered that animals with reduced IL-1β production had a lower incidence of pemphigus than the control group. This suggests that IL-1β promotes the occurrence or development of pemphigus. IL-1 knockout animals exhibited acantholysis, indicating that IL-1 may not be involved in the

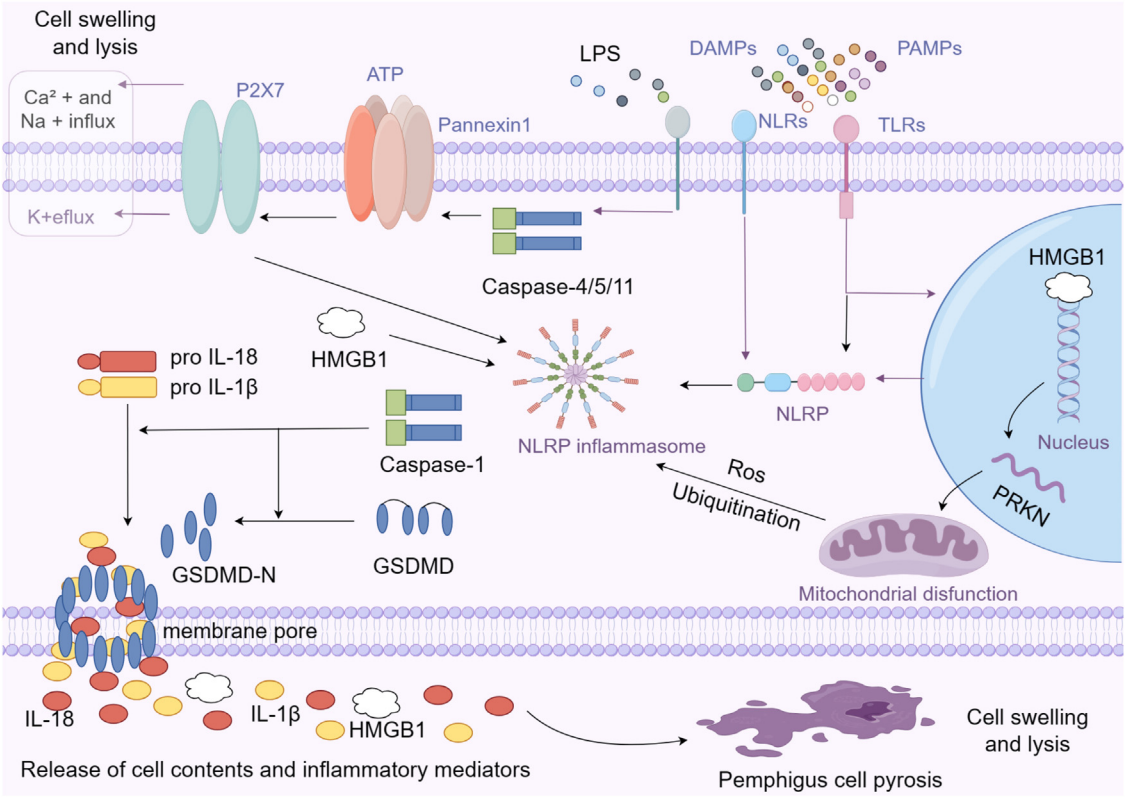

Figure 1 DAMPs and PAMPs are 'damage-associated molecular patterns' and 'pathogen-associated molecular patterns', respectively, that are recognized by pattern recognition receptors on cells, such as TLRs (Toll-Like Receptors) and NLRs (NOD-Like Receptors), to trigger and disseminate an immune response. Inflammasomes are multi-protein complexes that include NLRP proteins and are essential for innate immunity and the activation of inflammatory responses. Enzymes known as caspases are proteases that are crucial in inflammatory responses and programmed cell death. Caspase-1 and Caspase-4/5/11 are shown in the picture; they activate inflammasomes and cleave pro-inflammatory cytokines. GSDMD (Gasdermin-D): Upon cleavage by Caspase-1, GSDMD-N forms pores in the cell membrane, leading to the release of the cell's contents, including IL-1β, IL-18, and HMGB1. Upon stimulation by extracellular ATP, the P2 × 7 receptor opens and allows ions to flow, altering intracellular concentrations. This ionic change prompts the opening of Pannexin1 channels, facilitating the release of ATP and other inflammatory mediators. This ATP release and ion flux through P2 × 7 and Pannexin1 channels is a pivotal step in activating the inflammasome, leading to pyroptosis.

onset of pemphigus, but rather in the expansion of inflammation and injury.[22] In a study by Kailash C et al.,[23] serum IL-1 Receptor antagonist (Ra) levels increased in pemphigus patients in remission. This suggests that IL-1 Ra may inhibit the inflammatory effect of IL-1β and alleviate the disease. IL-1 inhibitors may also be effective in treating pemphigus.

Structural proteins and signaling molecules: HMGB1

High Mobility Group Box-1 (HMGB1) is a non-histone chromatin-binding protein found in the nuclei of all mammalian cells. HMGB1 is a protein that serves multiple biological functions, including regulating DNA structure and function within the cell and acting as a pro-inflammatory signaling molecule outside the cell. In the cell, HMGB1 participates in DNA replication, repair, transcription, and chromatin remodeling. When cells are damaged or inflamed, HMGB1 can be released outside the cell, acting as an extracellular signaling molecule involved in inflammation, tissue repair, and immune regulation. The release of HMGB1 is regarded as an important marker of cell damage and death, and it has the ability to activate the immune system, induce and enhance an inflammatory response. Pyroptosis causes the release of cell contents, including HMGB1, which activates the inflammasome, leading to the production and release of inflammatory factors such as IL-1β and IL-18. HMGB1, on the other hand, can activate immune cells and direct the development of an immune response by binding to a variety of receptors, including receptor RAGE (a receptor for advanced glycation end products) and TLRs (Shown in the right part of Fig. 1). This effect promotes the formation and progression of inflammation during pyroptosis.[24,25] Li et al. investigated serum HMGB1 levels as well as tissue expression of HMGB1 and its receptor RAGE in pemphigus patients. They discovered that serum HMGB1 levels were significantly higher in pemphigus patients than in bullous pemphigoid patients and healthy control populations, and serum HMGB1 levels were significantly higher in pemphigus patients before treatment than after treatment. HMGB1 is abundant in the epidermal cytoplasm of pemphigus patients, whereas HMGB1 expression in healthy skin and bullous pemphigoid is almost entirely confined to the nucleus.[26] The change in HMGB1 level is closely related to disease activ-

ity and treatment response, implying that HMGB1 may be an important part of the pathological mechanism of pemphigus, and that HMGB1 may be both a biomarker of disease activity and an indicator of treatment outcome.

Mitochondria-related functional proteins: Parkin

Parkin, encoded by the PRKN gene, is expressed in both the cytoplasm and the nucleus and plays a role in protein degradation and mitochondrial function maintenance. Parkinin regulates autophagy, which helps to maintain mitochondrial homeostasis. Dysfunctional mitochondria can produce Damage-Associated Molecular Patterns (DAMPs) and Reactive Oxygen Species (ROS), which are known to activate the inflammasome and cause pyroptosis. PRKN mutations or dysfunctions predispose to inflammation and create pyrogenic environments. Parkin proteins, on the other hand, are involved in the regulation of protein degradation in cells via the Ubiquitin-Proteasome System (UPS) and the autophagy pathway (Shown in the right part of Fig. 1). Parkin protein can ubiquitinate a variety of substrates, recognizing and promoting the degradation of markedly damaged or over-accumulated proteins, thereby influencing inflammatory signaling pathways.[27,28] Bumiller-Bini et al. used microarray hybridization and multivariate logistic regression to systematically study the allele and genotype frequencies encoding all 12 mature cell death cascades in 227 patients with pemphigus foliaceous and 194 controls. The pyrogenic cell death gene PRKN was discovered to be a protective factor for pemphigus foliaceus.[29] This suggests that the PRKN gene may play a protective role in pemphigus patients, as its normal function promotes mitochondrial health, reduces inflammatory response, and inhibits the scorch-death process. This discovery sheds new light on the pathogenesis of pemphigus.

Proteins with roles in responding to and modulating inflammation: NLR

Nucleotide-binding oligomerization domain-like receptors (NOD-like receptors) (also known as NLR) are a group of proteins with over 20 subtypes. These include NOD1, NOD2, NLRP1, NLRP3, and NLRC4 (also known as IPAF), which are intracellular Pattern Recognition Receptors (PRRs). These receptors activate inflammatory responses and cell death pathways in host defense mechanisms by recognizing endogenous molecules, bacteria, viruses, and toxic foreign bodies in the cytoplasm.[30,31] Furthermore, NLR can interact with other signaling proteins to form an inflammasome, which activates downstream inflammatory signaling pathways. The NLR protein family's inflammatory bodies activate Caspase, resulting in the maturation of Caspase-1 substrates like IL-1β and IL-18, which initiate immune and inflammatory responses. Shamsabadi et al. used real-time polymerase chain reaction to discover that NLRP1 and IPAF mRNA levels in patients with active pemphigus were significantly higher than in healthy controls.[15] The upregulation of NLRP1 and IPAF in pemphigus patients may indicate over-activation of these inflammatory bodies (Shown in the central part of Fig. 1). Inflammatory mediators like IL-1β and IL-18 may also contribute to skin inflammation and damage. These findings indicate that the NLR protein family which is related to pyroptosis may play an important role in the pathogenesis of pemphigus.

Membrane channel protein: P2XR

Membrane channel Protein P2X Receptor (P2XR) is a class of ion channel receptors made up of seven subtypes, P2 × 1–P2 × 7, that belong to the ATP-dependent ion channel on the cell surface. Extracellular ATP activates these receptors, causing Calcium ions (Ca^{2+}) and sodium ions (Na^{+}) to enter the cell and potassium ions (K^{+}) to leave. P2X receptors are more closely related to pyroptosis. Sustained activation of P2 × 7 causes extracellular ATP release, K + ion efflux, inflammasome activation, and Caspase-1 activation, which promotes IL-1β and IL-18 secretion. Furthermore, activating the P2 × 7 receptor increases membrane permeability and promotes the release of cell contents, such as pro-inflammatory factors[32,33] (Shown in the upper area of Fig. 1). These factors may cause or exacerbate pyroptosis. Malheiros et al. compared the genome-wide gene expression profiles of peripheral CD4+ T-cells between different subgroups of pemphigus foliaceus patients and healthy individuals, discovering that the P2XR gene was highly expressed in untreated pemphigus patients.[34] It is also proposed that ATP and P2X receptors play important roles in tissue inflammation and cell pyroptosis in pemphigus.

Relationship of pyroptosis and acantholysis

The relationship between pyroptosis and acantholysis may primarily revolves around the inflammatory response triggered by pyroptosis and its detrimental impact on skin tissue integrity. Pyroptosis is a form of programmed cell death that involves inflammasome activation, pore formation, and subsequent cell lysis. It is associated with various inflammatory and autoimmune conditions. Acantholysis refers to the loss of adhesion between keratinocytes in the epidermis, leading to blistering skin disorders. During pyroptosis, Gasdermin proteins form pores in the cell membrane, causing cell swelling and rupture. This process triggers the release of substantial quantities of pro-inflammatory cytokines, such as IL-1β and IL-18, fostering an inflammatory environment that can exacerbate skin conditions. These cytokines promote various immunological responses, including leukocyte migration and the production of other inflammatory mediators, which may further aggravate acantholysis[35] (Shown in Fig. 2). Pyroptosis is commonly activated in response to intracellular pathogens, resulting in skin inflammation. In this process, oxidative stress induces mitochondrial dysfunction and the generation of Reactive Oxygen Species (ROS), which exacerbates cellular damage and inflammation. Additionally, Nitric Oxide (NO) released during pyroptosis enhances the production of Matrix Metalloproteinases (MMPs) and inflammatory cytokines, disrupting the Extracellular Matrix (ECM) integrity and leading to skin lesions.[36–38] In chronic inflammatory skin diseases such as eczema, seborrheic dermatitis, or psoriasis, the exacerbation of symptoms can be attributed to the pro-inflammatory cytokines released during pyroptosis.[35,39,40] Persistent inflammation compro-

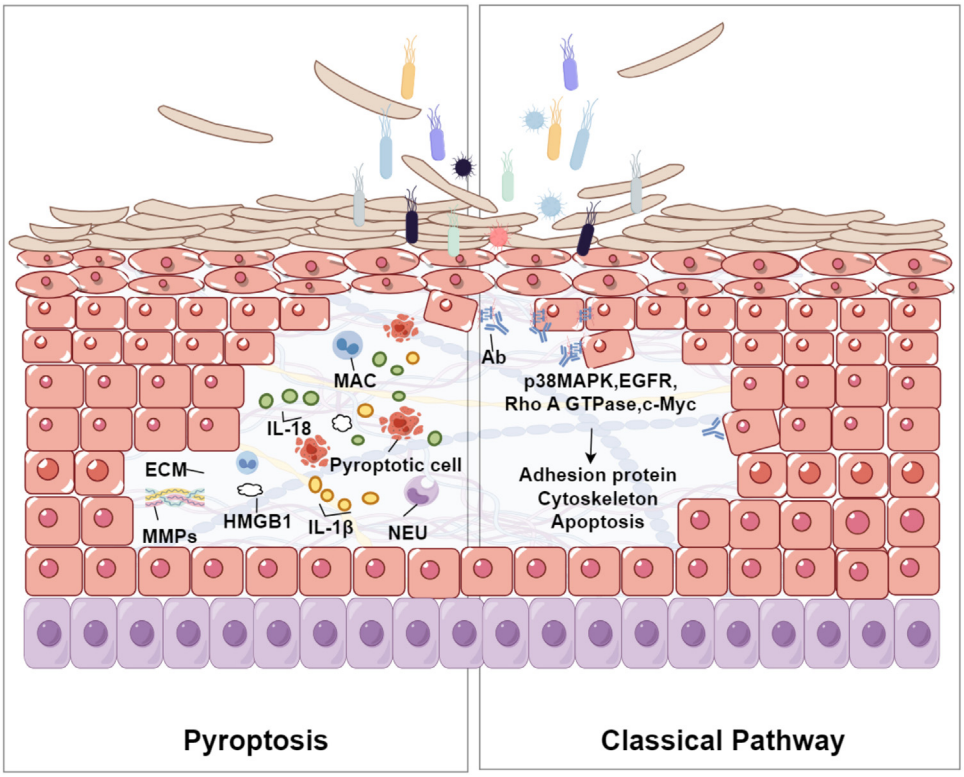

Figure 2 The relationship between pyroptosis and acantholysis within the epidermis. Pyroptotic cells, characterized by the formation of Gasdermin-mediated pores, release pro-inflammatory cytokines such as IL-1β and IL-18. These cytokines attract Neutrophils (NEU) and Macrophages (MAC), intensifying the inflammatory environment. The resultant oxidative stress and production of Matrix Metalloproteinases (MMPs) may degrade the Extracellular Matrix (ECM), weakening the structural integrity of the epidermis and leading to the detachment of keratinocytes, a process known as acantholysis. This figure illustrates the complex interplay between cellular death, inflammation, and tissue disruption in the pathogenesis of blistering skin disorders. The right part of the figure shows the classical pathway of acantholysis in pemphigus. Bacterial interaction triggers antibody production, activating signaling molecules (p38 MAPK, EGFR, Rho A GTPase, c-Myc), which affect the cytoskeleton and adhesion proteins, leading to cell detachment and apoptosis.

mises the structural integrity of the skin, rendering it more susceptible to acantholytic changes. Elevated levels of inflammatory cytokines, including IL-18 and IL-1β, have been documented in several skin disorders, suggesting their potential role in linking pyroptosis to acantholysis. These sources provide a comprehensive understanding of how pyroptosis contributes to the pathogenesis of acantholysis by releasing inflammatory mediators, causing oxidative stress, and resulting in tissue damage. This information offers valuable insights into potential therapeutic targets for treating related skin conditions.

Treating pemphigus with pyroptosis-related targets

Exploring the role of pyroptosis in pemphigus pathogenesis and its therapeutic implications requires digging deeper into Caspase activation and how Caspase inhibitors, particularly those targeting Caspase-1, can help treat the disease. Classically, autoantibodies that disrupt keratinocyte adhesion cause acantholysis and blisters in pemphigus. A recent study reveals that cell death processes, notably pyroptosis, contribute to its pathogenesis. Pyroptosis is triggered by Caspase family members like Caspase-1, Caspase-4, Caspase-5 and Caspase-11, which recognize intracellular pathogens or damage-related molecular patterns. Numerous animal, cellular, and human studies have demonstrated that Caspase activation is harmful in experimental pemphigus, and pancaspase inhibitors can block or diminish acantholysis and blister formation in pemphigus in vitro and in vivo, respectively.[41–45] Wang et al. used Trypan blue in vivo staining to evaluate cell mortality and found that YVAD-CHO, a Caspase-1 inhibitor, could decrease PV-IG-induced keratinocyte death and tissue acantholysis.[46] The effect of pyroptosis-specific Caspase-1 inhibitors supports the idea of pyroptosis in pemphigus pathogenesis and highlights the potential for targeting specific Caspases in pemphigus treatment.

Conclusion and prospects

Pemphigus refers to a class of autoimmune bullous skin illnesses in which intercellular adhesion is lost due to the generation of autoimmune antibodies. Recent research has revealed that innate immunity, including the recruitment of innate immune cells, the release of inflammatory mediators, and the activation of the complement system, also plays a

significant role in the pathological process of pemphigus. Pemphigus is primarily linked to abnormal adaptive immunity, particularly autoantibodies produced by B-cells. A type of planned cell death called pyroptosis is closely linked to inflammation, which is a result of both innate immune system and inflammatory body activation. In the development and progression of pemphigus, NLRP inflammatory bodies, Caspase, IL-1 and IL-18, PRKN, and P2X are considered to be implicated. In-depth research is still lacking to determine whether pyroptosis is linked to pemphigus skin infection and refractory erosion. This includes the significance of Gasdermin D, the key pyroptosis protein, being expressed in pemphigus and the mechanism by which pyroptosis-related molecules activate pyroptosis through a particular signaling pathway. It is also unclear whether pyroptosis broadens the inflammatory range of pemphigus. In vitro and in vivo, inhibitors of pancaspase, a pyroptosis-related molecule, prevent or lessen acantholysis and blister development in pemphigus. It has also been demonstrated that Caspase-1 inhibitors, an important pyroptosis enzyme, are useful in preventing the creation of vesicles; however, further experimental confirmation is required. More research is required to determine the potential of IL-1 receptor antagonists in the management of pemphigus.

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Authors' contributions

Jiazhen Chen: Conducted a comprehensive literature review, wrote the initial draft of the manuscript and created the figures.

Zezhi He: Created the figures and provided the necessary resources.

Xiangnong Dai: Contributed to the critical review and editing of the manuscript.

Sifan Lin: Contributed to the critical review and editing of the manuscript.

Jiahui Liu: Supervised the research and provided the necessary resources.

Xingdong Ye: Conceived the original idea and designed the framework of the study.

Conflicts of interest

None declared.

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SOCIEDADE BRASILEIRA DE DERMATOLOGIA

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SPECIAL ARTICLE

Anais Brasileiros de Dermatologia: who wrote this century-old history?☆

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Abstract The *Anais Brasileiros de Dermatologia* (ABD), an official publication of the Brazilian Society of Dermatology, has been published since 1925. ABD is considered the most influential dermatological journal in Latin America. By 2025, the journal will mark a significant milestone, celebrating a century of history. Over this time, it has published 99 volumes and 6,299 contributions from more than 10,800 authors. To analyze the trajectory of the journal, this study employs an applied research approach characterized by descriptive objectives and a quantitative nature. This research was based on a documentary procedure that encompassed all contributions already published in the journal. The main goal of the work was to identify the most prominent authors who have contributed to the journal and to map the largest co-authorship communities. The authors hope that this research serves as a formal recognition of the researchers who have written the history of the ABD.
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Introduction

The *Anais Brasileiros de Dermatologia* (ABD) is the authoritative scientific publication endorsed by the Brazilian Society of Dermatology. ABD stands out as one of the leading specialized journals in the field of dermatology, garnering recognition not only within Brazil but also on an international scale.[1] Established in 1925, the journal has remained steadfast in its commitment to disseminating scientific knowledge and fostering the progress of dermatology. Covering a diverse array of topics concerning skin, hair, and nail health, ABD continues to be a pivotal resource in advancing the understanding of dermatological sciences. Reaching the milestone of a century of contributions prompts reflection on the past and recognition of the researchers who have helped write this success story. Moreover, with 99 volumes published, the journal chronicles the evolution of dermatology in Brazil.

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Analyzing the history of a journal through significant milestones is a common practice in the literature. The Journal of Dental Research underwent a bibliometric analysis covering its 100-year history. The study identified the 100 most cited articles from this period. The findings highlight the journal's extensive impact and reveal shifts in citation patterns and research priorities over the past century.[2] Similarly, the Journal of Prosthetic Dentistry was subjected to a comprehensive bibliometric analysis to examine its characteristics over a 50-year period, from 1970 to 2019. Of the 11,989 records retrieved, 10,638 (92.9%) were included in the analysis.[3] Likewise, during its 20-year history, the *Centro de Ciências da Economia e Informática* (CCEI) Journal was analyzed, which includes all 420 published articles. The study identified the most influential authors and their associated research communities.[4] Analogously, the *Arquivos Catarinenses de Medicina* Journal was analyzed, covering all 1,173 articles published since its inception 65 years ago. The study identified the most prominent authors and their primary research communities.[5] To assess the current status and research trends in caries diagnosis, 816 documents published between 2013 and 2021 were analyzed from the Web of Science Core Collection database. The study aimed to perform a bibliometric analysis to identify contributing researchers, organizations, countries or regions, and journals, as well as to examine keyword co-occurrence and co-authorship networks.[6]

In parallel, other studies use Social Network Analysis (SNA) to obtain a deeper insight into the structure of collaboration among the authors. In medical education, it is acknowledged that SNA is underutilized. However, the method is argued to have significant potential, offering valuable insights that could enhance the experiences and outcomes of medical trainees and educators, ultimately benefiting patients.[7] SNA was also employed to visualize the co-authorship networks and scientific map of research outputs in clinical teaching and medical education. The research examined 1,229 publications on clinical teaching spanning a 40-year period, from 1980 to 2018.[8]

The ABD itself has been the subject of studies involving importance metrics, but the studies focused on journal impact indicators, without addressing aspects related to author metrics. An analysis of the trajectory of the ABD over a decade was done, from 2013 to 2022, and compared key bibliometric indices with those of Brazilian medical and international dermatological journals.[9] Previously, trends in the main bibliometric indicators of the ABD from 2010 to 2019 were investigated.[10]

In this context, the aim of this research is to analyze the century-long history of the ABD, identifying its most prominent contributors and mapping the largest co-authorship communities.

Material and methods

This study is an applied research with a descriptive objective and a quantitative nature. It involved a documentary procedure conducted on the websites of the ABD. This section delineates the methods employed in the study, encompassing the data collection process, the creation of the database, the generation of the co-authorship network, and the calculation of author metrics.

Dataset

Data was collected through the web scraping technique, which enabled the extraction of data from websites.[11] To automate this process, a scraper was implemented to download data from all published editions available on the journal's old website (http://www.anaisdedermatologia.com.br/edicoes-anteriores). The scraper was executed on December 24, 2024, at 15:56, performing a complete copy of the site's public data at that time. Data from volume 1, issue 1 (1925) to volume 95, issue 6 (2020) were downloaded, covering 96-years of the journal's history. The data from the Journal's new website (https://www.sciencedirect.com/journal/anais-brasileiros-de-dermatologia/issues) were manually downloaded, covering from volume 96 issue 1 (2021) to volume 99 issue 6 (2024). These steps involved the download of 99 volumes, encompassing a total of 6,299 contributions, which includes case reports, reviews, editorials, and full articles.

Afterward, the downloaded data underwent preprocessing to extract the names of the authors from each work, identifying 22,200 authors. A common issue in determining the impact is duplicate names, may arise from inconsistencies in the names used or name changes.[12] In this sense, the third step involved employing the Levenshtein algorithm (https://www.rdocumentation.org/packages/utils/versions/3.6.2/topics/adist) to calculate the distance between names, revealing several authors whose names had been written differently. For example, author Rubem David Azulay had his name written in the following alternative ways: R. D. Azulay, Dr. Rubem D. Azulay, Rubem D. Azulay, and Ruben D. Azulay. After standardizing the authors' names, the number of distinct authors was reduced from 22,200 to 10,829. This protocol for standardizing names has been applied in similar studies.[5,13]

Computing authors relevance

Finally, the collaboration network graph was generated, and author metrics were computed using the Gephi tool (https://gephi.org/). The concept of graphs is fundamental for understanding SNA. A graph is an abstract representation of a set of objects and their relationships.[14] In this work, the objects are the authors, and the relationships are co-authorship interactions. Key concepts of graphs for SNA include: 1) Nodes represent each author who has published in the journal; 2) Edges represent co-authorship relationships that occurred in the same paper; 3) Graph represents the co-authorship structure among all authors in the journal over its 99-years; 4) The graph is of the Undirected type, as the order of authors in each article was not considered; and 5) Edge Weights represent the number of co-authorships between two linked authors.

In this study, based on graph theory,[14] which serves as the theoretical foundation for SNA, the following metrics were calculated for the authors:

- Number of Publications (Pub): This metric reflects the total number of publications in which the author has participated, regardless of their position among the co-authors.
- Degree (Deg): This metric indicates how many different authors collaborated in co-authoring works with the author. The importance of the degree in a co-authorship network lies in its ability to reveal the collaborative behavior and networking patterns of authors within a research community. High-degree authors are often well-connected hubs within the research community and may have significant influence over the flow of information, ideas, and collaborations within their field.[15]
- Betweenness Centrality (BC): This metric indicates the relevance of an author as a connection between different research groups.[16] Elements with high betweenness centrality can be considered key players or influencers within the healthcare system.[17] These nodes may represent hospitals, healthcare providers, or diseases that play a crucial role in the dissemination of information, patient referrals, or the spread of diseases. This metric is also recognized as a robust measure for identifying the most relevant genes, making them potential candidates for drug-targeting purposes.[18,19]
- Page Rank (PR): Developed by Google, this metric was designed to determine the order in which web pages are displayed to users during searches. Recently, this metric has been used for identifying influential researchers in citation networks.[20,21] In the present work, PR is utilized to identify authors who hold leadership positions within the community of ABD.
- Community (Com): The identification of co-authorship communities was conducted using the Louvain method.[22] The community number indicates its position in the ranking of the largest communities, such that community 1 is the largest in terms of number of members, community 2 is the second largest, and so forth.

Results and discussion

Table 1 displays the authors who had at least thirty-one publications in the ABD. This threshold enabled the selection of the top 50 authors with the highest number of publications, representing 0.46% of the journal's 10,829 authors. The total number of publications by the top 50 authors is 2,550, out of a total of 6,299 publications by ABD up to its 99th edition. These numbers highlight the importance of the top 50 authors.

Table 1 is sorted in descending order of Publications, Degree, Betweenness Centrality, and Pagerank, indicating the respective co-authorship communities. In the Deg, BC, and PR columns, the values in parentheses indicate the author's potential ranking position if the respective column were used as the primary sorting criterion. In addition to these authors presented in the ranking, 57 authors were identified who had twenty or more articles published, 169 authors with ten to nineteen articles, 397 authors with five to nine articles; 2,182 authors with two to four articles, and 7,974 authors who participated in a single article, indicating that 73.64% of the authors published only once in the journal.

Due to space limitations, the authors chose to restrict the analysis to the top 5 highest values of each metric. Thus, according to number of publications, the importance over the 99-years of ABD is evident for the following five authors: Rubem David Azulay (Pos = 1) with 161 publications, Helio Amante Miot (Pos = 2) with 143 publications, Silvio Alencar Marques (Pos = 3) with 105 publications, Hiram Larangeira de Almeida Junior (Pos = 4), with 99 publications, and Renan Rangel Bonamigo (Pos = 5), with 87 publications. Just these authors contributed 595 publications, accounting for over 9.44% of the journal's total publications throughout its history. The median number of articles published by the top 50 ranked authors was 41.5 (p25–p75: 34–56), indicating a highly productive subgroup. In contrast, the overall average number of publications per author was much lower, 2.05 $\pm$ 4.59, with a median of 1 (p25–p75: 1–2). This substantial disparity suggests an exponential distribution, where a small number of highly productive authors contributed substantially to the total publication output.

In terms of degree, which represents the number of different co-authors collaborated with, the following authors stand out: Helio Amante Miot (Pos = 2) with 266 co-authors, Rubem David Azulay (Pos = 1) with 184 co-authors, Renan Rangel Bonamigo (Pos = 5) with 179 co-authors, Luna Azulay Abulafia (Pos = 21) with 162 co-authors, and Hiram Larangeira de Almeida Junior (Pos = 4) with 160 collaborations. The median number of coauthors among the top 50 ranked authors was 82 (p25–p75: 56–101). In comparison, the average number of coauthors across all authors was 6.2 $\pm$ 9.29, with a median of 4 (p25–p75: 3–6). This disparity highlights the more extensive collaborative networks of the top authors compared to the broader author pool.

The highest Betweenness Centrality values indicate authors who played a significantly relevant role in communication between different research communities, thereby integrating various communities within the context of ABD. In this metric, the following authors are highlighted: Helio Amante Miot (Pos = 2), Rubem David Azulay (Pos = 1), Luna Azulay Abulafia (Pos = 21), Bernardo Gontijo (Pos = 6), and Cesare Massone (Pos = 283). Despite a lower number of publications (Pub = 9), Cesare Massone, from Galliera Hospital in Genoa, Italy, achieves a high BC score due to his co-authorships with researchers from Brazil, Italy, and Austria. The median BC among the top 50 ranked authors was 0.008219 (p25–p75: 0.005179–0.017461). In contrast, the average BC across all authors was 0.000187 $\pm$ 0.001354 (p25–p75: 0–0). This significant difference underscores the central role of the top authors in connecting various segments of the research network.

The highest Pagerank values show the authors who have a leadership role in the ABD, likely resulting from their activities as mentors of new researchers in this area. In this metric, the most relevant authors are: Helio Amante Miot (Pos = 2), Hiram Larangeira de Almeida Junior (Pos = 4), Rubem David Azulay (Pos = 1), Renan Rangel Bonamigo (Pos = 5), and Silvio Alencar Marques (Pos = 3). The median PageRank (PR) among the top 50 ranked authors was 0.001049 (p25–p75: 0.000864–0.001482). In contrast, the mean PageRank across all authors was $9.23 \times 10^{-5} \pm 1.18 \times 10^{-4}$.

Relationships between these metrics provide insights into the profile of top-ranked authors. A weak positive

Table 1 Top 50 authors ranking.

Pos	Name	Pub	Deg	BC	PR	Com
1	Rubem David Azulay	**161**	(2) **184**	(2) **0.043302**	(3) **0.002593**	1
2	Helio Amante Miot	**143**	(1) **266**	(1) **0.048551**	(1) **0.003699**	5
3	Silvio Alencar Marques	**105**	114	0.017461	(5) **0.002118**	5
4	Hiram Larangeira de Almeida Junior	**99**	(5) **160**	0.018632	(2) **0.002874**	3
5	Renan Rangel Bonamigo	**87**	(3) **179**	0.024416	(4) **0.002485**	3
6	Bernardo Gontijo	78	95	(4) **0.030107**	0.001530	8
7	Neusa Yuriko Sakai Valente	76	133	0.012516	0.001980	6
8	Nelson Guimaraes Proenca	76	58	0.004664	0.001008	11
9	Juan Manuel Pineiro Maceira	63	158	0.019992	0.001939	1
10	Sinesio Talhari	62	100	0.022246	0.001561	10
11	Everton Carlos Siviero do Vale	61	56	0.007561	0.001060	8
12	Paulo Ricardo Criado	60	128	0.019865	0.001789	6
13	Antonio de Souza Marques	56	97	0.020951	0.001427	1
14	Nurimar Conceicao Fernandes	53	101	0.006272	0.001497	1
15	Antar Padilha Goncalves	50	9	0.000759	0.000246	13
16	Mariangela Esther Alencar Marques	49	93	0.003028	0.001346	5
17	Antonio Pedro Mendes Schettini	48	84	0.005235	0.001350	10
18	Luiz Carlos Cuce	48	63	0.010051	0.001027	23
19	Milvia Maria Simoes e Silva Enokihara	47	101	0.009096	0.001413	15
20	Sebastiao A Prado Sampaio	47	43	0.005636	0.000575	23
21	Luna Azulay Abulafia	44	(4) **162**	(3) **0.038265**	0.001622	2
22	Izelda Maria Carvalho Costa	44	63	0.005288	0.000956	12
23	Lucia Martins Diniz	43	55	0.005028	0.001120	1
24	Tancredo Alves Furtado	42	45	0.007044	0.000654	8
25	Glyne Leite Rocha	42	40	0.001813	0.000705	1
26	Alexandre Carlos Gripp	41	112	0.016335	0.001218	2
27	Leninha Valerio do Nascimento	41	67	0.005549	0.000769	2
28	Rosana Lazzarini	39	91	0.006285	0.001070	7
29	Absalom Lima Filgueira	38	50	0.008273	0.000664	1
30	Tania Ferreira Cestari	37	144	0.021105	0.001482	4
31	Fabiane Andrade Mulinari Brenner	37	89	0.012498	0.001173	9
32	David Rubem Azulay	36	85	0.010202	0.001165	2
33	John Verrinder Veasey	36	67	0.002917	0.000891	7
34	Lucio Bakos	35	81	0.008165	0.001021	3
35	Luciana Patricia Fernandes Abbade	35	64	0.005179	0.000892	5
36	Omar Lupi da Rosa Santos	34	94	0.015268	0.001058	1
37	Antonio Carlos Pereira Junior	34	61	0.004186	0.000812	1
38	Francisco Eduardo Rabello	34	16	0.000398	0.000183	1
39	Demetrio Peryassu	34	11	0.000437	0.000289	13
40	Juliano Vilaverde Schmitt	33	83	0.009619	0.000976	5
41	Vitor Manoel Silva dos Reis	33	72	0.005796	0.000837	11
42	Helena Muller	33	66	0.008979	0.000864	11
43	Elemir Macedo de Souza	33	50	0.006729	0.000724	18
44	Lorivaldo Minelli	33	39	0.003786	0.000732	21
45	Mario Cezar Pires	32	112	0.013097	0.001184	4
46	Carolina Talhari	32	76	0.022741	0.001040	10
47	Monica Santos	32	53	0.002048	0.000908	10
48	Itamar Belo dos Santos	32	49	0.003673	0.000917	14
49	Carlos Baptista Barcaui	31	84	0.010410	0.000937	1
50	Adriana Maria Porro	31	72	0.005599	0.000890	15

Pos, Position; Pub, Publications; Deg, Degree; BC, Betweenness Centrality; PR, PageRank; Com, Community.

correlation ($p = 0.474$) is observed between the number of Publications (Pub) and the number of unique coauthors (Deg). The Deg/Pub ratio among the top 50 authors varies widely, ranging from 0.18 to 3.89, with a median of 1.77 (p25–p75: 1.29–2.32). On one hand, Antar Padilha Gonçalves (Pos = 15) has a Deg/Pub ratio of 0.18 (9 coauthors/50 publications), reflecting his tendency to publish primarily without coauthors. A similar pattern is observed with Demetrio Peryassu (Pos = 39), whose ratio is 0.32. This profile is characteristic of authors who were more pro-

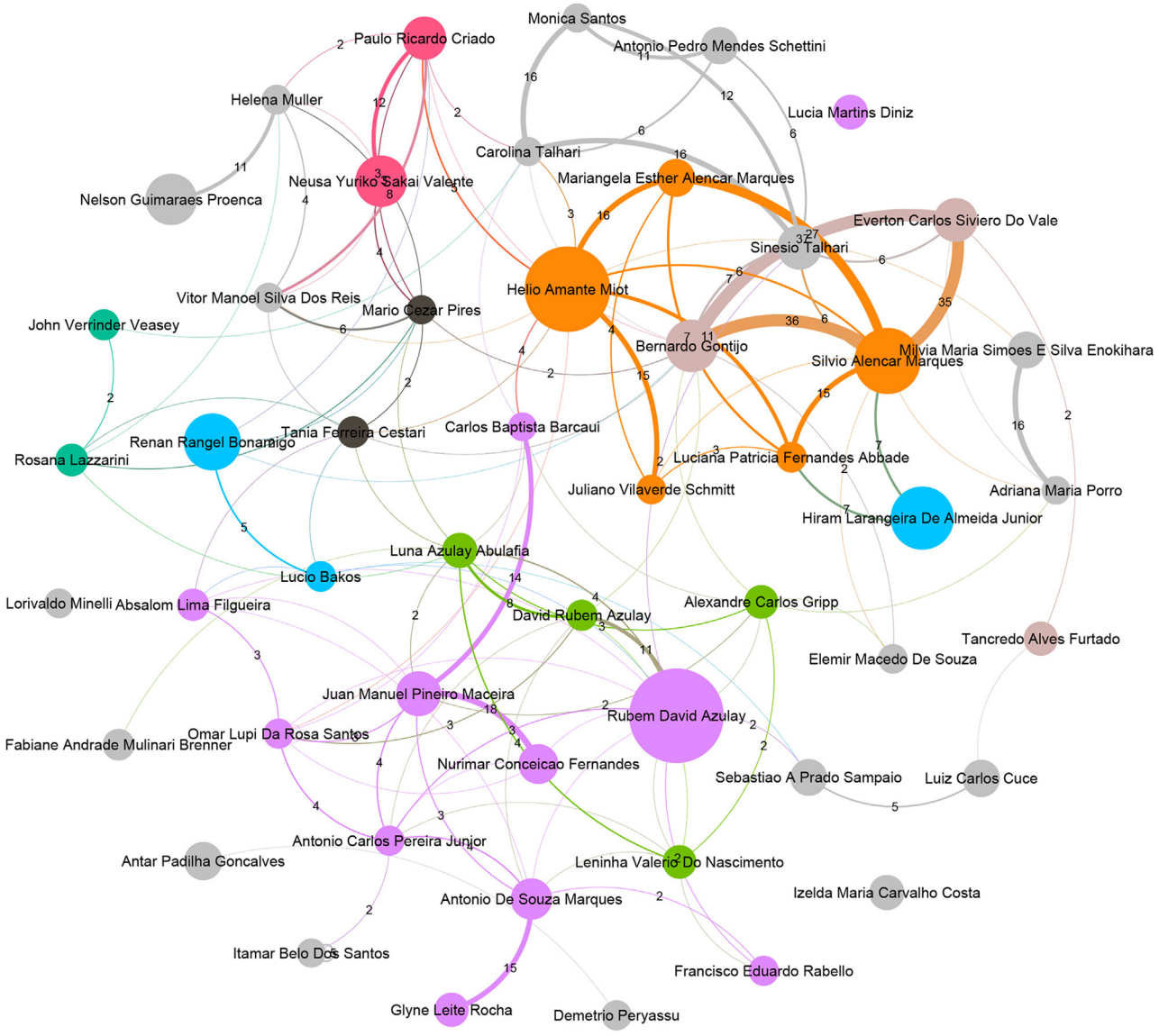

Figure 1 Top 50 authors and their co-authorship networks.

ductive during the earlier decades of ABD and are often regarded as influential figures in the history of Brazilian dermatology.[23,24] On the other hand, Tania Ferreira Cestari (Pos = 30) has a Deg/Pub ratio of 3.89, indicating collaboration with a diverse range of coauthors in her publications. As another example, Luna Azulay Abulafia (Pos = 21) has a ratio of 3.68. Higher ratios are more characteristic of authors with recent productivity, highlighting an increasing trend in interconnection and collaboration among researchers over time.

A weak positive correlation (p = 0.397) was observed between a number of publications and Betweenness Centrality (BC). The median BC/Pub ratio is 0.18×10^{-3} (p25–p75: 0.12×10^{-3} – 0.33×10^{-3}). Francisco Eduardo Rabello (Pos = 38) has the lowest BC/Pub ratio at 0.011×10^{-3}, while Luna Azulay Abulafia (Pos = 21) exhibits the highest ratio at 0.869×10^{-3}. This comparison further highlights the discrepancy between older and more recent authors. In contrast, a very strong positive correlation (p = 0.814) is observed between Deg and BC, reflecting the strong interdependence between a researcher's collaborative reach and their role as a connector within the network.

When analyzing the relationship between the number of Publications (Pub) and Page Rank (PR), a moderate positive correlation (p = 0.636) is identified. The median PR/Pub ratio is 0.26×10^{-3} (p25–p75: 0.20×10^{-3} – 0.29×10^{-3}). Antar Padilha Gonçalves (Pos = 15) has the lowest PR/Pub ratio at 0.049×10^{-3}, while Tania Ferreira Cestari (Pos = 30) exhibits the highest ratio at 0.40×10^{-3}. In contrast, a very strong positive correlation (p = 0.919) is observed between Deg and PR. This indicates that researchers with a broader collaborative network tend to have higher PageRank values, reflecting their centrality and influence within the co-authorship network. The strong relationship underscores the importance of collaborative reach in determining a researcher's prominence and visibility in the network.

Fig. 1 represents authors in the top 50 ranking and their co-authorships. This figure represents the core of ABD.

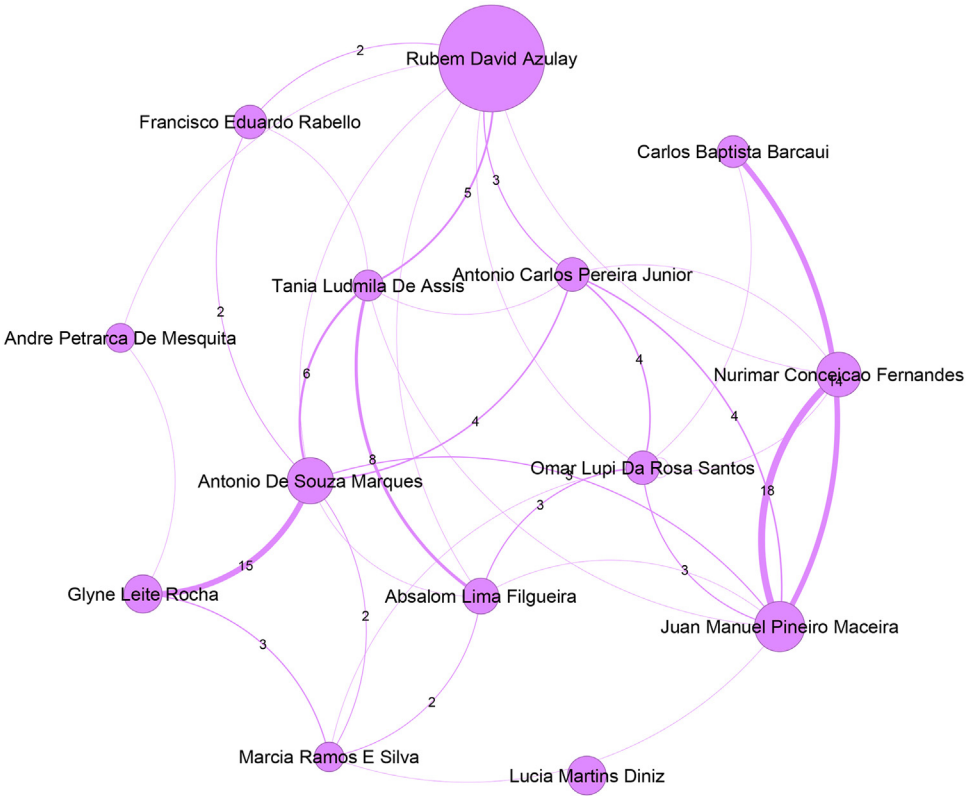

Figure 2 Top authors of the largest community, which contains 831 authors, are predominantly associated with the Universidade Federal do Rio de Janeiro.

Nodes in the graph represent authors, with their size proportional to the number of publications. Edges represent co-authorship collaborations, and their thickness indicates the frequency of these collaborations. Higher-weight edges often highlight frequent partnerships, suggesting long-term collaborations, joint projects, or shared research interests. A total of 33,596 co-authorship partnerships were identified, with the most frequent collaborations depicted in Fig. 1. The most frequent co-authorship was observed between Bernardo Gontijo (Pos = 6) and Everton Carlos Siviero do Vale (Pos = 11), with 37 joint publications. Additionally, Silvio Alencar Marques (Pos = 3) exhibited strong collaborative ties with both Bernardo Gontijo and Everton Carlos Siviero do Vale, co-authoring 36 and 35 publications, respectively. In summary, 43 co-authorships were recorded more than 10 times, while 3,655 co-authorships occurred more than once. Notably, nearly 89% of the collaborations, totaling 29,898, took place only once.

The colors of the nodes denote the primary coauthorship communities, with unique colors assigned to the eight largest communities. Communities ranked ninth and smaller are uniformly represented in gray.[5] These communities typically reflect specialized research areas or institutional affiliations. Notably, communities 1, 5, 10, and 2 together account for nearly half of the top 50 ranked authors, with 11, 5, 4, and 4 members, respectively.

Regarding the communities, the authors who are most relevant within the largest communities stand out. Aiming to focus the attention just on the main authors of each community, Figs. 2 to 10 present just authors who have 20 or more publications. Even the major networks have core members, demonstrating a pattern of close collaboration that has developed over time. The largest community, presented in Fig. 2, with 831 members, is led by the author Rubem David Azulay (Pos = 1), an emeritus professor at the Universidade Federal do Rio de Janeiro. This community contains 7.7% of the Journal authors and 22% of the authors in the ranking. The second largest community, shown in Fig. 3, comprises 549 authors and is led by Luna Azulay Abulafia (Pos = 21) from Universidade Estadual do Rio de Janeiro. The third largest community, displayed in Fig. 4, with 534 members, is led by Hiram Larangeira de Almeida Junior (Pos = 4), from Universidade Federal de Pelotas and Universidade Católica de Pelotas, and Renan Rangel Bonamigo (Pos = 5) from Universidade Federal do Rio Grande do Sul in Porto Alegre. The fourth largest community, displayed in Fig. 5, with 422 members, is led by Tania Ferreira Cestari (Pos = 30) from Universidade Federal do Rio Grande do Sul. Helio Amante Miot (Pos = 2) and Silvio Alencar Marques, both from Universidade Estadual Paulista, lead the fifth-largest community, which is composed of 349 authors, as presented in Fig. 6.

The sixth largest community, presented in Fig. 7, contains 334 authors, is led by Neusa Yuriko Sakai Valente (Pos = 7), from Universidade de São Paulo. Fig. 8 presents the seventh-largest community, which contains 320 authors, and is led by Rosana Lazzarini (Pos = 28), from Santa Casa de São Paulo. Bernardo Gontijo (Pos = 6), from Universidade Federal de Minas Gerais, leads the eighth largest community, which contains 315 authors and is presented in Fig. 9. The

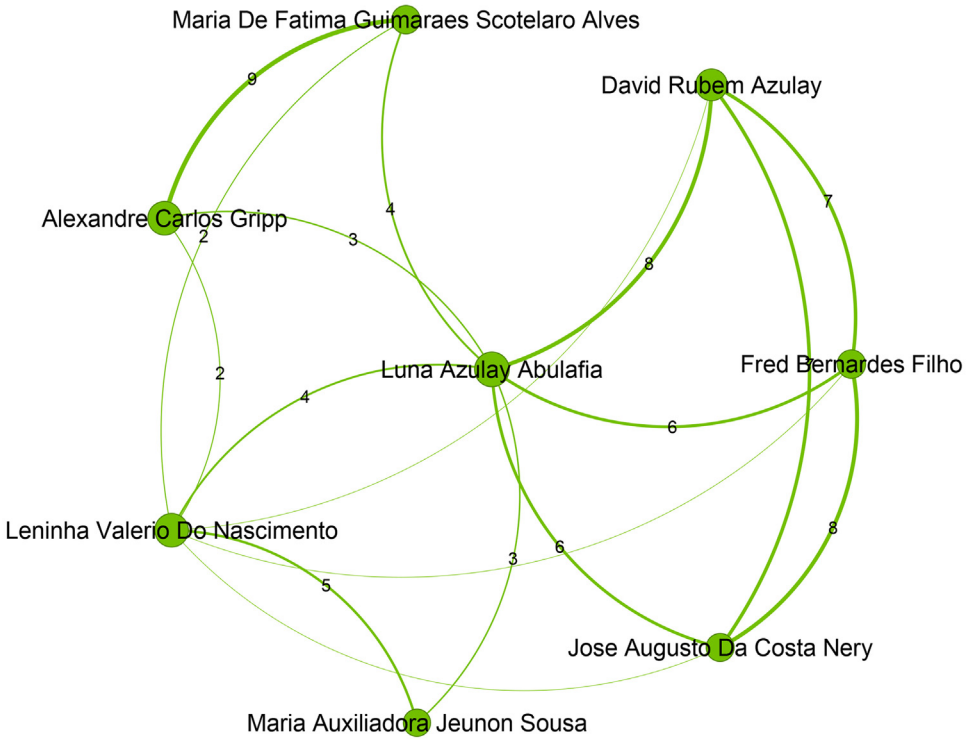

Figure 3 Top authors of the second largest community, which contains 549 authors, are mainly filiated with Universidade Estadual do Rio de Janeiro.

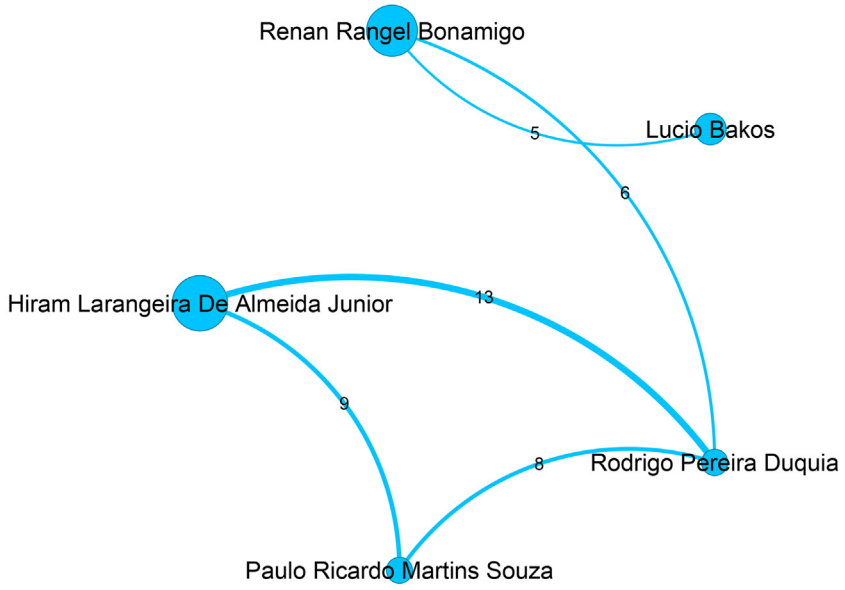

Figure 4 Top authors of the third largest community, which contains 534 authors, are mainly filiated with Universidade Federal do Rio Grande do Sul, Universidade Federal de Ciências da Saúde de Porto Alegre, and Universidade Federal de Pelotas.

ninth largest community, which has 297 authors, is depicted in Fig. 10 and is headed by Fabiane Andrade Mulinari Brenner, from Universidade Federal do Paraná. These nine main communities encompass 3,897 authors, representing 36% of the ABD's authors.

Although there is an international author, Cesare Massone (Pos = 283), among the top five in betweenness centrality, international authors are notably absent from the top 50 in the 100-year ranking. Despite its leadership in Latin America, the journal has historically been focused on Brazilian research, with limited interactions between Brazilian dermatologists and international collaborators. Additionally, publications by foreign authors gained prominence in earlier periods. This can be attributed to a relatively recent shift in editorial policy, implemented 20 years ago, aimed at broadening the base of national and international authors

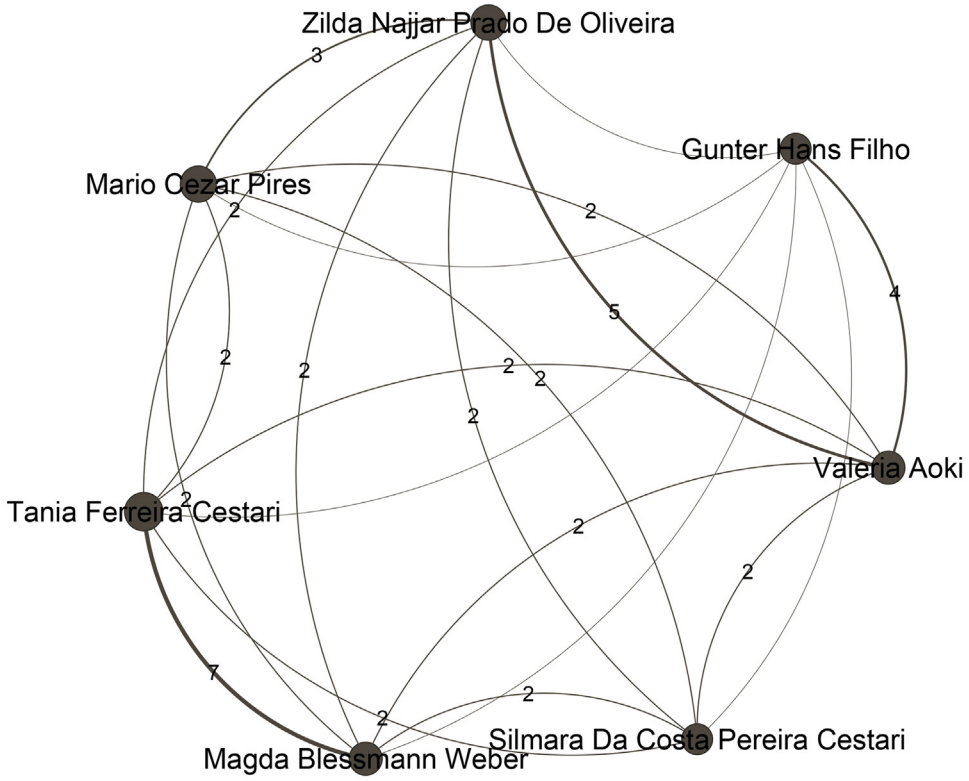

Figure 5 Top authors of the fourth largest community, comprising 350 authors, are associated with different institutions: Universidade Federal de São Paulo, Universidade Federal do Rio Grande do Sul, Universidade Federal do Mato Grosso do Sul, Universidade Federal de Ciências da Saúde de Porto Alegre, Hospital Sírio Libanês, and Hospital do Servidor Público Estadual de São Paulo.

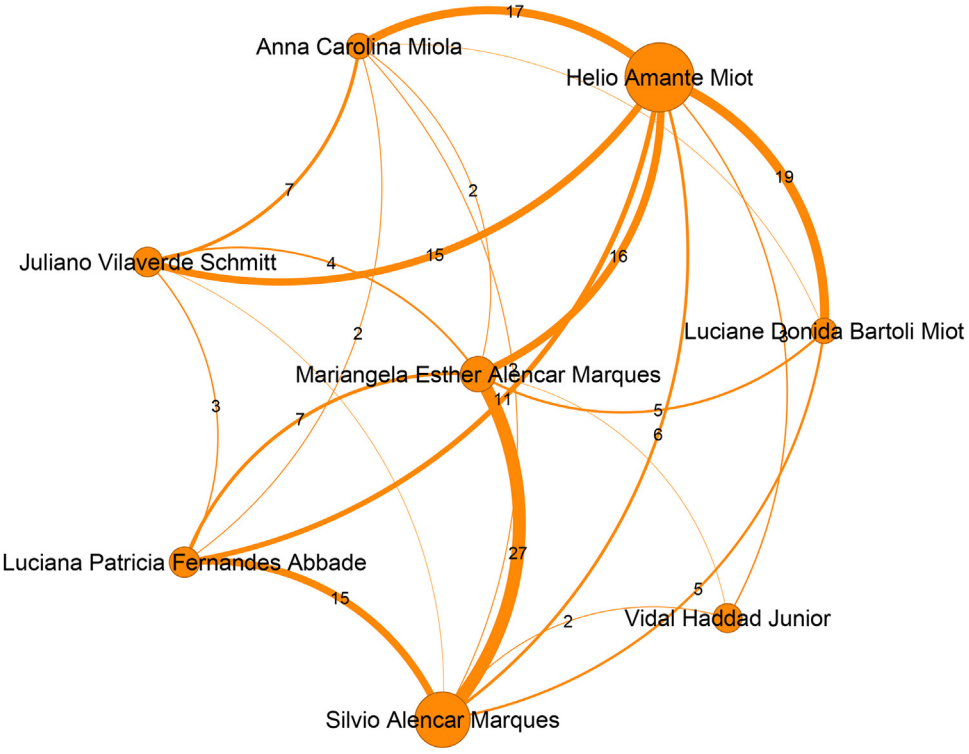

Figure 6 Top authors of the fifth largest community, holding 349 authors, are associated with Universidade Estadual Paulista.

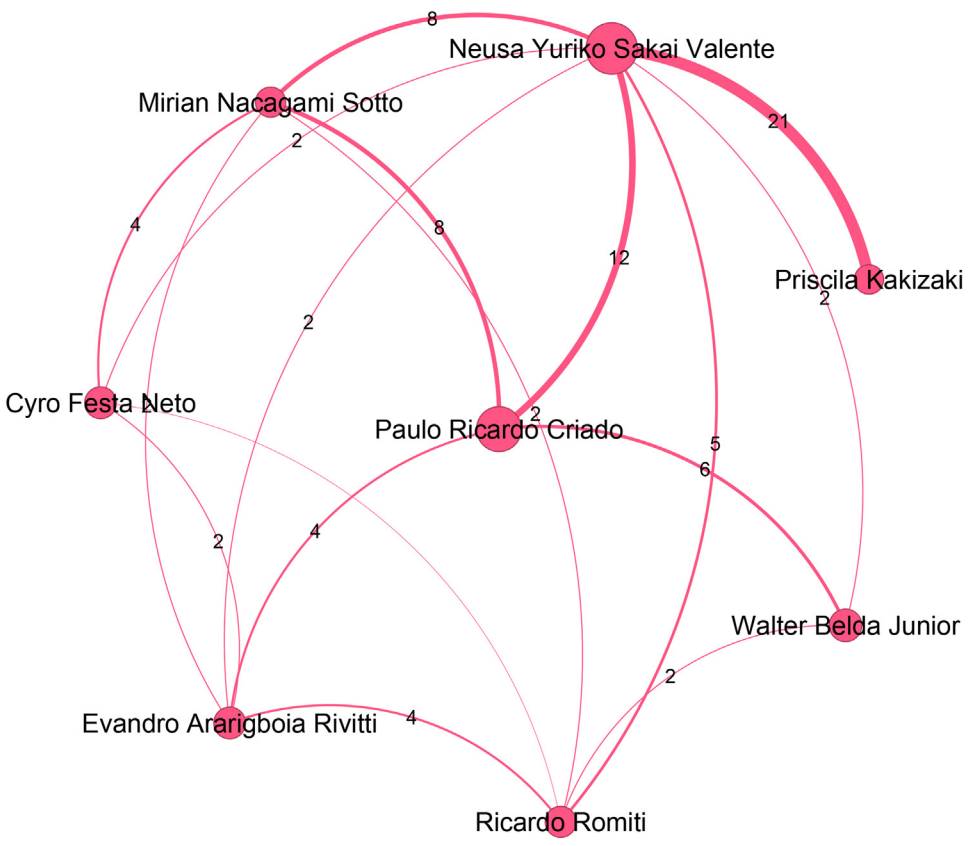

Figure 7 Top authors of the sixth largest community, consisting of 334 authors, are predominantly affiliated with the Universidade de São Paulo.

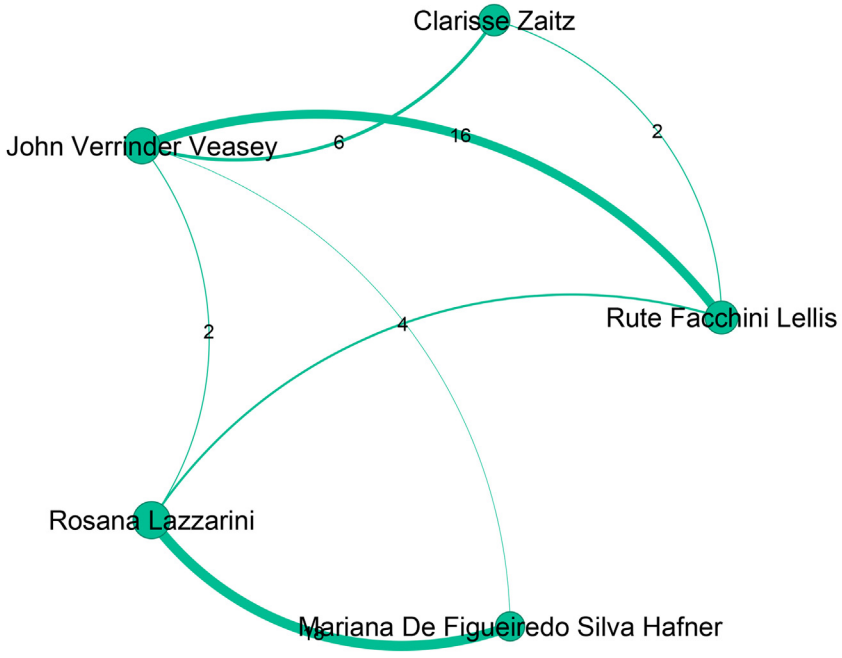

Figure 8 Top authors of the seventh largest community, which contains 320 authors, are primary affiliated with the Santa Casa de São Paulo.

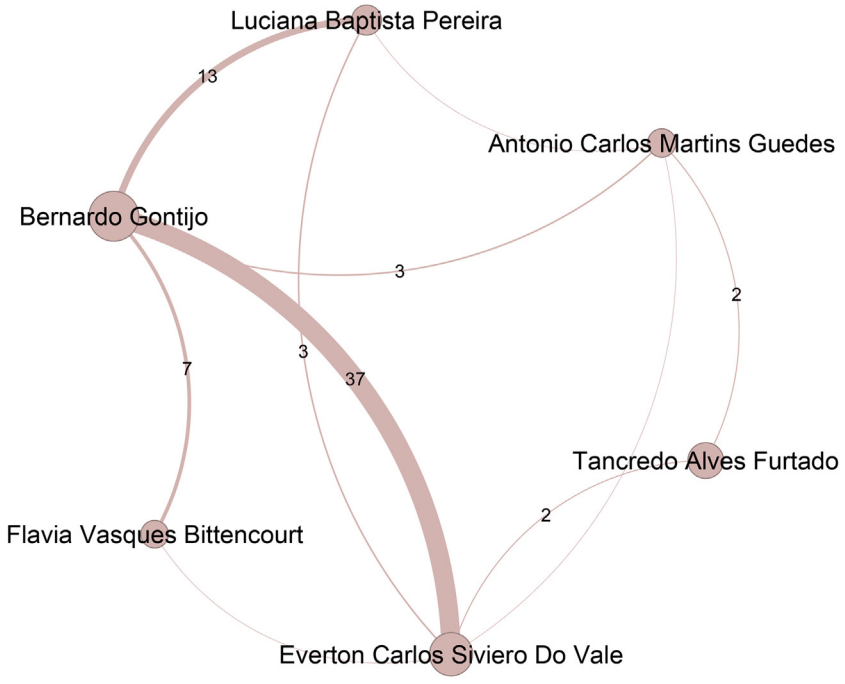

Figure 9 Top authors belonging to the eighth most extensive community, encompassing 315 authors, are mainly affiliated with the Universidade Federal de Minas Gerais.

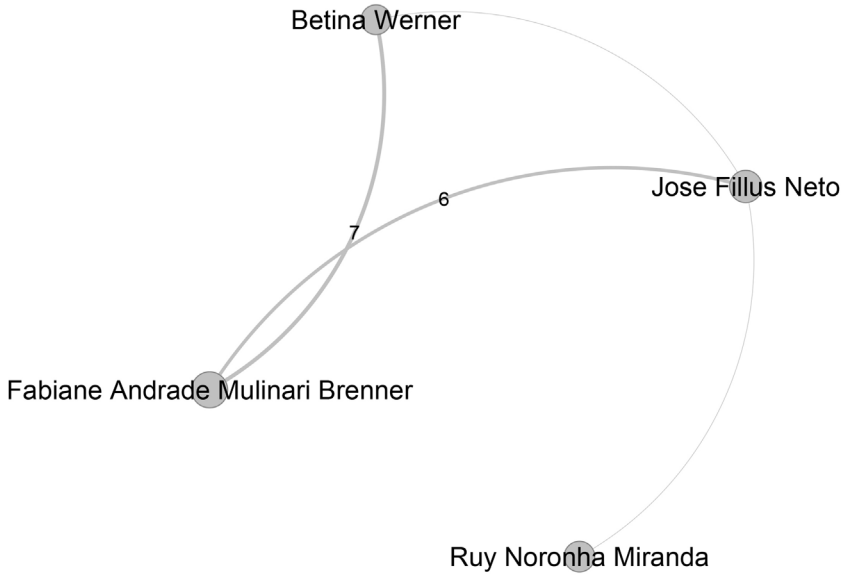

Figure 10 Top authors of the nineth largest community, which contains 297 authors, are primary affiliated with the Universidade Federal do Paraná.

and reviewers. This effort was further supported by the journal's indexing in LILACS since 1981, SciELO since 2003, and PubMed/Medline since 2009, which enhanced its visibility and accessibility to a wider audience.[1]

To evaluate the impact of editorial policy changes and initiatives aimed at enhancing the international visibility of ABD, the authors conducted a separate analysis focusing on the last 20 years (Table 2). This analysis identified one international researcher among the top 50 ranked authors: Toshiyuki Yamamoto (Pos = 29) from Japan, recognized as a notable foreign contributor. Despite this inclusion, the ABD ranking remains predominantly composed of Brazilian researchers, who continue to regard the journal as a key platform for disseminating their scientific work.

The limitations of this study include the lack of consideration for authorship order (e.g., first or last author), article type (e.g., case report, review, editorial, or full article), and article impact, as measured by citation rate. These limitations highlight gaps that should be addressed in future research by examining the influence of these factors on

Table 2 Ranking of the top 50 authors over the past 20-years (2005–2024).

Pos	Name	Pub	Deg	BC	PR
1	Helio Amante Miot	139	257	0.059630	0.004793
2	Silvio Alencar Marques	85	87	0.017733	0.002225
3	Renan Rangel Bonamigo	75	169	0.031555	0.003063
4	Hiram Larangeira de Almeida Junior	70	122	0.016010	0.002825
5	Neusa Yuriko Sakai Valente	67	114	0.013105	0.002310
6	Paulo Ricardo Criado	51	112	0.029076	0.002058
7	Bernardo Gontijo	51	62	0.018284	0.001357
8	Everton Carlos Siviero do Vale	49	35	0.003428	0.001061
9	Mariangela Esther Alencar Marques	43	79	0.003543	0.001525
10	Milvia Maria Simoes e Silva Enokihara	42	87	0.009567	0.001639
11	Antonio Pedro Mendes Schettini	42	76	0.006204	0.001569
12	Sinesio Talhari	39	71	0.015011	0.001509
13	Lucia Martins Diniz	38	53	0.008012	0.001425
14	Rosana Lazzarini	36	87	0.008908	0.001317
15	Izelda Maria Carvalho Costa	36	52	0.006545	0.001131
16	John Verrinder Veasey	35	66	0.004808	0.001182
17	Luciana Patricia Fernandes Abbade	34	64	0.007285	0.001182
18	Alexandre Carlos Gripp	32	81	0.010977	0.001210
19	Fabiane Andrade Mulinari Brenner	31	74	0.015064	0.001297
20	Juliano Vilaverde Schmitt	31	73	0.008647	0.001194
21	Carolina Talhari	30	72	0.037232	0.001278
22	Monica Santos	30	48	0.002046	0.001116
23	Luna Azulay Abulafia	29	140	0.043686	0.001701
24	Juan Manuel Pineiro Maceira	29	89	0.014520	0.001363
25	Carlos Baptista Barcaui	29	83	0.024486	0.001225
26	Adriana Maria Porro	29	69	0.008886	0.001118
27	Rute Facchini Lellis	29	62	0.003728	0.001027
28	Marilda Aparecida Milanez Morgado de Abreu	27	61	0.007407	0.001243
29	Toshiyuki Yamamoto	27	18	0.000003	0.000653
30	Maraya De Jesus Semblano Bittencourt	26	58	0.005795	0.001145
31	Fred Bernardes Filho	24	67	0.006301	0.001279
32	Tania Ferreira Cestari	23	110	0.016329	0.001378
33	Valeria Aoki	23	86	0.011628	0.001230
34	Ana Maria Roselino	23	62	0.013043	0.001070
35	Mario Cezar Pires	22	94	0.016492	0.001217
36	Zilda Najjar Prado de Oliveira	22	87	0.006758	0.001175
37	Betina Werner	22	44	0.006083	0.000779
38	Priscila Kakizaki	22	37	0.000678	0.000771
39	Magda Blessmann Weber	21	84	0.007522	0.001172
40	Maria De Fatima Guimaraes Scotelaro Alves	21	51	0.001566	0.000846
41	Luciane Donida Bartoli Miot	21	40	0.000629	0.000718
42	Anna Carolina Miola	21	38	0.000470	0.000672
43	Flavia Vasques Bittencourt	20	52	0.011120	0.000792
44	Mariana de Figueiredo Silva Hafner	20	31	0.000248	0.000625
45	Vidal Haddad Junior	20	26	0.002144	0.000466
46	Gunter Hans Filho	19	70	0.007991	0.000964
47	Sergio Henrique Hirata	19	65	0.019640	0.000893
48	Carlos D'Apparecida Santos Machado Filho	19	53	0.004576	0.000903
49	Flavia Regina Ferreira	19	32	0.003030	0.000786
50	Rodrigo Pereira Duquia	19	30	0.001435	0.000764

authors, research communities, and their respective topics of study.

Finally, following open science practices, the data generated in this work, along with high-resolution images of both the complete network and the main co-authorship communities, are available at https://github.com/sandrocamargo/publications/tree/main/abd25.

Conclusions

This study analyzed the century-long history of the ABD journal (1925–2024), encompassing 99 volumes and 6,299 articles authored by 10,829 distinct contributors. A ranking of the top 50 authors was constructed based on metrics

including publication count, collaboration degree, betweenness centrality, and PageRank. Among the findings, Rubem David Azulay was recognized as the author with the highest number of publications, while Helio Amante Miot emerged as the most influential contributor across the other metrics. Moreover, 73.64% of all authors published only once in the journal. The study also mapped the main co-authorship communities, detailing their size, key members, and institutional affiliations.

These results provide a detailed overview of the journal's historical contributions, recognizing individuals and communities that have significantly shaped its legacy over nearly a century.

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Authors' contributions

Helena Cargnelutti Grimaldi: Critical review of important intellectual content; interpretation of data; effective participation in the research guidance; final approval of the final version of the manuscript.

Sandro da Silva Camargo: The study concept and design; data collection and analysis; writing of the manuscript; final approval of the final version of the manuscript.

Conflicts of interest

None declared.

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SPECIAL ARTICLE

Latin American consensus on psoriasis severity classification☆

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KEYWORDS
Classification;
Consensus;
Delphi technique;
Patient acuity;
Psoriasis

Abstract:
Background: There are different classifications of psoriasis based on its clinical presentation, impact on quality of life, requirements for specific treatments, and other patient- or physician-reported outcomes. However, the lack of unified definitions has led to the severity of the disease being underestimated. Standardizing the classification of psoriasis will promote a better approach to the disease and facilitate care by professionals.
Objective: To present a consensus of experts in Latin America regarding the classification of psoriasis severity, based on the best available evidence and applicable to current medical practice in the region.
Methods: An independent methodological team, together with a group of clinical dermatologists representatives from different Latin American countries, developed a consensus with a modified Delphi methodology based on a systematic review of the literature. This consensus includes the classification of psoriasis, tools to define the severity of psoriasis, and other considerations in evaluating patients with psoriasis.
Results: Fifteen statements were formulated aimed at classifying the severity of cutaneous psoriasis and other forms of the disease, as well as tools to assess and define the severity of psoriasis and therapy considerations. Additionally, the consensus addresses implementation considerations.
Conclusion: The results of this consensus constitute a solid basis for a standard classification terminology for the varied clinical forms of psoriasis and their therapeutic implications. The importance of maintaining a personalized therapeutic approach, adjusted to each country's available resources and administrative realities, is highlighted.
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Introduction

Psoriasis is a chronic multisystemic inflammatory disease that affects between 0.1% and 1.5% of the world's population and is often associated with comorbidities such as psoriatic arthritis, metabolic syndrome, diabetes, cardiovascular disease, nephropathy, and bowel disease, among others.[1] The classic cutaneous presentation of psoriasis consists of scaly, localized, or widespread erythematous plaques that affect patients' quality of life and are amenable to long-term treatment.[2]

Psoriasis can be classified according to its clinical presentation, impact on patients' lives, and the need for specific treatments. Some authors propose that psoriasis could be cutaneous or systemic.[1] Other authors have described that psoriasis severity should include a combination of measures reported by the evaluator and the patient.[3] In clinical practice, the severity of psoriasis is often classified into two or three categories according to different criteria. Several tools are often used to assess the severity of psoriasis, such as the Psoriasis Area and Severity Index (PASI), the affected Body Surface Area (BSA), the Physician's Global Assessment (PGA) and other instruments that measure the severity of the disease and the effectiveness of the treatments used.[4] Other systems combine functional and psychosocial evaluations to obtain a more comprehensive assessment of the patient's condition and their degree of disease involvement.

Globally validated psoriasis severity categories are not currently recognized. Most reported classifications and definitions of disease severity and treatment response have been developed for clinical trials and have little use in clinical practice.[5] The lack of uniform definitions regarding the classification of psoriasis is primarily due to the heterogeneity of disease presentation and the variability of assessment tools. In this scenario, the severity of the disease may be underestimated, so it is necessary to specify the evaluation of psoriasis considering aspects such as the appearance of lesions in specific locations, symptoms, extent of the disease, comorbidities, indicated treatment, and impact on quality of life.[6]

In Latin America, there are guidelines[7] and consensuses[8–11] regarding the diagnosis and treatment of psoriasis, however, there is no uniform position on the classification of patients with psoriasis based on severity;

this is especially relevant in unclear situations, such as when there is a discordance between clinical scales and the impact on quality of life or disability.[4] Standardization of these concepts in psoriasis will promote better management of the disease and facilitate care by professionals.

Based on the best available evidence and medical expertise, this consensus offers definitions regarding the severity classification of psoriasis applicable to the current medical practice of dermatologists and rheumatologists in Latin America. This document considers the ethnic, social, cultural, and economic heterogeneity of the countries in the region, and its content should be adapted to the reality of each country and the individual circumstances of patients.

Methods

Consensus panel

An independent methodology team and a group of clinical dermatologists were part of the development group for this consensus. Representatives from Latin American countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Paraguay, and Peru) completed the deliberative panel. Participants were selected based on their clinical experience in the management of psoriasis. The development group defined the consensus topics and guided the search and selection of studies and the validation of the evidence included in the analysis. The entire panel discussed the recommendations, voted, and defined the final consensus statements.

Prior to consensus development, participants agreed to participate actively and provided a declaration of interest.

Evidence search

This consensus includes the classification of psoriasis, tools to define the severity of psoriasis, and other considerations when evaluating patients. A systematic literature review was conducted to identify the evidence to support the consensus analyses. The electronic databases MedLine and Embase were searched using strategies that included the following terms: ''psoriasis'' AND ''disease severity'' AND ''assessment'' OR ''classification''. All searches were performed in October 2022 and updated in April 2023. Clinical Practice Guidelines (CPGs), consensus, and evidence-based recommendation documents were included. Depending on the need for information, other types of documents, such as narrative reviews, cross-sectional studies, and expert opinion articles, were also considered if they provided accurate information on the topic of interest. Abstracts and grey literature were considered if they contained information of interest. There were language restrictions (English and Spanish). There were no publication date restrictions. In addition, the authors searched the websites of scientific societies, compilers, and developers of clinical practice guidelines.

Once identified studies were collected, two reviewers independently assessed them for inclusion according to the pre-established selection criteria. References were screened for title and abstract, and later in full text as deemed necessary, with discrepancies between reviewers resolved by consensus. The documents selected for inclusion were graded with the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool[12] and the Checklist for Analytical Cross-Sectional Studies from the Joanna Briggs Institute[13] according to the type of study. Supplementary Material 1 presents the search specifications, study selection, and quality of evidence.

Delphi methodology

The modified Delphi methodology was the basis for formal consensus. The methodology group developed a questionnaire based on the statements extracted from the selected references. The development group reviewed and validated the content of the questionnaire. The final version included 52 items related to the following topics: factors influencing psoriasis severity, classification of psoriasis, assessment tools, and other considerations.

The Delphi questionnaire was mailed to the entire panel of experts. Participants indicated their level of agreement with each statement using a 5-point Likert-type scale.[14] The methodological team collected the results of the first round, which were analyzed to determine the level of agreement. Second, the panel discussed the items for which there was no clear consensus and the controversial aspects, followed by anonymous synchronous voting. Supplementary Material 2 presents the specifications of the Delphi process. Fig. 1 illustrates the consensus development process.

Results and discussion

The evidence base for the consensus included seven clinical practice guidelines,[5,7,15–19] eight consensuses,[8,10,11,20–24] three reviews,[25–27] and two cross-sectional studies.[28,29] The evidence was analyzed and discussed as previously described, resulting in 15 guiding statements for psoriasis severity classification.

Psoriasis severity classification

Table 1 describes the psoriasis severity classification.

Cutaneous psoriasis

Cutaneous psoriasis severity categories help clinicians make treatment decisions and are often used as inclusion criteria in clinical trials. The evidence about classification is heterogeneous; some authors propose three categories (mild, moderate, and severe),[10,21,25,27] while others propose only two (mild and moderate-severe).[8,11,15] The inclusion of a ''moderate'' category is controversial. Although this category is not clearly defined, experts in practice recognize a group of patients who do not meet the criteria for maximum severity but do not respond to topical management or have greater clinical or quality-of-life impacts than those with mild disease.

Some experts believe clinical decisions do not change substantially between moderate and severe cases, while others see value in distinguishing these categories for better treatment access and description of cases. The classification in countries such as Argentina is typically divided into

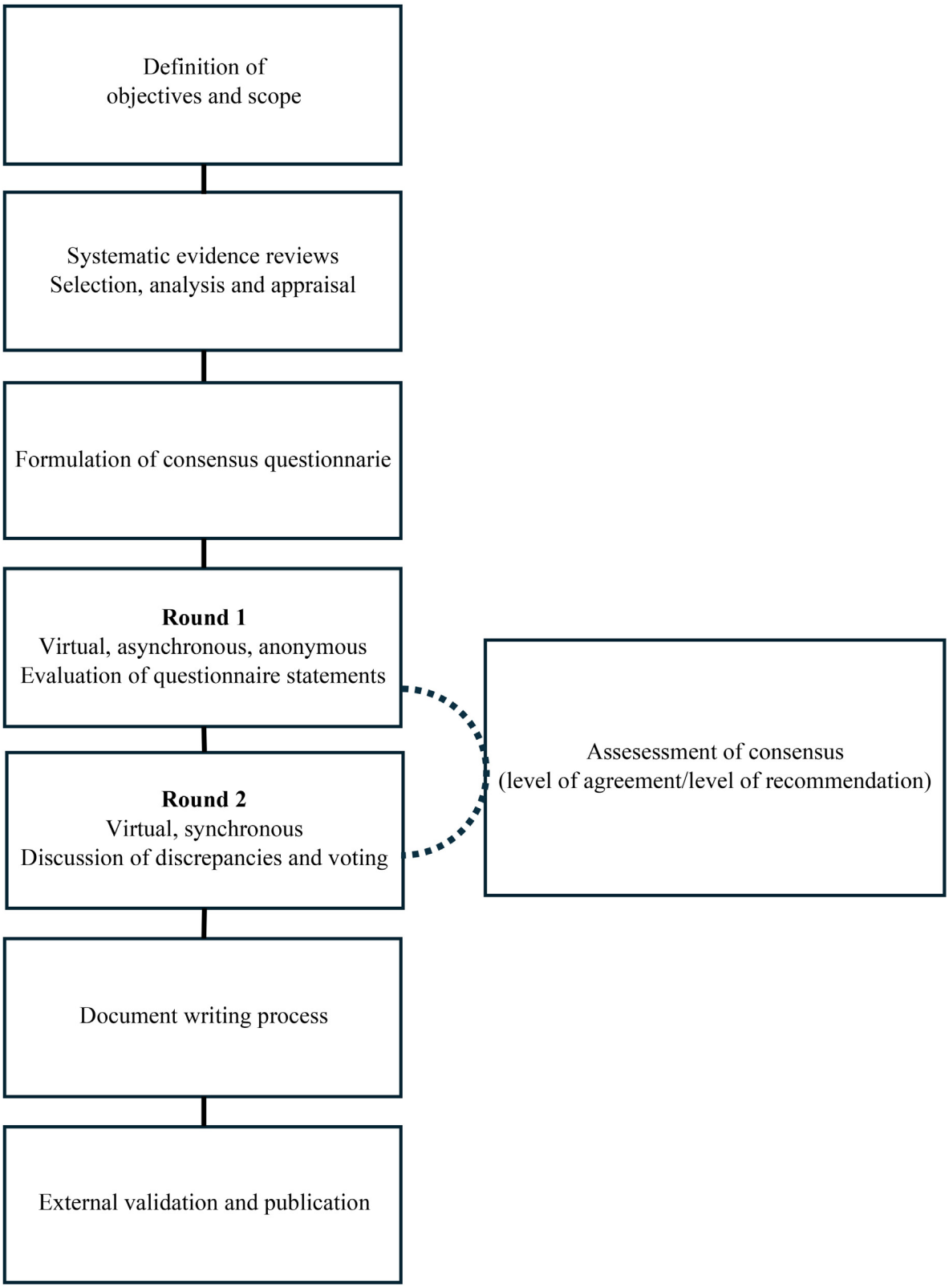

Figure 1 Consensus development on modified Delphi methodology.

mild and moderate-severe categories. In contrast, experts in Brazil and Colombia believe that specifying a ''moderate'' category could facilitate the use of more specific treatments, given the breadth of the PASI scale. While a more precise categorization could reduce barriers to accessing treatment, it might also have therapeutic implications, such

Table 1 Psoriasis severity classification.

Consensus statements on definitions of psoriasis severity	Agreement level
Cutaneous psoriasis	
Mild cutaneous psoriasis is defined as:	85%
PASI < 5 with DLQI < 5, or	
Control with topical therapy	
It does not meet moderate or severe criteria.	
Moderate cutaneous psoriasis is defined as:	64%
PASI ≥ 5 and < 10 or	
DLQI 5 ≥ 5 and < 10, or	
Lack of response to topical treatment	
It does not meet severe criteria.	
Severe cutaneous psoriasis is defined as:	
PASI ≥ 10, or	84%
DLQI ≥ 10, or	85%
Erythrodermic or pustular variants, or	79%
Involvement of special localizations (e.g. face, palms, soles, genitals, scalp and nails), or	94%
Association with psoriatic arthritis, or	93%
Requirement of biological systemic therapy.	94%
Scalp psoriasis	
Scalp psoriasis is classified as severe when it affects more than 50% of the scalp and presents at least one of the following: severe erythema, severe scaling, extensive infiltration, moderate or severe itching, evidence of hair loss with scaling, or lesions extending beyond the scalp (e.g., forehead involvement).	82%
Nail psoriasis	
Few-nail disease is defined as affecting three or fewer nails.	71%

PASI, Psoriasis Area Severity Index; DLQI, Dermatology Life Quality Index.

as imposing strict criteria for initiating treatments like methotrexate, conventional systemic therapy, or biosimilars. Additionally, differentiating between moderate and severe psoriasis could be useful for a more accurate description and analysis of cases by medical boards.

It is generally agreed that psoriasis severity classification should consider clinical evaluation (extent and inflammation) and quality of life, based on PASI and Dermatology Life Quality Index (DLQI) measurements, respectively. Involvement of special localizations (face, palms, soles, genitals, scalp, nails) and other forms (erythrodermic, and pustular variants) classify patients into the highest severity category. Comorbidities related to disease severity and treatment types (e.g., psoriatic arthritis, uveitis, inflammatory bowel disease) are also important considerations.

The classification of psoriasis is closely related to the type of treatment. Severe signs and symptoms, such as involvement of special localizations or intense pruritus, may require systemic treatment even if the PASI or BSA is < 10. A lack of response to topical treatment may lead to a moderate or severe psoriasis classification, depending on other factors of disease presentation and involvement (Table 2). Unless an individual assessment suggests otherwise, patients with moderate psoriasis should be prioritized for highly effective treatments, while for severe patients, this would be the only treatment option.

Other forms of psoriasis

According to an international consensus, nail psoriasis affecting three nails or fewer should be defined as a few-nail disease. This consensus also took into account the Nail Psoriasis Severity Index (NAPSI), defining mild nail disease as having a score of less than 20.[23] However, the complexity of the NAPSI scale and the lack of evidence for severity classification limit its widespread use and, in the opinion of the panel, do not allow the establishment of thresholds for categorizing the severity of nail disease in clinical practice.

In scalp psoriasis, the PASI may underestimate severity because it is weighted by the percentage of body surface area affected. A modified version of the PASI, known as the Psoriasis Scalp Severity Index (PSSI), has been developed for more accurate assessment, although it is not widely used in clinical practice. The Physician's Global Assessment (PGA) is commonly used in medical practice for scalp psoriasis but lacks specific definitions for each severity level.[21] Some experts have defined the severity of scalp psoriasis based on the extent of scalp involvement, as well as the presence and severity of erythema, scaling, itching, and the thickness of the lesions.[30]

The impact of scalp psoriasis on patients' well-being is increasingly recognized in evaluations. According to the panel of experts, the severity of scalp psoriasis should be assessed based on its effect on the patient. Generally, it is considered a severe condition when it affects more than half of the scalp and presents with one or more of the following: severe erythema, severe scaling, extensive infiltration, moderate to severe itching, and evidence of hair loss with flaking.

Table 2 Consensus statements on psoriasis therapy considerations.

Consensus statements on therapy considerations	Agreement level
Patients with psoriasis should be classified as topical or systemic therapy candidates.	82%
Candidates for systemic therapy are patients who meet at least one of the following criteria:	
BSA > 10%	
Involvement of special areas (face, palms, soles, genitals, scalp, or nails).	
Failure of topical therapy	88%
Evaluate associated comorbidities (psoriatic arthritis, uveitis, inflammatory bowel disease) or psoriatic arthritis to determine the treatment.	71%

BSA, Body Surface Area.

Table 3 Tools to assess and define psoriasis severity.

Consensus statements on psoriasis severity assessment	Agreement level
Assessment of the severity of psoriasis should include an objective assessment of the extent of the disease by the physician and a subjective assessment by the patient with regard to the impact on health-related quality of life.	94%
The PASI is the gold standard for assessing the clinical severity of plaque psoriasis because it is a widely validated and reproducible tool in adult patients with plaque psoriasis.	100%
The PASI should be assessed in patients with moderate to severe psoriasis as it correlates with other severity parameters such as the DLQI. Its percentage change helps assess the degree of improvement in psoriasis.	88%
Measurement of BSA can help assess the severity of psoriasis, stratify the patient's risk, and evaluate the response to treatment.	82%
The NAPSI is useful for assessing nail disease, functional or cosmetic impact, and treatment response.	71%
In specialized settings, and if practical in nonspecialized settings, it is recommended to use a validated tool to assess the impact of psoriasis on physical, psychological, and social well-being, such as the DLQI for adults or the CDLQI for children and young people.	100%
When using an assessment tool for a person with psoriasis, it is important to consider their age, disabilities, or limitations and provide support if necessary.	76%

PASI, Psoriasis Area Severity Index; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; NAPSI, Nail Psoriasis Severity Index; BSA, Body Surface Area.

Tools to assess and define psoriasis severity

Table 3 describes the tools used to assess and define the severity of psoriasis.

The severity of the physical effects of psoriasis can be measured using various clinometric tools. Evidence supports the use of scales such as PASI, PGA, and BSA. Clinical practice guidelines[7,16,17,19] and consensus[20] strongly recommend validated tools for assessing psoriasis severity.[18] PASI measures the severity of skin lesions (erythema, scaling, and induration) and the involvement in four regions (head and neck, upper limbs, trunk, and lower limbs) with scores ranging from 0 to 72.[17] It is commonly used to evaluate psoriasis severity and treatment response, with adequate correlation with other measures, but it has some disadvantages, such as complexity and low sensitivity to changes in less severe forms of psoriasis.[7]

The American Society of Dermatology recommends using the Body Surface Area (BSA) for mild psoriasis, while the PASI is recommended for moderate to severe psoriasis, either alone or in combination with PGA.[19] The PGA has a close correlation with the PASI[16] and is a validated tool for assessing physical severity with acceptable intraobserver and interobserver variability.[17] However, the panel does not consider the use of PGA relevant for classifying the severity of psoriasis. On the other hand, approximately one-third of the clinical experts in this consensus routinely reported using BSA, especially in patients with psoriasis with small plaques.

In a cross-sectional study, ten dermatologists evaluated nine psoriasis patients twice with the PASI, PGA, and BSA scales to evaluate the correlation in the classification of psoriasis.[28] Upon comparing the scales, it was found that the PGA had the highest interobserver reliability, while the BSA had the highest intraobserver reliability. The PASI showed intermediate values in terms of inter- and intraevaluation reliability. The authors concluded that none of the three assessment instruments showed an advantage over the others and recommended using several independent assessments simultaneously to evaluate the severity of psoriasis.

There are other tools that require further evaluation for assessing the severity of psoriasis, such as the Lattice System Physician's Global Assessment (LS-PGA), the Self-Administered Psoriasis Area Severity Index (SAPASI), and the Salford Psoriasis Index (SPI).[20] Another questionnaire, called REFLETS (REFlective Evaluation of Psoriasis Efficacy of Treatment and Severity), was developed to evaluate the severity of psoriasis and the efficacy of treatment based on disease evolution, symptoms, lesion characteristics, and the impact of psoriasis. It classifies the disease as mild, moderate, or severe, with moderate to high correlations with the PASI (*r*

= 0.35–0.70) and the DLQI (r = 0.36–0.82). However, as of the date of this manuscript, these results are only available in English and French.[29]

The heterogeneity of psoriasis makes it necessary to include the assessment of Health-Related Quality of Life (HRQL) and patient-reported outcome measures. The DLQI is the most frequently used, validated, and easy-to-apply tool in clinical practice.[17] This tool is recommended by the NICE group[18] to evaluate the impact of any type of psoriasis on physical, psychological, and social well-being. Other questionnaires used in research include the Short Form Health Survey (SF-36) and the Psoriasis Disability Index (PDI).[17]

In summary, the evaluation of patients with psoriasis should include measurement of both the clinical severity of the disease and its impact on the patient's quality of life. Both measures are important to ensure an appropriate approach to the disease.[17] In addition to assessing symptoms such as itching, skin pain, burning, and bleeding from skin lesions, high-impact and difficult-to-treat sites (such as the face, scalp, palms, soles, folds, nails, and genitals) should also be evaluated.[20] This comprehensive assessment should take into account any type of physical, visual or cognitive disability, language or communication difficulties, or other limitations, and should be adapted to the patient's age in order to obtain the most accurate results in estimating the severity of psoriasis.

Considerations for implementation

Psoriasis is a heterogeneous disease that requires a comprehensive assessment of aspects such as body surface involvement, erythema, infiltration and desquamation of skin lesions, localization of lesions in sensitive areas (e.g., face, nails, genitalia, palmoplantar), impact on quality of life, response to topical or systemic treatments, and comorbidities. In 2009, the Latin American Society of Psoriasis[10] established a holistic approach to assessing the severity of psoriasis, including other aspects, such as the patient's attitude towards the disease and the psychosocial impact, in addition to the usual ones. This consensus highlights the need to consider objective and subjective assessments of the burden of the disease from the perspective of the physician and the patient. Evaluations of psoriasis using tools that integrate these aspects are promising for improving the assessment of the severity of plaque psoriasis and the efficacy of treatment.

This document provides guidance on how to classify the severity of psoriasis according to current knowledge of the disease and suggests the preferred use of assessment tools that are available and widely used in the Latin American context. However, it is recognized that tools and assessment systems are constantly evolving to take into account all relevant aspects of the disease. Therefore, these recommendations should be updated in light of future knowledge of the disease, developments in practice, and the availability of resources for the assessment of psoriasis in the region.

Conclusions

The heterogeneity in the presentation of psoriasis and the variations in the severity assessment have contributed to the lack of a unified position in its classification. The medical-scientific community in Latin America has recognized this need for standardization and has been motivated to approach the subject in order to facilitate communication among health professionals and to promote a more accurate approach to psoriasis in the region. This consensus document reflects the current understanding of the disease and its various clinical manifestations based on the best available evidence for the evaluation of patients with psoriasis. This panorama of recommendations highlights the importance of maintaining a personalized therapeutic approach adapted to the available resources and administrative realities of each country. Some aspects of psoriasis severity remain controversial, and the results of this consensus provide a solid basis for establishing a standard classification for the different clinical forms of psoriasis and their therapeutic implications, which is expected to impact disease management positively.

External review and consensus update

A preliminary version of this manuscript, previously approved by the authors, was submitted for external peer review. The need to update this consensus should be evaluated in three years or sooner if necessary.

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Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.abd.2024.09.010.

Conflicts of interest

Angela Maria Londoño Garcia has been a speaker for Abbvie, Boehringer Ingelheim, Bristol, Eli Lilly, Janssen, Novartis, Pfizer.

Juan Raúl Castro Ayarza has been a speaker for AbbVie, Amgen, Eli Lilly, Janssen, Novartis, and Pfizer.

Manuel Darío Franco Franco has been a speaker for AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pharmalab, and Sanofi.

Cesar Fernando González Ardila has been a speaker for: AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, and Novartis.

Enrique Salvador Rivas Zaldivar has been a speaker for AbbVie and Novartis.

Paola Jimena Cardenas Rojas has been a speaker for AbbVie, Amgen, Elli Lilly, and Janssen.

Evelyn Giuliana Castro Vargas has been a speaker for AbbVie, Janssen and Tecnofarma.

Andrés Chavarriaga Restrepo has been a speaker for Amgen, Eli Lilly, Janssen, Novartis, Pfizer, Pharmalab.

Carolina Ivette Cortes Correa has been a speaker for Eli Lilly, Novartis, Bristol, Janssen.

Claudia de la Cruz Fernández has been a speaker or researcher for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer, Sandoz, UCB Pharma.

Cristina Mariela Echeverria has been a speaker for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, L'Oreal, Novartis, Pfizer, Sandoz, UCB Pharma.

André Vicente Esteves de Carvalho has been a speaker for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen and Novartis.

Benjamin Hidalgo Matlock has been a researcher for Cutera and Novartis.

Enrique Fabian Loaiza Sánchez has been a speaker for Janssen, Medicament, and Novartis.

Ricardo Romiti has been a speaker for AbbVie, Boehringer, Eli Lilly, Janssen, LEO Pharma, Novartis, Teva and UCB.

Fernando Valenzuela has been a speaker for AbbVie, Boehringer Ingelheim, Eli Lilly, Jannsen, LEO, and Novartis.

Other authors do not declare conflicts of interest.

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SPECIAL ARTICLE

Profile of dermatoses in extreme weather events: case series during floods in the state of Rio Grande do Sul, Brazil☆

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KEYWORDS
Climate changes;
Dermatology;
Extreme weather;
Floods;
Refugees;
Skin diseases

Abstract
Background: The skin is the first organ of the human body to be exposed to flood water, with local and possibly systemic consequences. There are no Brazilian data on dermatological diseases during recent climate catastrophes related in the country.
Objectives: To assess the demographic profile and dermatological diagnoses in people displaced from their homes and sheltered in collective housing and among rescue workers during the extreme climate crisis in the state of Rio Grande do Sul, Brazil, in 2024.
Methods: This was a cross-sectional and observational study. Information was collected in person or through records, retrospectively.
Results: Data were collected from 371 people with dermatological complaints, and a total of 423 dermatoses were diagnosed. The most prevalent dermatological diseases were dermatoparasitosis, pyoderma, and skin conditions due to trauma and/or injuries. The male gender was statistically associated with traumatic dermatoses/injuries, and females with pyoderma ($p < 0.05$).

☆ Study conducted at the Sociedade Brasileira de Dermatologia - Regional do Rio Grande do Sul, Porto Alegre, RS, Brazil.

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Conclusion: In the recent episode of extreme climate crisis in Brazil, infectious and traumatic dermatoses were the most prevalent among the affected persons. The role of dermatologists in providing care for this population, as well as guiding other colleagues in the management of skin diseases during the floods is highlighted.
Study limitations: The study was conducted in shelters, and some data were evaluated retrospectively. No complementary exams were used for diagnosis.
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Introduction

The state of Rio Grande do Sul (RS) in Brazil experienced the greatest climate crisis in its history in April and May 2024. Rainfall levels were extremely high, and institutional and civil society strategies were insufficient to prevent highly destructive scenarios – a catastrophe that caused extensive damage to the society.

The most serious and direct impact was on the lives of people affected by urban and rural flooding in certain areas of the state. By the end of May 2024, the number of recorded deaths was close to two hundred people, with many missing and more than 600,000 people displaced from their homes.[1]

Among those displaced were the ones rescued and those who moved from their homes and went to shelters – which were organized by an extensive network of private and public institutions – located in the capital city of Porto Alegre, and in other affected cities. The operation and logistics, from rescue to shelter maintenance, were carried out by volunteers and employees of public and private institutions.

Contact with flood water – from rivers, streams, lakes, lagoons, and canals – mixed with organic waste, different types of materials, and sewage, affected many displaced people and rescue workers. Moreover, the various circumstances associated with floods, such as accidents during transportation, incidents during rescues, exposure to cornered animals, landslides and collapsed structures affected many people (displaced persons and rescue workers).

Figs. 1–3 illustrate the immediate consequences of floods, affecting cities, people, flora and animals. Figs. 4 and 5 show rescue workers, the inside of a shelter and volunteer doctors.

The skin is the first organ of the human body to get in contact with flood water and skin health can be compromised, with local and eventually systemic consequences.[2]

This study, developed by volunteer dermatologists from the Brazilian Society of Dermatology – Rio Grande do Sul Sector, aimed to evaluate people affected by floods who developed dermatological diseases, providing important data for the knowledge of the scientific community and the society in general.

Method

With the aim of evaluating the profile of dermatoses among people displaced from their homes and sheltered in collective housing and among rescue workers, an observational, cross-sectional study of a series of cases was designed. Data were collected prospectively and retrospectively (files/medical records from shelters and/or volunteer doctors) by dermatologists and volunteer resident doctors, using a structured questionnaire. The research was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (CAAE 80193524900005327). The Informed Consent Form (FIC) was used for prospective cases and waived for retrospective cases.

Fig. 1 Flooding of Porto Alegre, on the Guaíba Lake – photograph by Douglas Rohers.

Fig. 2 Flooding of São Leopoldo, on the Sinos River – photograph by Douglas Garcia.

Fig. 3 Flooding, sewage and garbage in the city of Novo Hamburgo, on the local stream – photograph by Simone Feltes.

The collected variables evaluated comprised age, gender, city where the shelter was located, city where the rescue took place, type of service (in-person or online), participant condition (sheltered: persons displaced by the 2024 climate crisis in Rio Grande do Sul referring to a group of people affected by the floods; rescue worker: person who helped rescue people affected by the 2024 climate crisis in Rio Grande do Sul; sheltered and rescuer: sheltered person who became a rescue worker or rescuer who became a sheltered person) and dermatoses. These were classified as main dermatosis and other dermatoses (diagnosed during physical examination, but not the participant main disease). The dermatoses were grouped as infectious, inflammatory, traumatic/injury-related, and miscellaneous.

Operation and statistical analysis: a questionnaire prepared in Google Forms was completed by dermatologists and resident doctors, volunteers, who worked in shelters in the city of Porto Alegre and cities in the metropolitan region. The variables were entered into Excel and analyzed using a recent version of the SPSS software. The frequencies of dermatoses were evaluated in absolute numbers and percentages. The other variables were described in the univariate analysis. Associations between variables were evaluated using Pearson's chi-square test. The ANOVA method evaluated variances and the post-hoc tests (Tukey's test) were subsequently performed for distinct findings between groups of dermatoses. Significance levels were defined as $p < 0.05$.

Results

A total of 371 people were evaluated in different shelters in the city of Porto Alegre and the metropolitan region. During the study period, approximately 14,000 people were sheltered.[1]

Fig. 4 (A) Rescue worker during the floods in Rio Grande do Sul. (B) Inside of a shelter – photographs by Patrick Nascimento and Guilherme Ladwig Tejada, respectively.

Fig. 5 (A) Dermatology volunteers, with donations of medicines in the screening and reception area. (B) Dermatologists from SBD-RS united to help the homeless – photographs by Mariele Bevilaqua and SBD-RS, respectively.

Table 1 Main dermatosis (n = 371) and total dermatoses (n = 423), including the main one and those diagnosed during the physical examination, in the flooding period in Rio Grande do Sul, Brazil, 2024.

Dermatosis	Main dermatosis, n (%)	Total dermatoses, n (%)
Pediculosis	62 (16.7%)	65 (15.4%)
Trauma and injuries (including abrasions, lacerations, cuts caused by trauma)	57 (15.4%)	59 (13.9%)
Bacterial infections (impetigo, cellulitis, erysipelas, donovanosis, syphilis)	47 (12.7%)	60 (14.2%)
Other dermatoses with diagnosis	35 (9.4%)	43 (10.2%)
Superficial and deep mycoses (dermatophytosis, sporotrichosis)	34 (9.2%)	41 (9.7%)
Scabies	23 (6.2%)	26 (6.1%)
Insect bite	17 (4.6%)	20 (4.7%)
Dermatoviruses (herpes simplex and herpes zoster)	16 (4.3%)	17 (4%)
Contact dermatitis (including abrasions caused by pruritus due to flood water)	16 (4.3%)	20 (4.7%)
Unspecified dermatoses	16 (4.3%)	16 (3.9%)
Seborrheic dermatitis	11 (3%)	15 (3.5%)
Dog and cat bites	9 (2.4%)	9 (2.1%)
Pruritus without identifiable cause	8 (2.2%)	8 (1.9%)
Atopic dermatitis	5 (4%)	17 (4%)
Diaper rash	3 (0.8%)	4 (0.9%)
Onychocryptosis	2 (0.5%)	3 (0.7%)

Table 2 Main Dermatosis Groups according to gender in sheltered individuals and rescue workers during the flooding period in Rio Grande do Sul, Brazil, 2024 (n = 370).

Dermatoses	Females	Males	Total
Infectious[a]	107 (56.6%)	75 (41.4%)	182 (49.2%)
Inflammatory	26 (13.8%)	19 (10.5%)	45 (12.2%)
Trauma and wounds[a]	31 (16.4%)	52 (28.7%)	83 (22.4%)
Miscellaneous	25 (13.2%)	35 (19.3%)	60 (16.2%)
Total	189	181	370

[a] $p < 0.05$.

Age showed a normal distribution according to the Kolmogorov-Smirnov test, and the mean was 30.96 years, ranging from 0 to 83 years, with a standard deviation of 20.05 years. Among the participants, 189 (50.9%) identified themselves as females and 182 (48.8%) as males. One person (0.3%) preferred not to declare gender.

Three hundred and twenty-seven (88.1%) participants were evaluated retrospectively, through medical records, and 44 (11.9%) participants were prospectively evaluated. Of the total, 350 (94.3%) were sheltered people, 9 (2.4%) were rescue workers, and 12 (3.2%) were both sheltered and rescue workers. Care was provided in person for 362 people (97.6%) and via teleconsultation for 9 (2.4%) people.

As for the city of origin, 234 (63.1%) people were from Porto Alegre, 44 (11.9%) from cities in the metropolitan region, 3 (0.8%) from municipalities in the interior of Rio Grande do Sul, and 89 people (24%) did not have their city of origin identified.

Different types of dermatoses were diagnosed and the main dermatosis in each evaluated person was described. In addition to main dermatosis, 48 people had a second dermatosis diagnosed and three had three dermatoses. The total number of dermatoses in the 371 participants is shown in Table 1.

Dermatoses were grouped into infectious (n = 182 or 49.2%), inflammatory (n = 45 or 12.2%), traumatic/injuries (n = 83 or 22.4%) and miscellaneous/other dermatoses, varied or unspecified (n = 60 or 16.2%). Among those in the last group are ''skin lesions'' (unspecified), keloids, lupus, pemphigus, mouth ulcers, onychopathy, granulomas, skin cancer, burns, and vasculitis.

Table 2 shows the distribution of these groups according to gender (n = 370).

Figs. 6–9 show examples of the main conditions found, respectively: pediculosis, bacterial infection, injuries after trauma during rescues, and irritant dermatitis due to contact with water and debris.

Using Pearson's Chi-Square test, it was found that infectious dermatoses prevailed in females and the trauma/injury group in males ($p < 0.05$). The ANOVA analysis of variance showed that there were differences between the ages that affected the different groups of dermatoses ($p < 0.05$), and in the post-hoc tests, using the Tukey test, it was found that participants in the miscellaneous or unspecified group were older than in the three other groups, with $p < 0.05$. The mean ages among patients with infectious, inflammatory, and traumatic dermatoses were 29.4 years, 24.0 years, and 31.6 years, respectively, while those with miscellaneous or unspecified dermatoses had a mean age of 40.3 years.

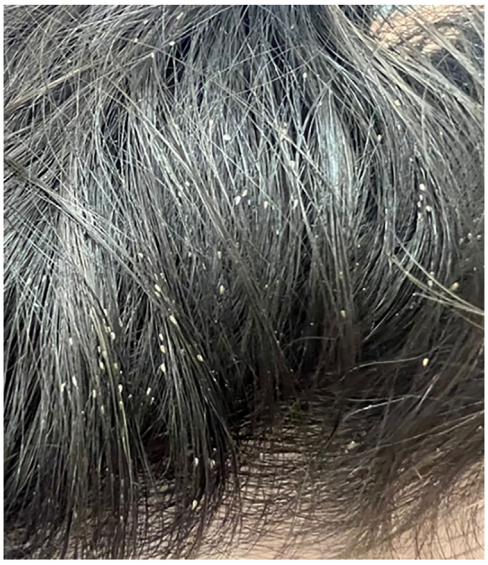

Fig. 6 Pediculosis (nits), the most often diagnosed condition in shelters.

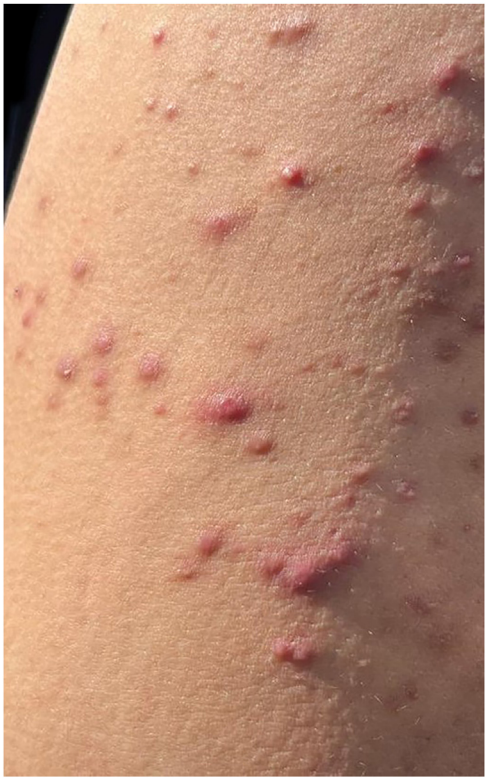

Fig. 7 Folliculitis in a rescue worker.

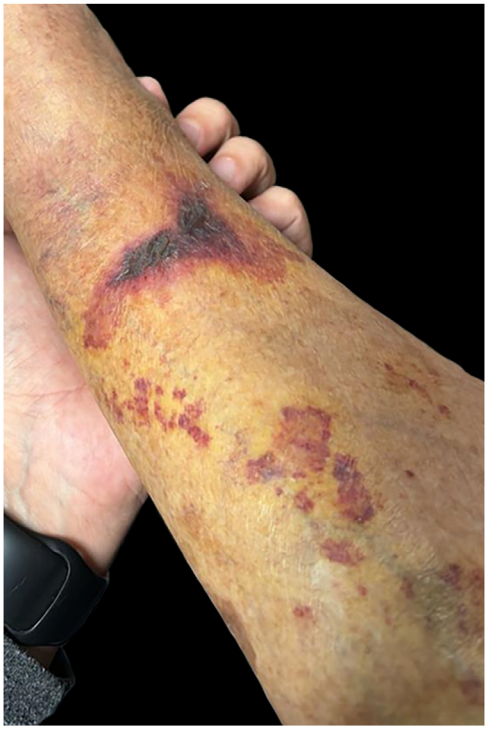

Fig. 8 Bruises from trauma, after rescue.

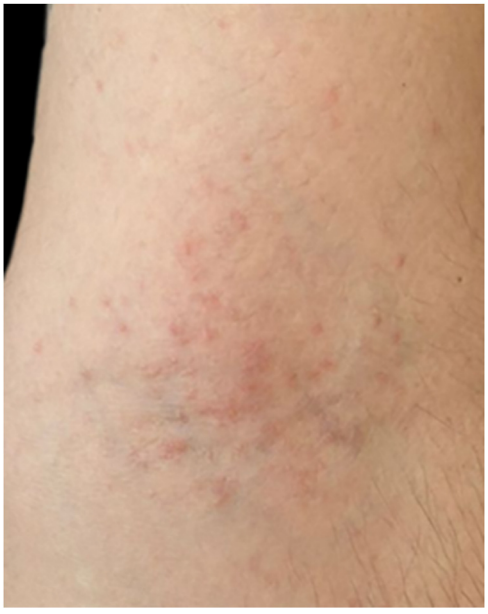

Fig. 9 Irritant dermatitis after contact with flood water.

Discussion

Floods are water overflows caused by hydrometeorological and geophysical disasters, and are the most frequent type of climate disaster (accounting for 40% of calamities) at the global level, with more than 50,000 deaths recorded in the last decade.[3]

In addition to the direct humanitarian disaster, with loss of life and the appearance of climate refugees, the consequences of floods include urban and rural destruction and economic damage hampering the restructuring of the multiple pillars of the affected societies.

The scenario of an increase in the occurrence of extreme events is set, with rising temperatures, rising sea levels, and greater rainfall – in intensity and frequency – as warned by science for decades, and it is up to all social forces in countries and global governance institutions to lead a process aimed to achieve a slowdown in these events, an urban

reconfiguration and a social and humanitarian protection network for those potentially and effectively affected.

In addition to the major global climate events of the 21st century – such as those that occurred in Bangladesh (2004), the United States of America (2005), Haiti (2010), Japan (2011), Thailand (2011), and Pakistan (2010)[3–5] – what occurred in Brazil, during the last days of April and in the month of May 2024, was recognized as the greatest climate disaster in the country. The above-average rainfall in the state of Rio Grande do Sul within a very short period of time raised the levels of important rivers and these caused serious flooding and inundation. Among the cities affected were the state capital, Porto Alegre, the cities of the metropolitan region, those in the Taquari River Valley, those bordering the Jacuí River, and those in the southern region of the state and on the coast close to Lagoa dos Patos, such as Rio Grande and Pelotas.[1]

More than two million people were affected in some way, in almost all of the cities in the state of Rio Grande do Sul; more than 600,000 people were displaced, there were more than a hundred deaths, and a large number of missing persons were recorded. Fauna and flora, road structures, residential and commercial buildings, educational and health systems, and different areas of the economy were severely affected by the extreme climate crisis in RS.[1]

In the context of floods, a series of pathogenic factors present as potentially harmful for human health. There is potential contamination of drinking water and food reservoirs, contact with waste and chemical materials, and exposure to microbial agents mainly through the respiratory and digestive systems, and through contact and breakdown of the skin-mucosal barrier. Additionally, psychological implications are very present and should be among the health conditions to be monitored.

Among the most frequently found diseases are those affecting the skin, mucous membranes, and skin appendages. In a study carried out in Pakistan, 28% of those affected by flooding had skin conditions.[7] The period between the fourth and 28th day after the disaster is the period of greatest risk for wound and trauma infection and the spread of infectious diseases. In addition to skin infections, changes caused by immersion, contact dermatitis, and exacerbation of pre-existing skin conditions are well-documented manifestations after flood disasters.[8]

Another study with firefighters who rescued the victims of the Katrina hurricane in the United States in 2005 and had contact with flood water showed that skin rashes were the most often reported symptoms among those affected, followed by respiratory and gastrointestinal symptoms.[9] Moreover, it was observed that symptoms were more frequent in those who had prolonged contact with the water and among those who had contact with the water through the nose/mouth or eyes.[9]

The fact that the skin is immediately exposed to a series of products from contaminated water, added to the difficulty of maintaining hygiene in flood conditions, facilitates the onset of skin diseases, which can be grouped into the categories of inflammatory, infectious, traumatic and miscellaneous diseases.

In the current literature on the subject, the most common dermatoses in each group are:[6,7,10–12]

- Inflammatory: Contact dermatitis, pruritus, miliaria, pruritus;
- Infectious/Infestations: Bacterial/pyoderma (impetigo, cellulitis, folliculitis, furunculosis, carbuncle, abscesses), fungal (dermatophytosis, candidiasis, deep mycoses), parasitic diseases (scabies, pediculosis, cutaneous hookworm, cutaneous leishmaniasis, amoebiasis, strongyloidiasis, filariasis, onchocerciasis, trypanosomiasis, among others), cercarial dermatitis. The etiologies vary according to local geography and infectious epidemiology;[6,7,10–12]
- Traumatic: Lacerations, cut-bruise injuries (bleeding and secondary infections as consequences);
- Miscellaneous: Reactions to mosquito, ant, and arthropod bites (which can cause local and systemic reactions), dog bite injuries (which can be infected by canine flora and/or transmit serious diseases, such as rabies), snakebites and their consequences, immersion foot syndrome, and psychodermatoses.

In addition to these groups of dermatological diseases, there are pre-existing conditions that are aggravated by the climate disaster (such as atopic dermatitis, psoriasis, urticaria/angioedema, connective tissue diseases, autoimmune bullous diseases) and those that can be induced later, due to the influence of post-disaster psychological conditions, such as vitiligo, alopecia areata, psoriasis and urticaria.[8,9]

Two dermatological conditions of greater clinical-epidemiological relevance following the floods should be highlighted:

- Inflammatory: Contact dermatitis is the most common inflammatory syndrome. The skin barrier, affected by prolonged immersion and contact with products that cause epithelial damage, allows greater permeability, and various substances come into contact with the inner skin. An acute, immediate inflammatory response is induced by the keratinocyte release of inflammatory mediators. Depending on the duration and composition of the water, the acute phase lasts for days with symptoms such as burning (more than pruritus), erythematous, vesicular, and eroded lesions. The hands and feet are the most affected areas. The possibility of superimposing infections occurs.[12]
- Skin infections/infestations: The introduction of microbial agents via the cutaneous-mucosal integument is a major concern during and after floods. Bacterial infections are most often polymicrobial. The main causes of mild or severe pyoderma are *Staphylococcus sp*, *Corynebacterium sp*, *Aeromonas sp*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus*, *Clostridium*, Burkholderia pseudomallei, Vibrio sp (flooding by seawater), *Leptospira*, *Streptococcus sp*, *Chromobacterium violaceum*, *Mycobacterium ulcerans* and other non-tuberculous mycobacteria. Clinically, there may be lesions of impetigo, cellulitis/erysipelas, abscesses, nodules, gummas and ulcerated tumors.[10,12,13]

Among fungal infections, the most prominent are those caused by dermatophytes, non-dermatophytes, yeasts, and agents of deep mycoses, such as *Fonsecaea pedrosoi*, *Blastomyces spp*, *Mucor spp*, *Rhizopus spp*, *Absidia spp*. Clinically, tinea pedis/interdigitalis/manuum/inguinum are the most common forms of presentation, as dermatophyte infections predominate.[12,13]

The overlap of agents is very common, including bacterial and fungal infections in the same site.[11–13]

Among the infestations, scabies and pediculosis stand out, both of which have their spread facilitated by the large human population in collective housing after a disaster.[10]

Scabies can cause intense pruritus and become a risk for serious bacterial infections, particularly in people who were previously immunosuppressed due to nutritional conditions, diseases, or medications. Pediculosis is cited as the most frequent infestation, affecting adults, and particularly children. As excoriations are common, it also becomes a risk for overlapping infections.[10]

After identifying dermatological diseases, it is important that therapeutic management be rapidly implemented to prevent their spread and worsening.[13]

The present study describes dermatological findings in a series of cases during the largest climate crisis in a large Brazilian region. The age profile of those sheltered and/or rescue workers was identified (mean and median age around 30 years, with a wide age range), both males and females being equally affected. A total of 371 people with dermatoses were evaluated. Among the main dermatoses present or identified on physical examination, a total of 423 dermatological diagnoses were made by the medical team. Dermatologists evaluated the patients prospectively or retrospectively, using forms/medical records, which were filled out by doctors, whether dermatologists or not. Other limitations of the study include the fact that the diagnosis was always clinical, as there was no possibility of using complementary exams and, as it was not a cohort study (longitudinal), there was no follow-up of the patients in the medium to long term (other dermatoses could have appeared within weeks or months).

Among the dermatoses identified, pediculosis, bacterial infections and/or traumatic infections/injuries stand out. After classification as inflammatory, infectious, traumatic, and miscellaneous, it was observed that infectious diseases were the most frequent, corresponding to almost half of the total.

Pediculosis – the most frequent dermatosis diagnosed in this study – certainly stood out due to the characteristics of the shelters, where very close grouping of people was extremely common. Besides scabies, it was found that more than 20% of the people were affected by some dermatoparasitosis.

Trauma and injuries resulting from floods and rescue operations were the second most prevalent condition as the main dermatosis, followed by bacterial infections. Additionally, a wide range of other dermatological diseases, many inflammatory and miscellaneous, including pre-existing ones, were observed.

Inflammatory dermatoses – much highlighted in the literature – appeared, but without much prominence. There was probably underdiagnosis in this group since the study did not cover the entire range of affected individuals and diagnoses were made based on people that sought medical assistance.

The impossibility of using complementary diagnostic resources and/or evaluation by non-specialist doctors probably contributed to the fact that a number of dermatoses included in the miscellaneous group were not diagnosed with certainty, and were listed as ''unspecified dermatoses'' (n = 16 or 3.9% of the total).

Regarding the observed associations, infectious dermatoses were more frequent in females and the trauma/injury group in males ($p < 0.05$). There is no way to be certain of the reasons for these differences, but it can be assumed that men were more intensely involved in rescue operations and that women were in contact with contaminated water for longer periods.

For decades, science has indicated that society and governments should organize actions that have an impact on the planet climate and its viability. According to Menegat R, Porto ML, Carraro CC and Fernandes LAD, there are necessary measures to empower governance in promoting global sustainability, including: a) Implementing public sector policies that promote sustainable resource management and social development, and b) Committing the private sector, through agreements and programs, to respect and support local strategies for sustainable development in areas in which they invest and operate.[14]

Children and the elderly, as well as individuals with comorbidities or immunosuppression, are at greater risk of suffering from flood-related illnesses.[8] It has also been shown that the lower-income population is more vulnerable to the effects of disasters, as are the black and Hispanic populations, usually because they live in areas that are more susceptible to the effects of water.[8] In fact, public policies to improve the general health of these populations and, especially, their housing conditions, including viable housing alternatives that reduce the occupation of high-risk areas, are of fundamental importance.

This study has unique characteristics and historical singularity: it was developed in the midst of an extreme climate crisis, reflects a large movement of volunteer dermatologists and the Brazilian Society of Dermatology, Rio Grande do Sul sector, and despite its intrinsic limitations, it can become a reference for future actions that may be necessary. As limitations, it is known that the research was carried out in shelters, with part of the data evaluated retrospectively. Moreover, complementary exams were not used in the diagnoses and it also did not include patients who required hospitalization.

Conclusion

In the largest episode of extreme climate crisis in Brazil, the floods and inundations in the state of Rio Grande do Sul in 2024, Dermatology was a very important specialty in the care of those affected, as various skin diseases occurred, mainly infectious ones (particularly pediculosis, bacterial diseases, mycoses and scabies), traumatic/wound-related and inflammatory diseases. Infectious skin diseases were more prevalent in women, while traumatic skin diseases were more prevalent in men.

The authors reinforce the role of dermatologists in this context, providing care to those affected, as well as guiding other colleagues in the management of skin diseases occurring during the floods.

Authors' contributions

Analupe Webber: Actively contributed to data collection and approved the final version of the manuscript.

Cíntia Cristina Pessin: Actively contributed to data collection and approved the final version of the manuscript.

Gabriela Agne Magnus: Actively contributed to data collection and approved the final version of the manuscript.

Guilherme Ladwig Tejada: Actively contributed to data collection and approved the final version of the manuscript.

Isadora da Rosa Hoefel: Actively contributed to data collection and approved the final version of the manuscript.

Jacqueline Sarmento Fernandes: Actively contributed to data collection and approved the final version of the manuscript.

Juliana Catucci Boza: Actively contributed to data collection and approved the final version of the manuscript.

Juliano Peruzzo: Actively contributed to data collection and approved the final version of the manuscript.

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Rosemarie Mazzuco: Actively contributed to data collection and approved the final version of the manuscript.

Taciana Dal'Forno Dini: Actively contributed to data collection and approved the final version of the manuscript.

Vanessa Santos Cunha: Actively contributed to data collection and approved the final version of the manuscript.

Veronica Hamann Aita: Actively contributed to data collection and approved the final version of the manuscript.

Renan Rangel Bonamigo: Actively contributed to data collection and approved the final version of the manuscript.

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Conflicts of interest

None declared.

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LETTER - RESEARCH

First case of *Trichophyton indotineae* in Brazil: clinical and mycological criteria and genetic identification of terbinafine resistance☆

Dear Editor,

Terbinafine-resistant dermatophytes are currently a global health problem, particularly *Trichophyton indotineae*. Terbinafine, a potent antifungal agent against dermatophytes, inhibits the enzyme squalene epoxidase (SQLE), restricting fungal growth by interfering with ergosterol biosynthesis; point mutations in the *SQLE* genes are the main cause of antifungal resistance.[1] *T. indotineae*, formerly known as *Trichophyton mentagrophytes* variety VIII, frequently shows mutations in the *SQLE* gene.[2,3] The present report describes the first case of a patient diagnosed in Brazil with dermatophytosis caused by terbinafine-resistant *T. indotineae*.

A 40-year-old male individual, without comorbidities, originally from Brazil and living in London, reported pruritic erythematous-desquamative lesions on the lower limbs and buttocks that began in January 2024 (Fig. 1). He reported frequent short trips during the second half of 2023; to Austria, Slovakia, Hungary, and Poland in August, and to Scotland and Turkey in November and December. He sought dermatological care in Piracicaba (state of São Paulo, Brazil), where direct mycological examination revealed the presence of hyaline septate hyphae, and the culture using Sabouraud agar and Mycosel® showed growth of *T. mentagrophytes*. He was diagnosed with dermatophytosis and in March 2024 he was prescribed 500 mg/day of terbinafine for 14 days.

Although there was no clinical improvement, the patient returned to London; in May 2024 he came back presenting lesions in the same locations (Fig. 2). On this occasion,

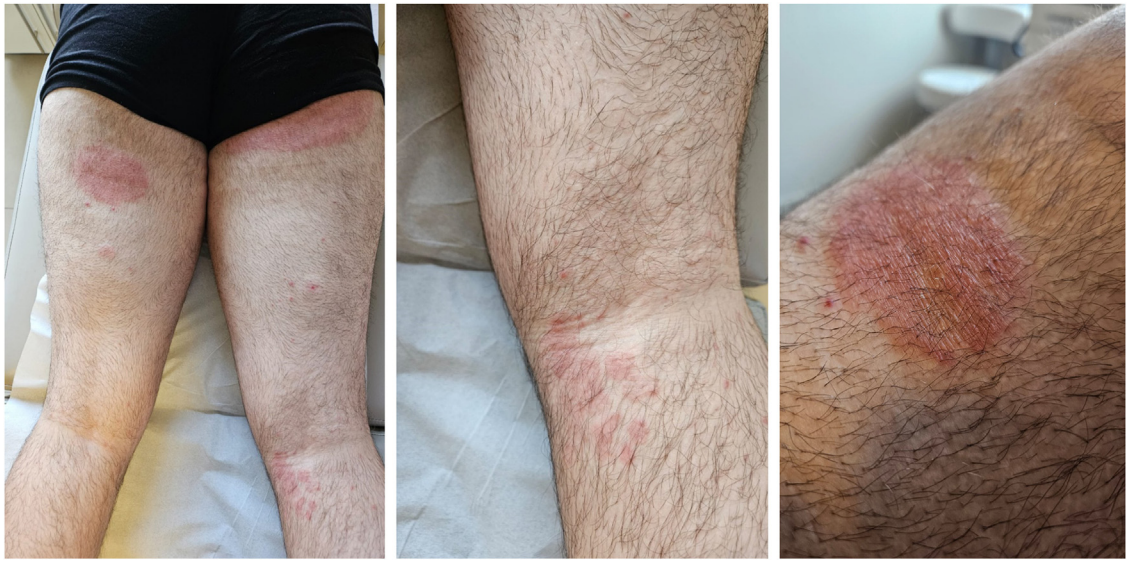

Figure 1 Clinical aspect of dermatophytosis lesions caused by *Trichophyton indotineae* affecting the posterior region of the lower limbs.

☆ Study conducted at the Dermatology Clinic, Hospital da Santa Casa de São Paulo, São Paulo, SP, Brazil.

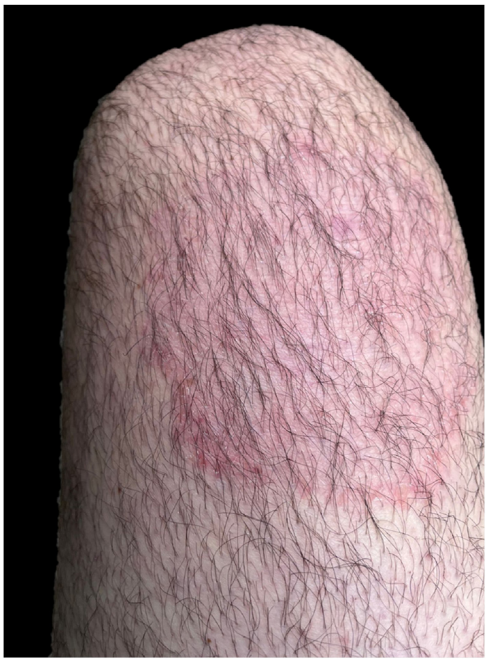

Figure 2 Clinical aspect of dermatophytosis recurrence caused by *Trichophyton indotineae* affecting the anterior surface of the right thigh.

itraconazole 200 mg/day was prescribed for 14 days, with complete clinical remission. However, the patient developed recurrence after treatment was discontinued, and fluconazole 150 mg/day was prescribed for seven days, which proved ineffective. With a new cycle of treatment using itraconazole at the same dosage, the patient showed the same result: good initial response followed by recurrence four days after treatment was discontinued. A skin scraping specimen was collected for new mycological analysis, and treatment with itraconazole was prescribed again. The condition improved, the patient returned to England and once again was lost to dermatological follow-up. In this scenario of (i) disseminated dermatophytosis refractory to terbinafine but susceptible to itraconazole, (ii) microbiological evidence suggestive of the *T. mentagrophytes*/*T. interdigitale* species complex, and (iii) history of frequent international travel, it was strongly suggested that this was a case of *T. indotineae*. This suspicion was confirmed using the material from the second collection, identifying the isolate as *T. indotineae* resistant to terbinafine and fluconazole through analysis of mycological exams (Fig. 3) associated with DNA sequencing of the internal transcribed spacer (ITS) region of ribosomal DNA. The *SQLE* gene was also amplified and sequenced using the described primers.[4] The sequences were deposited in GenBank under access numbers PQ634380 (*T. indotineae*) and PQ655447 (*SQLE*). The sequences used are shown in Fig. 4. In addition, an antifungal susceptibility test for terbinafine, fluconazole, and itraconazole was performed using the *in vitro* broth microdilution reference method described by EUCAST (E.DEF 9.4).

The assessed isolate is resistant to terbinafine and fluconazole, with minimum inhibitory concentration (MIC) values of $\geq$16 μg/mL (upper limit value) and 8 μg/mL, respectively; and susceptible to itraconazole (MIC value of 0.064 μg/mL). Sequencing results revealed two terbinafine resistance mutations ($Phe^{397}Leu$ and $Thr^{414}His$).

In the last decade, *T. indotineae* has caused large outbreaks of severe and difficult-to-treat infections worldwide. Lesions may be atypical with multiple morphologies, including concentric erythematous, desquamative, papulosquamous and pustular plaques, in addition to conditions modified by the use of topical corticosteroids.[5]

Cases of terbinafine-resistant *T. indotineae* described are often introduced by immigrants from endemic countries.[5,6] The high rate of inter-human transmission is a strong contributor to its spread, where familial cases account for about 50% of patients, and sharing of fomites is a common denominator.[5–8] However, few cases have been reported to date, mainly due to misidentification and underreporting.[6] This may be the scenario in Brazil, where terbinafine-resistant dermatophytosis may be overlooked, since the etiological identification of dermatophytes remains a challenge, as DNA sequencing is not routinely used in the diagnosis of superficial mycoses.

The emergence of terbinafine-resistant *T. indotineae* is noteworthy, considering its frequency of up to 75% compared to 44% for *T. rubrum*.[9,10] This phenomenon may be

Figure 3 Mycological examinations of *Trichophyton indotineae*. (A) Direct microscopic examination (with 10% KOH) under optical microscopy (×400) showing branched septate hyaline hyphae and arthroconidia. (B) Macromorphology of fungal culture in Sabouraud medium showing velvety white front and light yellow pigment on the back. (C) Micromorphology under optical microscopy (×400), stained with lactophenol blue, showing the presence of numerous pyriform and clavate microconidia and septate, spindle-shaped macroconidia.

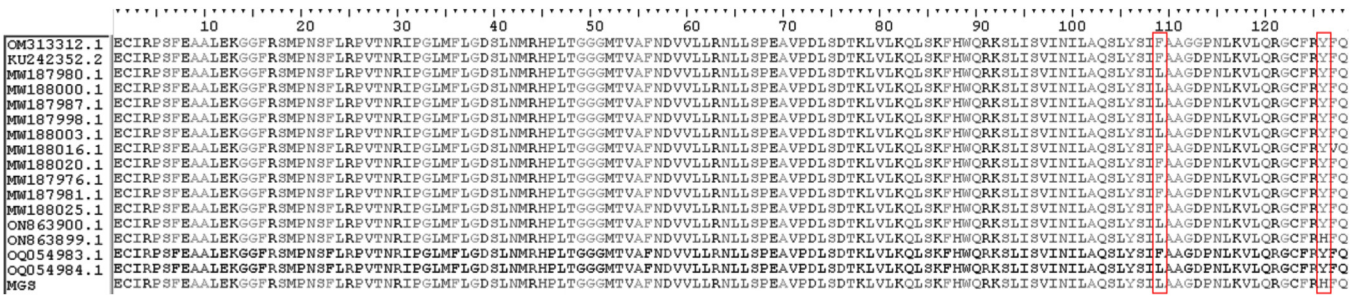

Figure 4 *SQLE* gene alignment under CLUSTAL multiple sequence alignment in BioEdit. The amino acid sequences of *SQLE* from the *T. indotineae* isolate IMT-1778 (MGS) were compared with the reference sequence of the *T. mentagrophytes* strain TIMM2789 (GenBank acc. number KU242352.) and the *T. interdigitale* isolate DK-Tinterdig-WT (GenBank acc. number OM313312.1), as well as *SQLE* sequences of terbinafine-resistant *T. indotineae* strains (GenBank acc. numbers MW187976, MW187980, MW187981, MW187987, MW187998, MW188000, MW188003, MW188016, MW188020, MW188025, ON863900, ON863899, OQ054983 and OQ054984). The amino acid substitutions that were found to be different in IMT-1778-MGS isolate are depicted, and their positions are shown in red boxes.

linked to (i) inappropriate use of antibiotics, antifungals, and corticosteroids; (ii) climate change and indiscriminate use of pesticides; and (iii) the return of intense migratory movements seen after the COVID-19 pandemic.[7,8]

In summary, the present case is the first report of dermatophytosis caused by *T. indotineae* in Brazil, with the typical evolution of therapeutic resistance to several antifungals and terbinafine resistance associated with mutations in the *SQLE* gene. Phenotypic and genotypic characterizations were essential for adequate diagnosis and therapeutic choice, but terbinafine resistance complicates treatment options and highlights the need for better surveillance, prevention strategies, and alternative therapeutic approaches.

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None declared.

Authors' contributions

John Verrinder Veasey: Design and planning of the study; collection of data, or analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Renata Diniz Jacques Gonçalves: Collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; approval of the final version of the manuscript.

Guilherme Camargo Julio Valinoto: Approval of the final version of the manuscript; critical review of the literature.

Gustavo de Sá Menezes Carvalho: Approval of the final version of the manuscript; critical review of the literature.

Giovanna Azevedo Celestrino: Collection of data, or analysis and interpretation of data; critical review of the literature.

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Gil Benard: Collection of data, or analysis and interpretation of data; critical review of the literature.

Maria Gloria Teixeira Sousa: Design and planning of the study; collection of data, or analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; effective participation in research orientation; critical review of the literature; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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In vitro characterization of biofilm produced by *Fusarium oxysporum*, an onychomycosis agent[☆]

Dear Editor,

Onychomycosis caused by Non-Dermatophyte fungi (NDMs), such as *Fusarium* spp., is more prevalent than previously thought, especially in warmer climates.[1] Furthermore, onychomycosis has currently been attributed to fungi organizing themselves into a biofilm form.[2] Biofilm is a complex microbial community, highly adhered to the nail and surrounded by a matrix that provides protection and antifungal resistance.[2,3]

The research group has been studying the genus *Fusarium* spp. as an agent of onychomycosis in immunocompetent hosts. The authors reported its high prevalence in the studied region, established clinical and laboratory criteria for this genus as a causal agent of onychomycosis, and determined the susceptibility profile to the systemic antifungals most commonly used in Brazil.[4] Later, the authors proved that *Fusarium* spp. uses nail keratin as a single source of nutrients[5] and began studies on the etiopathogenesis of fusarial onychomycosis based on an *ex vivo* model using sterile human nail fragments.[3]

More recently the authors reported, for the first time, that *Fusarium oxysporum* is able to form biofilm on the human nail as the only nutritional source.[6,7] Also, the authors describe the volatile organic molecule 2-Ethyl-1-Hexanol (2 EH) as a quorum-sensing component capable of modulating such biofilm.[8] These findings were relevant to confirm the etiopathogenesis of fusarial onychomycosis. However, it did not reveal the proper characteristics of the biofilm formed under nutritional support. Thus, the current study aimed to characterize the *in vitro* biofilm formation of *F. oxysporum*, evaluating its natural ability, during 7-days with controlled nutrient availability.

This study was conducted with *F. oxysporum* CMRP2925 isolated from a previously described onychomycosis case.[4] The isolate was reactivated to confirm its purity and identification, before assays, and was cultured on Sabouraud Dextrose Agar (SDA; DifcoTM, MI, USA) for 7-days at 25 °C. Biofilms were prepared according to Galletti et al.,[9] with some modifications. A suspension containing 1×10^7 conidia mL^{-1} was prepared in RPMI Medium 1640 (Gibco, NY, USA), with L-glutamine, sodium bicarbonate, 0.165 M 3-(N-morpholino) propanesulfonic acid (pH 7.2), and 2% glucose. This suspension was placed into 96-well flat-bottomed microtitration plates and incubated at 35 °C in a shaker at 110 rev min^{-1}, for 7-days. Every 24 h, the culture medium was renewed by removing 100 μL of old broth and adding the same volume of fresh RPMI. During the seven days, biofilms were evaluated under different aspects, as previously described.[6,9] Briefly, cell viability was assessed by counting Colony Forming Units (CFU), quantification of total biomass by Crystal Violet, metabolic activity by the reduction assay of tetrazolium salt, 2,3-(2-methoxy-4-nitro-5-sulphophenyl)-5-([phenylamino]carbonyl)-2H Tetrazolium hydroxide (XTT), characterization of the Extracellular Matrix (ECM), and visualization of biofilm structure by Scanning Electron Microscopy (SEM).

[☆] Study conducted at the Universidade Estadual de Maringá, Maringá, PR, Brazil.

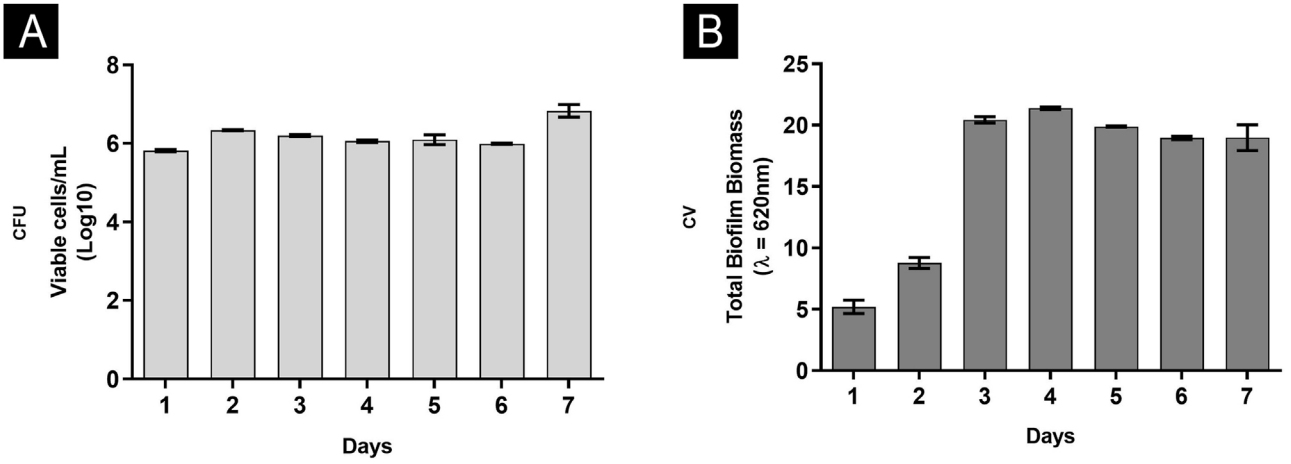

Fig. 1 Characterization of biofilm produced by *F. oxysporum* on flat-bottomed polystyrene plates from one to seven days, in RPMI medium. (A) Number of viable cells by counting Colony-Forming Units (CFU); (B) Total biomass by Crystal Violet staining (CV).

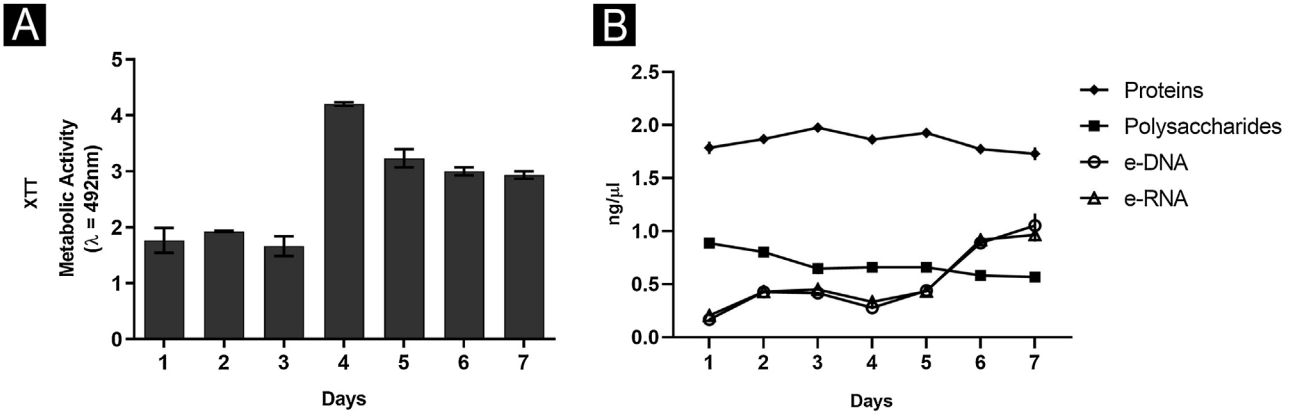

Fig. 2 Characterization of biofilm produced by *F. oxysporum* on flat-bottomed polystyrene plates from one to seven days, in RPMI medium. (A) Metabolic activity by XTT reduction; (B) Quantification of Extracellular Matrix (ECM): proteins, polysaccharides, extracellular DNA and RNA.

Overall, the biofilm's characteristics were similar, drawing a parallel between greater nutritional support with RPMI and nails only.[6] In both situations, it was possible to show that the third and fourth days were critical. In rich medium and neutral pH, the number of CFU remained constant at all times (Fig. 1A), since the first day, with an increase in metabolic activity on the third day, stabilizing from this moment. A similar profile was found for proteins and nucleic acids. Interestingly, polysaccharides were significantly consumed until the third day, continuing to decline gradually until the seventh day. On the other hand, using the nail as a nutritional source had observed an increase in CFU until the third day, a high metabolic activity only on the fourth day, while the increase in proteins and carbohydrates occurred late, corroborating the results of nucleic acids.[6] These differences can be attributed to the availability of nutrients, with daily renewal of the RPMI medium (food at will), and the fact that in the nail (restricted food), the fungus itself needed a period of adaptation.

In addition, a progressive increase in the amount of biomass was observed (Fig. 1B) between the first and third day, followed by stability, which seems to be associated with the consumption of polysaccharides (Fig. 2), a fundamental component during the development and maintenance of the biofilm. Taking into account that the CFU remained stable, this increase was attributed to the large production of ECM, in a rich environment. The increase in metabolic activity (Fig. 2) is reflected in protein and nucleic acid synthesis, mainly eRNA. Protein production appears to be crucial in the process of biofilm formation and support of the entire system.[6,10] This idea is reinforced by the high levels of XTT and eDNA, from the fourth day onwards, since this nucleic acid is needed in activities that demand cellular energy, such as the construction of a mature biofilm.[10] The biofilm structure begins by forming a cell monolayer and within seven days the highly complex three-dimensional structure was observed (Fig. 3A and B).

Thus, it is logical to assume that the ability of *F. oxysporum* to produce biofilm is intrinsic. The nutritional support seems just to facilitate the first hours of its formation, in addition to favoring the production of a greater amount of biochemical components associated with the maturation and stability of the biofilm. Therefore, the experience draws attention to the natural abilities of this fungus, pre-

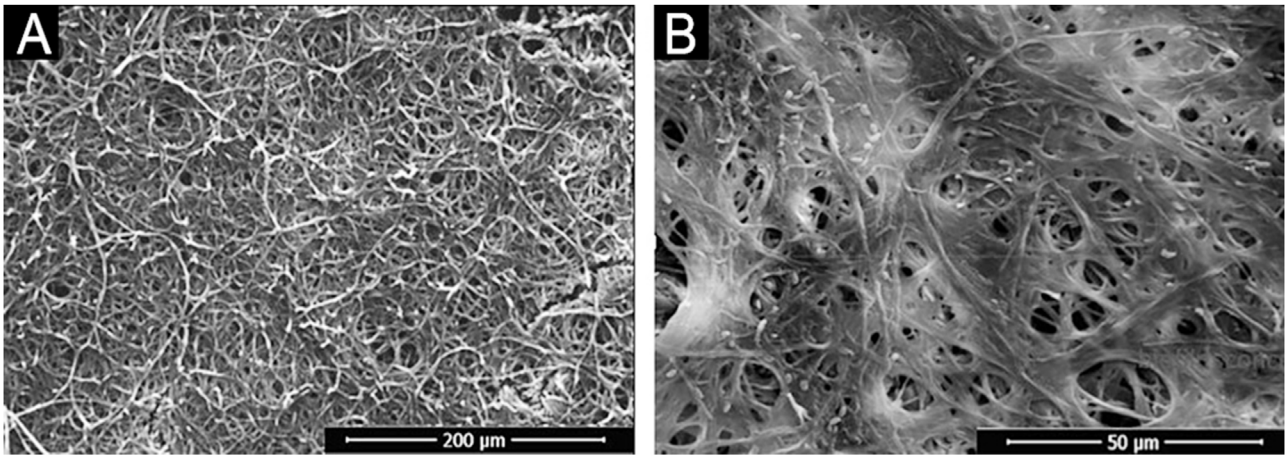

Fig. 3 SEM illustration of four-day *F. oxysporum* biofilm structure. (A) Highlighting the structural organization of the biofilm, the intertwining and compaction of the hyphae (500×); (B) Higher magnification, showing the extracellular matrix produced (2000×).

viously restricted to the environmental, agricultural, and animal interest. Probably, the natural selection induced by pesticides facilitated its adaptation to human tissues. The authors were able to show its virulence potential (here the efficiency in producing biofilm) is maintained regardless of the addition of nutritional support. This behavior therefore allows us to consider the genus *Fusarium* spp. as a primary pathogen of interest in dermatology.

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Authors' contributions

Terezinha Inez Estivalet Svidzinski: Came up with the research idea, planned the experiments, and proofread them.

Isabella Letícia Esteves Barros: Came up with the research idea and planned the experiments; Performed the experiments and analyzed the data; Wrote the manuscript.

Flávia Franco Veiga: Performed the experiments and analyzed the data.

Conflicts of interest

None declared.

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Latent tuberculosis infection in patients with psoriasis using immunobiologicals: an observational study☆

Dear Editor,

Immunobiologicals are an increasingly important therapy in the context of inflammatory diseases, mainly in dermatology, with numerous approved medications.[1,2] However, the use of these agents is associated with immunosuppressant effects and, consequently, increases the risk of reactivation of latent infections, such as tuberculosis (TB).[2]

Recent guidelines recommend carrying out TB screening before starting treatment with any immunobiological agent, using the tuberculin skin test (TST) or interferon gama release assay (IGRA), as well as being repeated annually in high-risk patients. For patients who are not considered at high risk, this screening is particularly important for those receiving anti-tumor necrosis factor (TNF) agents.[3] Despite the recommendation, this is not done frequently in practice, so the objective of the present study was to evaluate the prevalence of TB infection (assessed via TST) in patients receiving immunobiological therapy for psoriasis.

This study was carried out at the Regional Hospital of Presidente Prudente, São Paulo, Brazil, and was started only after the project was approved by the Research Ethics Committee of the University of West Paulista (Protocol: 65581122.0.0000.5515 – December 18, 2023) and only those who signed an informed consent form were enrolled. Patients aged 18 years or older who were diagnosed with psoriasis, who were receiving immunobiological agents for at least 6 months, and who had undergone TST before the start of treatment were included. Patients with immunosuppressive diseases or a history of previous TB were excluded.

The TST result was considered negative when there was no induration formation or if it was smaller than 5 mm. The presence of an induration with a diameter greater than or equal to 5 mm when the previous TST was zero or an increase of 10 mm or more from the value of the previous TST, if it was positive, was considered to indicate a positive result. These values were used on the basis of the guidelines of the Brazilian Ministry of Health.[4,5] Although IGRA is a test with greater specificity in diagnosing latent tuberculosis infection (LTBI), it has a high cost and is currently available in Brazil through the Unified Health System (SUS) only for certain selected conditions.[6]

A total of 85 patients with psoriasis were evaluated and the immunobiologicals used were anti-Interleukin (IL) agents (77.6%), with 25 patients using ustekinumab, 30 using secukinumab and 11 using risankizumab, and anti-TNF agents (22.4%), with 18 patients using adalimumab and 1 patient using etanercept. In 46 patients (63%) there was concomitant use of methotrexate. Table 1 presents demographic and clinical characteristics of psoriasis patients. Table 2 presents the data on the characteristics of the patients with positive results for the second TST. No statistically significant associations were observed for any of the characteristics evaluated.

The second TST was positive, with a diagnosis of LTBI being made in 10 patients (11.7%), of whom 9 used an anti-IL agent (5 secukinumab, 3 ustekinumab, and 1 risankizumab) and only 1 patient used an anti-TNF agent (adalimumab). Despite the higher prevalence of LTBI in patients using anti-ILs, there was no statistical significance, probably because the vast majority of patients included in the study were using anti-ILs. This result is similar to a study also carried out in Brazil with rheumatological patients using anti-TNF, where the TST became positive in 12.3% of patients.[7]

Of the 10 patients who were positive on the second TST, 8 were negative on the first TST, suggesting that they may have acquired the infection while using immunobiological agents. This is probably due to the fact that the region where the study was carried out has a high prevalence rate of TB. Among the 9 positive patients who used anti-ILs, 4 had previously used an anti-TNF agent (1 infliximab and 3 adalimumab), which makes it impossible to infer which medication the positivity would be implicated in or whether it occurred due to the sum of the effects of the two therapies. It is important to highlight that none of the patients developed active TB.

The tuberculin skin test has certain limitations and may present false-positive results due to BCG vaccination and exposure to nontuberculous mycobacteria. The effects of BCG vaccination on TST results are smaller after 15 years. Therefore, a strong positive test, with an induration equal to or greater than 15 mm, has a greater chance of indicating TB infection than occurring as a result of the vaccine.[8] As the BCG vaccine in Brazil is administered in the first year of life and the patients included in this study were over 18 years old, TST observed positivity has to be understood as a real latent TB infection. Furthermore, most patients had results greater than 15 mm, which also strengthened that the test positivity was due to real infection. False negatives can also occur due to problems with the reagent, inaccurate administration or interpretation of the test, or tuberculin anergy in children and immunocompromised patients, including those who used methotrexate.[5] However, these possibilities were considered remote, as the PPD kits were used within their

☆ Study conducted at the Hospital Regional de Presidente Prudente, Universidade do Oeste Paulista, Department of Dermatology, Presidente Prudente, SP, Brazil.

Table 1 Demographic and clinical characteristics of psoriasis patients using immunobiologicals.

Characteristics	Options	n (%)
Sex	Male	44 (51.8%)
	Female	41 (48.2%)
Age	Minimum	25
	Maximum	86
	Mean ± standard deviation	54.2 ± 14.1
Skin color	White	53 (67.1%)
	Brown	21 (26.6%)
	Black	4 (5.1%)
	Yellow	1 (1.3%)
Time of psoriasis diagnosis in years	Minimum	3
	Maximum	43
	Median (IIQ)	9 (5.7–12.0)
Total time of use of immunobiologicals in months	Minimum	11
	Maximum	170
	Median (IIQ)	42 (26–60)
Immunobiological in use	anti-IL	66 (77.6%)
	anti-TNF	19 (22.4%)
Concomitant use of methotrexate	Yes	46 (63.0%)
	No	39 (37.0%)
Previous use of anti-TNF	Yes	32 (37.6%)
	No	53 (62.4%)
First TST	Negative	74 (87.1%)
	Positive	11 (12.9%)
2nd TST was positive or increased > 10 mm	Yes	10 (11.8%)
	No	75 (88.2%)
Time elapsed between TSTs in months	Minimum	9
	Maximum	156

TST, Tuberculin Skin Test; IIQ, Interquartile Range.
Note: Values presented in the form of simple frequencies and percentages for categorical variables, and for quantitative variables as mean ± standard deviation for those that presented normality and median (IIQ) for those that did not present normality. Percentages and summary measures were calculated for the total valid responses for each variable.

validity period and kept in a suitable environment, the test was carried out by the same trained professional, and the only cause of immunosuppression in these patients was the previous or current use of methotrexate and immunobiologicals.

A significant limitation of this study is that it was carried out in a single institution and with a small sample. Other limitations are that some patients concomitantly used methotrexate or previously used anti-TNF agents, all of which may influence the LTBI outcome.

In conclusion, we demonstrated the development of LTBI in an important proportion of patients receiving immunobiologicals. Furthermore, no patient developed active TB, which may demonstrate the possible safety of this group of immunobiologicals. We emphasize the need for periodic assessment of TB during immunobiological treatment, especially in endemic countries, such as those in Latin America, to carry out early detection and avoid active disease.

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Authors' contributions

Mariana Baptista Angeluci: Design and planning of the study; collection, analysis and interpretation of data; drafting and editing of the manuscript; critical review of the literature; approval of the final version of the manuscript.

Marilda Aparecida Milanez Morgado de Abreu: Design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; approval of the final version of the manuscript.

Ana Cláudia Cavalcante Esposito Lemos: Design and planning of the study; effective participation in research orientation; approval of the final version of the manuscript.

Eduardo Vinicius Mendes Roncada: Collection of data; effective participation in research orientation; approval of the final version of the manuscript.

Cristhiana Kise Saito: Analysis and interpretation of data; drafting and editing of the manuscript; approval of the final version of the manuscript.

Felipe Puga Barbosa: Collection of data; statistical analysis; approval of the final version of the manuscript.

Table 2 Association between the positive result of the 2nd tuberculin skin test or an increase greater than 10 mm with the demographic and clinical characteristics of psoriasis patients using immunobiologicals.

Characteristics		2nd TST positive or increased > 10 mm		p-value
		Yes	No	
Sex	Male	5 (50.0%)	39 (52.0%)	0.905
	Female	5 (50.0%)	36 (48.0%)	
Age		54.3 ± 16.1	54.2 ± 13.9	0.986
Skin color	White	6 (75.0%)	47 (66.2%)	1.0
	Brown	2 (25.0%)	19 (26.8%)	
	Black	0 (0.0%)	4 (5.6%)	
	Yellow	0 (0.0%)	1 (1.4%)	
Time of psoriasis diagnosis in years		8.5 (6.2–13.7)	9.5 (5.0–12.0)	0.629
Total time of use of immunobiologicals in months		26 (22.7–50.0)	44 (30.5–60.0)	0.238
Immunobiological in use	anti-IL	9 (90.0%)	57 (76.0%)	0.445
	anti-TNF	1 (10.0%)	18 (24.0%)	
Concomitant use of methotrexate	Yes	5 (50.0%)	41 (65.1%)	0.359
	No	5 (50.0%)	22 (34.9%)	
Previous use of anti-TNF	Yes	4 (40.0%)	28 (37.3%)	1.0
	No	6 (60.0%)	47 (62.7%)	
First TST	Negative	8 (80.0%)	66 (88.0%)	0.611
	Positive	2 (20.0%)	9 (12.0%)	
Time elapsed between TSTs in months		27.5 (26.0–47.2)	41 (21.0–55.5)	0.843

TST, Tuberculin Skin Test.
Note: Values presented as Mean ± Standard Deviation for the age variable, median (IIQ) for the other quantitative characteristics, and simple frequencies (%) for the categorical variables. P-values referring to the Chi-Square or Fisher's exact test (when appropriate) for categorical variables, the Mann-Whitney test for comparison between medians, and T-Student test for age.

Conflicts of interest

None declared.

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Mid-term effectiveness, safety, and potential predictors of response of upadacitinib in patients with moderate-to-severe atopic dermatitis: a multicenter observational retrospective study☆

Dear Editor,

The treatment of atopic dermatitis (AD) still presents a therapeutic challenge. The recent approval of targeted therapies has opened new pathways for treatment, with upadacitinib, a selective Janus kinase (JAK) 1 inhibitor,[1] standing out as a solid candidate. Clinical trials[1] and real-world studies[2–7] have demonstrated the efficacy and safety of upadacitinib in managing moderate-to-severe AD. These studies highlight its potential to achieve significant improvements in disease severity and patient-reported outcomes.[2–7] However, the variability in patient response requires further investigation into predictors of therapeutic success and the potential impact of early-intervention on long-term disease modification. This study aims to evaluate the mid-term effectiveness and safety of upadacitinib in a real-world setting and identify potential predictors of response in patients with moderate-to-severe AD.

A retrospective non-interventional multicenter study was conducted at the dermatology departments of nine Spanish hospitals from June 2023-to-June 2024. It included adolescents and adults with moderate-to-severe AD treated with upadacitinib 15 or 30 mg in a daily practice setting. No concomitant systemic medication was prescribed. Baseline patient data included age, gender, comorbidities, disease duration, and previous treatments. Disease severity was measured using the Eczema Area and Severity Index (EASI), Body Surface Area (BSA), Investigator Global Assessment (IGA) for AD, and pruritus Numerical Rating Scale (NRS) at Weeks-4, -16, and -24. Quality of life was assessed with the Dermatology Life Quality Index (DLQI). Minimal Disease Activity (MDA)[8] response (EASI ≤ 3 and peak pruritus NRS ≤ 1) was evaluated at week-24. Drug-related adverse events were recorded throughout the study. The primary endpoint was to analyze the influence of variables (gender, BMI, years of diagnostic delay, presence of atopic comorbidities, cardiovascular risk factors, involvement of special areas, number of previous treatments, and dupilumab exposure) on therapeutic response at week-24. The secondary endpoint was to analyze the evolution of response in terms of absolute EASI, BSA, IGA, DLQI, and pruritus NRS scores at Weeks-4, -16, and -24, and the safety profile of the drug. Descriptive statistics were used to evaluate the characteristics of the sample. The Shapiro-Wilk test was used to assess the normality of the variables. Continuous variables were expressed as mean and Standard Deviation (SD). Qualitative variables were expressed as relative frequency distributions. To explore potential associated factors, multiple linear regression was used, considering the absolute reduction in EASI and NRS as the dependent variables. Statistical significance was considered if p-values were less than 0.05.

Table 1 Baseline characteristics of the patients.

n = 63	
Age (years) (SD)	42.65 years (18.42)
Gender (Female)	43.64%
Family history of AD	29.27%
BMI (Kg/m^2) (SD)	24.11 (8.05)
Years of diagnostic delay (SD)	4.56 (6.16)
Atopic comorbidities	69.09%
Food allergy	25.93%
Rhinitis	50.91%
Asthma	41.82%
Cardiovascular risk factors	30.91%
Special areas	85.45%
Hands eczema	56.36%
Facial/Neck	74.55%
Genital	20.00%
Basal EASI (SD)	18.98 (7.25)
Basal Peak pruritus NRS (SD)	7.60 (1.61)
Basal IGA (SD)	3.10 (0.62)
Number of previous treatments (SD)	1.35 (0.95)
Previous classical treatments or phototherapy	
Cyclosporine	43.64%
Methotrexate	9.09%
Azathioprine	9.09%
Mycophenolate	3.29%
Phototherapy	12.73%
Previous advanced treatments	
Dupilumab	44.3%
Tralokinumab	3.64%
Baricitinib	1.82%
Abrocitinib	1.82%
Time of exposure (months) to upadacitinib (SD)	11.92 (8.38)

BMI: Body Mass Index; EASI: Eczema Area and Severity Index; NRS: Numerical Rating Scale; IGA: Investigator Global Assessment.

Sixty-three patients with a mean age of 42.65-years (SD = 18.42) were included. Patients' characteristics are detailed in Table 1. Upadacitinib was the first systemic treatment for 16.1% of patients. Most patients (60.5%) received a daily dose of upadacitinib of 30 mg. Only 5.5% of patients switched from 30 mg to 15 mg once achieving optimal response. The mean exposure to upadacitinib 15 or 30 mg was 11.9 months (SD = 8.38). Treatment responses in terms of EASI, IGA, BSA, DLQI, and peak pruritus NRS are detailed in Table 2. No significant differences were observed between patients treated with 15 vs. 30 mg doses and those previously treated with dupilumab vs. not treated. We did

☆ The present study was carried out in the following hospitals from the Valencian Community, Spain: Hospital Universitario Doctor Peset, Hospital Lluís Alcanyís of Xátiva, Hospital Universitario y Politécnico La Fe, Hospital Universitario Virgen de los Lirios, Hospital Arnau de Vilanova, Hospital General Universitario of Castellón, Hospital de la Ribera, Hospital Frances de Borja, Hospital Clínico Universitario de Valencia.

Table 2 Treatment response to upadacitinib during the follow-up period.

	Basal Mean[a] (SD)	Week 4 Mean (SD)	Week 16 Mean (SD)	Week 24 Mean (SD)
EASI (SD)	18.98 (7.25)	3.02 (3.81)	1.15 (2.22)	0.84 (2.27)
BSA (SD)	24.66 (15.78)	3.94 (4.77)	1.84 (3.96)	0.85 (2.74)
DLQI (SD)	16.48 (6.42)	3.30 (5.27)	1.48 (2.64)	0.77 (1.92)
IGA (Value and %)	3–4 (87.5%)	3–4 (4.8 %)	3–4 (4.5%)	3–4 (2.5%)
	2 (12.5%)	2 (12.2%)	2 (8.5%)	2 (5.5%)
		0–1 (83%)	0–1 (87%)	0–1 (93%)
Peak pruritus NRS (SD)	7.60 (1.61)	1.61 (1.87)	0.70 (1.30)	0.45 (1.25)

EASI, Eczema Area and Severity Index; BSA, Body Surface Area; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; NRS pruritus, Numeric Rating Scale for pruritus.
[a] The mean and standard deviation were used, except for IGA.

Table 3 Multiple linear regression model exploring the influence of variables (gender, BMI, years of diagnostic delay, presence of atopic comorbidities, cardiovascular risk factors, involvement of special areas, number of previous treatments, and dupilumab exposure) on therapeutic response in terms of EASI at week 24.

EASI/Variables	Coef	Std Err	T	p>|t|	[0.025	0.975]
Intercept	21.4782	4.598	4.674	0.0	12.384	30.572
Gender	−1.6871	1.211	−1.393	0.165	−4.078	0.704
BMI (Kg/m^2)	−0.0332	0.296	−0.112	0.911	−0.616	0.55
Years of diagnostic delay	0.3592	0.142	2.528	0.013	0.078	0.64
Family history	2.7874	1.322	2.108	0.036	0.175	5.4
Atopic comorbidities	−1.1373	1.225	−0.928	0.355	−3.554	1.279
CVD risk factors	2.7548	1.557	1.769	0.09	−0.409	5.718
Special areas	1.4782	1.598	0.925	0.357	−1.679	4.635
Number of previous treatments	0.9873	0.472	2.092	0.038	0.053	1.921
Dupilumab	−0.1421	0.296	−0.48	0.632	−0.724	0.439

BMI, Body Mass Index, CVD, Cardiovascular Disease.

not observe differences in the effectiveness of upadacitinib among different phenotypes of AD. MDA[8] criteria at week-24 were achieved by 55.5% (95% CI 42.72–67.28) of patients. Among the variables analyzed, the number of years of diagnostic delay (p = 0.013) and the number of previous treatments (p = 0.038) showed a statistically significant association with EASI response, and the number of previous treatments (p = 0.010) showed a statistically significant association with pruritus NRS at week-24, respectively. The presence of a family history of AD was associated with a statistically significant increase in the EASI score (p = 0.036) (Table 3 and Table 4). Twenty patients were followed up until week-52 and presented a mean absolute EASI of 2.57 (SD = 5.21), 90% of IGA 0–1, and NRS pruritus of 0.89 (SD = 1.94). 75% (95% CI 64.31–85.69) of them achieved MDA[8] defined by EASI $\leq$ 3 and NRS pruritus $\leq$ 1. The safety profile of upadacitinib was favorable. Infections or Major Adverse Cardiovascular Events (MACEs) were not reported. Five patients experienced transient and isolated lymphopenia (750–1000 mm^3), which resolved spontaneously. During the follow-up, no patient discontinued the drug.

In our series, treatment with upadacitinib in patients with moderate-to-severe AD showed significant mid- and long-term efficacy. These results are similar to those already reported in clinical trials and major real-world series.[1–8] Our patients exhibited severe disease profiles and resistance to multiple systemic therapies, including biologics, which contrasts with the profiles typically seen in clinical trials.[1] Additionally, by week-16, more than 50% of patients achieved MDA (defined in our series as EASI $\leq$ 3 and peak pruritus NRS $\leq$ 1), a more stringent response criterion recently proposed by Silverberg JI et al.,[8] which encompasses clinical response and Patient-Reported Outcomes (PROs). The MDA percentage increased to 75% by week-52. We wanted to highlight that despite the high proportion of patients achieving substantial improvements in EASI, peak pruritus NRS, and IGA index, the number of years of diagnostic delay and the number of previous treatments could negatively influence therapeutic response, highlighting the importance of early treatment.[9] This reinforces the recent hypothesis surrounding advanced and long-standing cases, that the main cytokines involved in cutaneous inflammation, particularly Th2-cytokines (Interleukin [IL]-4, IL-5, IL-13, IL-31)/JAK-1 pathway may also be implicated in promoting itch at the neuronal level (neuroinflammation), thus chronicling the process.[10] This raises the question of whether early intervention for AD could lead to a modification of the disease, either in severity or in future persistence.[9] This study has some limitations, with the main one being derived from its observational and retrospective nature, which does not allow missing data to be retrieved. Additionally, only patients who used upadacitinib for at least 24-weeks were analyzed, and those who discontinued the drug were not assessed. This may overestimate the rates of success and safety in the current sample other limitations include the small sam-

Table 4 Multiple linear regression model exploring the influence of variables (gender, BMI, years of diagnostic delay, presence of atopic comorbidities, cardiovascular risk factors, involvement of special areas, number of previous treatments, and dupilumab exposure) on therapeutic response in terms of pruritus NRS at week 24.

Pruritus NRS/Variables	Coef	Std Err	*t*	p>|*t*|	[0.025	0.975]
Intercept	4.4782	0.598	7.491	0.0	3.298	5.659
Gender	−0.6871	0.455	−1.51	0.133	−1.587	0.213
BMI (Kg/m^2)	0.0332	0.116	0.287	0.774	−0.195	0.261
Years of diagnostic delay	0.0592	0.056	1.056	0.293	−0.051	0.169
Family history	0.4874	0.518	0.94	0.349	−0.534	1.509
Atopic comorbidities	−0.6373	0.482	−1.322	0.188	−1.588	0.313
CVD risk factors	0.7548	0.626	1.206	0.23	−0.482	1.991
Special areas	0.4782	0.618	0.774	0.44	−0.742	1.698
Number of previous treatments	0.4873	0.186	2.62	0.01	0.122	0.853
Dupilumab	0.0421	0.116	0.362	0.717	−0.187	0.271

BMI, Body Mass Index, CVD, Cardiovascular Disease.

ple size and the statistical adjustments performed, which may impact the accuracy and generalizability of the results. In conclusion, upadacitinib is presented as an effective alternative in the treatment of moderate-to-severe atopic dermatitis, with significant improvements observed in both mid- and long-term follow-up. Despite the promising results, early intervention remains crucial due to the potential negative impact of diagnostic delays and multiple previous treatments on therapeutic response.

Authors' contributions

Francisco Javier Melgosa Ramos: Contributed to the conception, design, data collection, interpretation, writing-draft preparation and review of the present work.

Carlos Abril Pérez: Contributed to the conception, data collection, interpretation and review of the present work.

Santiago Guillén Climent: Contributed to data collection, interpretation and review of the present work.

María Matellanes Palacios: Contributed to data collection, interpretation and review of the present work.

Juncal Roca Ginés: Contributed to data collection, interpretation and review of the present work.

Javier Sabater Abad: Contributed to data collection, interpretation and review of the present work.

Eduardo Bernia Petit: Contributed to data collection, interpretation and review of the present work.

Andrés Casanova Esquembre: Contributed to data collection, interpretation and review of the present work.

Andrea Estébanez Corrales: Contributed to data collection, interpretation and review of the present work.

Victor González Delgado: Contributed to the conception, design, data collection, interpretation, writing-draft preparation and review of the present work.

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Multilocus sequence typing of *Treponema pallidum* in male patients with genital ulcers in a public sexually transmitted infections clinic: a new allele and almost complete macrolide resistance[☆]

Dear Editor,

Syphilis is a sexually transmitted infection of polymorphic evolution caused by the *Treponema Pallidum* subspecies *pallidum* (TP). Mucocutaneous, neurological and cardiovascular systems are the most affected and mother-to-child transmission can occur at any stage of pregnancy.[1] The World Health Organization (WHO) estimated 6.3 million yearly cases in the world. In Brazil, syphilis increased from 33.9 cases in 2015 to 74.2 cases per 100,000 inhabitants in 2019.[2]

TP is non-cultivable with standard culture methods. In clinical practice, the diagnosis is presumptive using serological tests. Different Polymerase Chain Reactions (PCR) techniques have been used for diagnosis[3] and DNA sequencing is increasingly used to study genetic diversity, dynamics of transmission, virulence, and patterns of resistance.[4] Genotyping by Multilocus Sequence Typing (MLST) on the chromosomal loci TP0136, TP0548, and TP0705 allows better discrimination of TP strains and permits the creation of an epidemiological analysis database (https://pubmlst.org/organisms/treponema-pallidum). Different loci, distinct alleles, and their combination define the allelic profile and the Sequence Type (ST). The analysis of the 23SrRNA gene can complement the identification of mutations (A2058G or A2059G) that are related to resistance to macrolides.[5]

The objective of our study is detecting and genotype TP in by MLST Genital Ulcers Presumptive of Syphilis (GUPS).

We analyzed exudate GUPS samples obtained from male patients aged 18 years and over, seen at a public STI clinic in Porto Alegre, Brazil, from July 2019 to March 2019. Sample collection: dry cotton swab. DNA extraction: PureLink® Genomic Kit (Invitrogen®, Thermo Fisher Scientific). Detection: PCR amplification of 260 bp of the tpp47 gene with DNA using the *primers* KO3 (5'-GAAGTTTGTCCCAGTTGCTGCTTT-3') and KO4 (5'-CAGAGCCATCAGCCCTTTTCA-3'). Amplification: *Taq platinum* DNA polymerase (Invitrogem, Fisher Scientific, USA) and Thermocycler PTC96 (Bioer Technology, China). PCR product analysis: electrophoresis in agarose gel (0.05% ethidium-bromide). MLST analysis: sequencing chromosomal loci (TP0136, TP0548, and TP0705) as described previously by Vrbová et al.,[4] Evaluation of A2058G and A2059G mutations in the 23S rRNA gene: nested PCR. Sequencing analysis: Bioedit software (Tom Hall, USA). Genotyping analysis: scheme including TP0136, TP0548, and TP0705 loci,[4] using the public database platform for molecular typing and microbial genome diversity (PubMLST, available at https://pubmlst.org/organisms/treponema-pallidum). Resistance-related sequencing analysis: sequence annotation corresponding to positions 2058 and 2059 in rRNA gene of *Escherichia coli* (accession nº V0033, GenBank). Positive and negative controls were used in each round. Ethical approval: School of Public Health, state of Rio Grande do Sul (nº 3,232,889).

Forty-three participants were recruited. Ages ranged from 19 to 66 years. All of them were residents of the metropolitan area of Porto Alegre. In 32 (74%) of the 43 DNA samples analyzed, we detected TP specific sequences. In

[☆] Study conducted at the Sanitary Dermatology Outpatient Unit, Secretaria Estadual de Saúde, Porto Alegre, RS, Brazil.

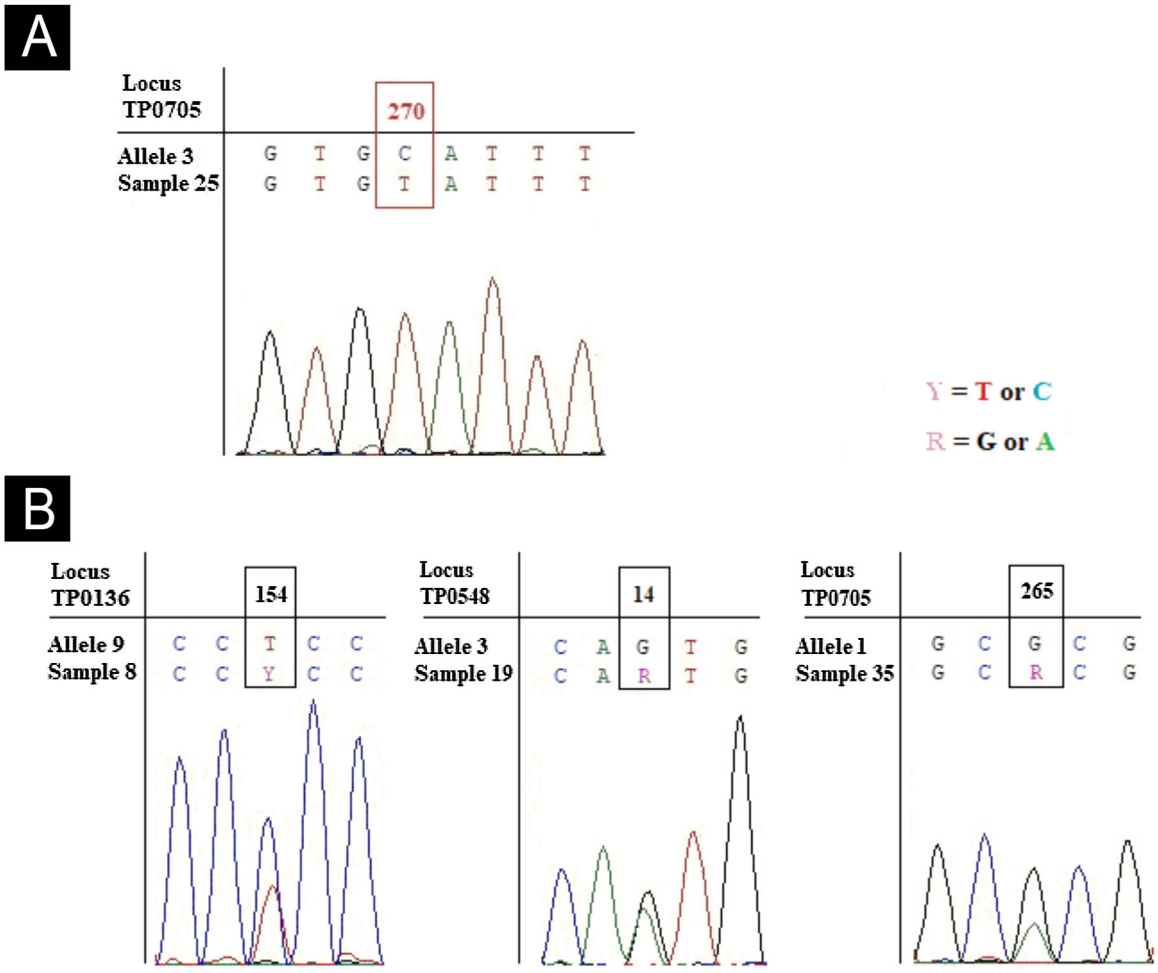

Figure 1 **New allele** for TP0705 and three heterozygous peaks for TP0136, TP0548 and TP0705 loci. (A) Chromatogram of sample 25 shown the new allele variant called here of 11, characterized by an SNV at position 270 (C→T) using the allele 3 (most similar sequence) as reference. (B) Chromatograms of three samples showed heterozygous peak for TP0136 locus at position 154 (C and T), TP0548 at position 14 (G and A) and TP0705 at position 265 (G and A). The alleles used as reference are the most similar sequence observed in PubMLST database.

30 (94%) of the 32 at least one locus of the MLST scheme was successfully sequenced. We successfully sequenced the same proportion 23SrRNA gene. We obtained quality sequencing of TP0705 in 22 samples, as well as for TP0136 and TP0548. The combination of successfully sequenced locus among samples varied. We identified three allele variants for TP0136, two for TP0548, and three for TP0705. We identified a new allele for TP0705 in the only sample characterized as genotypically susceptible to macrolides (designated allele 11) which differed from allele 3 at loci position 270 (C270T). Three other samples presented heterozygous peaks (two peaks), at positions 154 for TP0136, 14 for TP0548, and 265 for TP0705 (Fig. 1). The results of TP typing, the identified alleles, the genotypic resistance profile, and the clonal complex are presented in Table 1.

We obtained Sequence Types (ST), which are attributed to fully characterized haplotypes (three MLST loci), for 11 samples and the most frequent (8/11;72,7%) was the profile 1.3.1 (ST 1). Profile 28.7.3 has not yet attributed an ST in PubMLST platform. We classified samples that had at least one locus successfully sequenced in a clonal complex by approximation. This classification was based on the number of sequenced isolates containing the allele(s) stored in the PubMLST database (Table 2). We identified two clonal complexes of strains: 6 (20%) of 30 isolates were classified as Nichols-like and 22 (73%) as SS14-like. It was not feasible to assign a clonal complex to the two samples that only had the TP0705 locus successfully sequenced. One sample was characterized as allele 3, while the other exhibited a newly identified allele designated as allele TP0705-22 (Fig. 1).[5] Regarding resistance-related mutations, out of the 30 samples that were adequately characterized, only one did not have the A2058G mutation in the 23S rRNA gene and therefore classified as susceptible.

The TP DNA was detected in approximately two-thirds of the samples. They belonged to the SS14-like or Nichols-like clonal complexes. A new allele was identified in the two samples not classified in a clonal complex (x.x.3 and x.x.11).[5] The haplotype containing this allele had only the TP0705 locus characterized. This locus can share identical alleles among strains from SS14 and Nichols-clades, which makes it difficult to assign a clonal complex.

Table 1 Genotyping of *T. pallidum* by Multi-Locus Sequence Typing (MLST) of studied samples.

Sample ID	TP0136	TP0548	TP0705	23S rRNA[a]	MLST[b]	ST[c]	Clonal Complex
1	1	3	1	R	1.3.1	1	SS14-like
7	nd	nd	1	R	x.x.1	–	SS14-like[d]
8	9[f]	7		R	9.7.x	–	Nichols-like[d]
9	1	3	–	R	1.3.x	–	SS14-like[d]
10	1	nd	1	R	1.x.1	–	SS14-like[d]
11	1	3	1	R	1.3.1	1	SS14-like
12	1	3	nd	R	1.3.x		SS14-like[d]
13	nd	3	nd	R	x.3.x		SS14-like[d]
14	nd	nd	nd	R	–	–	nd
15	nd	nd	nd	R	–	–	nd
16	28	7	3	R	28.7.3	–	Nichols-like
17	nd	nd	1	R	x.x.1	–	SS14-like[d]
18	1	3	1	R	1.3.1	1	SS14-like
19	1	3[f]	nd	R	1.3.x	–	SS14-like[d]
20	1	3	nd	R	1.3.x		SS14-like[d]
21	nd	7	3	R	x.7.3	–	Nichols-like[d]
22	9	7	3	R	9.7.3	26	Nichols-like
23	nd	nd	3	nd	x.x.3	–	nd
25	nd	nd	11[e]	S	x.x.11	–	nd
27	1	3	nd	R	1.3.x	–	SS14-like[d]
28	1	3	1	R	1.3.1	1	SS14-like
29	28	7	3	R	28.7.3	–	Nichols-like
30	1	3	1	R	1.3.1	1	SS14-like
31	nd	nd	1	R	x.x.1	–	SS14-like[d]
32	1	3	1	R	1.3.1	1	SS14-like
34	1	nd	1	Nd	1.x.1	–	SS14-like[d]
35	1	nd	1[f]	R	1.x.1	–	SS14-like[d]
36	28	7	3	R	28.7.3	–	Nichols-like
38	1	3	nd	R	1.3.x	–	SS14-like[d]
39	1	3	1	R	1.3.1	1	SS14-like
40	1	3	1	R	1.3.1	1	SS14-like
42	nd	3	1	R	x.3.1	–	SS14-like[d]

nd, Not determined.
[a] 23S rRNA gene encoding resistance to macrolide antibiotics: S, Sensitive; R, Resistant with mutation A2058G.
[b] Allelic profiles based on TP0136, TP0548 and TP0705 loci sequences.
[c] ST, Sequence Type, according to the PubMLST database for *Treponema pallidum subsp. Pallidum*.
[d] Clonal complex classified by approximation.
[e] New allele.
[f] Alleles with heterozygous peak in one position of the sequence.

Table 2 Clonal complex of incomplete genotypic profiles based on number of samples present in PubMLST database.

Profile searched in the database	n of samples SS14-like	n of samples Nichols-like	n of samples without CC assignment	CC considered in this study
1.3.x	463	0	1	SS14-like
1.x.1	639	0	10	SS14-like
9.7.x	0	38	0	Nichols-like
x.3.1	477	0	4	SS14-like
x.3.x	482	0	6	SS14-like
x.7.3	0	41	3	Nichols-like
x.x.1	683	0	20	SS14-like
x.x.3	22	86	7	nd

CC, Clonal Complex.

All but one of our DNA-positive samples presented the A2058G mutation in the 23S rRNA gene, which provides resistance to the macrolide class of antibiotics.[6] Our findings corroborate those of Grillová et al.[7] and Giacani et al.,[8] which demonstrated a high and increasing proportion of this mutation. We identified the same clonal complexes in 20% of the samples of this study (Clonal Complex SS14 or the Nichols-like). We found three MLST fully characterized profiles of TP (1.3.1; 9.7.3; 28.7.3).

The negative samples to TP DNA can be explained: 1) Some patients did not have syphilis; 2) Microorganisms in the lesions reduced over time; and 3) The previous use of topical and systemic antibiotics. The small sample size prevented the study associations of different genotypes with demographics, sexual practices, or geographic origin of participants since the SARS-CoV2 epidemic hindered the enrollment of participants. The development of studies with larger sample sizes will be able to provide additional information that is crucial for the control of syphilis.

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Authors' contributions

Leonardo Souza Esteves: Responsible for the conception and design, carried out bioinformatic sequencing analysis and genotyping, provided comments and edits and approved the final draft prior to submission.

Vera Mileide Trivellato Grassi: Responsible for the conception and design, provided comments and edits and approved the final draft prior to submission.

Liliane Trivellato Grassi: Carried out reference organizing, provided comments and edits and approved the final draft prior to submission.

Maria Rita Castilhos Nicola: Participated in data collection and management, provided comments and edits and approved the final draft prior to submission.

Marcia Susana Nunes Silva: Responsible for the conception and design, provided comments and edits and approved the final draft prior to submission.

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Mauro Cunha Ramos: Responsible for the conception and design, provided comments and edits and approved the final draft prior to submission.

Conflicts of interest

None declared.

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Negative impact of striae gravidarum in maternal mental health☆

Dear Editor,

Striae distensae or ''stretch marks'', referred to in pregnancy as striae gravidarum (SG) are considered minor problems, which do not affect the physical health of mothers or babies. However, they remain after pregnancy, with expensive, painful, and mostly ineffective treatments.[1]

SG most commonly appear between the 24th and the 27th week of gestation.[2] They may be of cosmetic concern reducing quality of life.[1–4] Chronic dermatological changes are associated with lower self-esteem.[5–7]

The present study aimed to evaluate the association between SG and depressive and anxiety symptoms in the third trimester of pregnancy in women in Southern Brazil.

This is a cross-sectional study nested in a population-based cohort study, which included 840 pregnant women living in Pelotas (Brazil). City sectors were visited to invite pregnant women up to 24 weeks to participate. The first evaluation (baseline) occurred via home interviews. The data of the present study refer to the second evaluation, which occurred sixty days after the first evaluation.

SG was self-declared and confirmed by the interviewers. Pregnant women were asked about the presence or the increase of SG in the abdomen, thighs, or breasts. Four variables were considered: presence and/or increase of SG (yes/no), SG in the abdomen (yes/no), on the thighs (yes/no) and on the breasts (yes/no).

The validated Brazilian Portuguese version of the Beck Depression Inventory-Second Edition (BDI-II) was used. The cutoff point considered was 0–12 for the absence and 13 points or more for the presence of depressive symptoms.

The validated for the Brazilian Portuguese version of Beck Anxiety Inventory (BAI) was used. The cutoff point considered was 0–10 for the absence of symptoms and 11 points or more for the presence of anxiety symptoms.

We accessed also a third variable of Combined Anxiety-Depressive Symptoms (CADS), according to the cutoff points mentioned above.

For the socio-economic status, the classification proposed by the Brazilian Association of Research Companies. The classes were grouped as follows: A + B, C and D + E. ''A + B'' refers to the highest and ''D + E'' to the lowest economic classes.

A Body Mass Index (BMI) nomogram was used to calculate obesity based on the Atalah criteria, which classifies BMI according to gestational age.[8] In the present study, we considered women with obesity ($\geq$30.1 kg/m^2) and without obesity ($\leq$30 kg/m^2).

The Food Insecurity (FI) level was measured using the validated Brazilian Food Insecurity Scale (EBIA), adapted from the US Household Food Security Survey Measure (HPSSM). It estimates an individual's experience and perception of hunger.[9] The variable was dichotomized into the presence or absence of food insecurity.

The questionnaire asked also: education level (up to 8/9 years or more), age (up to 27/28 or more), previous pregnancy (yes/no), planned pregnancy (yes/no), previous depression (yes/no), and gestational age on the day of the interview.

The univariate analysis was performed by calculating simple and relative frequencies. The Chi-Square test was used for the bivariate analysis. The adjusted analysis was performed using logistic regression, adjusted for socioeconomic level, schooling, age, gestational age, previous pregnancy, planned pregnancy, obesity, food insecurity and previous depression. The variables related to the presence SG were separately inserted in the regression model for being highly correlated. Statistical significance was set at $p < 0.05$ in all tests.

This study was approved by the Ethics Committee of the University under protocol number 1.729.653. All participants signed an informed consent.

Table 1 shows socio-demographic, gestational, physical and mental health and food insecurity characteristics of participants associated with depressive and anxiety symptoms. A total of 840 pregnant women were evaluated.

In the bivariate analysis, the prevalence of depressive symptoms was significantly higher among women with a previous pregnancy ($p = 0.026$), those who experienced

☆ Study conducted at the Universidade Católica de Pelotas, Pelotas, RS, Brazil.

Table 1 Socio-demographic, gestational, physical and mental health characteristics, and food insecurity associated with depressive and anxiety symptoms in pregnant women.

Variables		Depressive symptoms (BDI ≤ 13)		Anxiety symptoms (BAI ≥ 11)		Mixed anxiety-depressive symptoms (BDI ≤ 13 + BAI ≤ 11)	
	n total (%)	n (%)	p-value	n (%)	p-value	n (%)	p-value
Socio-economic class[a]			0.837[b]		0.412[b]		0.483[b]
A + B	216 (26.2)	51 (23.6)		70 (32.4)		35 (16.2)	
C	473 (57.5)	113 (23.9)		152 (32.2)		93 (19.7)	
D + E	134 (16.3)	33 (24.6)		50 (37.3)		27 (20.1)	
Education (years of study)			0.308		0.942		0.707
Up to 8	263 (31.3)	58 (22.1)		87 (33.1)		46 (17.5)	
≥9	577 (68.7)	146 (25.3)		192 (33.3)		113 (19.6)	
Age (years)			0.172		0.106		0.179
Up to 27	463 (55.1)	104 (22.5)		143 (30.9)		76 (16.4)	
≥28	377 (44.9)	100 (26.5)		136 (36.2)		83 (22.1)	
Previous pregnancy			0.026		0.091		0.002
No	357 (42.5)	73 (20.4)		107 (30.1)		48 (13.5)	
Yes	483 (57.5)	131 (27.1)		172 (35.6)		111 (23.0)	
Planned pregnancy			0.113		0.002		0.011
No	462 (55.0)	122 (26.4)		145 (38.9)		87 (23.3)	
Yes	378 (45.0)	82 (21.7)		134 (28.8)		72 (15.5)	
Obesity			0.627		0.734		0.601
No	596 (71.3)	142 (23.8)		196 (32.9)		114 (19.2)	
Yes	240 (28.7)	61 (25.4)		82 (34.2)		45 (18.8)	
Previous depression			<0.001		<0.001		<0.001
No	511 (60.8)	49 (9.6)		87 (17.1)		29 (5.7)	
Yes	329 (39.2)	155 (47.1)		192 (58.4)		130 (39.5)	
Food insecurity			0.001		0.002		0.003
No	578 (68.8)	122 (21.1)		172 (29.8)		90 (15.6)	
Yes	262 (31.2)	82 (31.3)		107 (40.8)		69 (26.3)	
Total	840 (100)	204 (24.3)	–	279 (33.3)	–	159 (19.0)	–

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.
[a] Variables with missing data.
[b] p-linearity.

previous depression (p < 0.001) and those who were food insecure (p = 0.001). Anxiety symptoms were significantly higher with unplanned pregnancy (p = 0.011), with previous depression (p < 0.001) and those who were food insecure (p = 0.003). CADS were significantly associated with previous pregnancy (p = 0.002), unplanned pregnancy (p = 0.001), previous depression (p < 0.001) and those who were food insecure (p = 0.003) (Table 1).

Thirty-two percent (270) had SG, 23.7% (n = 199) had on the abdomen, 11.5% (n = 97) on the breasts, and 7.4% (n = 62) on the thighs. In women with SG (270) prevalence of depressive symptoms was 29.3% (79), 37.8% (102) for anxiety symptoms and 23.0% (62) for CADS, which were significantly higher when compared with pregnant women without SG (Table 2).

The bivariate analysis showed that all variables related to SG were significantly associated with a higher prevalence of depression, anxiety and CADS (Table 2).

In the logistic regression, was observed that pregnant women with SG were 60% more likely to experience depressive symptoms (PR = 1.6, 95% CI 1.1–2.4, p = 0.018) and 90% more likely to have CADS (PR = 1.9, 95% CI 1.2–3.1, p = 0.005) compared to those without SG. Involvement of the abdomen was 60% more likely to experience depressive symptoms (PR = 1.6, 95% CI 1.1–2.5, p = 0.017) and 90% more likely to have CADS (PR = 1.9, 95% CI 1.1–3.2, p = 0.010). Similarly, SG on the breasts had 2.3 times more depressive symptoms (PR = 2.3; 95% CI 1.3–4.0, p = 0.002), 1.7 times more anxiety symptoms (PR = 1.7, 95% CI 1.0–2.9, p = 0.033) and 3.1 times more CADS (PR = 3.1, 95% CI 1.7–5.9, p < 0.001). Conversely, the odds of having depressive symptoms were 2.9 times higher with SG on the thighs (PR = 2.9, 95% CI 1.6–5.4, p = 0.001) and 3.9 times higher for those with CADS (PR = 3.9, 95% CI 1.8–8.1, p < 0.001). The association of SG on both the abdomen and thighs with anxiety symptoms was not statistically significant (p > 0.05), as shown in Table 3.

Our results showed that pregnant women with SG had a higher prevalence of depressive symptoms, anxiety symptoms and CADS, even after adjusting for all possible confounding factors. Although anxiety and depressive symptoms are frequent during pregnancy, no previous studies have reported their association with SG.

Some studies have evaluated Quality of Life (QoL) and SG.[1] It is known that chronic skin diseases significantly reduce QoL and are risk factors for mood disorders. Peo-

Table 2 Prevalence of Striae Gravidarum (SGs) associated with depressive and anxiety symptoms in pregnant women.

Variables		Depressive symptoms (BDI ≤ 13)		Anxiety symptoms (BAI ≤ 11)		Mixed anxiety-depressive symptoms (BDI ≤ 13 + BAI ≤ 11)	
	n (%)	n (%)	p-value	n (%)	p-value	n (%)	p-value
Presence and/or increase of SG in pregnancy			0.021		0.055		0.110
Yes	270 (32.1)	79 (29.3)		102 (37.8)		62 (23.0)	
No	570 (67.9)	125 (21.9)		177 (31.1)		97 (17.0)	
SG on abdomen			0.005		0.027		0.037
Yes	199 (23.7)	63 (31.7)		79 (39.7)		51 (25.6)	
No	641 (76.3)	141 (22.0)		200 (31.3)		108 (16.9)	
SG on breasts			0.004		0.014		0.015
Yes	97 (11.5)	35 (36.1)		43 (44.3)		30 (30.9)	
No	743 (88.5)	169 (22.7)		236 (31.8)		129 (17.4)	
SG on thighs			0.001		0.009		0.007
Yes	62 (7.4)	26 (41.9)		30 (48.4)		21 (33.9)	
No	778 (92.6)	178 (22.9)		249 (32.0)		138 (17.8)	

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; SG, Striae gravidarum.

Table 3 Logistic regression analysis of the prevalence of depressive and anxiety symptoms according to the presence and/or increase of Striae Gravidarum (SG) during pregnancy.

Variables	Depressive symptoms (BDI ≤ 13)		Anxiety symptoms (BAI ≤ 11)		Mixed anxiety-depressive symptoms (BDI ≤ 13 + BAI ≤ 11)	
	PR (95% CI)	p-value	PR (95% CI)	p-value	PR (95% CI)	p-value
Presence and/or increase of SG during pregnancy[a]		0.018		–		0.005
Yes	1.6 (1.1; 2.4)		–		1.9 (1.2; 3.1)	
No	1.0		–		1.0	
SG on abdomen[a]		0.017		–		0.010
Yes	1.6 (1.1; 2.5)		–		1.9 (1.1; 3.2)	
No	1.0		–		1.0	
SG on breasts[a]		0.002		0.033		<0.001
Yes	2.3 (1.3; 4.0)		1.7 (1.0; 2.9)		3.1 (1.7; 5.9)	
No	1.0		1.0		1.0	
SG on thighs[a]		0.001		0.069		<0.001
Yes	2.9 (1.6; 5.4)		3.2 (0.9; 11.3)		3.9 (1.8; 8.1)	
No	1.0		1.0		1.0	

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; PR, Prevalence Ratio; CI, Confidence Interval; SG, Striae gravidarum.
[a] Variables adjusted for socio-economic class, education, age, previous pregnancy, planned pregnancy, obesity, previous depression, food insecurity and gestational trimester.

ple with chronic skin disease may become depressed due to difficult treatments and have reduced QoL.[6,7]

Yamaguchi et al.[1] were the first researchers to assess the impact of SG on QoL, using the SKINDEX-29. The authors found that SG has an effect on QoL of pregnant women similar to other chronic skin diseases.

Yamaguchi et al.[2] evaluated some preventive measures taken by pregnant women for SG and QoL for emotion and observed that women who followed preventive measures to control the presence of SG showed a lower QoL for emotion than pregnant women who did not, this may indicate that the use of skin moisturizers, due to negative emotions caused by their skin condition, are anticipating a preventive effect against the stretch marks.

Karhade et al.[3] evaluated pregnant women with a questionnaire adapted from the Dermatology Life Quality Index and concluded that 75% of women were concerned about the permanency of the lesions and 74% were willing to seek treatment for SG, and most of them had attempted to prevent them with topical treatment.

Our results showed the association between SG and depressive and anxious symptoms during pregnancy independently of the affected body region (abdomen, breast or thighs). SG is not only an aesthetic discomfort, but could trigger mood disorders.

Authors' contributions

Talita Pereira Calheiros: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; critical review of the literature; critical review of the manuscript.

Bárbara Borges Rubin: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Jéssica Puchalski Trettim: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature, critical review of the manuscript.

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Conflicts of interest

None declared.

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Serum levels of vitamin D in people with albinism from Brazil☆

Dear Editor,

Oculocutaneous albinism is an autosomal recessive disorder caused by mutations in the TYR, AOC2, TYRP1, and SLC45A2 genes, leading to reduced or absent melanin production in melanocytes.[1] Melanin absorbs and scatters ultraviolet radiation (UVR) and visible light in the skin.[2] Due to the lack of melanin, individuals with albinism are highly susceptible to the harmful effects of UVR, making sun protection a priority to prevent actinic damage and malignant skin neoplasms.[1,3,4] Photoprotection reduces vitamin D (VD) production by blocking its synthesis in the skin.[3,5] Since people with albinism strictly avoid the sun, they are thought to be at risk for low VD levels.[6,7]

Vitamin D is a fat-soluble vitamin mainly obtained from endogenous skin production and, to a lesser extent, from the diet. Most serum VD comes from the conversion of 7-dehydrocholesterol into vitamin D3 in the skin through UVB radiation.[8] Besides its role in bone metabolism, VD participates in the functions of almost all body systems.[9] Deficiency has been linked to various diseases, making it important to detect and treat VD deficiency in high-risk groups.[10]

The primary objective of this study was to evaluate serum VD levels in people with albinism who were advised on strict photoprotection and without oral VD supplementation. The secondary objective was to determine the impact of other variables on serum VD levels. This is a prospective cross-sectional observational study conducted at the Dermatology Sector of Santa Casa de São Paulo. Participants were randomly recruited from the Pró-Albino Program. Inclusion criteria included having albinism and no VD supplementation for at least six months. Exclusion criteria included pregnancy and certain comorbidities.

Blood collections were carried out from September 2020 to August 2022. São Paulo has high solar radiation throughout the year, with an average UVB index of 11. Collections were conducted without considering the four climatic seasons. Participants signed informed consent forms, and the project was authorized by the Research Ethics Committee of the Faculty of Medical Sciences of Santa Casa de São Paulo.

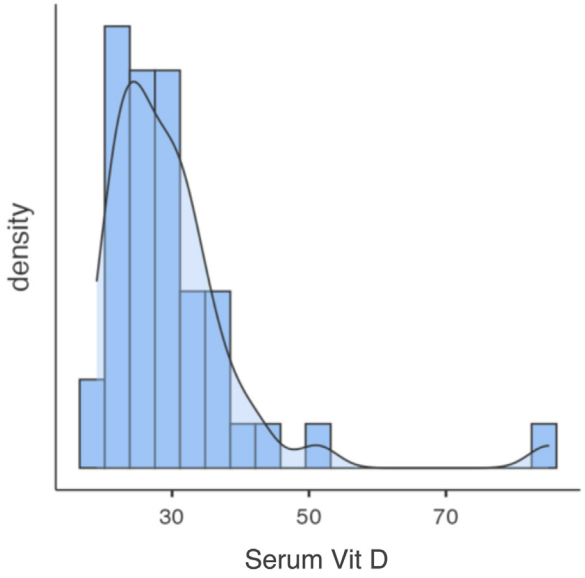

Fig. 1 Distribution of vitamin D levels in the sample. The average serum level of 25(OH)D in the sample was 30 ng/mL, with 97.6% of participants having levels above 20 ng/mL, 60% 25(OH)D levels below 30 ng/mL, and 40% above 30 ng/mL, with a maximum value of 85 ng/mL.

Participants were interviewed using a sun exposure questionnaire. Daily sun exposure, sunscreen use, mechanical photoprotection measures, and occupation were evaluated. Skin photoaging was assessed using the GLOGAU scale, adapted for albinism, and dietary VD intake was evaluated using a food frequency questionnaire. Demographic and clinical data were collected during medical consultations.

Data considered included age, sex, socioeconomic level, place of birth, skin color, hair color, eye color, smoking, Body Mass Index (BMI), and physical activity. Five milliliters of venous blood were collected for VD analysis. Serum 25(OH)D levels were measured using the ARCHITECT-OH-Vitamin-D chemiluminescence microparticle immunoassay. Data were analyzed using Jamovi® in an *R* environment.

Continuous data were summarized by mean values, confidence intervals, and standard deviation. Categorical data were described by their absolute frequency and proportion. Continuous data were tested for normality using the

Table 1 Results of constitutional variables.

	N	95% Confidence interval			Standard deviation	Minimum	Maximum
		Mean	Lower limit	Upper limit			
Age	42	27.74	22.03	33.44	18.306	3	67
Weight	42	61.75	53.03	70.47	27.982	13.20	115.00
Height	42	1.51.	1.44	1.58	0.232	1.00	1.83
BMI	42	24.97	22.81	27.13	6.921	12.69	35.13

Details of the constitutional variables (age, weight, height and BMI) found in the 42 individuals in the sample.

☆ Study conducted at the Irmandade da Santa Casa de Misericórdia de São Paulo, SP, Brazil.

Table 2 Variables studied and their relationship with serum 25(OH)D levels.

Predictor	Estimates	Standard error	*t*	p
Intercepto	24.43451	7.17522	3.40540	0.002
Vitamin D total	−1.66e-4	0.00277	−0.05997	0.953
White hair color				
White hair – others	0.02573	4.02660	0.00639	0.995
Green eye color				
Green eyes – others	3.02581	4.96927	0.60890	0.547
Daily sun exposure from 6 am to 6 pm – more than 30 min				
More than 30 min – less than 30 min.	0.00130	5.78696	2.24e-4	1.000
Use of sunscreen lotion				
Yes – No	2.75324	6.34766	0.43374	0.667
Sun damage level (choice = type 1 [level])				
Non verified – Verified	2.15289	3.97541	0.54155	0.592

None of the variables tested in this model interfered with the serum levels of 25(OH)D.

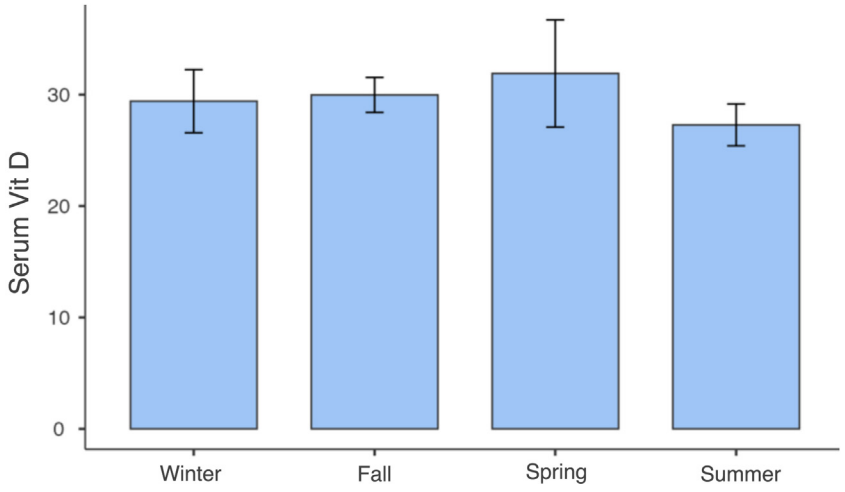

Fig. 2 Serum vitamin D levels in different climatic seasons. Vitamin D levels were similar between seasons. The data were subjected to a one-way ANOVA test, which confirmed that there was no statistically significant difference in vitamin D levels between the seasons (p = 0.687).

Shapiro-Wilk test, and parametric or non-parametric tests were applied accordingly.

The sample consisted of 42 individuals with an average age of 22.03 years, average weight of 61.8 kg, average height of 1.51 m, and average BMI of 25 (Table 1). Gender distribution was similar, with 52.4% female. The most common skin color was white (76.3%), and the most common parental skin color was brown (53.4%). Most participants reported using sunscreen (85.7%) and practicing photoprotective measures. The average serum 25(OH)D level was 30 ng/mL.

Only one participant had VD levels below 20 ng/mL, with 97.6% having levels above 20 ng/mL and 40% above 30 ng/mL (Fig. 1). No significant correlations were found between serum VD levels and variables such as age, sex, skin color, physical activity, or photodamage degree (Table 2). Vitamin D levels were similar between seasons. The data were subjected to a one-way ANOVA test, which confirmed that there was no statistically significant difference in vitamin D levels between the seasons, p = 0.687 (Fig. 2).

Only three studies published in the literature specifically evaluated serum vitamin D levels in people with albinism, all of which were carried out in African countries. Namely, these three studies concluded that serum levels of vitamin D in people with albinism, when compared to those with pigmented skin, were higher, even with the supposed photoprotection.[4,5,7] Similar findings were observed in this Brazilian study, with most participants having normal VD levels despite photoprotective measures. The lack of correlation between VD levels and analyzed variables might be due to the small sample size. More extensive studies with larger samples and detailed analysis could provide further insights.

Serum VD levels in the studied population with albinism were within the sufficiency range, even without oral supplementation and despite photoprotective measures. These values were not influenced by the analyzed variables. People with albinism in regions with high solar radiation are likely not at risk for VD deficiency, and normal VD values should be considered equivalent to the general population. Empirical supplementation is not indicated unless based on individual

needs assessed through clinical investigation and periodic measurements.

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Authors' contributions

Carolina Reato Marçon: Approval of the final version of the manuscript; Critical literature review; Data collection, analysis and interpretation; Effective participation in research orientation; Manuscript critical review; Preparation and writing of the manuscript; Statistical analysis; Study conception and planning.

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Conflicts of interest

None declared.

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Successful treatment of severe diffuse alopecia areata with abrocitinib☆

Dear Editor,

Alopecia areata (AA) is a chronic autoimmune disorder characterized by non-scarring hair loss.[1] Clinically, various patterns of hair loss may be observed. Among them, diffuse AA is a unique subtype, described as widespread scalp hair thinning, which brings a significant psychological burden for the patients.[2] Systemic treatment for severe AA is limited, but Janus kinase (JAK) inhibitors (baricitinib and ritlecitinib) have recently shown promising results in clinical trials and have been approved by the Food and Drug Administration (FDA) for the treatment of severe alopecia areata.[1] Other JAK inhibitors, in particular abrocitinib, a highly selective JAK1 inhibitor have been approved for the treatment of moderate-to-severe atopic dermatitis (AD).[3] but no, clinical trials have been conducted to investigate its theraptherapeutic potential in AA.

In this letter, we report a case series of patients with severe AA who showed improvement following treatment with abrocitinib. Six patients with severe AA, who were treated at our hospital between July 2023 and June 2024, were included in this report. These patients, who had a Severity of Alopecia Tool (SALT) score $\geq$50, indicating severe AA, either had no response to systemic glucocorticoids or refused their use. They received 100 mg of abrocitinib daily for at least 12-weeks. If the patient has recovered at 12-weeks, the dosing interval is incrementally extended. Patient characteristics were assessed at baseline and SALT scores were measured every 4-weeks.

The patients' average age was 38.4 $\pm$ 8.7 years (range, 27–52), with a duration of AA ranging from 1.5 to 6 months (average 3.1 $\pm$ 1.7 months). Detailed demographics and clinical characteristics are summarized in Table 1. At baseline, the mean SALT score was 56 $\pm$ 7.8 (range, 50–70), and after 8-weeks of treatment, all patients achieved a SALT score $\leq$20. Two-thirds of the patients (4/6) experienced complete recovery within 12 weeks (SALT score = 0), with an average final SALT score of 2 $\pm$ 3.6 (range, 0–9). Table 1 also illustrates the clinical improvements observed during the treatment period. Fig. 1(A–C) presents representative figures of these patients at baseline and 12-weeks after treatment. Notably, abrocitinib was well-tolerated with no adverse events reported.

To our knowledge, these are the first clinical experiences evaluating the role of abrocitinib for the treatment of severe diffuse AA, and our patients showed a rapid response to abrocitinib. Past studies have reported successful treatment of abrocitinib in several AA cases with concomitant AD.[4] Additionally, there is a hypothesis that diffuse AA may be related to hypersensitivity and an increase in serum IgE level.[2] All six of our six patients had a history of allergic rhinitis and one had moderate AD, where, four of six patients exhibited high serum IgE levels, suggesting that concurrent atopic diseases might predict a positive response to abrocitinib treatment. It is noteworthy to consider that two patients' conditions worsened after reducing their medication, so further exploration is needed on how to proceed

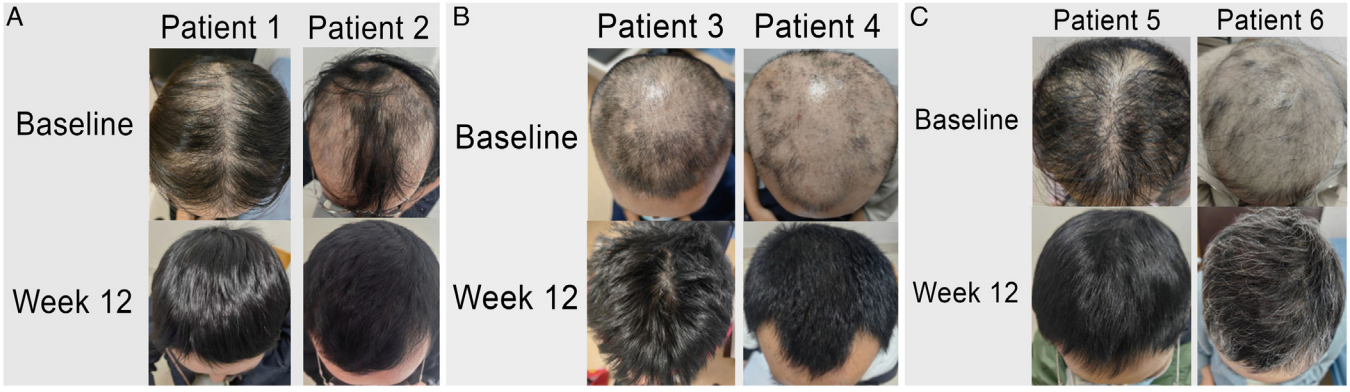

Fig. 1 (A–C) Representative figures of AA patients at baseline and 12-weeks after treatment.

☆ Study conducted at the Huashan hospital, Fudan University, Shanghai, China.

Table 1 Clinical characteristics and SALT scores of patients.

Patients (no.)	Sex	Age, years	Disease duration, months[a]	IgE level (KUA/L)[b]	Atopic diseases	Initial SALT score	SALT score at week 4	SALT score at week 8	SALT score at week 12	SALT score at week 24
1	F	35	1.5	121	AR	54	36	4	0	5
2	M	27	6	576	AR	60	34	16	9	4
3	F	42	4	47.2	AR	50	14	2	0	3
4	M	41	2	225	AR, AD	70	31	2	1	0
5	F	33	3	136	AR	52	16	4	0	0
6	F	52	2	20.1	AR	50	20	4	0	0

F, Female; M, Male; AR, Allergic Rhinitis; AD, Atopic Dermatitis; SALT, Severity of Alopecia Tool.
[a] The disease duration is determined from the most recent exacerbation.
[b] A serum total IgE level >60 KUA/L was defined as elevated.

with drug reduction. We advocate for further investigation through randomized controlled trials to assess the efficacy and safety of abrocitinib for severe AA.

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Authors' contributions

Zheng Li: Investigation; resources; visualization; writing-original draft.

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Ke Tao: Investigation.

Ying Miao: Investigation.

Chunya Ni: Investigation.

Youyu Sheng: Investigation.

Jinran Lin: Funding acquisition; project administration; resources; writing-review & editing.

Wenyu Wu: Conceptualization; project administration; funding acquisition; resources.

Conflicts of interest

None declared.

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LETTER - CLINICAL

Efficacy of upadacitinib in the management of atopic dermatitis, Crohn's disease, and hidradenitis suppurativa: one treatment, multiple indications☆

Dear Editor,

Atopic dermatitis (AD) and Crohn's disease (CD) are chronic inflammatory diseases that share pathophysiological similarities, although their immunopathological mechanisms have not been fully elucidated.[1]

Janus kinase inhibitors (JAKi) have proven to be effective in the treatment of inflammatory and autoimmune diseases, including AD and CD.[2] Moreover, the literature reports a predisposition for a bidirectional association between AD and CD.[1] This article discusses two cases of the association of AD and CD treated with upadacitinib, achieving control of both diseases.

Case 1. A 47-year-old female patient presented AD and asthma since childhood. At 39 years old, she developed CD, and received mesalazine, prednisone, and antibiotics. In 2019, there was worsening of CD with enterorrhagia, diarrhea, vomiting and weight loss. The fecal calprotectin level was 56 mcg/g (RV < 50 μg/g) and treatment with ustekinumab was started.

In 2021, she had an AD exacerbation, with erythematous-crusted lesions, lichenification and excoriation on the neck, limbs, scalp, and erythematous-desquamative lesions on the hands (Fig. 1A). Disease activity scores were high: Scoring Atopic Dermatitis (SCORAD) of 45 and Dermatology Life Quality Index (DLQI) of 20.

She used cyclosporine 300 mg/day with initial improvement but showed a loss of response after three months. Upadacitinib 15 mg/day was initiated with significant improvement in AD and CD, with a fecal calprotectin level of 10 mcg/g. After seven months, ustekinumab was discontinued due to CD control, and she currently has SCORAD of 0 and DLQI of 0 (Fig. 1B).

Case 2. A 19-year-old male patient presented AD and asthma in childhood and was diagnosed with CD in 2015. He had severe acne and hidradenitis suppurativa (HS) in 2019, treated with isotretinoin. He had previously used mesalazine, adalimumab, and prednisone for CD and has been using ustekinumab since 2020.

In 2022, he had simultaneous worsening of AD and HS: fistulized nodules on the face, abdomen, axillae, and buttocks (Fig. 2). He had intense pruritus and exudative erythematous-squamous lesions, on the face, hands, thighs, and feet. The IgE level was 1006 kU/L and fecal calprotectin was >3000 μg/g. DLQI was 18 and SCORAD was 65.4. An ileocolonoscopy showed deep ulcers and inflammation in the right colon (Fig. 3).

Upadacitinib 15 mg/day was started with complete improvement of the skin lesions (Fig. 2). The patient showed clinical remission of CD, with fecal calprotectin normalization at 35 μg/g and ileocolonoscopy showing endoscopic remission (Fig. 4).

Upadacitinib is a JAK1i, currently approved for AD treatment in Brazil and for AD and CD in the USA. Despite the absence of protocols/guidelines for the concomitant treatment of multiple inflammatory diseases, the profile of inhibited interleukins potentially encompasses associated diseases.[1]

Mendelian randomization studies and meta-analyses have highlighted a bidirectional relationship between AD and CD and other inflammatory/autoimmune diseases, such as rheumatoid arthritis.[1] Among the mechanisms that could explain the association are shared predisposing factors such as stress, obesity, lack of breastfeeding, urbanization, and diet.[3]

Inadequate inflammatory responses to intestinal or cutaneous microorganisms, leading to disruption of the external environment protective barrier, be it intestinal epithelium or epidermis, together with dysbiosis and colonization by pathogenic microorganisms, provide possible explanations.[3–5]

Genetic predisposition may play a role, as genes that predispose to AD regulate T-cell differentiation and function, as

☆ Study conducted at the Division of Dermatology, Department of Internal Medicine, Faculty of Medicine, Universidade de São Paulo, Ribeirão Preto, SP, Brazil.

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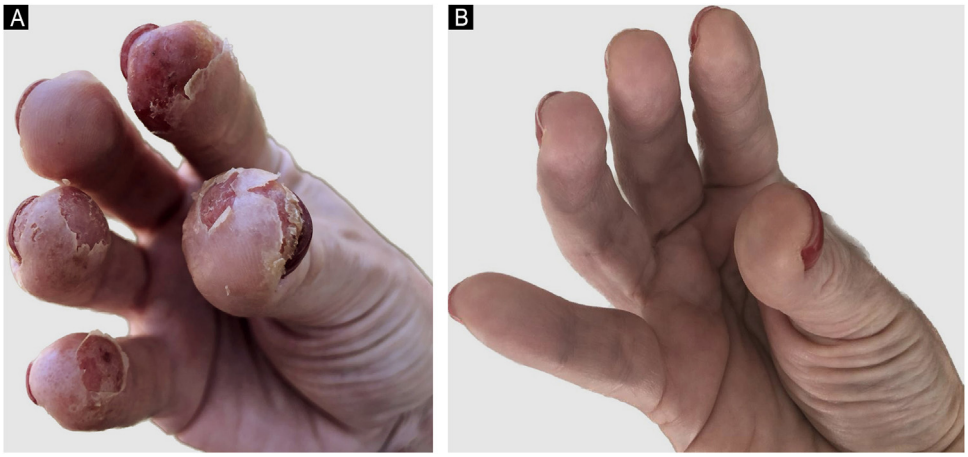

Fig. 1 Case 1 (A) shows extensive erythematous and desquamative lesions, especially on the digital pulps of the right hand, with some crusts; (B) complete improvement of the skin lesions after upadacitinib.

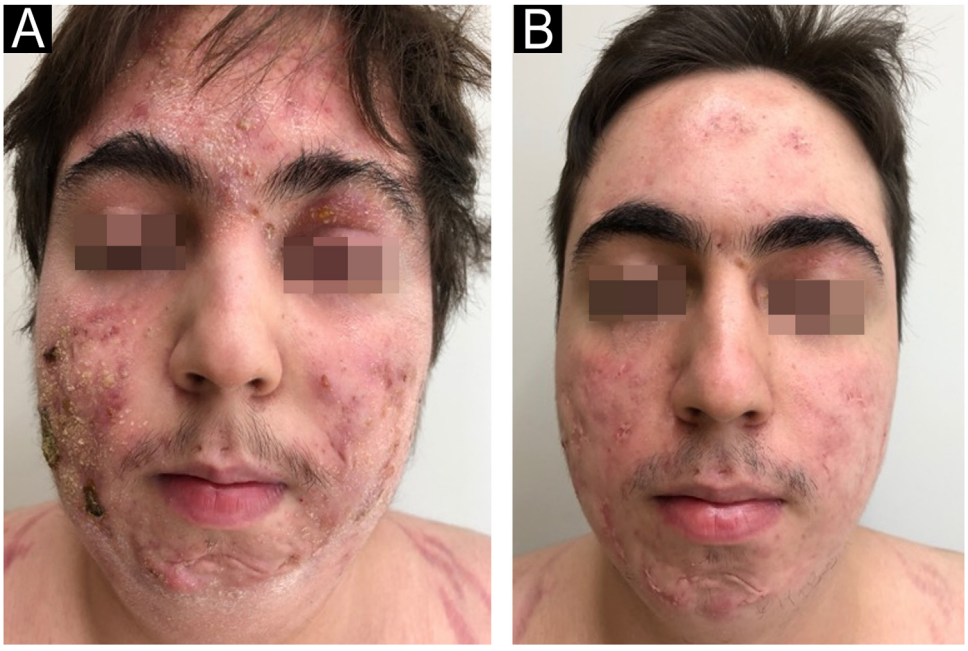

Fig. 2 Case 2 (A) multiple lesions with erythema, desquamation, crusts, and also nodules, some containing secretion; (B) almost complete improvement of the inflammation, leaving unaesthetic scars on the face, especially in places where there were nodules.

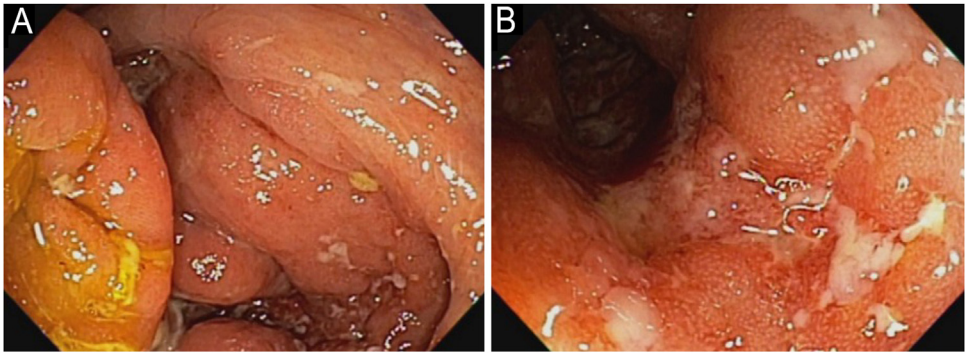

Fig. 3 Ileocolonoscopy before upadacitinib treatment. The ileocecal valve (A) and cecum (B) show multiple deep ulcers, indicative of active Crohn's disease.

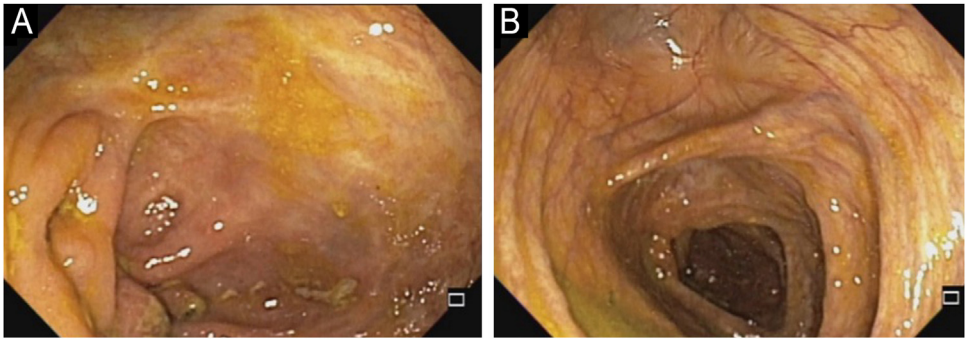

Fig. 4 Ileocolonoscopy after treatment with upadacitinib. The ileocecal valve (A) and the cecum (B) show complete mucosal healing.

well as certain components of the innate immune system, and some genes are shared with other diseases, such as CD.[6]

The shared T-cell-mediated inflammation in AD and CD is noteworthy: one-third of AD patients exhibit immune autoreactivity, particularly those with chronic or persistent disease.[7] Exaggerated Th1 and Th17 responses promote autoimmunity and contribute to the chronicity of CD, and are also implicated in AD persistence. It has been speculated that chronic inflammation in AD may foster sustained Th1/Th17 inflammation and predispose to diseases such as CD.[8,9]

The understanding of the pathophysiology and epidemiology does not yet provide a precise explanation for the association between these diseases. However, one must remain vigilant to improve therapeutic approaches. The prospect of treating inflammatory pathologies with a single medication represents remarkable progress, as drug interactions and unwanted side effects are reduced. Although the reported cases demonstrate promising results in the treatment of multiple inflammatory diseases with upadacitinib, further studies are required to confirm its long-term safety and efficacy. Until more evidence emerges, it is essential that therapy be individually and carefully monitored.

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Authors' contributions

Roberto Bueno-Filho: Design and planning of the study; collection of data, or analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Daniel Lorenzini: Design and planning of the study; collection of data, or analysis and interpretation of data; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; approval of the final version of the manuscript.

Rogério Serafim Parra: Collection of data, or analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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LETTER - CLINICAL

Golimumab-induced lichen planus pigmentosus in a patient with ulcerative colitis☆

Dear Editor,

Tumor necrosis factor alpha (TNF-alpha) inhibitors have proven efficacy in managing various immune-mediated inflammatory conditions. Five TNF-alpha inhibitors are currently available: infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab. Generally, TNF-alpha inhibitors demonstrate favorable tolerability profiles but are linked to specific adverse reactions, notably cutaneous manifestations.[1,2] These include injection/infusion-related responses, skin infections, neoplasms, and immune-mediated manifestations.[2] In this report, we present a rare case of lichen planus pigmentosus potentially triggered by golimumab administration.

A 43-year-old male patient, undergoing golimumab treatment (100 mg monthly) for a year due to a history of ulcerative colitis, presented with a progressive facial hyperpigmentation evolving over six months. The patient, with Fitzpatrick skin phototype IV, worked a desk job and had minimal sun exposure. He denied any prior history of facial or mucosal hyperpigmentation and confirmed no prior usage of topical treatments or daily cosmetic products. On physical examination, diffuse pruritic, brown-colored hyperpigmen-

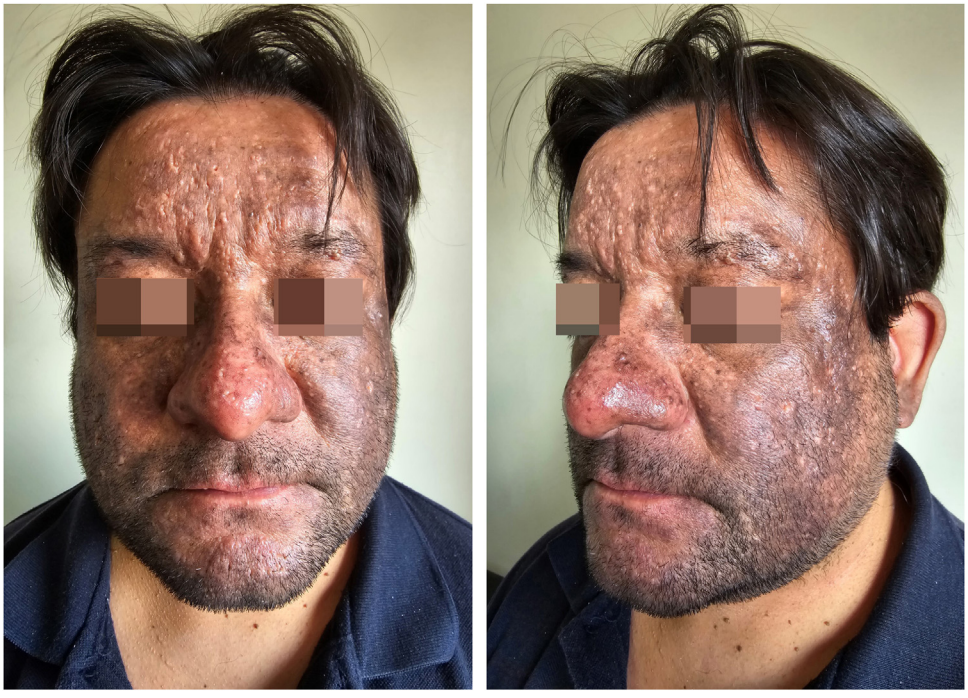

Fig. 1 Brown-gray patches with purplish hue on the face. Note eyelids involvement.

☆ Study conducted at the Universidad de los Andes, Santiago, Chile.

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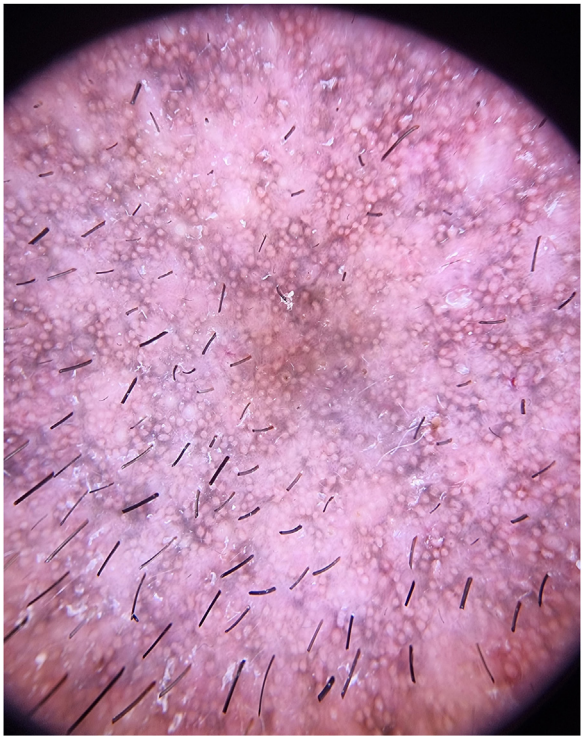

Fig. 2 Dermoscopy. Grayish-brown hyperpigmentation with a lichenoid pattern encircling follicular openings and isolated bright white rosette-like structures.

tation was observed across the face, involving the eyelids but sparing the nasal tip, devoid of scaling or erosions (Fig. 1). The patient exhibited intact mucous membranes and appendages. The dermoscopic evaluation revealed a diffuse grayish-brown hyperpigmentation with a lichenoid pattern encircling follicular openings and isolated bright white rosette-like structures (Fig. 2).

Considering the clinical context and the progressive extension of lesions, a histopathological study was conducted, indicating findings of superficial and periadnexal lymphoplasmacytic dermatitis with a focal lichenoid interface and dermal melanosis, consistent with pigmented lichenoid dermatitis (Fig. 3).

Further investigation revealed no other known triggers for lichen planus pigmentosus, such as hepatitis B or C virus, mustard oil, henna, nickel, or hair dye. A standard European patch test was performed, which returned negative results. Topical immunomodulatory therapy was initiated and suspecting a cutaneous adverse reaction secondary to golimumab usage, a reassessment by Gastroenterology was warranted. Golimumab was suspended and changed to adalimumab; this decision was influenced by the fact that, in the public health system to which the patient belongs, only TNF-alpha inhibitors (golimumab, adalimumab, infliximab) are economically covered for the treatment of refractory or severe ulcerative colitis. Currently, the patient has been on adalimumab for 4 months. The lesions have shown a slight reduction (Fig. 4); however, the pruritus has significantly diminished, despite the patient discontinuing the topical immunomodulatory therapy without medical guidance.

The majority of documented cases involving immune-mediated cutaneous eruptions associated with TNF-alpha inhibitors commonly represent the onset of psoriasis or psoriasiform drug reactions.[1] However, albeit rare, there is an increasing number of reports associating TNF-alpha inhibitors with the onset of lichenoid eruption.[3] Among these reported cases, the frequency of occurrences was highest with infliximab, followed by etanercept, adalimumab and certolizumab, in decreasing order.[4,5] No previously reported cases of a lichenoid eruption attributed to the use of golimumab were found in the English or Spanish literature upon investigation.

The pathophysiology of anti-TNF-alpha-induced lichenoid eruption remains unclear. However, some authors propose that TNF-alpha inhibition in specific genotypes may lead to the upregulation of opposing cytokines, such as interferon-alpha. This upregulation could activate T-cells and dendritic

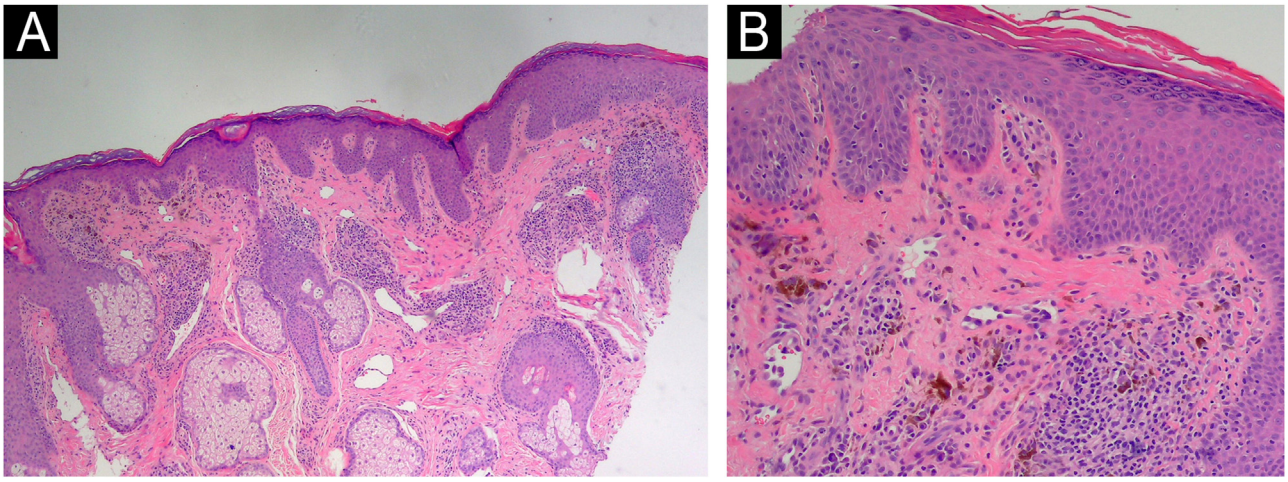

Fig. 3 Histopathological examination of the skin biopsy shows features consistent with pigmented lichenoid dermatitis. (A) The epidermis exhibits irregular hyperkeratosis and acanthosis, with a perivascular and perifollicular lymphoplasmacytic infiltrate in the dermis, accompanied by abundant melanophages (Hematoxylin & eosin, ×100). (B) Civatte bodies are also present (Hematoxylin & eosin, ×200).

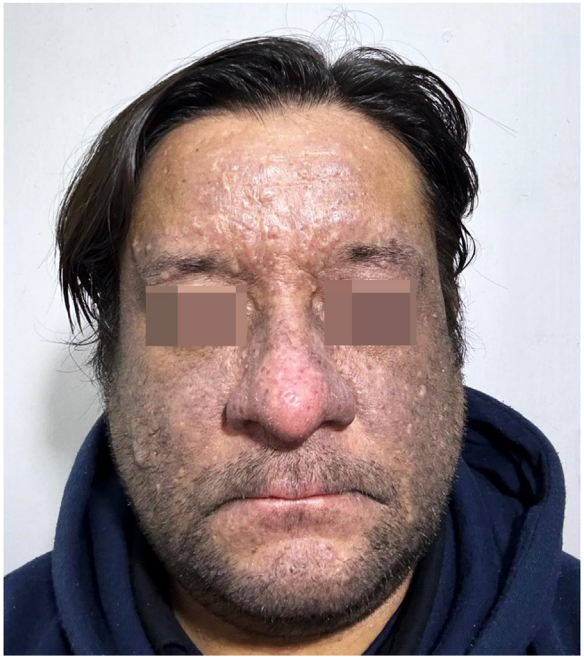

Fig. 4 Facial hyperpigmentation after 4 months of adalimumab therapy, showing a slight reduction following the discontinuation of golimumab.

cells, triggering an inflammatory response that may induce lichen planus.[6]

Reporting rare adverse effects of these medications, increasingly used in clinical practice, is crucial to establishing pharmacovigilance registries. These registries help to understand the long-term implications of treatment with TNF-alpha inhibitors, which are increasingly used and currently extend beyond the timeframe of randomized controlled trials.

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Authors' contributions

Daniela Alfaro-Sepúlveda: The study concept and design, data collection, or analysis and interpretation of data, writing of the manuscript or critical review of important intellectual content, effective participation in the research guidance, intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases, critical review of the literature and final approval of the final version of the manuscript.

Claudio Escanilla: The study concept and design, data collection, or analysis and interpretation of data, writing of the manuscript or critical review of important intellectual content, effective participation in the research guidance, intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases, critical review of the literature and final approval of the final version of the manuscript.

Fernando Valenzuela: The study concept and design, data collection, or analysis and interpretation of data, writing of the manuscript or critical review of important intellectual content, effective participation in the research guidance, intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases, critical review of the literature and final approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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LETTER - CLINICAL

Immunotherapy-induced psoriasis successfully treated with Guselkumab in a patient with metastatic gastric cancer☆

Dear Editor,

Programmed Death-1/Programmed Death Ligand-1 (PD-1/PD-L1) and Cytotoxic T-Lymphocyte Associated Protein-4 (CTLA-4) are regulatory proteins that inhibit T-cell activity.[1] Immune checkpoint inhibitors remove the blockade of the immune system, allowing T-cells to act against malignant cells.[1,2] Due to the inactivation of these co-inhibitory receptors, immune-mediated adverse events may arise, affecting the gastrointestinal tract, lungs, endocrine system, kidneys, liver, eyes, musculoskeletal system, nervous system, and skin.[3] Among cutaneous lesions associated with anti-PD-1 and anti-CTLA-4 drugs, maculopapular rash, psoriasis, pruritus, vitiligo, bullous pemphigoid, Stevens-Johnson syndrome/toxic epidermal necrolysis, and other less common disorders (drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, Sweet syndrome, pyoderma gangrenosum, dermatomyositis, vasculitis) were described.[4] Immunotherapy-related psoriasis occurs *de novo* or as an exacerbation of previous psoriasis.[5] We describe a case of immunotherapy-induced psoriasis in a patient with metastatic gastric cancer successfully treated with Guselkumab.

A 62-year-old male presented with plaques with moderate infiltration and mild scaling on the back, frontal, and pre-auricular regions for two months (Fig. 1). He had

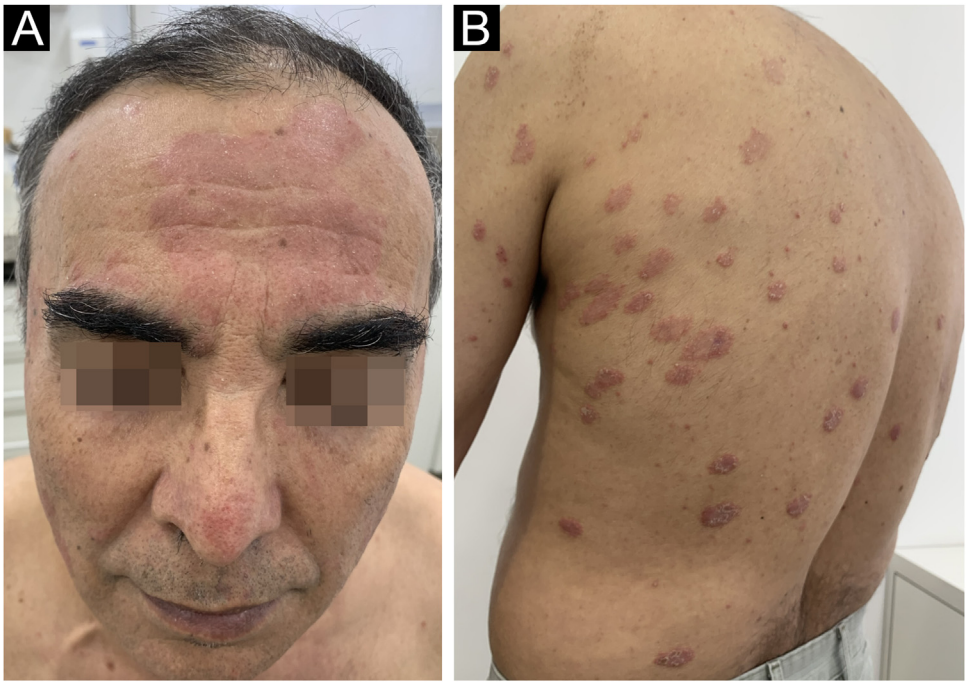

Fig. 1 Erythematous and scaling plaques on the forehead (A), and back (B).

☆ Study conducted at the Hospital Alemão Oswaldo Cruz, São Paulo, SP, Brazil.

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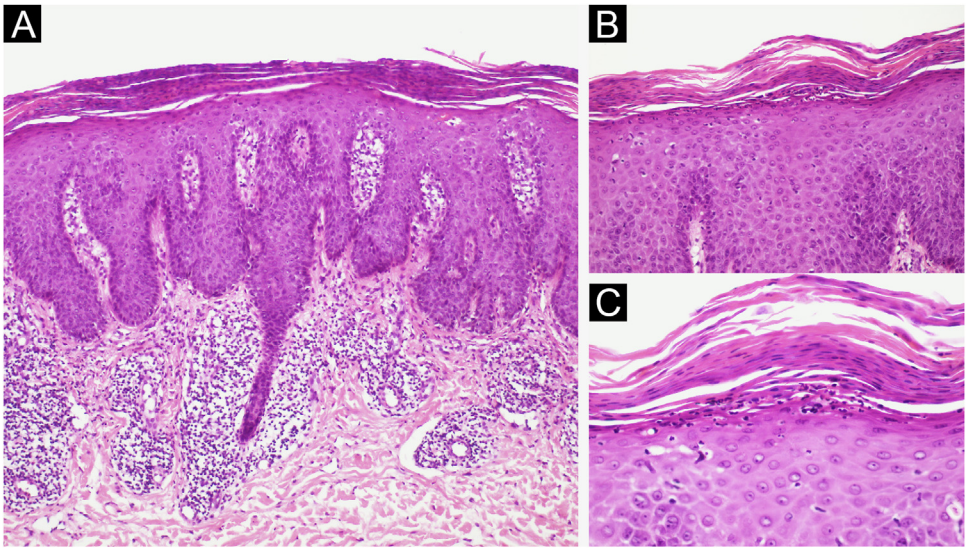

Fig. 2 (A) Regular acanthosis, hypogranulosis, parakeratosis, dilated capillaries in the papillary dermis (Hematoxylin & eosin, ×100). (B) Parakeratosis and Munro's microabscesses (B, Hematoxylin & eosin, ×200). (C) Higher magnification showing parakeratosis and Munro's microabscesses (C, Hematoxylin & eosin, ×400).

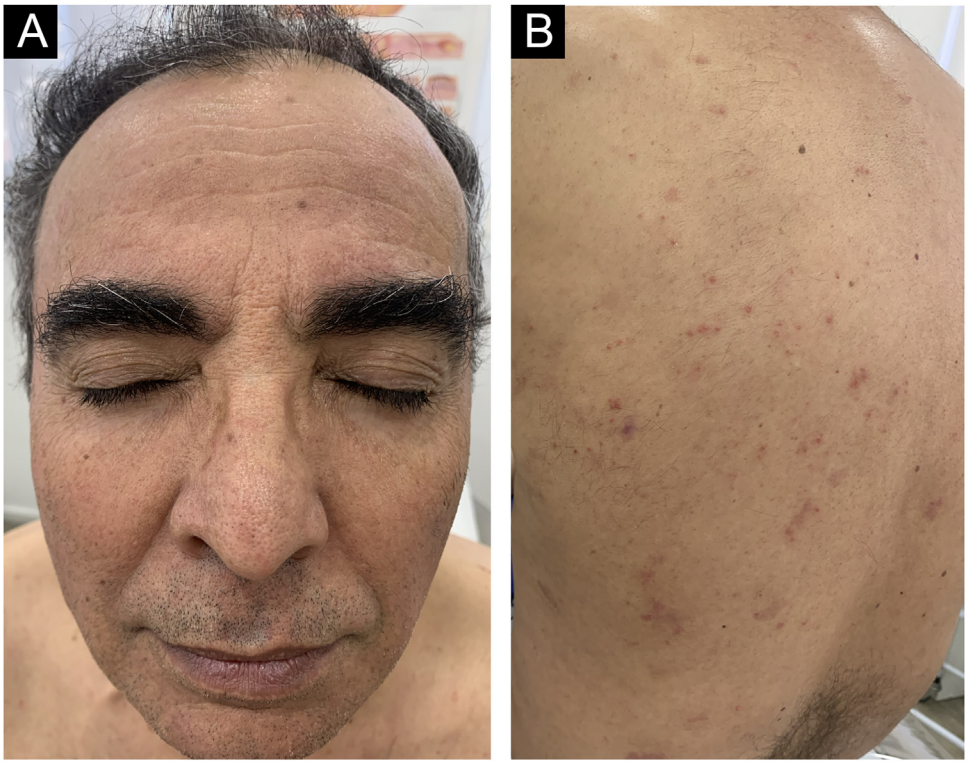

Fig. 3 Significant improvement of skin lesions after 2 doses of Guselkumab.

a previous diagnosis of stage IV gastric adenocarcinoma with liver metastasis and has been treated with nivolumab 240 mg every two weeks for six months with partial response. He had no history of previous cutaneous diseases and denied a family history of immune-mediated disorders. The hypothesis of nivolumab-induced psoriasis was raised. Skin biopsy revealed regular acanthosis, hypogranulosis, parakeratosis, dilated capillaries in the papillary dermis, and Munro's microabscesses compatible with psoriasis (Fig. 2). Skin lesions were refractory to topical steroids and due to intense pruritus, the patient stopped cancer treatment. Because of the lack of response to topical steroids, difficulty in adhering to phototherapy, and contraindication for the use of acitretin and methotrexate due to liver metastasis, the patient started Guselkumab 100 mg at weeks 0-, 4-, and every 8-weeks. After two applications, significant improve-

ment was observed (Fig. 3). After 12-months skin lesions completely resolved, but malignant disease progressed with new liver lesions. Nivolumab was restarted, and skin remains clear with no significant adverse events due to Guselkumab.

Psoriasis associated with immune checkpoint inhibitors occurs in approximately 0.5% of patients.[6] It may occur *de novo* (70%) or as an exacerbation of previous psoriasis (30%), and skin lesions usually appear 5–12-weeks after the start of immunotherapy.[5]

Immune checkpoint inhibitors increase T-cell response against tumor cells, and the increased release of pro-inflammatory T-helper 1 (Th1) and 17 (Th17) cytokines may result in exacerbation or induction of psoriasis.[7]

A large retrospective study analyzing 7008 patients who developed cutaneous immune-related adverse events secondary to anti-PD-1 or anti-PD-L1 for treatment of different malignant diseases showed a strong association between the development of cutaneous lesions, including psoriasis, and response to immune-checkpoint inhibitors.[8] Some studies show that guttate lesions and psoriasis affecting >10% of the body surface area are associated with better immunotherapy responses, but pruritus is a negative predictor of response.[5]

Treatments reported for immunotherapy-induced psoriasis include topical steroids, calcipotriol, phototherapy, and systemic therapies. The most common systemic agent administered is acitretin since it does not have immunosuppressive effects.[5] The impact of biologics on the treatment of psoriasis in cancer patients is not fully understood. Most evidence shows no increased risk of cancer in patients with psoriasis, rheumatoid arthritis, or inflammatory bowel disease treated with anti-tumor necrosis factor-alpha, anti-interleukin 17, anti-interleukin 12 and/or 23, or Janus-kinase inhibitors.[9,10]

Guselkumab is a fully human monoclonal antibody that inhibits interleukin 23 by binding to its subunit p19. The use of Guselkumab in patients with previous diagnoses of cancer has been investigated in small case series.[9,10]

We reported the case of *de novo* psoriasis secondary to immune-checkpoint inhibitor therapy that was successfully treated with Guselkumab with rapid response and no significant adverse events. We highlight the importance of treating immune-mediated adverse events secondary to immunotherapy since the use of this type of drug is increasing rapidly due to its efficacy in different types of cancers, and we must be aware to treat these patients to provide a good quality of life and prevent from discontinuing or reducing the dosage of cancer treatment.

Authors' contributions

Denis Miyashiro: The study concept and design; data collection, or analysis and interpretation of data; Writing of the manuscript or critical review of important intellectual content; Effective participation in the research guidance; Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; Critical review of the literature; Final approval of the final version of the manuscript.

Thiago William Carnier Jorge: Data collection, analysis, and interpretation of data; Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; Critical review of the literature; Final approval of the final version of the manuscript.

André Luís da Silva Hirayama: Data collection, analysis, and interpretation of data; Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; Critical review of the literature; Final approval of the final version of the manuscript.

José Antonio Sanches: The study concept and design; Effective participation in the research guidance; Final approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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LETTER - CLINICAL

Mpox in a patient with AIDS: clinical management with tecovirimat and surgical correction of unaesthetic scars*

Dear Editor,

A 33-year-old male patient, single, born and raised in Manaus, Amazonas, Brazil, sought medical care due to ulcerated lesions on the face, chest, upper limbs, gluteal region, and anorectal mucosa (Figs. 1 and 2). He also reported recurrent fever and anal pain. He had been treated with several medications, such as anti-inflammatory drugs, topical, and systemic antibiotics, for over a month, without response. He had no neurological or respiratory symptoms and denied comorbidities.

Laboratory tests were requested, and the main results were: qPCR for Monkeypox – detectable virus; Anti-HIV – reactive; VDRL – 1:256; cerebrospinal fluid analysis – no findings suggestive of neurosyphilis; colonoscopy – ulcerative proctitis (Fig. 1). The anatomopathological examination of the ulcerated skin lesion showed epidermal necrosis, ballooning of keratinocytes, Guarnieri inclusion bodies and a dermal inflammatory infiltrate consisting of histiocytes, lymphocytes and neutrophils (Fig. 3).

The initial treatment included benzathine penicillin, a single dose of 2.4 million IU, with a subsequent adequate decrease in VDRL; and antiretrovirals (Dolutegravir, Lamivudine and Tenofovir), in addition to supportive measures.

Given the worsening of the skin lesions, anal pain, and extension of the anorectal involvement, the patient was hospitalized in isolation, submitted to colostomy and, seven days after admission, started treatment with tecovirimat, 600 mg every 12 hours, for 14 days.

Approximately 20 days after starting therapy with tecovirimat, associated with systemic antibiotic therapy for secondary infection, healing of the skin lesions was observed (Fig. 2), without adverse events.

The regression of the skin ulcers evolved with hypertrophic scars, mainly in the glabella and labiomental region. At this stage, surgical repair was indicated, performed ten months after hospital discharge.

Initially, excision and correction of the labiomental scar were performed with an advancement flap and the creation of a Burow's triangle (Fig. 4). Subsequently, the glabella scar was corrected.

Mpox is caused by the Monkeypox virus – a double-stranded DNA virus belonging to the Orthopoxvirus genus, Poxviridae family. Clinically, vesicopustular, ulcerative-crusted, or ulcerative-vegetative lesions are observed; fever, myalgia, headache, and lymphadenopathy may be present.[1,4–9]

The disease has been endemic in African countries for decades, causing occasional outbreaks restricted to the continent. However, in 2022, and more recently in August 2024, international epidemic outbreaks were recorded, with the spread of strains 2b and 1b respectively, and the World Health Organization (WHO) declared the disease a ''Public Health Emergency of International Concern'' in both scenarios. Strain 1b, detected in the Democratic Republic of the Congo, has been shown to be more virulent and lethal, with a particularly severe evolution in immunocompromised individuals, children, and pregnant women. There are no records of the circulation of this strain in Brazil to date. Since 2022, more than 10,000 confirmed or probable cases of Mpox have been reported in Brazil, including 16 deaths in immunosuppressed individuals.[5,10]

Before the outbreaks observed in 2022, it was assumed that transmission was mainly related to contact with skin lesions and the respiratory tract. However, the demonstration of the presence of the virus in semen and rectum indicated sexual transmission as a risk factor, mainly among men who have sex with men (MSM); 91% of the patients with Mpox are male and more than 50% are MSM. Mpox is also a risk factor for HIV – coinfection occurs in more than 40% of the cases.[2,3]

The patient in this report was diagnosed with HIV, with CD4 T-lymphocytes at 44 cells/mm^3 and a viral load of 94,000 copies/mL, at the time of the Mpox diagnosis. Sexual history revealed unprotected anal sex with other men.

Patients who are coinfected with Mpox and HIV, mainly with a low CD4 + T count (< 200 cells/mm^3), have a longer disease duration. The lesions may be larger and have a necrotic appearance, as observed in this case. Bacterial infections, sepsis, and death may also occur. Some authors

* Study conducted at the Fundação Hospitalar Alfredo da Matta, Manaus, AM, Brazil.

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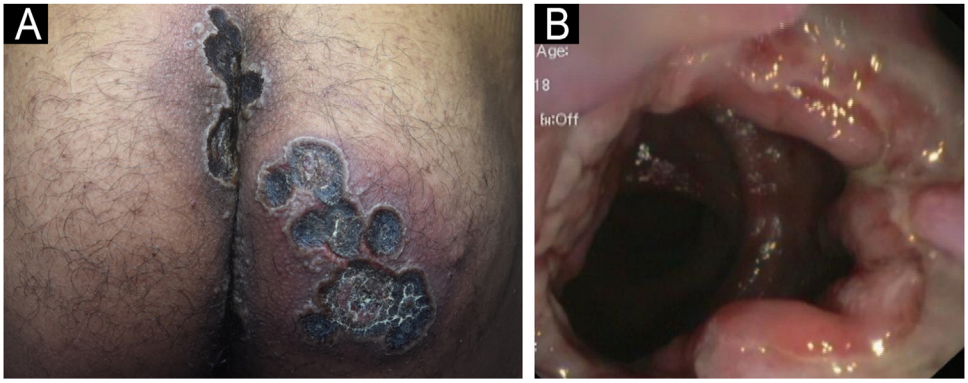

Figure 1 (A) Ulcero-necrotic lesions on the buttocks. (B) Colonoscopy image: ulcerative proctitis.

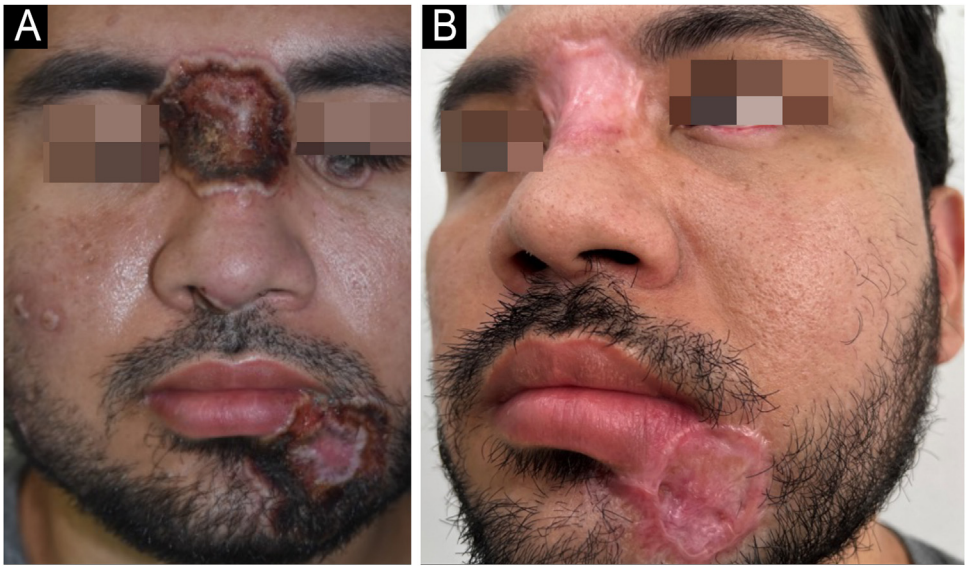

Figure 2 (A) Vesicopustular lesions in the malar region; ulcer in the lower eyelid, glabella and labiomental region. (B) Two months after treatment.

consider Mpox to be an opportunistic infection or an AIDS-defining disease.[3]

Mpox treatment consists of general care and supportive measures. Recently, on an emergency basis, the Centers for Disease Control and Prevention (CDC) authorized the use of tecovirimat, brincidofovir, cidofovir, and trifluridine (ophthalmic solution). In Brazil, in 2022, the National Health Surveillance Agency (Anvisa, *Agência Nacional de Vigilância Sanitária*) approved the compassionate use of tecovirimat only in severe cases of the disease, as in the case reported herein. This drug inhibits the VP37 protein, responsible for virion enveloping, preventing viral replication. It is presented in 200 mg capsules, for oral administration, at a dose of 600 mg, every 12 h, for 14 days, for adults weighing >40 kg. In adolescents and children weighing at least 13 kg, the daily dose is adjusted according to weight. The most common adverse effects are headache, nausea, and gastrointestinal symptoms. There is no need to adjust the dose for patients with liver disease; the drug is not recommended for patients with kidney disease with creatinine clearance <30 mL/min.[6,7]

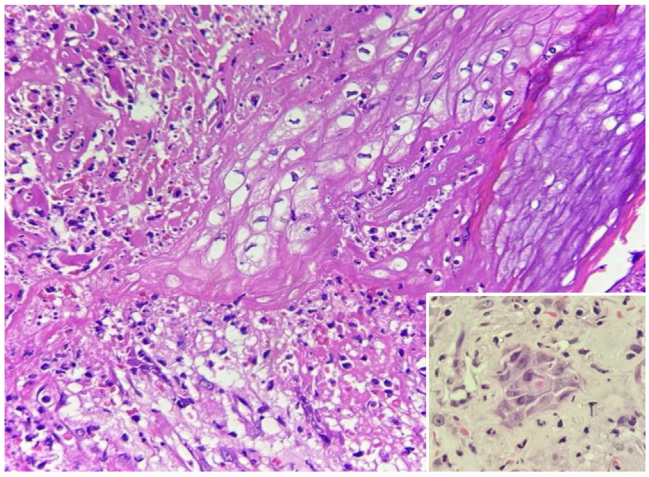

Figure 3 Histopathology: ballooning of keratinocytes (Hematoxylin & eosin, ×400). Inset: Guarnieri's inclusion bodies.

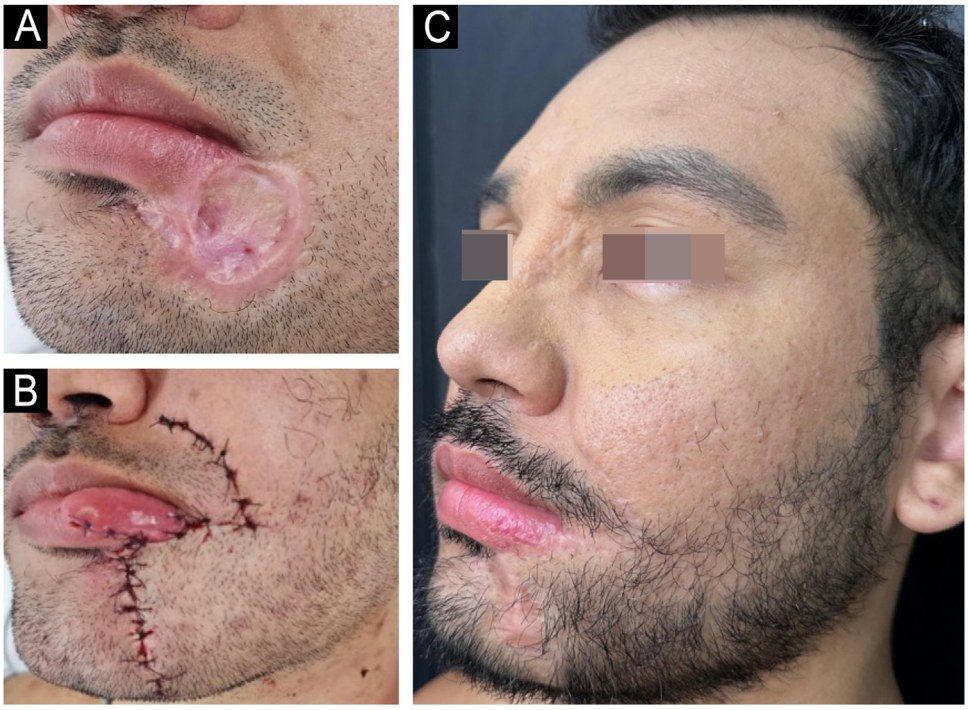

Figure 4 (A) Scar in the left labiomental region. (B) Immediate postoperative period. (C) Late postoperative period.

The efficacy of tecovirimat against Mpox was established in animal models, and there is limited safety and pharmacokinetic data in humans. In these animal-based studies, tecovirimat showed the ability to significantly reduce mortality rates among animals exposed to Mpox, achieving survival rates of no less than 90%.[7]

Mpox causes significant morbidity and mortality, mainly related to unaesthetic scars. Surgical excision, with or without adjuvant treatments, constitutes an efficient and low-cost therapeutic alternative.[3,8] In the present case, the scars were excised, with satisfactory results (Fig. 4C).

The increase in the number of cases of Mpox has raised concern among health authorities worldwide. Cutaneous manifestations are evident and the role of dermatologists in the early diagnosis is essential. Isolation measures, contact control, mandatory notification, educational and prevention efforts, together with public health policies are essential to reduce the risk of spreading the virus.

Mpox represents a global challenge, requiring greater public awareness of the disease and more studies related to specific treatments and vaccines.

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Authors' contributions

Kananda Kesye Sousa Nunes: Design and planning of the study; drafting and editing of the manuscript; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

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Beatriz Costa Cardoso: Drafting and editing of the manuscript; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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LETTER - CLINICAL

Nail involvement due to immunoglobulin G4 (IgG4)-related disease in a person living with HIV*☆

Dear Editor,

Immunoglobulin-4 (IgG4)-related disease is an immune-mediated disorder characterized by the presence of a lymphoplasmacytic infiltrate rich in IgG4-positive tissue plasma cells and elevated serum IgG4. This condition causes inflammation with fibrosis and presents with symptoms that vary depending on the affected organ. It usually affects the pancreas, salivary glands, lacrimal glands, biliary tract, and peritoneum. Cutaneous involvement is rare and occurs most frequently in the jaw, mental protuberance, and cervical region, and this is the first description in the literature involving the nail apparatus.[1]

A 47-year-old man, living with HIV, with a CD4 count of 349 cells and an undetectable viral load, complained of progressive nail changes over the past two months, which were asymptomatic and did not improve after self-medication with ointments. In his past history, he had been previously treated for pulmonary tuberculosis and onychomycosis. On examination, edema was observed in the proximal nail fold, with ulceration of the nail bed and complete absence of the nail plate of the fourth finger of the right hand, in addition

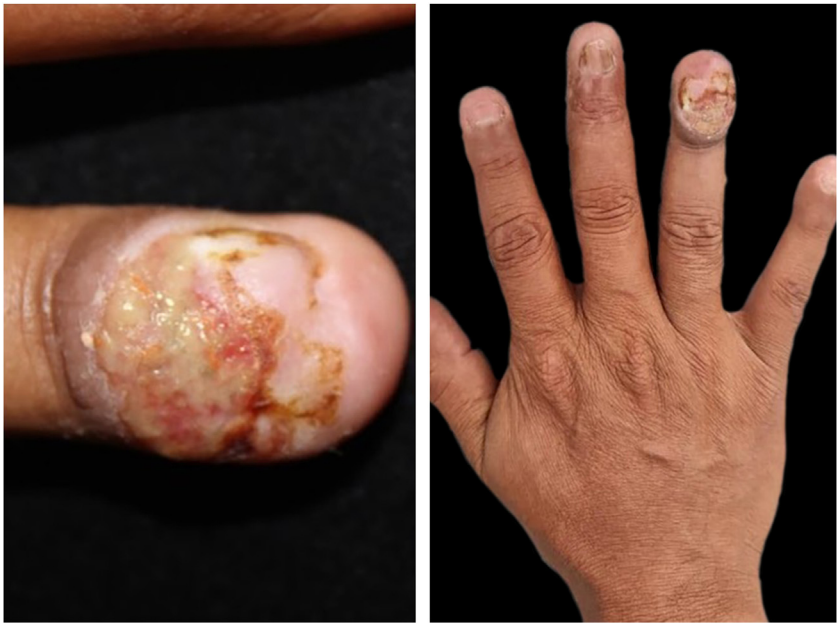

Fig. 1 Clinical manifestation of IgG4-related disease in the nail: (A) significant involvement of the nail apparatus with edema in the proximal nail fold, nail bed ulceration, and complete absence of the nail plate. (B) Onychodystrophy is seen in the other nail plates.

☆ Study conducted at the Fundação de Medicina Tropical Doutor Heitor Vieira Dourado (FMT-HVD), Manaus, AM, Brazil.

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to onychodystrophy in the other nails (Fig. 1). Onychoscopy of the lesion showed irregular vascularization of the nail bed (Fig. 2). There were no other skin lesions or alterations in the lymphatic, cardiovascular, respiratory or gastrointestinal tract systems.

A skin biopsy was performed and sent for tissue microscopy, culture and histopathology. The microbiological examination was negative for fungi and AFB. The histopathological examination showed ulceration and a lymphoplasmacytic infiltrate in the connective tissue, interspersed with granulocytes, eosinophils and extensive areas of fibrosis. Immunohistochemistry confirmed the presence of IgG4+ plasma cells > 200/high power field (HFP), with an IgG4+/IgG ratio > 40% (Fig. 3). Additional histochemistry did not reveal fungal or bacterial organisms. Moreover, serum IgG4 was increased: 434 mg/dL. Laboratory tests, with the exception of ESR (10 mm), were normal or negative: complete blood count; biochemistry; VDRL; Anti-LA; C-anca; P-anca; Anti-DNA and CRP. There was no bone involvement on the X-ray. Computed tomography scans of the chest, abdomen and pelvis were performed, which detected architectural distortion in the lung apices, due to bands of atelectasis and bronchiectasis in between, in addition to multiple calcified retroperitoneal lymph node enlargements, suggesting previous granulomatous infection. The patient underwent two sessions of intralesional infiltration with triamcinolone acetonide 2.5 mg/mL, after which there

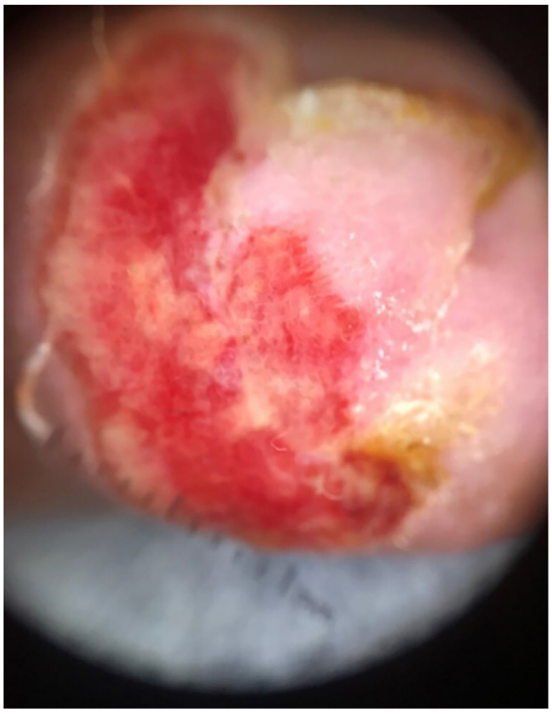

Fig. 2 Onychoscopy of IgG4-related nail disease: erosion and irregular vascularization of the nail bed.

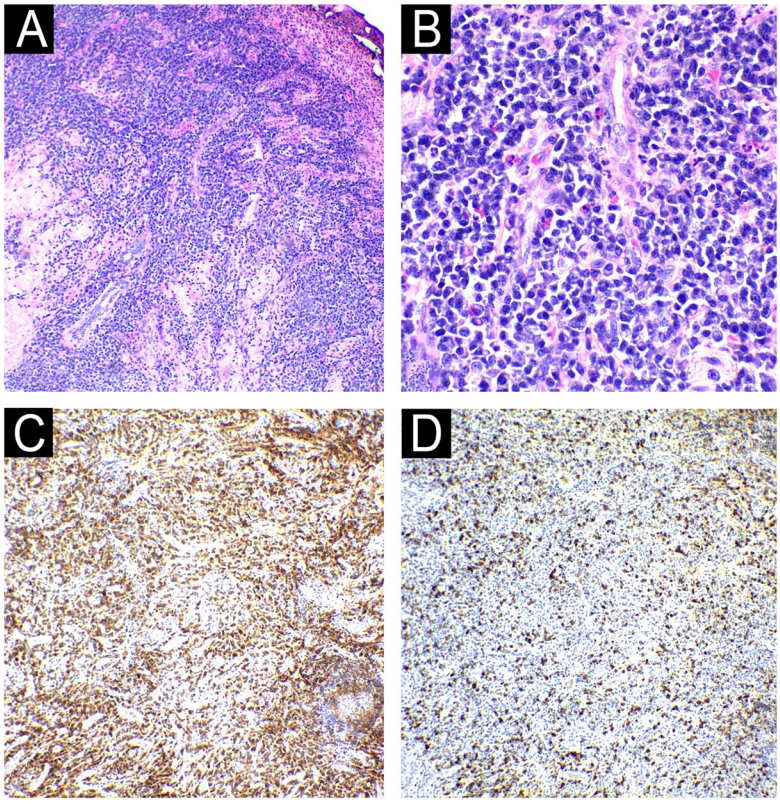

Fig. 3 Histopathology of the nail lesion: (A) Ulceration and dense perivascular, periadnexal and interstitial inflammatory infiltrate in the connective tissue, both superficial and deep, amid areas of fibrosis (Hematoxylin & eosin ×40). (B) Inflammatory infiltrate consisting predominantly of plasma cells, interspersed with lymphocytes and eosinophils. (Hematoxylin & eosin ×100). Immunohistochemistry showing an increased IgG4/IgG ratio with >200 IgG4-positive plasma cells per high-power field (in C, IgG; in D, IgG4).

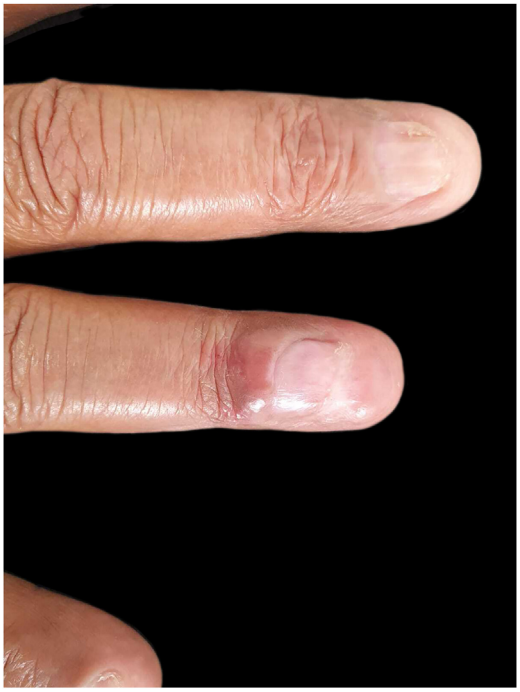

Fig. 4 Result of treatment of IgG4-related nail disease: significant improvement with functional maintenance of the finger.

was complete improvement of the lesion, without loss of limb functionality (Fig. 4) and continues to be monitored by a multidisciplinary team.

Cutaneous involvement in IgG4-related disease refers to tumor lesions due to a local inflammatory process in the skin. The prevalence of cutaneous lesions in this condition varies from 4.2% to 6.3% and they are most commonly described as subcutaneous papules, plaques or nodules in the head and neck region associated with systemic disease, in middle-aged men.[2] Primary presentation in the skin, as in the present case, is extremely rare.[3] Recently, a similar case was reported in the literature of a patient living with HIV, with the cutaneous form of IgG4-related disease, showing a single ulcerated lesion in the inguinal region, without any involvement of other organs.[4]

According to the 2020 Consensus Review and Diagnostic Criteria for IgG4-related disease, the following criteria must be present to establish its diagnosis: 1) Clinical and radiological characteristics: one or more organs demonstrating diffuse or localized edema or a characteristic mass or nodule; 2) Serological diagnosis: serological IgG4 levels > 135 mg/dL; and 3) Pathological diagnosis: two of the following findings: a) Dense infiltrate of lymphocytes and plasma cells with fibrosis; b) IgG4+/IgG plasma cell ratio > 40% and number of IgG4 cells > 10 per high-power field; c) Presence of storiform fibrosis or obliterative phlebitis.[2] The diagnosis is definitive when it includes all three domains; probable, when it includes only the clinical and pathological criteria; and possible, when it includes the clinical and serological criteria.[5] Since the patient met all the criteria a definitive diagnosis of IgG4-related disease was established.

Systemic steroids are the first-line agents for inducing disease remission, but they present high recurrence rates after discontinuation. Other treatments previously described include surgical excision, topical corticosteroids, azathioprine, rituximab, and methotrexate.[6–8] Since the reported patient showed only nail involvement, it was believed that local therapy would be sufficient, and systemic therapy was not necessary. The patient continues to be monitored by a multidisciplinary team.

In summary, by describing this atypical case, the authors expect to contribute to increasing the diagnostic suspicion of IgG4-related disease regarding the differential diagnoses of nail diseases. Additionally, the importance of accurate clinical-pathological correlation to attain a precise diagnosis is reinforced.

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Authors' contributions

Valéria Lukenczuk Said: Design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; statistical analysis; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature.

Monique Freire: Critical review of the literature; collection, analysis and interpretation of data; effective participation in research orientation; approval of the final version of the manuscript.

Tiago Vencato da Silva: Analysis and interpretation of data; approval of the final version of the manuscript.

Virginia Vilasboas Figueiras: Critical review of the literature; analysis and interpretation of data; approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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LETTER - CLINICAL

Pyoderma gangrenosum diagnosed in a high-risk myelodysplastic neoplasm patient with trisomy 8: a rare case report☆

Dear Editor,

Pyoderma gangrenosum (PG) is a neutrophilic autoinflammatory dermatosis linked to dysregulated immune responses in genetically predisposed individuals. It involves elevated cytokines like TNF-α and interleukins (IL-1α, IL-17, IL-23), leading to cutaneous ulcers.[1,2] PG is often associated with systemic conditions such as rheumatoid arthritis, inflammatory bowel disease, and myelodysplastic neoplasms/syndrome (MDS), particularly in cases with trisomy of chromosome 8.[3] This genetic abnormality may heighten inflammatory pathways, contributing to the severity of PG.[4] PG frequently precedes MDS onset, suggesting its potential as a predictor of underlying hematologic disorders, although no cases linking high-risk MDS with trisomy 8 and PG were found.[5,6]

Here, a 69-year-old female patient was admitted to a Brazilian tertiary hospital's emergency room with a one-month history of fatigue, lower limb pain, fever, and pancytopenia, showing a hemoglobin level of 7.4 g/dL, white blood cell count of 1830, and platelet count of 107,000 (Table 1). Initially, a bone marrow aspirate examination was conducted to explore the cause of the pancytopenia. The results revealed an 18% blast count (Table 1), indicating the possibility of MDS, specifically classified as the refractory anemia with excess blasts-2 (RAEB-2) subtype. A karyotype analysis was performed, which showed 47,XX,+8[11]/46,XX[1] (Fig. 1), classifying the patient as very high risk according to the Revised International Prognostic Scoring System (IPSS-R).

She had a skin plaque on her left calf that evolved into a hemorrhagic blister, then an ulcer with irregular edges (Fig. 2). Initial treatments with piperacillin/tazobactam and vancomycin for a suspected infection did not lead to lesion improvement. A biopsy of the leg lesions revealed an infiltrate of mature neutrophils with epidermal ulceration consistent with PG (Fig. 3). The patient was prescribed dapsone 100 mg daily for 45 days to treat the lesion, with scheduled outpatient follow-ups. After completing the treatment, the lesions regressed, as shown in Fig. 4, and dapsone administration was discontinued.

However, after two weeks, the patient's hematological condition deteriorated, presenting with a hemoglobin level of 7 g/dL, white blood cell count of 28,000 (including 846 neutrophils and 26,000 blasts), and platelet count of 17,000 (Table 1). A subsequent myelogram revealed a blast percentage of 37% (Table 1), leading to a diagnosis of secondary acute myeloid leukemia (sAML) (Table 1). The patient was prescribed venetoclax100 mg and azacitidine 100 mg for 5 days with spaced by 21 days between applications for the treatment of sAML. Unfortunately, the patient died after 2 months of treatment due to a hemorrhagic stroke, which was attributed to severe thrombocytopenia. The study was carried out in accordance with CARE guidelines.

Our results demonstrated that the association of PG with hematologic disorders, particularly high-risk MDS and the presence of trisomy 8, suggests a deeper genetic and immunological connection that may influence both the presentation and treatment outcomes of affected patients. The first-line therapy for pyoderma gangrenosum is glucocorticoids, typically initiated at high doses (1–2 mg/kg) during the acute phase.[7] However, this protocol was not followed due to the lack of feasible outpatient follow-up. Another possible therapeutic option is immunosuppression; however, neutropenia was considered a contraindication due to the high risk of infection, one of the leading causes of death in AML.[8]

Dapsone, beyond its use for bacterial infections as an inhibitor of bacterial folic acid synthesis, acts on myeloperoxidase-peroxide halide-mediated cytotoxicity – a component of the neutrophil respiratory burst. It also inhibits the synthesis of chemotactic lipids and interferes with chemotaxis, reducing neutrophil migration to lesions. This medication was selected for treatment due to its wide availability and low cost if self-purchased, and its manageable side effects at low doses, such as areas of hyperpigmentation – an acceptable trade-off compared to the risk of glucocorticoid-induced osteoporosis or high infection risk with immunosuppressants. Furthermore, the patient had no

☆ Study conducted at the Universidade Federal do Ceará, Fortaleza, CE, Brazil.

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Table 1 Clinical and Laboratory Variables Before and After Progression to Acute Myeloid Leukemia (AML) in Myelodysplastic Neoplasm/Syndrome (MDS) Patients with Pyoderma Gangrenosum (PG).

Clinical Laboratory Variables	Before Progression	After Progression	Usual Range[a]
Hemoglobin (g/dL)	7.4	7	8 to <10
White blood cell count ($\times 10^9$/L)	1.830	28.000	4.000–11.000 cells/μL
Neutrophils ($\times 10^9$/L)	805	846	$\geq$800 $\times$ 10^9/L
Platelet (/mm^3)	107.000	17.000	$\geq$100.000
Blasts (%)	18%	37%	0–30%

[a] Based on Revised International Prognostic Scoring System (IPSS-R).

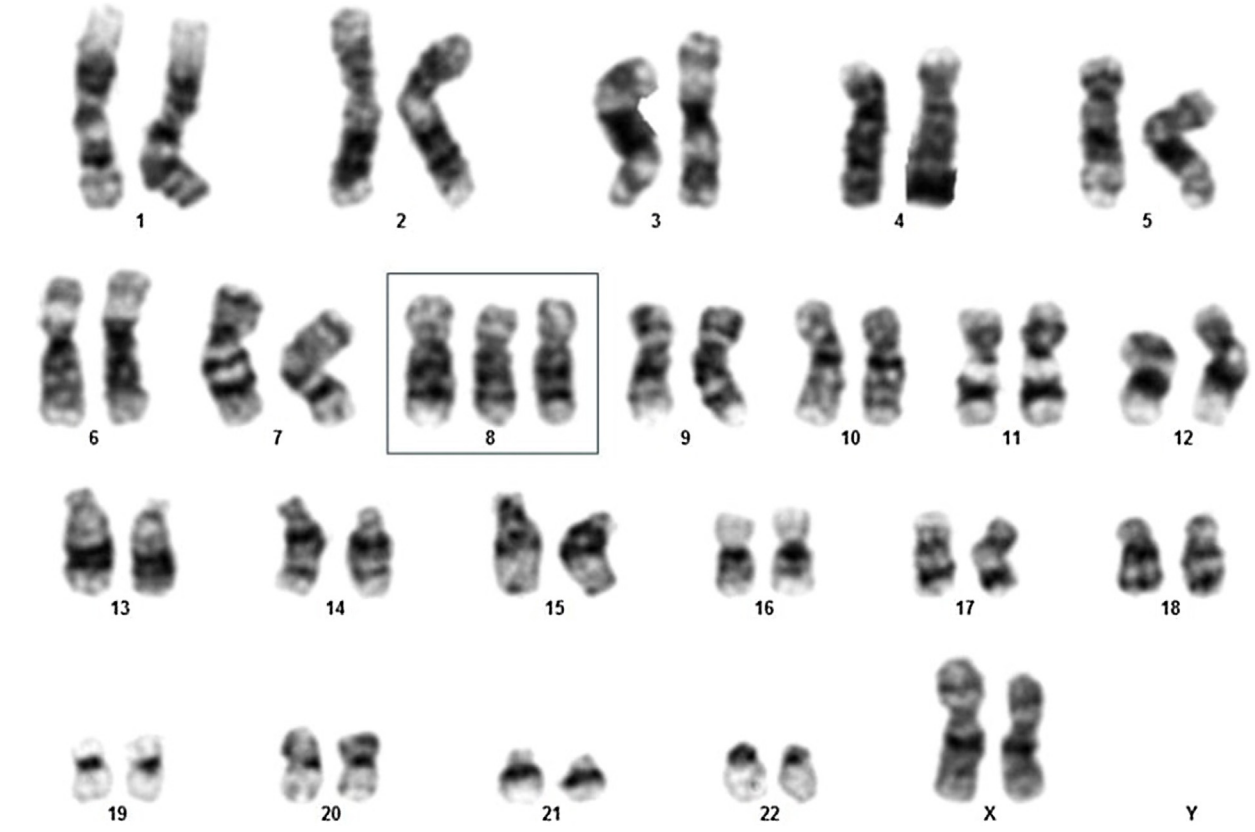

Fig. 1 Karyotype analysis of elderly female myelodysplastic neoplasm/syndrome patient demonstrating 47,XX,+8[11]/46,XX[1].

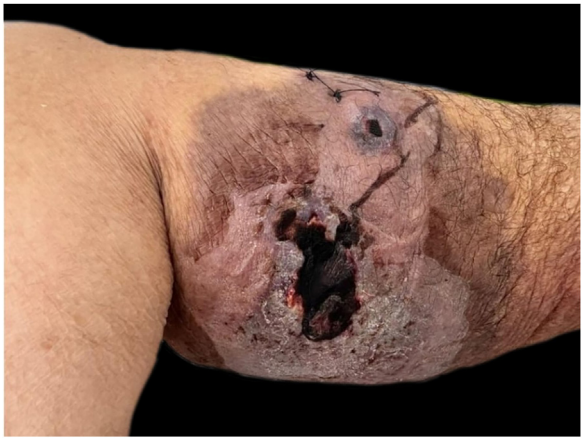

Fig. 2 Lesion ulcerative with violaceous aspect on borders consistent with pyoderma gangrenosum diagnosis.

known drug interactions, and the prescriber had prior experience successfully using dapsone for PG, achieving lesion remission. The prescribing physician must tailor therapeutic approaches individually, considering each patient's needs, adherence potential, risks, and social circumstances to optimize recovery.

Additionally, similarly to our case, Haga and colleagues[9] discuss mucocutaneous PG due to trisomy 8 neutrophilic infiltrates in an 87-year-old Japanese male patient with MDS, illustrating the complex pathophysiology that underlies this association and potentially guiding therapeutic decisions. Our case reinforces the clinical hypothesis that PG could be considered an external manifestation of the underlying hematologic disorder's complexity and severity. The aggressive nature of the skin lesions in PG, characterized by their rapid onset and resistance to conventional treatments, may parallel the progression of hematologic malignancies from

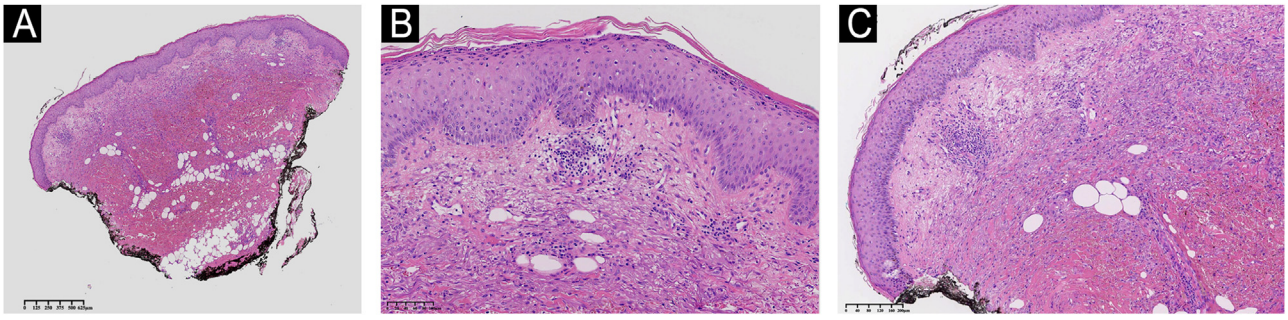

Fig. 3 Histologic section of skin showing hyperkeratosis in the stratum corneum. The epidermis exhibits mild acanthosis. The dermis shows moderate inflammatory infiltrate characterized by lymphoplasmacytic leucocytes, with significant associated tissue hemorrhage. There is mild perivascular inflammation, without evidence of vasculitis. Absence of edema in the papillary dermis. (A) Low power of the histological section of skin demonstrating hyperkeratosis, mild inflammation and hemorrage. (B) Hyperkeratosis in the stratum corneum and mild acanthosis in the epidermis. (C) Moderate inflammatory infiltrate with a perivascular distribution and with tissue hemorrhage in the dermis. Hematoxylin & eosin staining.

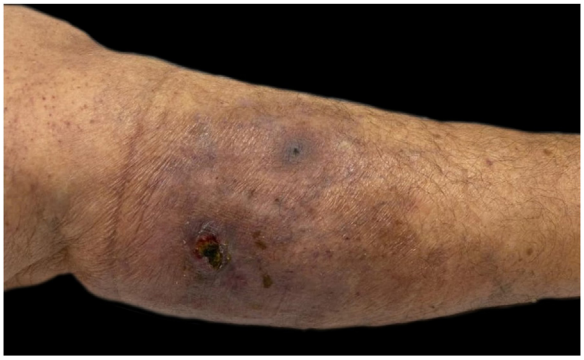

Fig. 4 Pyoderma gangrenosum lesion regression after dapsone treatment.

a more indolent state to an aggressive, acute phase. Thus, PG might not only serve as a marker for the presence of an underlying hematologic disorder but could also indicate a turning point in the disease trajectory towards a more aggressive and less responsive state.

This hypothesis is supported by the notion that both PG and the progression of MDS to sAML involve dysregulated immune responses and inflammatory pathways. The genetic abnormalities associated with MDS, such as trisomy 8, could further exacerbate this dysregulation, leading to the manifestation of PG as a direct consequence of the underlying disease's progression. Moreover, the evolution of MDS to sAML, marked by an increase in blast cells and worsening cytopenias, might be mirrored in the skin by the worsening or uncontrolled progression of PG lesions.

In summary, we report for the first time a rapid response of PG lesion regression in a Brazilian patient with RAEB-2 MDS with trisomy 8 treated with dapsone. To date, data on high-risk MDS patients with trisomy 8 are rare in cohort studies and clinical follow-up. This case report highlights the association of the patient's immunological impairment with MDS, likely caused by the presence of trisomy 8, which may have triggered PG as a dermatological manifestation. Finally, this association underscores the intricate interplay between genetic abnormalities and immune dysregulation in the pathogenesis of hematological disorders with cutaneous manifestations, warranting further investigation and consideration in the clinical management strategies of MDS patients.

Authors' contributions

Renato Mendes Martins: The study concept and design; data collection or processing; analysis or interpretation; literature search; writing; final approval of the final version of the manuscript.

Howard Lopes Ribeiro Junior: The study concept and design; analysis or interpretation; literature search; writing; final approval of the final version of the manuscript.

Natália Feitosa Arrais Minete Mendonça: The study concept and design; data collection or processing; writing; final approval of the final version of the manuscript.

Fábio Rocha Fernandes Távora: Data Collection or processing; analysis or interpretation; writing; final approval of the final version of the manuscript.

Ronald Feitosa Pinheiro: The study concept and design; data collection or processing; analysis or interpretation; writing; final approval of the final version of the manuscript.

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Conflicts of interest

None declared.

Acknowledgments

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LETTER - CLINICAL

Treating Parry-Romberg syndrome with hyaluronic acid: insights after 2.5 years of successive treatments☆

Dear Editor,

An 18-year-old female patient with a previous diagnosis of Parry-Romberg syndrome (PRS) since childhood was referred to our clinic for facial symmetrization. The patient was on methotrexate 15 mg/week, with no evidence of disease progression in recent years. She had previously undergone autologous fat grafting with ephemeral and unsatisfactory results.

On dermatological examination, she presented signs of cutaneous and muscular atrophy on the right side of her face, resulting in asymmetry in the height of the eyebrows, and atrophy in the right zygomatic, subocular, mandibular, and mental regions. In the right subocular region, cutaneous atrophy manifested as hypopigmentation and exposure of the dermal vascular network (Fig. 1A).

For facial symmetrization, hyaluronic acid filler (Restylane, Galderma Laboratoires, Upsala) was chosen.

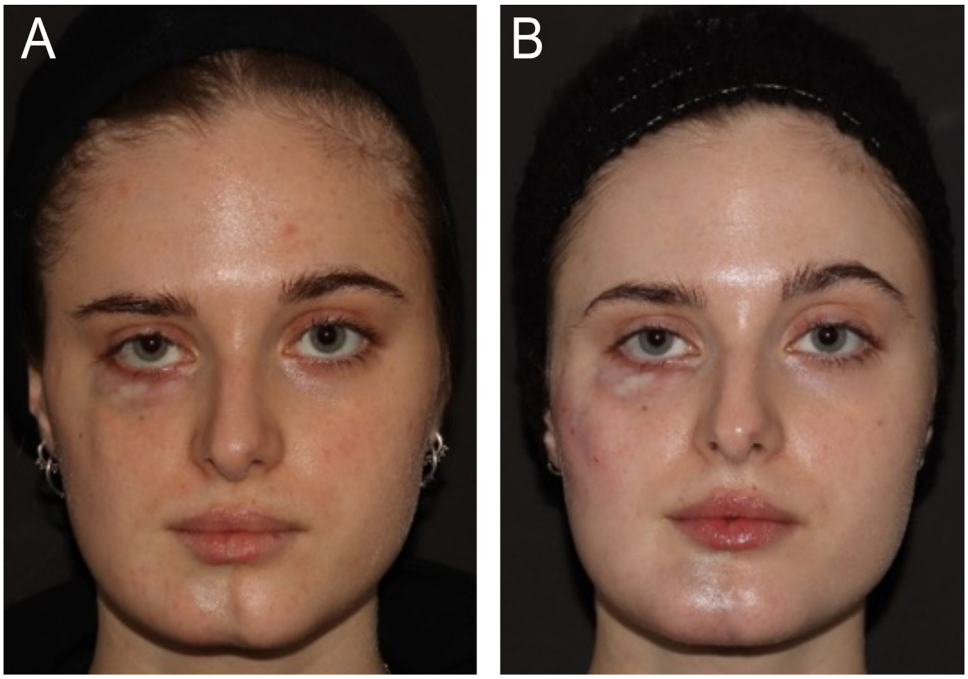

Figure 1 (A) Baseline in April 2021 showing skin and deep planes atrophy of the right hemiface in a patient with Parry-Romberg syndrome. (B) The patient after the last filler treatment in February 2024, showed improved facial symmetry, especially in the zygomatic region, tear trough, and chin. Between the first and last photos, 12 treatments were performed with a median volume of 2 mL per session, every 60 days. The tear trough region was treated with a 25 G blunt cannula using Restylane Lidocaine deeply, and the zygomatic region, and chin were treated both supraperiosteally (with a 27 G needle using Restylane Lyft) and in the deep subcutaneous region (with blunt cannula 22 G using Restylane Defyne).

☆ Study conducted at the Margarethenklinik, University Hospital of Basel, Basel, BS, Switzerland.

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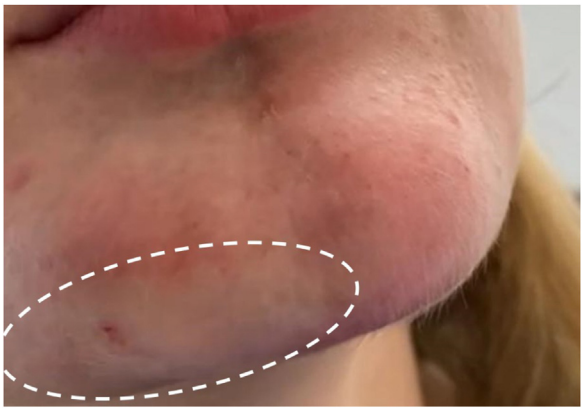

Figure 2 Blanching of the right lateral chin region (dotted area) during hyaluronic acid injection, indicating likely ischemia in the area.

From the first treatment in April 2021, where 6.6 mL of Hyaluronic Acid (HA) was injected, to February 2024, the patient returned for 12 additional sessions. The time between treatments ranged from 46 to 153 days (median 60 days), and the volume of hyaluronic acid per session varied between 0.75 and 3 mL (median 2 mL). All treatments were guided by ultrasound.

The hyaluronic acid injections were administered only to the affected hemiface. The treated regions included the lateral and medial zygomatic areas, tear trough, and chin. The treatment details are described in Fig. 1B.

In two sessions, hyaluronidase was needed in the chin area to correct irregularities caused by hyaluronic acid migration.

During one treatment in the chin area, signs of local ischemia were observed (Fig. 2). However, the patient reported that this same region periodically and spontaneously exhibited these signs even before the first hyaluronic acid injection. Indeed, Doppler ultrasound performed during the procedure did not show arterial occlusion. The symptoms regressed after a few hours of treatment, even without hyaluronidase injection.

Parry-Romberg Syndrome is a rare acquired neurocutaneous disease of unknown etiopathogenesis, typically characterized by progressive hemifacial atrophy. It is commonly characterized as an autoimmune disorder within the spectrum of diseases associated with localized scleroderma *en coup de sabre*. This classification is substantiated by evidence of inflammatory histopathology, the presence of serum autoantibodies, the coexistence of other autoimmune conditions, and positive responses to immunosuppression. Extracutaneous disease manifestations, including neurologic, ocular, and oral pathology, are common,[1] but was not the case with our patient.

The classic treatment for facial symmetrization is autologous fat grafting, which was not indicated in our case due to the patient's previous dissatisfaction. Hyaluronic acid filling has been previously reported in the literature in four cases of PRS.[2–4] In none of them the treatment was guided by ultrasound, and none reported to be on immunosuppressive treatment. There was no report of disease progression

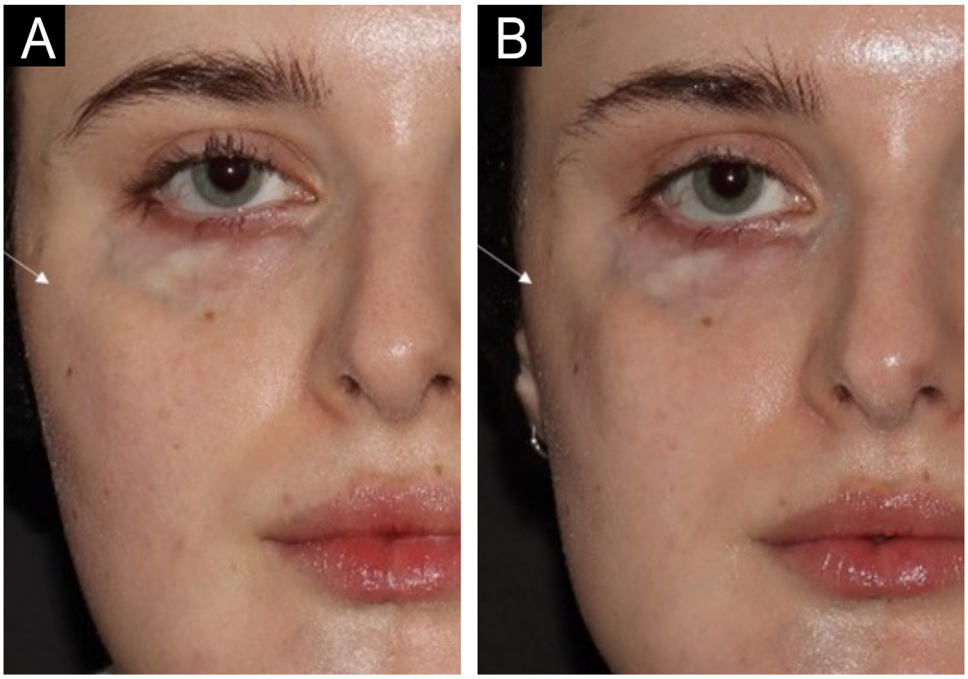

Figure 3 The same patient with an 80-day interval. On the day of the first photo (A), 0.9 mL of Restylane Defyne was injected into the right zygomatic region (result not shown). Despite this, in photo B, 80 days after the injection, the zygomatic region (white arrow) appears visibly more depressed than in the previous photo. This absorption pattern was observed over the three years of follow-up, which may represent accelerated hyaluronic acid absorption.

associated with aesthetic treatment. No infections, rejections, or other complications related to this treatment were observed.

The use of hyaluronic acid in patients with morphea/scleroderma spectrum diseases was reviewed in 2020.[5] The retrospective analysis of 488 reported cases, treated with different brands and types of HA, did not result in disease progression.

Some peculiarities were observed in the treatment of this patient: The average time for complete absorption of hyaluronic acid after injection varies depending on the molecular composition of HA,[6] but treatment repetition is expected to be between 6- and 12 months for healthy individuals. In our case, treatment was repeated approximately every two months. Fig. 3 shows the volume reduction in the right zygomatic region only 80 days after the hyaluronic acid injection. This leads us to question whether there is a higher turnover of injected HA as part of the disease in PRS.

Besides the difficulty of moving the cannula during the procedure, tissue rigidity, associated with periodic vasospasms, could pose a higher risk of vascular compression by HA. Additionally, the spontaneous cutaneous vasospasms in these patients may be a confounding factor for real vascular occlusion by HA during the procedure. Performing the procedure guided by ultrasound can help in differentiation. Tissue rigidity could also explain the frequent migration of HA, which, when compressed by muscle movement against adjacent tissues, might herniate to areas with less resistance. This difficulty may be even greater in the chin area, where muscle fibers and subcutaneous fatty tissue are naturally interwoven, making the tissue more compact. In this sense, favoring products with greater tissue integration could be a good treatment strategy.

Considering the importance of facial symmetrization in the quality of life and given the low incidence of adverse effects, hyaluronic acid can be a good option in PRS. However, due to the technical difficulty associated with treating PRS, it is recommended to be performed by experienced professionals with extensive anatomical knowledge and prepared to handle vascular and infectious events.

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None declared.

Authors' contributions

Roberta Vasconcelos-Berg: The study concept and design; writing of the manuscript and critical review of important intellectual content; final approval of the final version of the manuscript.

Barbara Varella Maire: Data collection, analysis and interpretation of data; critical review of the literature.

Alexander A. Navarini: Writing of the manuscript and critical review of important intellectual content; final approval of the final version of the manuscript.

Conflicts of interest

Roberta Vasconcelos-Berg is a speaker and consultant for Galderma Laboratoires. Barbara Varella Maire and Alexander A. Navarini have no conflict of interest to declare.

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LETTER - DERMATOPATHOLOGY

A case of labyrinthine pattern basal cell carcinoma☆

Dear Editor,

Basal cell carcinoma (BCC) is the most common type of malignant skin tumor and presents with various histopathological subtypes. One of these subtypes exhibits a complex cord-like arrangement of tumor cells, described as a labyrinthine pattern. Reports on BCC with a labyrinthine pattern are primarily limited to textbook descriptions.[1] Here, we report such a case coexisting with nodular BCC.

An 80-year-old woman was referred to our hospital for excision of a lesion on her right forearm. The lesion had appeared 5 years previously and had gradually enlarged without any treatment. Clinical examination revealed a well-demarcated, elastic hard black nodule with some scales, measuring 14 × 14.5 mm, with good mobility over the underlying tissue, on the inner side of her right forearm (Fig. 1). Dermoscopy revealed large blue-gray ovoid nests, of multiple blue-gray globules, and shiny white areas. Under local anesthesia, the nodule was excised, and a full-thickness skin graft was performed. At a 4-month postoperative follow-up, there was no recurrence.

Histopathological examination revealed a raised, protruding lesion with well-defined tumor nests of varying sizes within the dermis, some of which were continuous with the epidermis. Melanin granule deposition was prominent in the tumor nests and stroma (Fig. 2A). Nodular BCC was also identified. There were no findings indicative of differentiation into sebocytes or elements of hair papilla-like structure (Fig. 2B). The tumor nests exhibited a complex cord-like arrangement, referred to as a labyrinthine pattern. Mucinous spaces were observed between the cord-like tumor nests, with minimal presence of blood vessels and fibroblasts. The labyrinthine pattern was observed in approximately 70% of the entire tumor cell population (Fig. 2C–D). Immunohistochemical findings showed diffuse BerEP4 expression in tumor cells (Fig. 3), and S-100 expression in approximately 5%. Adipophilin, GCDFP-15, CEA, EMA, vimentin, Melan A, and CK20 were not expressed in the tumor cells.

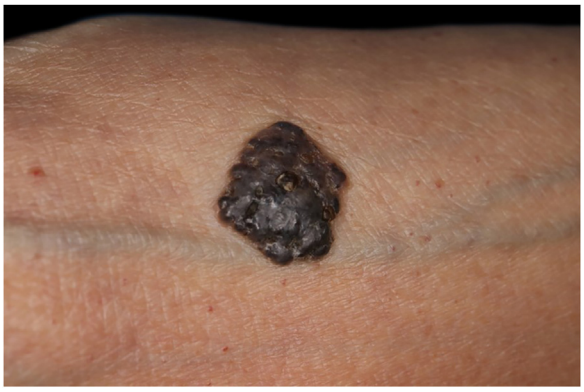

Figure 1 Clinical features of a well-demarcated, partially keratinized, elastic hard black nodule on the forearm.

The present case needs several histopathological differential diagnoses, including sebaceous adenoma, sebaceous carcinoma, trichoblastoma, and malignant melanoma.[2] Sebaceous adenomas and carcinomas are known to have characteristic cellular arrangements, like rippled patterns, as shown in Table 1[3]; and distinguishing between them can sometimes be difficult. In this case, the results of immunohistochemistry revealed positive findings for BerEP4 but negative for S100, adipophilin, GCDFP-15, CEA, EMA, vimentin, and Melan A. Therefore, immunohistochemical staining facilitated differential diagnosis from other tumors. The absence of differentiation into sebocytes or elements of hair papilla-like structure, as well as the diffuse expression of BerEP4, led to the diagnosis of labyrinthine pattern BCC coexisting with nodular BCC. Trichoblastoma was excluded in that follicular germinative cells were absent.

While reports on the labyrinthine pattern in BCC are scarce, there have been 18 reported cases exhibiting carcinoid-like patterns and rippled patterns, all of which coexisted with nodular BCC, and in 15 out of the 18 cases, the lesions predominantly occurred on the face.[2,4–7] Additionally, sebaceous adenomas and trichoblastomas with carcinoid-like patterns and rippled patterns have been reported to show apocrine gland differentiation,[8,9] but tubular structures in BCC with rippled patterns have not been reported to show signs of apocrine gland differentiation.[7]

☆ Study conducted at the Fukushima Medical University, Fukushima, Japan.

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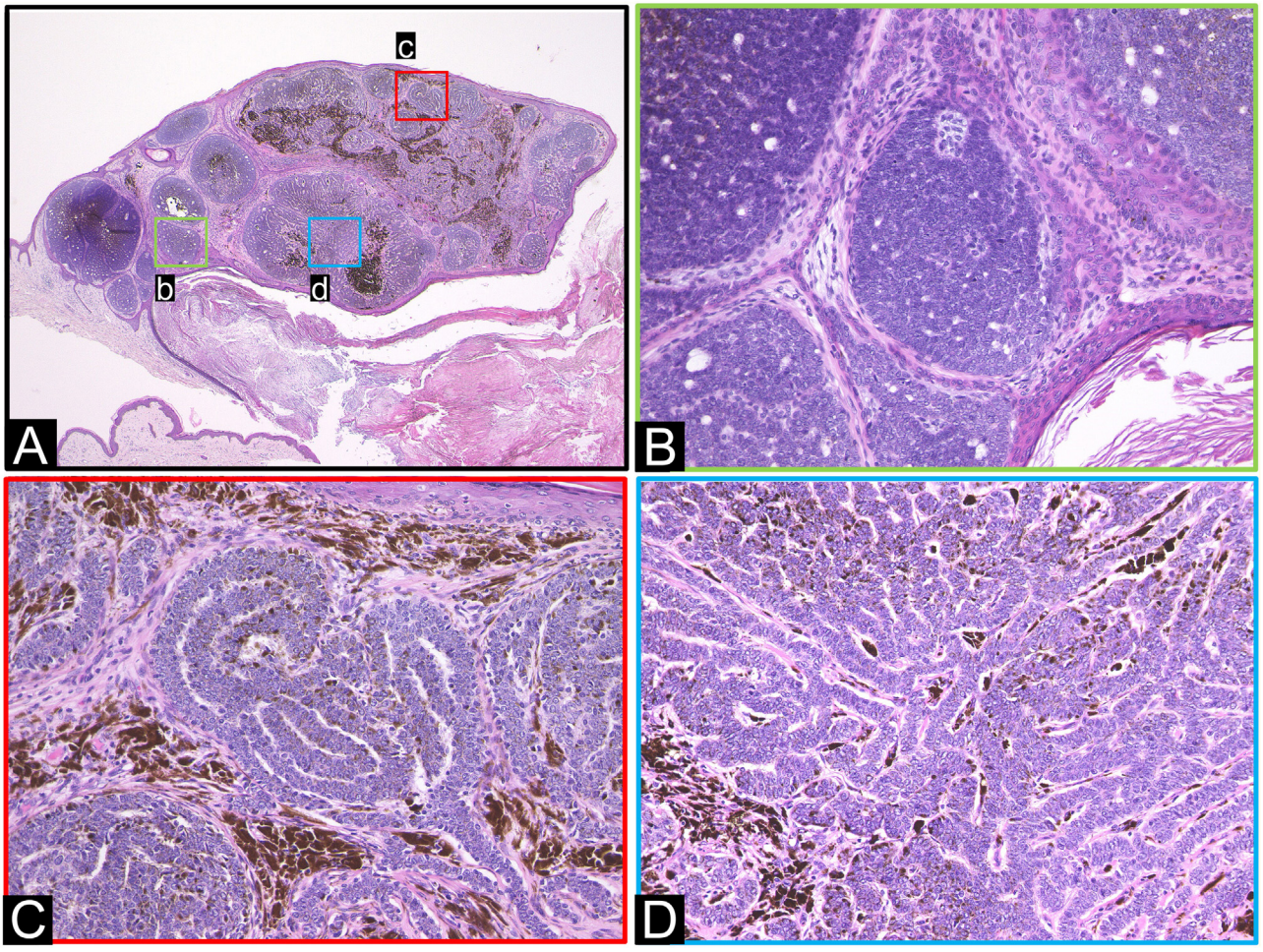

Figure 2 Histopathological features. (A) Protruding lesion with well-defined large and small tumor nests within the dermis. (B) Region of nodular BCC. (C–D) Tumor cells exhibit a complex cord-like arrangement, forming a pattern described as labyrinthine. (Hematoxylin & eosin; A: ×20, B: ×200, C: ×200, D: ×200).

Table 1 Differences in cellular arrangement.

Labyrinthine Pattern	Tumor cells exhibit a complex cord-like arrangement, forming a pattern described as labyrinthine. Edematous changes are observed between the tumor nests, but mesenchymal components such as blood vessels and fibroblasts are scarcely seen.
Carcinoid-like Pattern	Tumor cells are arranged in cords, ribbons, rosettes, and networks, displaying a histological appearance similar to carcinoid tumors. Mesenchymal components such as blood vessels and fibroblasts are interspersed between the tumor nests.
Rippled Pattern	Regions where nuclei are arranged in palisades alternate with anuclear regions in one direction, creating a rippled pattern. Cytoplasm without blood vessels is observed between the tumor nests.

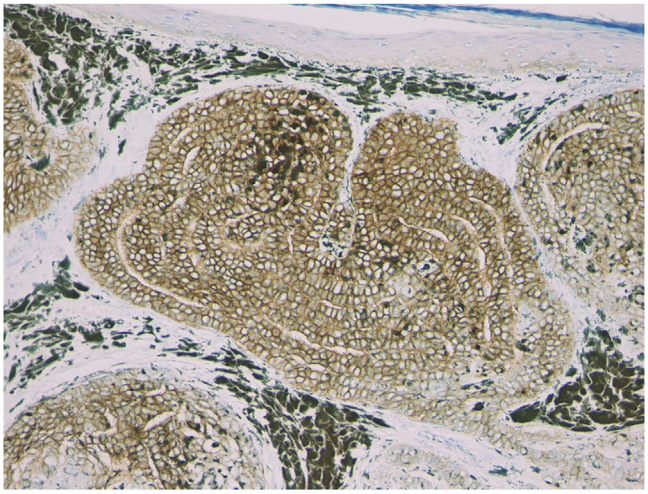

Figure 3 Immunohistochemical features showing diffuse immunoexpression of BerEP4. (×200).

This suggests that tumors exhibiting the same patterns may lose their differentiation potential in malignant BCC, in contrast to benign sebaceous adenomas and trichoblastomas.[7] The coexistence of nodular BCC was also observed in the present case, but there were no findings indicating apocrine gland differentiation.

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None declared.

Authors' contributions

Takehiro Nakamura: The study concept and design; data collection, or analysis and interpretation of data; writing of the manuscript or critical review of important intellectual content; data collection, analysis and interpretation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; final approval of the final version of the manuscript.

Toshiyuki Yamamoto: The study concept and design; effective participation in the research guidance; critical review of the literature; final approval of the final version of the manuscript.

Conflicts of interest

None.

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LETTER - DERMATOPATHOLOGY

Merkel cell carcinoma coexisting with squamous cell carcinoma☆☆

Dear Editor,

Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma, the origin of which is still debated.[1] It is a highly aggressive neoplasm, with a predilection for sun-exposed areas, mainly the head and neck, most commonly affecting elderly patients with no gender predilection.[2]

Due to its rarity, association with other skin neoplasms is possible, the most commonly described being the association with squamous cell carcinoma (SCC).[3,4]

A 78-year-old female patient reported the appearance of a lesion on her right upper limb approximately four months before, with progressive growth. She denied other previous neoplastic lesions.

On physical examination, the lesion had an erythematous base, was slightly infiltrative, presented an hematic crust and keratotic surface, and showed atypical vessels on dermoscopy.

An excisional biopsy of the lesion was performed, with the following diagnostic hypotheses: basal cell carcinoma, amelanotic melanoma, or Merkel cell carcinoma. Histopathology and immunohistochemistry showed Merkel cell carcinoma associated with moderately differentiated and invasive squamous cell carcinoma, with free surgical margins (Figs. 1 and 2). There was positivity for neuroendocrine markers such as synaptophysin (MRQ-40) and chromogranin (LK2H10) in the Merkel cell carcinoma, besides positive cytokeratin 20 (clone SP33) with a ''dot'' pattern – these markers were negative in the squamous cell carcinoma. There was also negative TTF1 (clone 8G7G3/1), and positive cytokeratin 5/6 (D5/16B4) and p63 (clone 4A4) in the squamous cell carcinoma (Fig. 3). On physical examination, the patient showed no signs of lymph node enlargement and was referred to Oncology for clinical staging and treatment. The tumor polyomavirus status was not tested or reported.

Merkel cell carcinoma, or primary neuroendocrine carcinoma of the skin, is a rare and aggressive malignant neoplasm. It was first reported by Toker in 1972 as ''trabecular carcinoma''.[5] In 2008, the polyomavirus associated with Merkel cell carcinoma was discovered, called Merkel cell polyomavirus (MCPyV).[6] Clinically, its presentation usually consists of an asymptomatic plaque or nodule, pink or reddish-blue in color, sometimes ulcerated, and showing rapid growth. Histopathologically, it presents as an ill-defined dermal nodule that can infiltrate fatty tissue, fascia, and muscle. It is characterized by the monotonous proliferation of small, round to oval cells with basophilic nuclei and dispersed nuclear chromatin.[1,3,7] It expresses neuroendocrine markers, including chromogranin, synaptophysin, neuron-specific enolase, and CD56 in immunohistochemical studies.[8,9] Another expressed marker – and the most specific one, with a ''dot'' pattern – is CK20.[1] Staining for TTF1 is usually negative.[4]

MCC may occasionally be associated with other skin neoplasms. The most common association, although rare, is between MCC and *in situ* or invasive squamous cell carcinoma. The rarity of the lesion has prevented the correct quantification of the association, since most of the published data come from case reports.[3] A recent multi-institutional study analyzed 136 MCCs and found a 10% frequency of MCC association with *in situ* or invasive SCC, compared with two other series in the literature: one in which this percentage was 10.34% and the other 6.25%. These studies describe all associations between MCC and SCC, which include (1) intraepidermal MCC within an *in situ* SCC, (2) MCC with *in situ* SCC, and (3) MCC associated with *in situ* and invasive SCC. Additionally, other studies report ''mixed tumors'' and divergent differentiation in MCC – presence of squamous differentiation.[1]

The presence of polyomavirus has been widely studied in MCC. A study published in 2009 that investigated the presence of polyomavirus in MCC using various techniques showed that immunohistochemical testing using the monoclonal antibody CM2B4 proved valid, since all tumors immunoreactive with CM2B4 were positive in the polymerase chain reaction (PCR) technique. Also in this study, seven MCCs associated with SCC were evaluated and all were positive for CK20, but negative for CM2B4 (both in the neuroendocrine and squamous cell components).[10] Associated with the fact that both neoplasms share common risk fac-

☆ Study conducted at the Hospital do Servidor Público Estadual de São Paulo, São Paulo, SP, Brazil.

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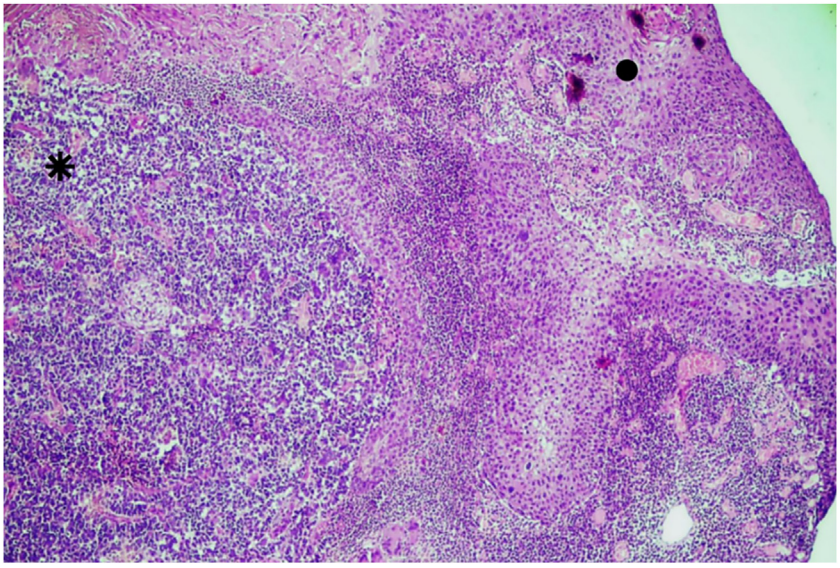

Fig. 1 Squamous cell carcinoma (●) coexisting with Merkel cell carcinoma (✳). Hematoxylin & eosin, ×40.

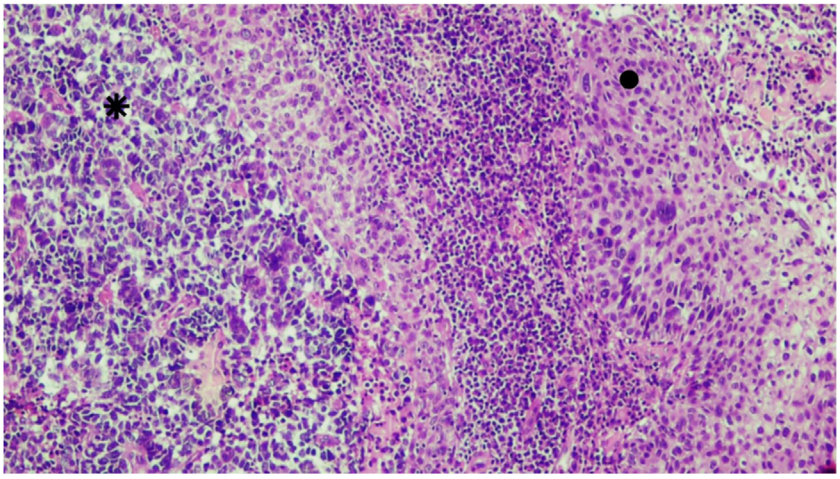

Fig. 2 Squamous cell carcinoma (●) coexisting with Merkel cell carcinoma (✳). Hematoxylin & eosin, ×100.

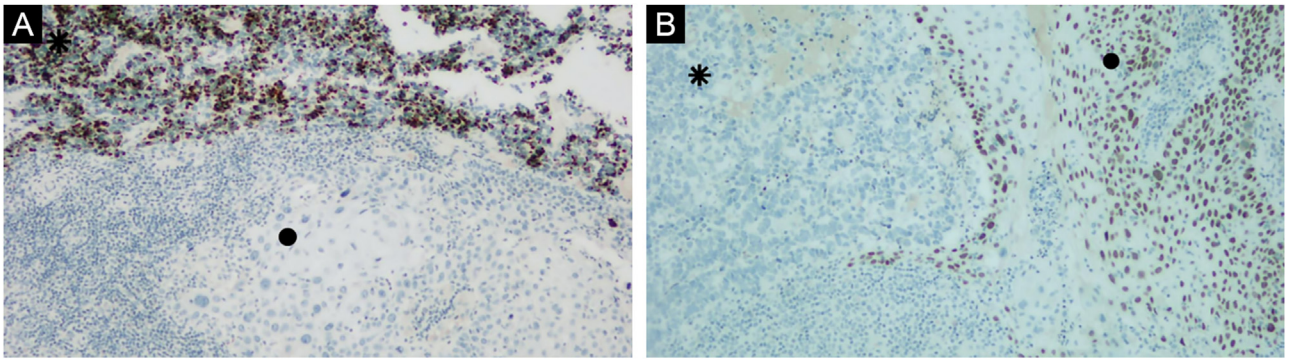

Fig. 3 (A) CK20 positive ''dot'' pattern in Merkel cell carcinoma (✳) and negative in squamous cell carcinoma (●). CK20 (SP33), ×100. (B) P63 negative in Merkel Cell Carcinoma (✳) and positive in squamous cell carcinoma (●). P63 (4A4), ×100.

tors, such as sun exposure, low phototype and advanced age, it may be suggested that MCC associated with SCC may develop through a polyomavirus-independent pathway.

The present report describes a case of Merkel cell carcinoma associated with invasive squamous cell carcinoma. Despite its rarity, such an association, already reported in

the literature, raises aspects about its histogenesis, which are still the subject of studies and discussion.

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Authors' contributions

Mariana Abdo de Almeida: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

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Bruna Nascimento Arruda Scabello: Approval of the final version of the manuscript; drafting and editing of the manuscript; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the manuscript.

Conflicts of interest

None declared.

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LETTER - TROPICAL/INFECTIOUS AND PARASITIC DERMATOLOGY

Borderline lepromatous leprosy with lymph node infiltration: Dermatology helps to clarify challenging diagnoses☆

Dear Editor,

Eliminating the occurrence of leprosy (L) is a global goal of the WHO. For this purpose, combating the disease in Brazil is of utmost importance, since the country accounts for 13% of the absolute number of new cases of the disease worldwide.[1]

Early identification of possible cases of L in the community, whether by general practitioners, medical doctors of different specialties, or dermatologists, is essential to reduce the spread of the disease and combat sequelae related to late diagnosis. Therefore, it is essential to invest in diagnostic training for the medical community, nurses and community health agents.[2]

It is necessary, however, to keep in mind that many cases do not follow the classic disease presentation, making the diagnosis difficult, which also makes it necessary to get to know disease presentations in which the manifestations go beyond the involvement of cutaneous and neurological sites.

The present report describes a 48-year-old male patient with testicular pain radiating to the inguinal region, chills, insomnia, night sweats and spontaneous weight loss of 9 kg in two months. On physical examination, the patient had bilateral inguinal lymphadenopathy, with mobile lymph nodes, with a parenchymal appearance, measuring 3 cm in diameter, without involvement of other lymph node chains. On ultrasound examination, the enlarged inguinal lymph nodes presented a reactive architecture. There was also splenomegaly on the abdominal ultrasound. The blood count showed lymphopenia.

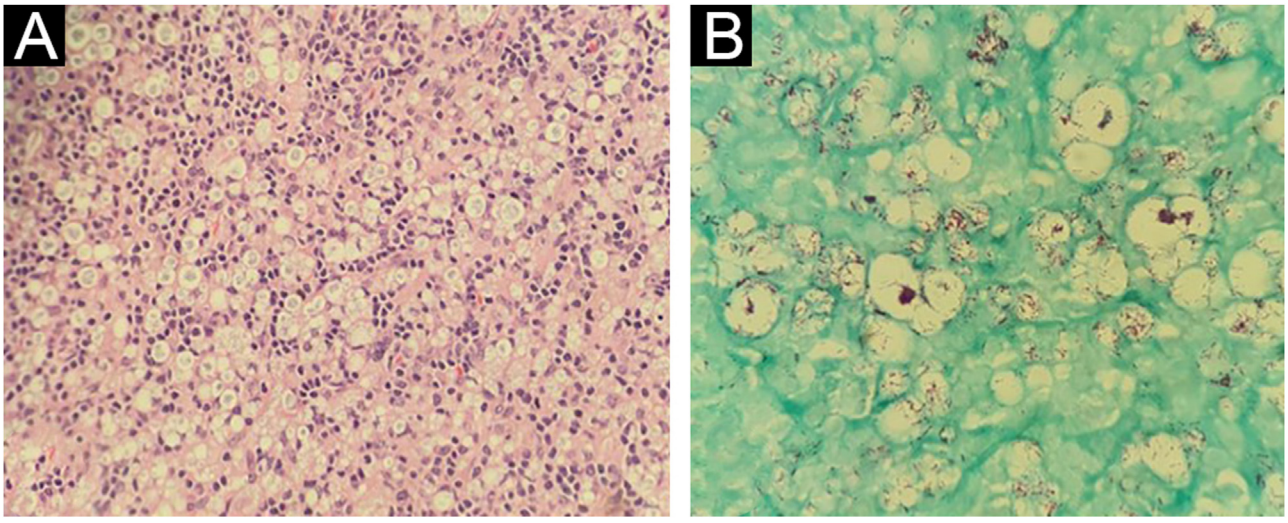

Fig. 1 Inguinal lymph node histopathology – (A) Presence of a diffuse histiocytic infiltrate, lymph node stroma disorganization and presence of typical lymphocytes (Hematoxylin & eosin, ×40); (B) Presence of numerous acid-fast bacilli, organized in clusters within xanthomatous histiocytes (Fite-Faraco, ×100).

☆ Study conducted at the Department of Infectology, Dermatology, Imaging Diagnosis and Radiotherapy, Faculty of Medicine, Universidade Estadual Paulista, Botucatu, SP, Brazil.

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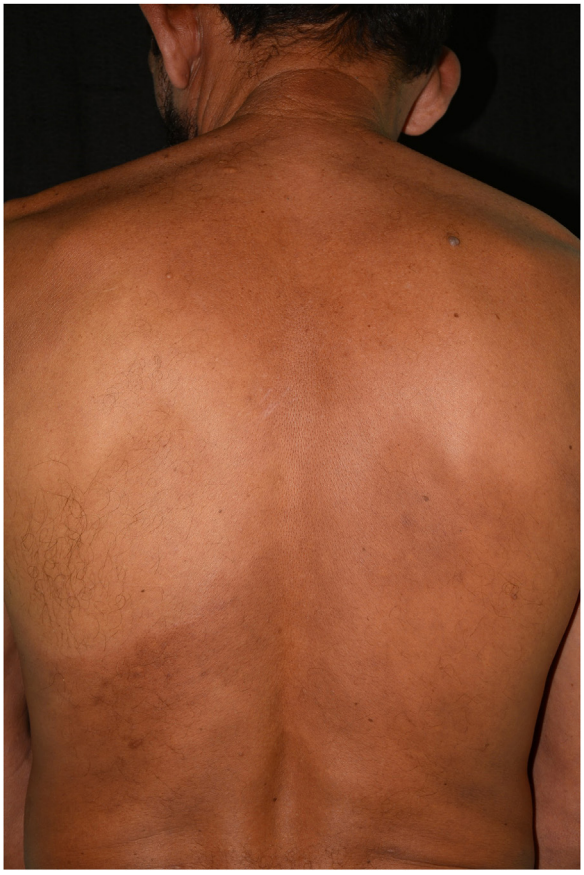

Fig. 2 Hypochromic spot affecting the scapular and infrascapular region, extending to the left costal region, anesthetic on esthesiometry examination. On the periphery of the lesion, a discreet, poorly delimited erythematous-brownish area is observed.

The internal medicine team hypothesized non-Hodgkin's lymphoma as the diagnosis, and a biopsy of one of the lymph nodes was performed. Histopathology showed lymph node stroma disorganization with a marked number of histiocytes. On Fite-Faraco staining, numerous acid-fast bacilli organized in clusters were observed, confirming the diagnosis of lymph node involvement by L (Fig. 1).

During the consultation with Dermatology, a hypochromic patch on the left infrascapular region was observed on physical examination, which was anesthetic on esthesiometry examination (Figs. 2 and 3). Additionally, the entire perilesional area showed apparent diffuse cutaneous infiltration. Painless thickening of the ulnar nerves bilaterally and discrete infiltration of the earlobes were also observed.

Biopsies were performed in the hypochromic infrascapular lesion, considered a suspicious lesion on physical examination, and in the perilesional region with discrete infiltration. Histopathology of the hypochromic area showed a discrete perivascular inflammatory infiltrate, negative for bacilli on Fite-Faraco staining. The histopathological findings of the infiltrated perilesional region, however, were epidermal rectification (Grenz zone), associated with the presence of disorganized perineural granulomas in the dermis, rich in xanthomatous histiocytes containing numerous bacilli, confirming the involvement by *Mycobacterium*

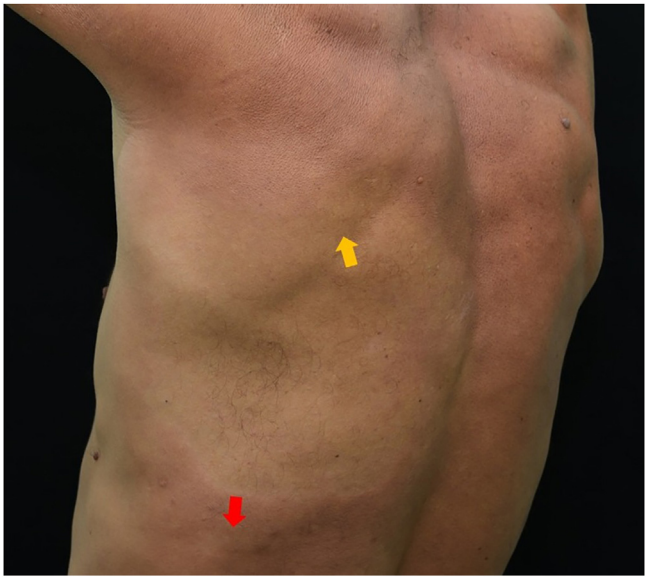

Fig. 3 Hypochromic spot affecting the scapular and infrascapular region, extending to the anesthetic left costal region. The yellow arrow points to the biopsied area of suspected leprosy. The red arrow points to an area of discrete peripheral infiltration, which was also biopsied.

leprae (Fig. 4). So the hypochromic spot suspected for leprosy was, in reality, an area of the skin less affected by the disease on histopathology, when compared to the more severely affected area.

Bacilloscopy was investigated, and the detected bacilloscopic index was 4.4. Once the diagnosis of borderline lepromatous L was confirmed, treatment with multibacillary multidrug therapy (MB-MDT) was initiated.

Leprosy is considered a ''great disease imitator'', showing a wide variety of clinical manifestations, which can represent a diagnostic challenge in certain situations.[3] There are reports of L mimicking diseases such as sarcoidosis, cutaneous lymphomas, Jessner's lymphocytic infiltrate and connective tissue diseases.[4] The great variability of the clinical presentation reflects the hosts immunological spectrum in relation to *M. leprae* infection, which may show Th1 and Th2 pattern immune responses in polar clinical forms or both patterns in interpolar forms.[5]

Lymph node involvement in leprosy patients may occur as part of the visceral involvement in multibacillary patients. On histopathology, the reticuloendothelial system shows involvement and infiltration by *M. leprae* in a spectral pattern, similar to what occurs in the skin lesions. In lepromatous L, liver involvement occurs in 85% of cases and spleen involvement in approximately 41%, similar to what happened in the present case.[6]

There are reports of cases in which lymphomas simulate lepromatous L, or even the coexistence of both diseases.[4,7,8] However, in the case described herein, the hypothesis of non-Hodgkin's lymphoma was ruled out by the absence of atypical lymphocytosis in the blood count, as well as by the histopathology of the affected lymph nodes.

It is worth remembering that approximately one-third of patients diagnosed with multibacillary L may present with type II leprosy reaction (LR2) at the time of diagno-

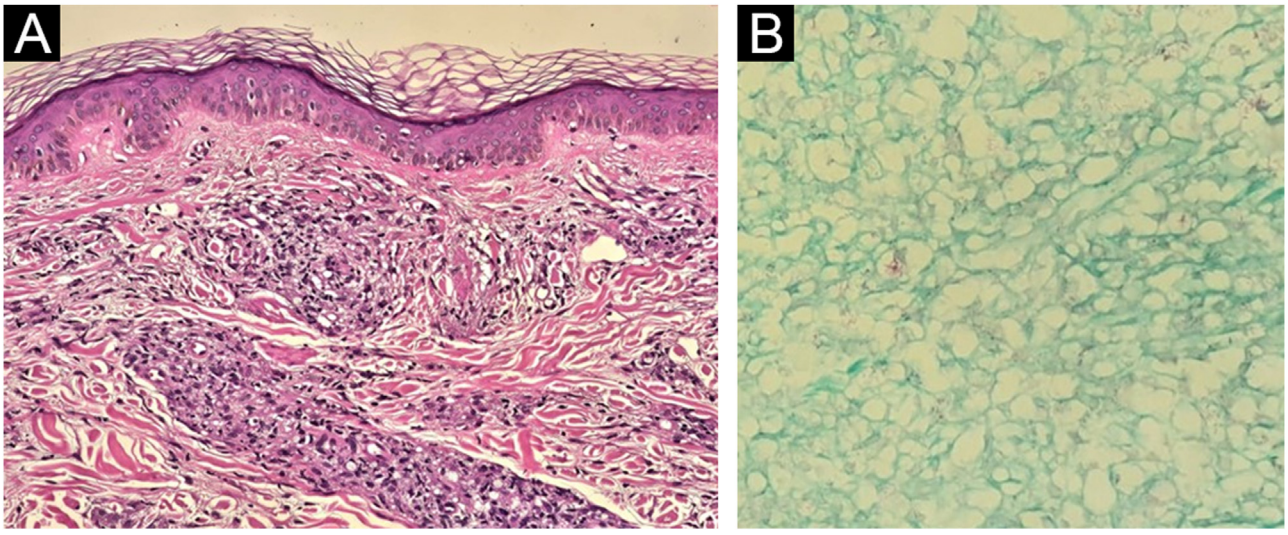

Fig. 4 Histopathology of the region adjacent to the hypochromic spot seen in Figs. 2 and 3: on the left, the presence of a Grenz zone and poorly organised granulomatous infiltrate, containing many xanthomatous histiocytes (Hematoxylin & eosin, ×100); on the right, presence of intact bacilli organized in clusters (Fite-Faraco, ×40).

sis, which makes it necessary to exclude the possibility of LR2 with lymph node infiltration in cases with lymph node enlargement.[9] In the case described herein, the absence of pain, fever, neurological symptoms or lesions typical of erythema nodosum leprosum led to the suggestion of probable lymph node involvement in a patient with borderline lepromatous L. Additionally, there were no necrotic areas nor polymorphonuclear cell infiltration in the lymph nodes involved, as is usually observed in patients with lymph node leprosy reactions.[10] In fact, four months after starting treatment, the patient developed erythematous nodules diffusely throughout the skin and neurological symptoms (significant pain on palpation of the ulnar nerves bilaterally and worsening of the palmoplantar esthesiometric examination), confirming the diagnosis of type 2 leprosy reaction following specific treatment.

In conclusion, it is essential that physicians closely monitor the possibility of involvement by leprosy bacilli in organs other than the skin and the peripheral nervous system. It is of utmost importance to emphasize the need to interrupt the chain of transmission, especially in multibacillary patients, such as the described case, so that, after diagnostic definition, they can be treated with multibacillary multidrug therapy.

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Authors' contributions

Victor Henrique Murback dos Reis: Design and planning of the study; collection of data, analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; approval of the final version of the manuscript.

Anna Carolina Miola: Design and planning of the study; drafting and editing of the manuscript or critical review of important intellectual content; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

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Simone de Pádua Milagres: Design and planning of the study; drafting and editing of the manuscript or critical review of important intellectual content; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Joel Carlos Lastória: Design and planning of the study; drafting and editing of the manuscript or critical review of important intellectual content; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Juliano Vilaverde Schmitt: Design and planning of the study; drafting and editing of the manuscript or critical review of important intellectual content; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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LETTER - TROPICAL/INFECTIOUS AND PARASITIC DERMATOLOGY

Pyoderma gangrenosum-like sporotrichosis: case series of three patients and literature review☆

Dear Editor,

Sporotrichosis is a subacute or chronic subcutaneous mycosis caused by thermodimorphic fungi of the genus *Sporothrix*.[1] Although the diagnosis of the classic form is relatively straightfoward, other variants pose a significant diagnostic challenge. Morphologically, it can simulate keratoacanthoma, erysipelas, sarcoidosis and pyoderma gangrenosum (PG). The term pyoderma gangrenosum-like sporotrichosis (PGLS) is used to describe extensive ulcerative forms.[2–11] Three new cases are reported and previously published cases are reviewed.

A 48-year-old female patient presented with a painful ulcer on her right thigh for three months, with progressive enlargement and satellite lesions (Fig. 1). She had autoimmune hepatitis and had been treated with prednisone 1 mg/kg/day and azathioprine 3 mg/kg/day for five years. Tissue cultures were negative, and histopathology had shown granulomatous, suppurative panniculitis and vascular aggression. Given the hypothesis of PG, the patient received intravenous pulse therapy with methylprednisolone (1 g/day for three days) without improvement. As there was no response, a new biopsy was performed on the edge of the same lesion, one week after pulse therapy. Yeast-like structures stained with PAS (periodic-acid Schiff) were found in the subcutaneous tissue on histopathology (Fig. 2A). Simultaneously, patient's pet cat was diagnosed with sporotrichosis through secretion culture (Fig. 2B). As the patient had hepatorenal syndrome, treatment with potassium iodide (2 g/day) was chosen despite being immunosuppressed. The patient showed almost complete healing within three months of treatment (Fig. 1), when she presented decompensation of the liver condition and died. Although potassium iodide-associated hepatotoxicity is rare, it may occur in patients with pre-existing liver disease. However, the Gastroenterology team correlated the outcome to the worsening of the underlying disease.

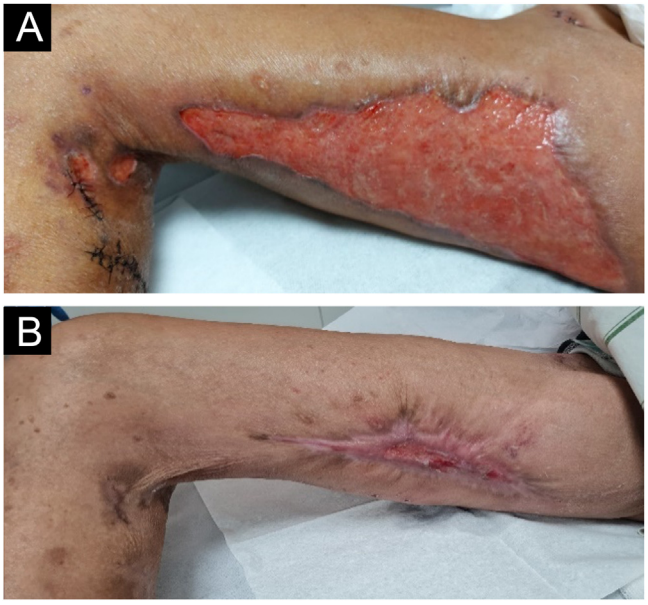

Figure 1 Pyoderma gangrenosum-like sporotrichosis. (A) Ulcer in the medial region of the right thigh with satellite lesions along the lymphatic tract. (B) Significant clinical improvement of the lesion after three months of treatment with potassium iodide.

The second patient, a 49-year-old male, had a painful ulcer in the right antecubital fossa with satellite lesions and perilesional lymph node enlargement of one-month evolution (Fig. 3A). He had psoriatic arthritis and diabetes mellitus. He had been treated with infliximab 3 mg/kg for four years, sulfasalazine 2 g/day for three years, and prednisone 20 mg/day for six months. Based on the initial suspicion of ecthyma gangrenosum, clindamycin and ciprofloxacin were administered for one month, without improvement. Subsequently, *Sporothrix sp.* was isolated from the ulcer fragment and sent for culture. Histopathology revealed abscessed granulomas, but the fungal culture was negative. Itraconazole was started, but the patient developed hepatorenal syndrome, which led to drug discontinuation. As an alternative, potassium iodide (3 g/day)

☆ Study conducted at the Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.

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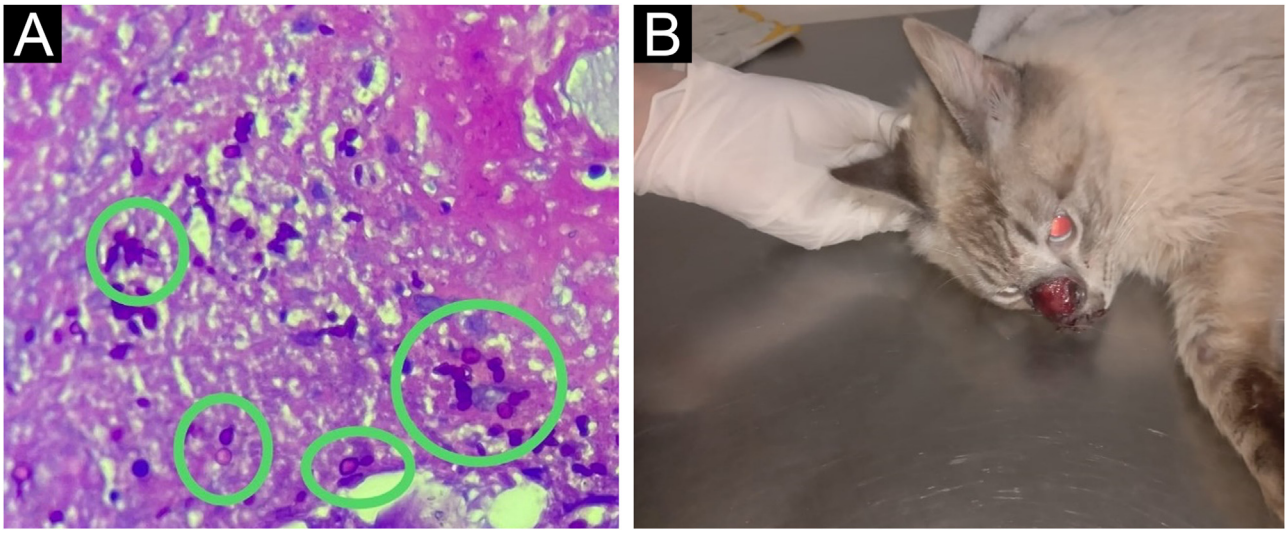

Figure 2 (A) Oval and elongated yeast-like structures in the deep dermis. (PAS, ×400). (B) Patient's cat with nasal ulceration diagnosed as sporotrichosis.

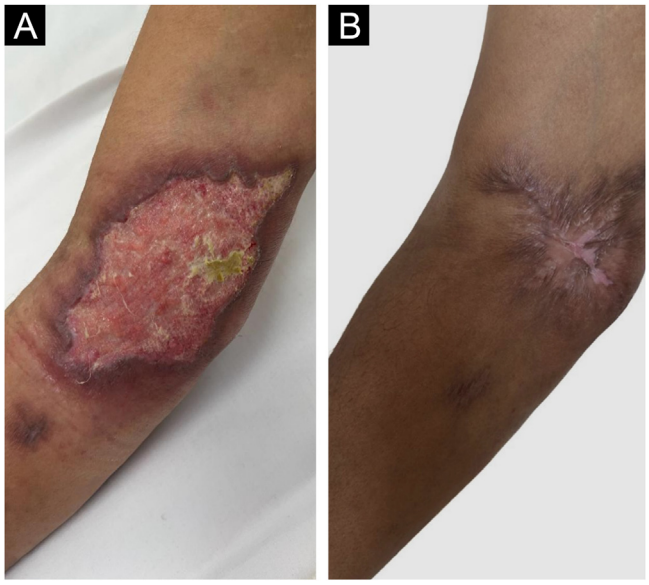

Figure 3 Pyoderma gangrenosum-like sporotrichosis. (A) Ulcer in the right antecubital fossa with satellite lesion. (B) Healing of the lesion after two months of treatment with potassium iodide.

was administered for two months, with healing of the ulcer (Fig. 3B).

The third patient, a 39-year-old male individual, presented a painful, ulcerated lesion with a cribriform appearance and satellite abscessed papules and nodules on the left leg of three-week evolution (Fig. 4A). Initial treatment with amoxicillin combined with clavulanate, clindamycin, vancomycin, and cefepime yielded no improvement. The patient had Crohn's disease and had received methotrexate 20 mg/week for four years and infliximab 5 mg/kg for two years. Given the initial hypothesis of PG, dapsone 100 mg/day was added for 30 days. Histopathology showed a neutrophilic inflammatory infiltrate and leukocytoclasia, abscessed granulomas and rare yeast-like spindle-shaped structures. In the culture, there was *Sporothrix sp*. growth, confirming the diagnosis. Itraconazole (200 mg/day) and potassium iodide (2 g/day) were started concomitantly, with healing after four months (Fig. 4B).

Extensive ulcerative forms of sporotrichosis are rarely described and occur especially in immunosuppressed patients. The term PGLS has been adopted due to the clinical and histopathological similarities with PG: phagedenic ulcers with erythematous edges, cribriform morphology and neutrophilic infiltrate.[3] The initial approach to PG requires the exclusion of differential diagnoses through biopsy and culture. However, the search for pathogens is not always positive at first. The lack of response to immunosuppressants should motivate a diagnostic review. Furthermore, fungal structures are difficult to observe, making the diagnosis of sporotrichosis even more difficult.[3] In this context, the culture of secretions or tissue fragments is extremely important,[11] as well as a detailed anamnesis, especially regarding the presence of felines and risk activities, such as gardening.

Only 10 published cases of PGLS were found in the English-language literature in PUBMED (Table 1). More than half (n = 6) were published in the last six years, which may reflect an improvement in diagnostic accuracy or an increase in incidence, mainly due to the growing population of immunosuppressed patients. The cases reported herein were under immunosuppression.

Interestingly, they had ulcers with a larger axis in the lymphatic drainage direction, while PG ulcers often have a more rounded shape. Satellite lesions occurred in the three cases and may help formulate the hypothesis of sporotrichosis.

Although potassium iodide is not the first therapeutic choice for immunosuppressed patients, it can be used as monotherapy when there are contraindications to other treatments.[3,4] In view of the experience in the first two cases, due to the synergistic drug effect and the report

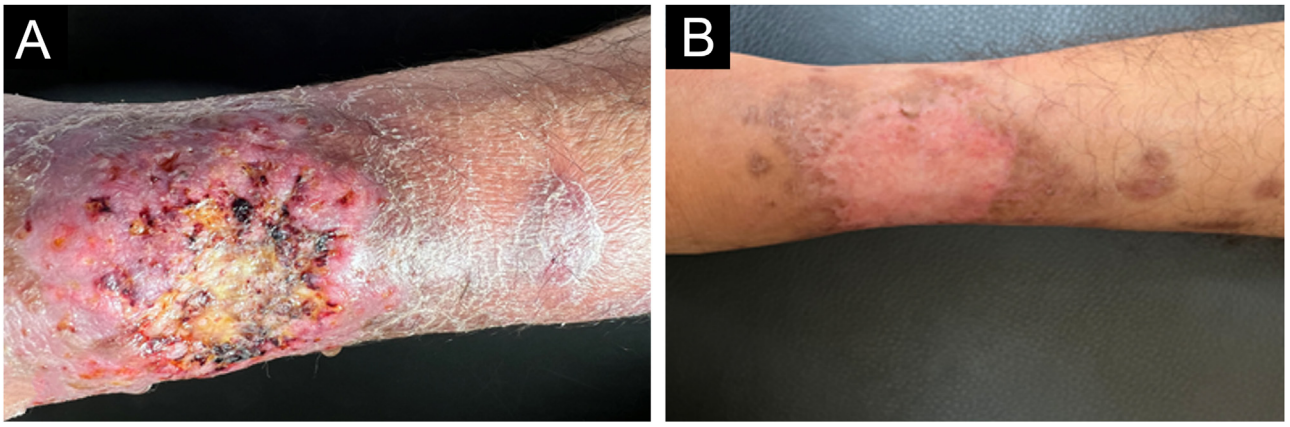

Figure 4 Pyoderma gangrenosum-like sporotrichosis. (A) Ulcer on the left leg with satellite lesions. (B) Healing of the lesion after four months of treatment with itraconazole and potassium iodide.

Table 1 Cases published in the literature (PUBMED database, English language until July 2024).

	Gender/ Age	Immunosuppression/ Comorbidities	Lesion sites	Initial treatment	Diagnostic method	Treatment	Clinical outcome
Stroud et al. 1968[1]	M/62	Metastatic squamous cell carcinoma	R forearm	Await the investigation, despite the clinical suspicion of PG	+Tissue culture	Amphotericin B 25 mg/day for five days; potassium iodide added for 2 days	Death after seven days of treatment for AKI
Spiers et al. 1986[2]	M/46	No	Abdomen	Tetracycline, erythromycin, PDN, DDS, AZA	+Tissue culture	Potassium iodide 3 g/day	Clinical cure after two months
Wan-Qing et al. 1991[3]	F/56	Corticosteroid therapy for rheumatoid arthritis	L buttock and thigh	MDT for TB; PDN; DDS	+Secretion culture	Potassium iodide (6–8 g/day)	Clinical improvement of the lesions. Death after two weeks due to pneumonia.
Byrd et al. 2001[4]	F/59	No	R leg	Systemic ATBs, PDN, AZA and cyclosporine	+Tissue culture; +PAS in AP	Itraconazole 600 mg/day, 18 months	Clinical cure after three months.
Lima et al. 2017[5]	F/39	No	Abdomen and R arm	PDN, immunosuppressors infliximab	+Tissue culture; +PAS yeast-like structures in AP	Liposomal amphotericin B (400 mg/day) six weeks + itraconazole 400 mg/day for 12 months	Clinical cure.
Charles et al. 2017[6]	F/57	Obesity and asthma	R arm	Levofloxacin, ceftriaxone, PDN, penicillin and topical clobetasol	+Tissue culture; +PAS yeast-like structures in AP	Itraconazole 400 mg/day	Clinical improvement and loss to follow-up
Takazawa et al. 2018[7]	M/47	Ulcerative colitis using mesalazine	R leg	Topical corticoids	+Tissue culture; +PAS yeast-like structures in AP	Potassium iodide 0.5 g for two weeks and 1 g for three weeks	Clinical cure in five weeks.

Table 1 (*Continued*)

	Gender/ Age	Immunosuppression/ Comorbidities	Lesion sites	Initial treatment	Diagnostic method	Treatment	Clinical outcome
White et al. 2019[8]	M/62	Coronary artery disease	L thigh	Cephalexin, PDN, cyclosporine, ustekinumab, immunoglobulin	+Tissue culture and blood culture	Liposomal amphotericin B (5 mg/kg/day); itraconazole 600 mg/day; amphotericin (4 mg/kg/day); posaconazole 300 mg/day	Clinical cure after six months.
Saeed et al. 2019 [9]	F/35	Alcohol abuse and type II diabetes	Legs, arms and abdomen	PDN, doxycycline	+Tissue culture; +PAS yeast-like structures in AP	Liposomal amphotericin B (5 mg/kg/day); posaconazole 300 mg/day; itraconazole 600 mg/day	Clinical cure after 12 months.
Tai et al. 2020 [10]	M/78	Not reported	L arm	Cyclosporine, mycophenolate mofetil, PDN, ustekinumab and immunoglobulin	+Tissue culture	Itraconazole 200 mg/day for four months, developed liver and kidney failure, potassium iodide was started	Clinical cure after four months.
Case 1	F/48	Autoimmune hepatitis/use of PDN and AZA	R thigh	Systemic antibiotics and methylprednisolone	+PAS yeast-like structures in AP; +epidemiology	Potassium iodide 2 g/day for three months	Clinical improvement, death after three months due to hepatorenal syndrome.
Case 2	M/49	Psoriatic arthritis, atrial fibrillation, arterial hypertension, dyslipidemia, diabetes mellitus, use of infliximab, sulfasalazine, prednisone, amiodarone, warfarin	R antecubital fossa	Clindamycin and ciprofloxacin	+Tissue culture; Negative for yeast structures in PAS and Grocott	Itraconazole 200 mg/day, developed hepatorenal syndrome, started potassium iodide 3 g/day	Clinical cure after two months.
Case 3	M/39	Crohn's disease using methotrexate, infliximab and loperamide	L leg	Amoxicillin + clavulanate, clindamycin, vancomycin and cefepime, dapsone	+Tissue culture	Itraconazole 200 mg/day and potassium iodide 2 g/day	Clinical cure after four months.

PDN, Prednisone; AZA, Azathioprine; DDS, Dapsone; ATB, Antibiotics; PAS, Periodic Acid of Schiff; AP, Anatomopathological; MDT, Multidrug therapy; TB, Tuberculosis; AKI, acute kidney insuficiency.

of the emergence of itraconazole-resistant *S. brasiliensis* isolates,[1] the association was chosen for the third patient.

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Authors' contributions

Lucas Campos Garcia: Study design, critical review, drafting and editing of the manuscript, review of the literature, approval of the final version of the manuscript.

Marianne de Sousa Nunes Soares: Drafting and editing of the manuscript, review of the literature.

Gustavo Gomes Resende: Drafting and editing of the manuscript, review of the literature.

Luciana Baptista Pereira: Study design, critical review, drafting and editing of the manuscript, review of the literature, approval of the final version of the manuscript.

Conflicts of interest

None declared.

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LETTER - THERAPY

Generalized pustular psoriasis (von Zumbusch) flares successfully treated with Spesolimab. Report of two cases and review of the literature☆

Dear Editor,

Generalized pustular psoriasis (GPP) is a severe, rare autoinflammatory disease characterized by recurrent widespread erythema and sterile pustules that can coalesce to form lakes of pus.[1] Its prevalence in Brazil is estimated to be between 0.7 and 0.9 cases per 100,000 inhabitants.[2] The treatment of GPP is challenging, as traditional antipsoriatic medications, including biologics, have limited evidence of efficacy in GPP. Recently, the anti-IL36R biologic, spesolimab, has shown promise.[1] This study reports the first two Brazilian cases of GPP treated with spesolimab.

Case 1

A 27-year-old woman reported a history of recurrent flares of erythematous lesions associated with pustules since the age of 11. She was diagnosed with GPP at the age of 21, during the second trimester of pregnancy, when she developed a generalized condition with systemic symptoms requiring hospitalization, and GPP was confirmed by skin biopsy. At that time, cyclosporine was initiated, resulting in complete control of the lesions. During outpatient follow-up, cyclosporine was discontinued in search of alternatives for maintenance treatment. The use of methotrexate showed improvement in the condition; however, localized pustular lesions persisted. The induction of the medication risankizumab resulted in a new flare, which was contained by the use of cyclosporine. At 27-years-old, the patient experienced a new flare, with diffuse erythema, desquamation, numerous pustules, pain, edema, malaise, and significant impairment of quality of life. On this occasion, an infusion of 900 mg of spesolimab was administered, resulting in an extremely rapid response in both cutaneous and systemic symptoms. Within 24 hours, all pustules had dried up, and there was a sensation of reduced edema, and remission of pain, with only the crusts of the pustules and milder erythema compared to the previous day persisting. At the follow-up visit one week later, there were no pustules, only erythema in the areas where the lesions had been most intense (Figs. 1 and 2). The patient maintained complete remission of the lesions, with no lesions observed during 16 weeks of follow-up.

Case 2

A 66-year-old woman presented with complaints of erythematous lesions with pustules, progressing to fever and dissemination of the lesions over the past week. She reported previous episodes with similar characteristics, which were treated with systemic corticosteroids and antibiotics. Based on the ERASPEN diagnostic criteria and the skin biopsy, she was diagnosed with GPP.[3] Acitretin, cyclosporine, and corticosteroids were used in sequence, without achieving clinical control. In an attempt to manage the condition, 900 mg of spesolimab was administered intravenously. One week after the infusion, there was a partial response (GPPASI = 10.2 and GPPGA = 2), and a second dose of 900 mg of spesolimab was administered. The patient showed a rapid response to the medication in the following week (GPPASI = 3 and GPPGA = 1) and maintained complete remission of the lesions, with no flares during 12-weeks of follow-up (Figs. 3 and 4).

Discussion

GPP is characterized by a sudden eruption of sterile pustules on erythematous base with systemic symptoms.[4] Disease flares can be idiopathic or triggered by external factors such as infections, discontinuation of systemic corticosteroids, pregnancy, and use of certain immunobiological drugs.[5,6] The pathogenesis involves the exaggerated activation of the IL-36 Receptor (IL-36R). The cytokines IL-36α, IL-36β, and IL-36γ activate IL-36R, while the IL-36 Receptor antagonist (IL-36Ra) modulates the action of IL-36 cytokines. These cytokines stimulate the inflammatory response, and activation of neutrophils, macrophages, dendritic cells, and T-cells.[4] The IL-36RN gene encodes the IL-36Ra protein that contributes to suppressing the action of IL-36 cytokines. Mutation of this gene triggers exaggerated signaling of IL-36 cytokines. Mutations in this gene have been identified in both isolated cases[7] and familial cases[8] of GPP. Spesolimab, a novel anti-IL36R medication, has shown efficacy in treating GPP flares and was approved by ANVISA in March 2023. The Effisayil-1 trial showed that spesolimab cleared all lesions within a week in 54% of the patients vs. 6% in the placebo group).[1] A review showed that there is limited evidence regarding the use of other biological drugs to treat GPP compared to spesolimab.[9] This drug represents a safe and efficient alternative compared to traditional treatments such as immunosuppressants and retinoids.

☆ Study conducted at the Hospital Universitário Evangélico Mackenzie, Curitiba, PR, Brazil.

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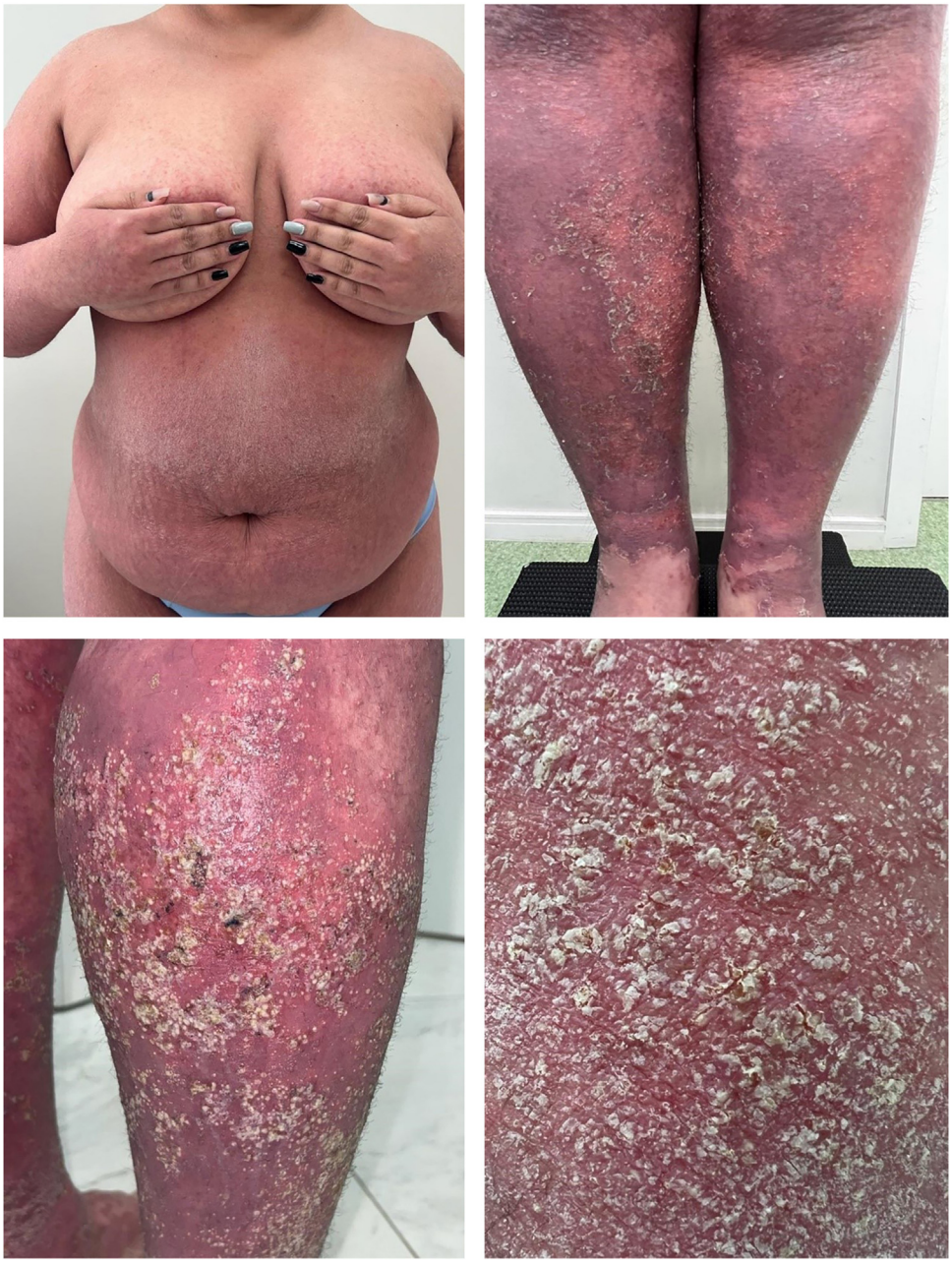

Fig. 1 Patient in flare before the infusion – GPPASI = 54.2 and GPPGA = 4.

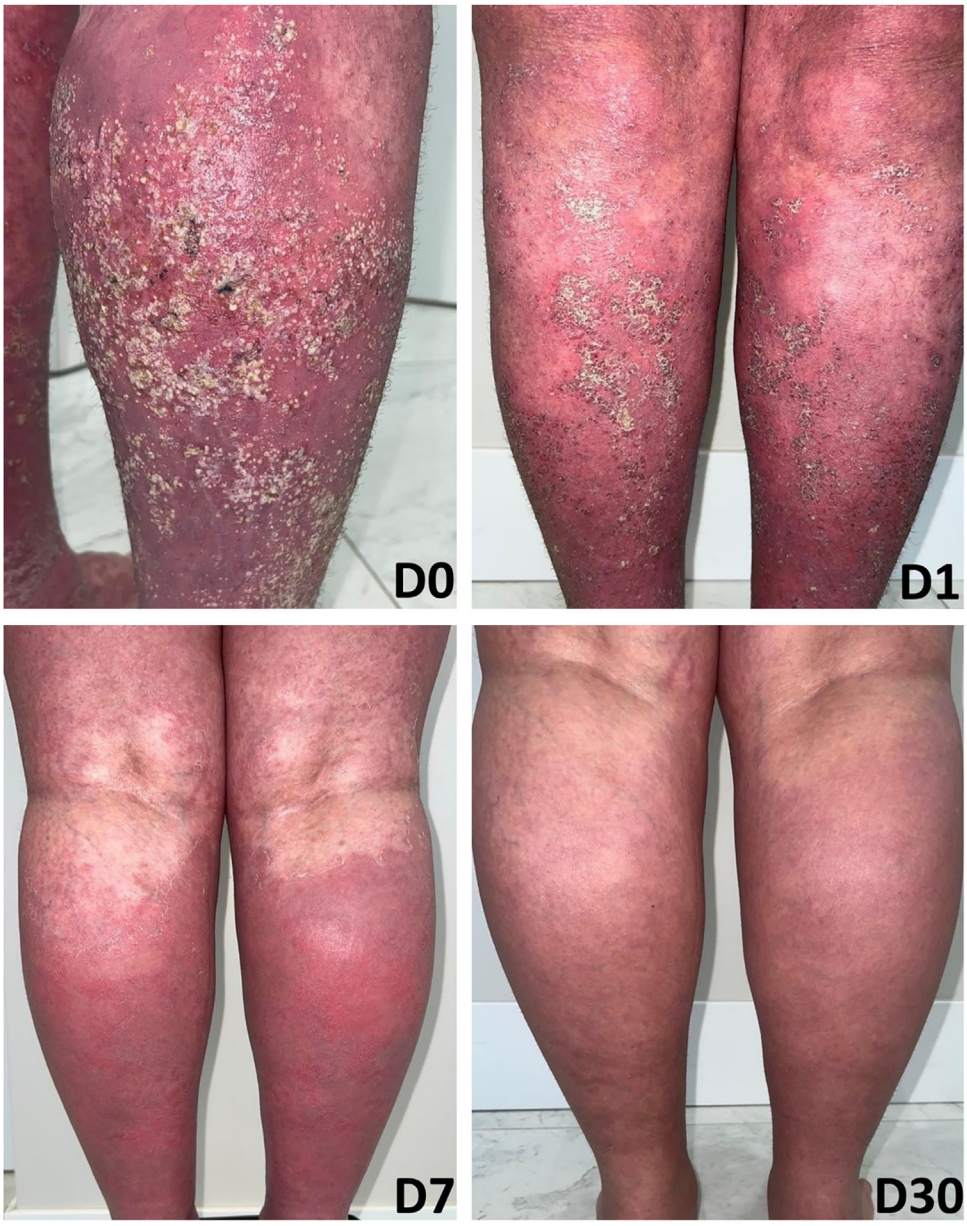

Fig. 2 Sequential images before the infusion; one day; one week; and one month after the infusion.

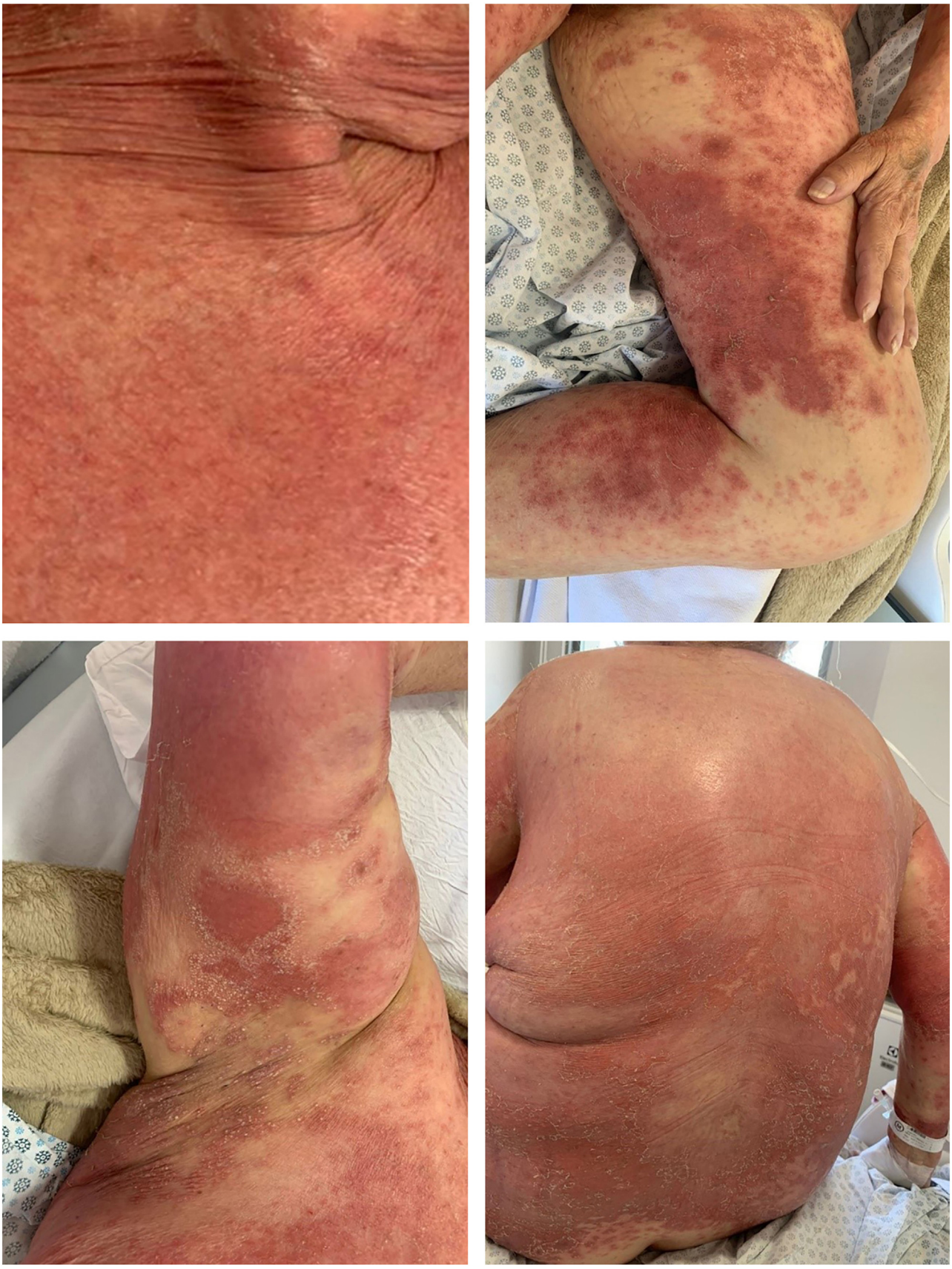

Fig. 3 Patient during hospitalization in flare – GPPASI = 23.1 and GPPGA = 3.

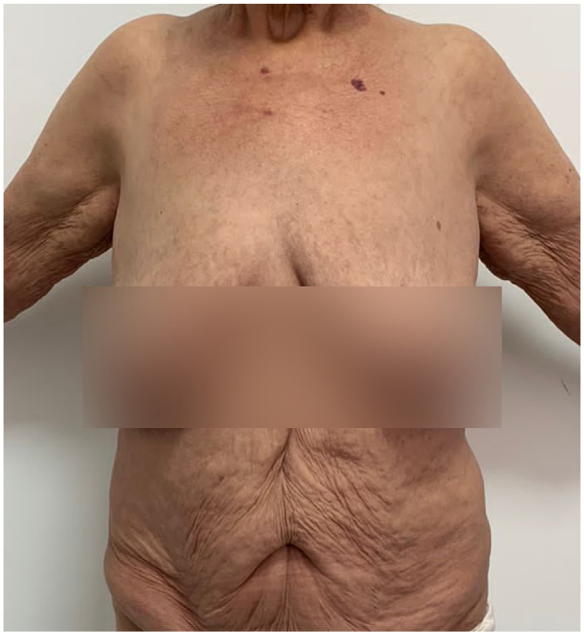

Fig. 4 One week after 2 doses of spesolimab administered at weekly intervals.

Conclusion

GPP is a severe dermatosis that can be confused with other diseases, making diagnosis and treatment challenging. Traditional therapies can cause significant side effects. Spesolimab, an anti-IL36R medication, emerges as a promising and safe alternative in the treatment of GPP, providing rapid improvement of cutaneous and systemic symptoms. It is suggested that further research and the inclusion of spesolimab in established treatment protocols for generalized pustular psoriasis be considered.

Disclaimer

Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to Boehringer Ingelheim substances, as well as intellectual property considerations.

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Authors' contributions

Raquel Steglich: Approval of the final version of the manuscript; intellectual participation in propaedeutic and/or therapeutic management of studied cases; preparation and writing of the manuscript ; manuscript critical review.

Felipe Saboia: Critical literature review; data collection, analysis and interpretation; preparation and writing of the manuscript.

Lincoln Helder Zambaldi Fabricio: Approval of the final version of the manuscript; intellectual participation in propaedeutic and/or therapeutic management of studied cases.

Eoda Steglich: approval of the final version of the manuscript; intellectual participation in propaedeutic and/or therapeutic management of studied cases.

Anber Tanaka: Approval of the final version of the manuscript; intellectual participation in propaedeutic and/or therapeutic management of studied cases; manuscript critical review.

Conflicts of interest

Raquel Steglich: Abbvie – lecturer; Boehringer-Ingelheim – lecturer; Janssen – advisory board, lecturer.

Felipe Saboia: None.

Lincoln Fabricio: Abbvie – lecturer, investigator; Bayer – lecturer; Bioderma – lecturer; Biolab – lecturer; Galderma – lecturer; Hypera Pharma – lecturer; Isdin – lecturer; Janssen – lecturer, investigator; La Roche-Posay – lecturer; LEOPharma – lecturer; Pfizer – lecturer; GSK – lecturer; Novartis – lecturer, investigator; Sanofi – lecturer, investigator; Ache – lecturer.

Eoda Steglich: None.

Anber Tanaka: Abbvie – advisory board, consultant, lecturer, investigator; Boehringer-Ingelheim – advisory board, consultant, lecturer, investigator; Eli-Lilly – advisory board, consultant, lecturer, investigator; Janssen – advisory board, consultant, lecturer; Leo Pharma – advisory board, consultant, lecturer; Novartis – advisory board, consultant, lecturer; investigator; UCB Biopharma – advisory board, consultant, lecturer; Pfizer – lecturer, advisory board; Sanofi – lecturer.

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LETTER - THERAPY

Pembrolizumab-induced Stevens-Johnson syndrome☆

Dear Editor,

Immunotherapy represents an important advance in the treatment of malignant neoplasms, and melanoma was the first disease for which its use was approved; over time it has gained other indications. Its therapeutic principle is the activation of T-lymphocytes, overcoming their inhibition with monoclonal antibodies targeted at proteins or receptors with an inhibitory effect.[1] The 2018 Nobel Prize in Medicine was awarded to the discoverers of the possibility of releasing T-cells in oncological treatment, starting a new era.

In 2011, ipilimumab (an anti-CTLA-4 antibody) was approved for the treatment of metastatic melanoma, followed by the approval of nivolumab and pembrolizumab in 2014 (both anti-PD-1), all of them for melanoma.[1] It was subsequently approved for other neoplasms, as well as combined therapy with two antibodies, with a synergistic effect, such as ipilimumab + nivolumab for melanoma in 2015.[1]

Its adverse effects are due to aggression of non-neoplastic tissues by activated T cells, the most common being thyroiditis (in 10% of patients receiving anti-PD-1 and up to 20% receiving combined therapy consisting of ipilimumab and nivolumab), hypophysitis (5% to 10% of patients; it is more common with ipilimumab) and adrenal insufficiency.[2] Colitis, rheumatological conditions

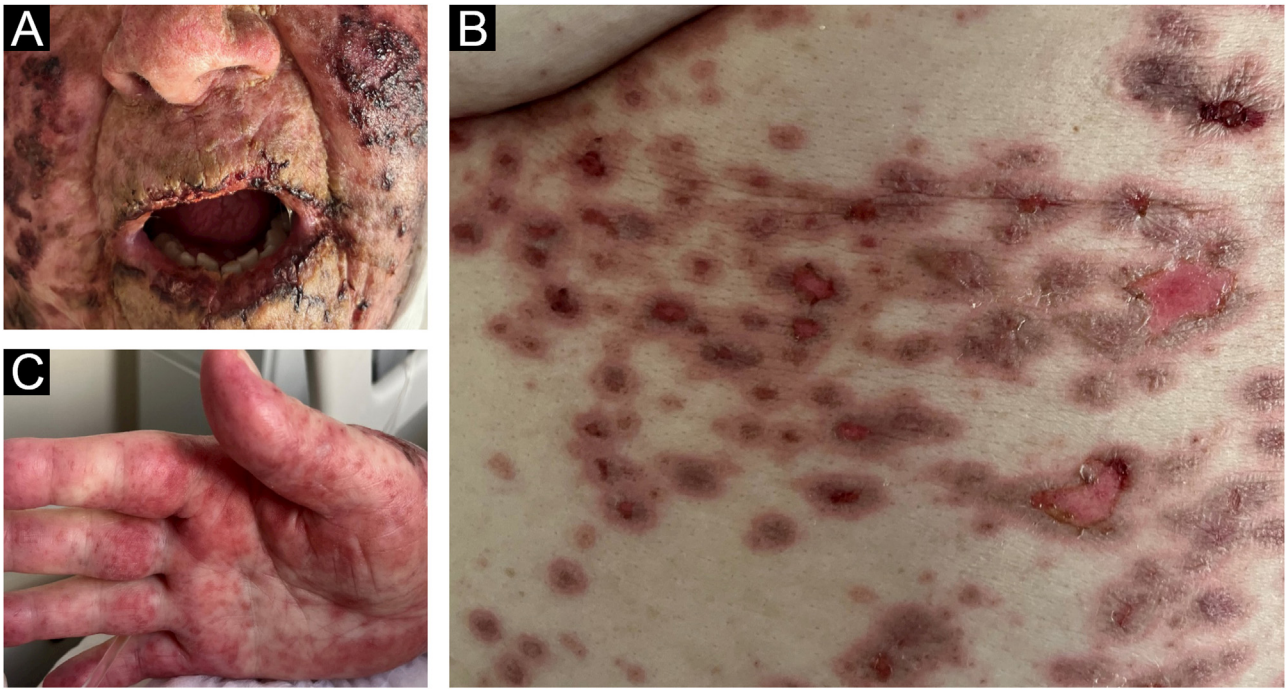

Fig. 1 (A) Erosions on the labial mucosa and malar regions. (B) Palmar lesions. (C) Target-like lesions on the abdomen.

☆ Study conducted at the Universidade Federal de Pelotas, Pelotas, RS, Brazil.

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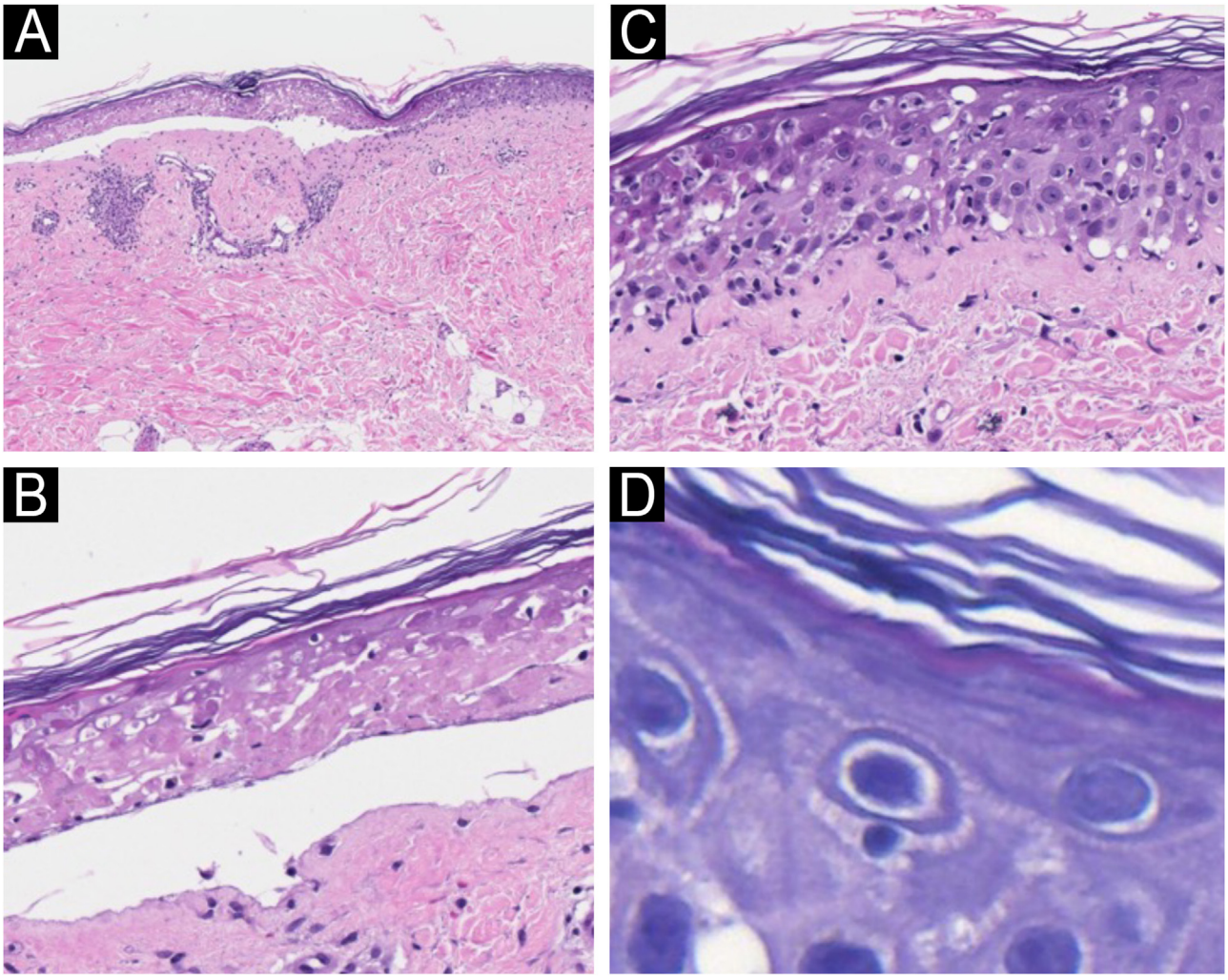

Fig. 2 Light microscopy with hematoxylin & eosin. (A) Epidermal detachment and light inflammatory reaction in the dermis (×100). (B) Detail of epidermal necrosis in the center of the lesion (×200). (C) Detail of the periphery of the lesion with isolated necrosis of keratinocytes and lymphocytic exocytosis (×200). (D) Lymphocyte satellitosis at the periphery of the lesion (×400).

(resembling rheumatoid arthritis, polymyalgia rheumatica, polymyositis and Sjögren's syndrome), neurological and cardiac manifestations (myocarditis has a high mortality rate in these patients) are also described.

The skin may also be affected, with manifestations ranging from pruritus to exanthema, psoriasis, lichen planus, bullous pemphigoid, and even severe reactions in the Stevens-Johnson/Lyell syndrome spectrum.[2,3] Vitiligo is more common in patients treated for melanoma, suggesting immunity against neoplastic and epidermal melanocytes.[2]

The present report describes an 83-year-old female patient, previously hypertensive, with a history of thymoma excision in 2022. Two years later, she presented a vegetative lesion on the right heel, and histopathology revealed an undifferentiated malignant neoplasia, extending to the reticular dermis. Immunohistochemistry was positive for melanocytic markers, confirming the diagnosis of melanoma. Given the difficulty of the surgical approach, therapy with pembrolizumab was indicated by the oncology team. Ten days after she started treatment, she developed painful crusts in the oral cavity (Fig. 1A) associated with palmar lesions (Fig. 1C). As the condition progressed, target-like lesions with central erosion appeared (Fig. 1B).

The patient was hospitalized and received systemic corticosteroid therapy. Despite the use of systemic antibiotics, the patient developed sepsis and died.

A biopsy of a target-like lesion was performed and histopathology revealed prominent necrosis of the epidermis with its detachment (Fig. 2A). A detailed examination identified epidermal necrosis in the area of the bulla (Fig. 2B). In the transition to the unaffected area, there was necrosis of keratinocytes and the presence of numerous lymphocytes in the epidermis (Fig. 2C). On high magnification, several satellitosis figures were seen in this same area (Fig. 2D). The dermis exhibited scarce perivascular lymphocytic inflammatory infiltrate.

Immunohistochemistry (IHC) with anti-CD3, CD4, CD8 and CD20 antibodies, aimed to identify the lymphocyte subtypes involved, showed light dermal infiltrate of CD3, CD4 and CD8-positive cells; no positivity was seen for CD20 (Fig. 3). Detailed examination showed that the dermal infiltrate was predominantly composed by CD3 and CD4 positive cells and

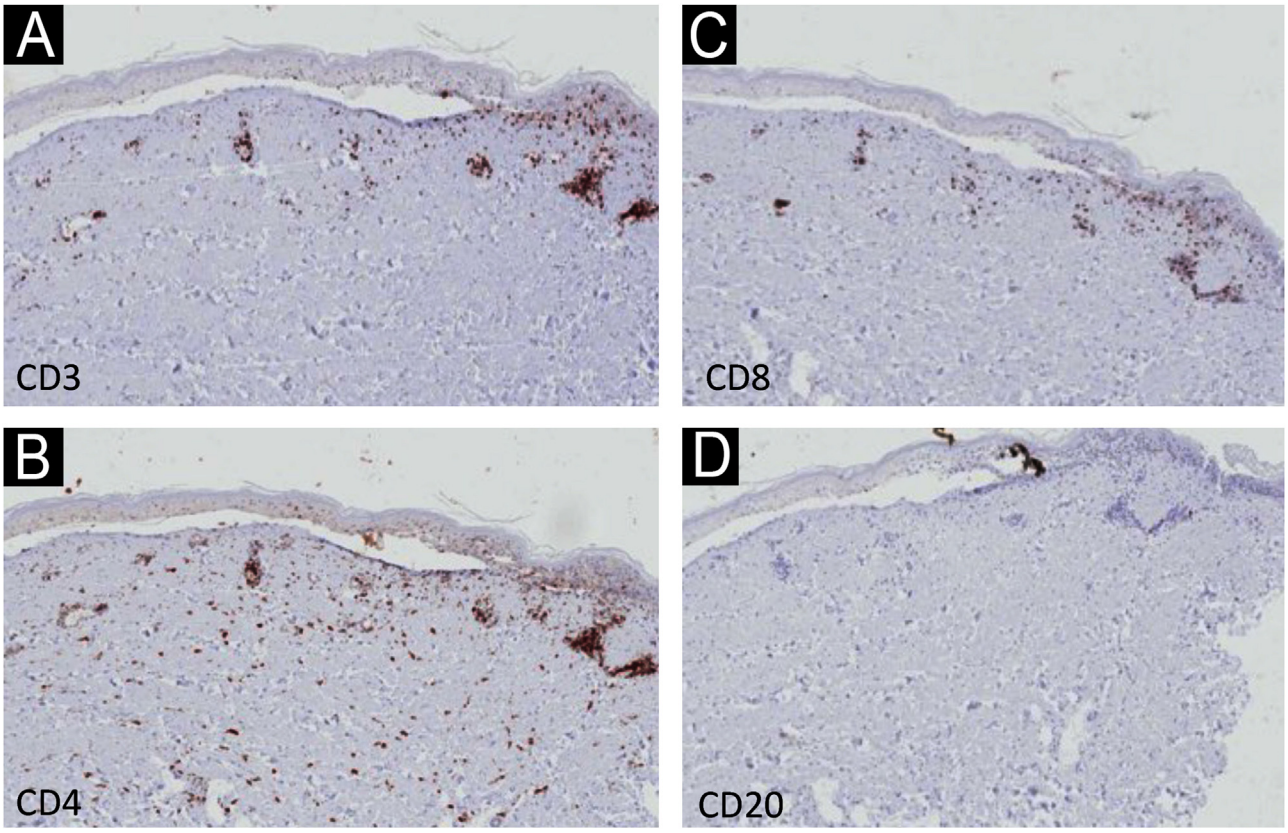

Fig. 3 Immunohistochemistry – low magnification (×40) showing light dermal infiltrate with positivity for CD3, CD4 and CD8 cells (A–C), and negativity for CD20 (D).

a smaller number of CD8 cells (Fig. 4). In the epidermis, the infiltrate was more pronounced with CD3-positive cells followed by CD8-positive cells (Fig. 4). The B lymphocyte marker, anti-CD20, was negative.

Given the clinical possibility of paraneoplastic pemphigus, indirect immunofluorescence was performed on rat bladder and normal skin, which resulted negative.

There are numerous reports of Stevens-Johnson syndrome associated with the use of pembrolizumab similarly to what was seen in the reported patient, sometimes after only one dose of immunotherapy,[4–7] but it can happen even after the ninth dose.[8] There are also similar reports with other monoclonal antibodies used in immunotherapy.

The histopathological findings in the present report are similar to those previously described, with epidermal necrosis and little dermal infiltration.[9] There is only one IHC report demonstrating a predominance of CD8 cells, in slight disagreement with the present findings of epidermal predominance of CD3 cells over CD8-positive cells; the CD3 protein participates in the activation of CD8-positive cells, and their co-expression may occur.[9] It is necessary to examine more cases with IHC to better understand these findings.

The satellitosis found in the present case is characteristic of T-cell-mediated diseases, such as graft-versus-host disease, and demonstrates the activation of T cells by immunotherapy.[10]

The IHC findings confirm epidermal aggression by T-lineage cells.

The literature on pembrolizumab-induced Stevens-Johnson syndrome refers to different neoplasms, outcomes, and intensities, including an association with other autoimmune diseases,[7,8] which may contribute to the severity of this condition, and therefore, dermatologists should be aware of these possibilities.

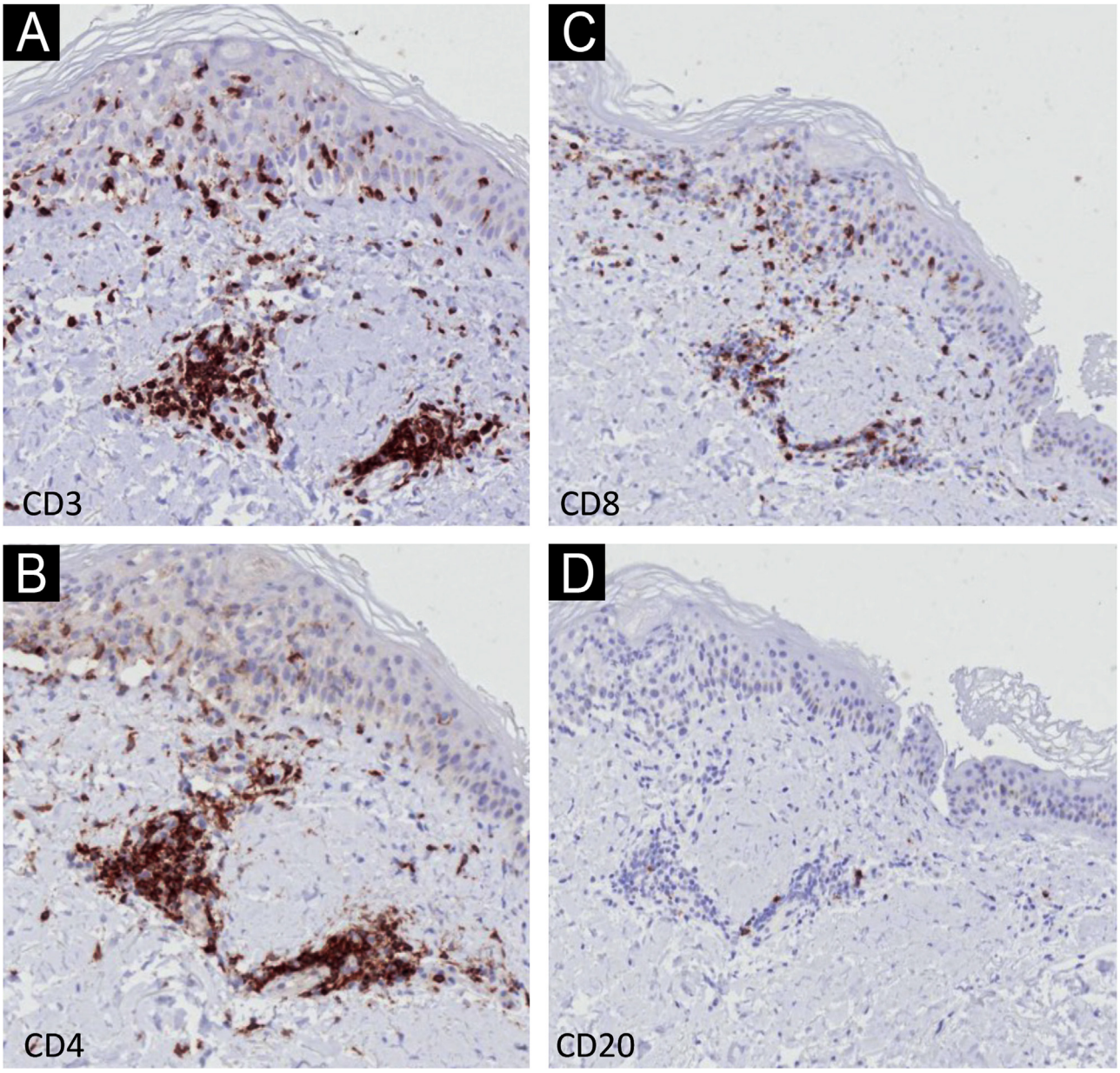

Fig. 4 Immunohistochemistry – detail (×400) showing stronger positivity in the dermis for CD3 and CD4 (A and B) and in the epidermis for CD3 (A) and CD8 (C). Negativity for CD20 (D).

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Authors' contributions

Hiram Larangeira de Almeida Jr: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Debora Sarzi Sartori: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Aline Paganelli: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; critical review of the literature; critical review of the manuscript.

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Conflicts of interest

None declared.

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LETTER - THERAPY

Rapid improvement in a recurrent generalized pustular psoriasis patient ineffective to Ixekizumab following Spesolimab therapy☆

Dear Editor,

Generalized pustular psoriasis (GPP) is a rare and dangerous subtype of psoriasis characterized by recurrent episodes of widespread erythema with numerous sterile pustules, often accompanied by varying degrees of systemic inflammatory manifestations.

A 52-year-old female presented with recurrent erythema and pustules accompanied by pain for 2 years, exacerbated after discontinuing oral medications for the past 2 days, along with generalized fatigue, then she was admitted to our department for inpatient treatment. Prior to admission, she relied on long-term oral acitretin (10–20 mg once daily), prednisone acetate tablets (10 mg three times daily) to control her condition, and received injections of ixekizumab (anti-IL-17A) (80 mg every 2-weeks) for a total of 12-weeks, but the skin lesions did not completely improve, and the pustules continued to recur. Upon physical examination, her temperature was normal, with swelling of the limbs and diffuse erythema almost covering the entire body, containing densely distributed pinpoint-sized pustules. Local skin temperature was elevated with evident tenderness. Generalized Pustular Psoriasis Physician Global Assessment (GPPGA: 11), Generalized Pustular Psoriasis Area and Severity Index (GPPASI: 38.3). Her white blood cell count (13.52×10^9/L), neutrophil count (11.33×10^9/L), neutrophil percentage (83.8%), and CRP (45.75 mg/L) were elevated upon admission, accompanied by decreased albumin (35.5 g/L). Then we performed a skin biopsy and combined the clinical and pathological findings (Fig. 1 A and B), she was diagnosed with GPP. With the patient's consent, we completed the prebiologic screening and administered a single dose of 900 mg spesolimab intravenously over 90 minutes, the patient experienced no discomfort during or after the injection process. Within 24 hours of Spesolimab treatment, almost complete clearance of pustules was observed, with the erythema darkening in color and beginning to desquamate (GPPGA: 5, GPPASI: 11.7) (Fig. 2 A and B) Five days later, the patient's

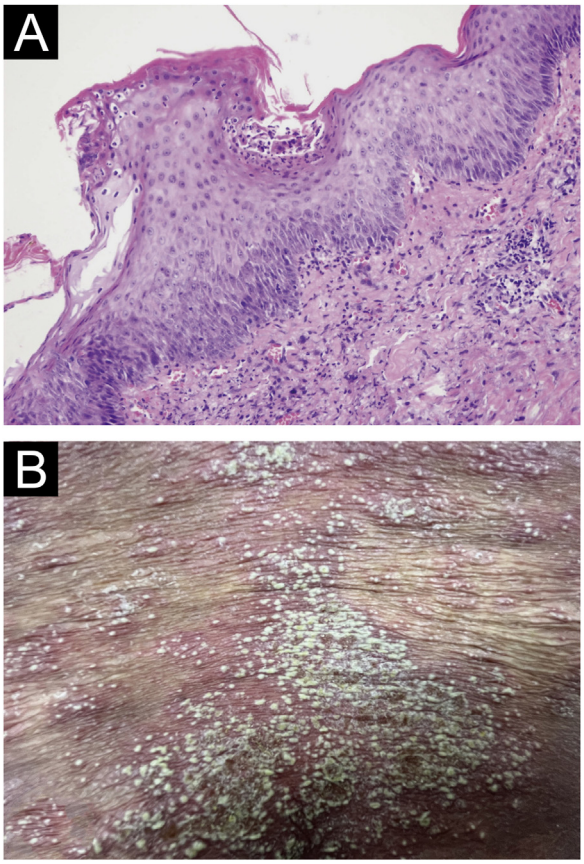

Figure 1 (A) Biopsy results from the skin folds under the breast: Epidermal hyperkeratosis with mild parakeratosis, focal neutrophilic aggregates forming microabscesses in the stratum corneum, thinning of the granular layer, acanthosis in the spinous layer, mild spongiosis in the spinous layer, and dermal perivascular infiltration of inflammatory cells including lymphocytes, histiocytes, and neutrophils (Hematoxylin & eosin, ×200); (B) Localized pustules at admission.

☆ Study conducted at the Institute of Dermatology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.

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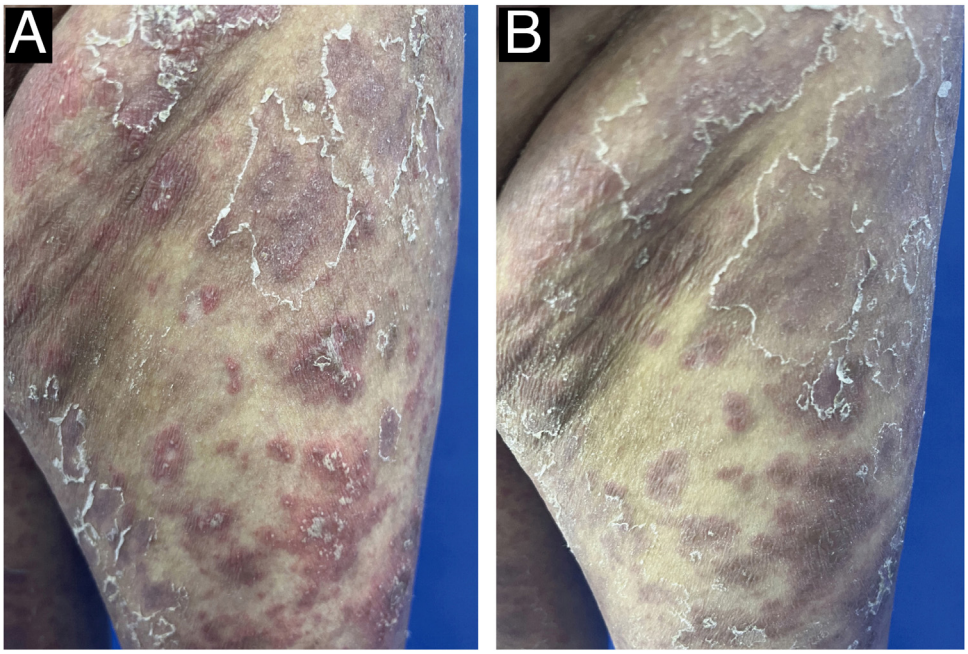

Figure 2 (A) Skin lesions on the left thigh 1-day before Spesolimab treatment; (B) Changes in skin lesions on the left thigh 1 day after Spesolimab treatment.

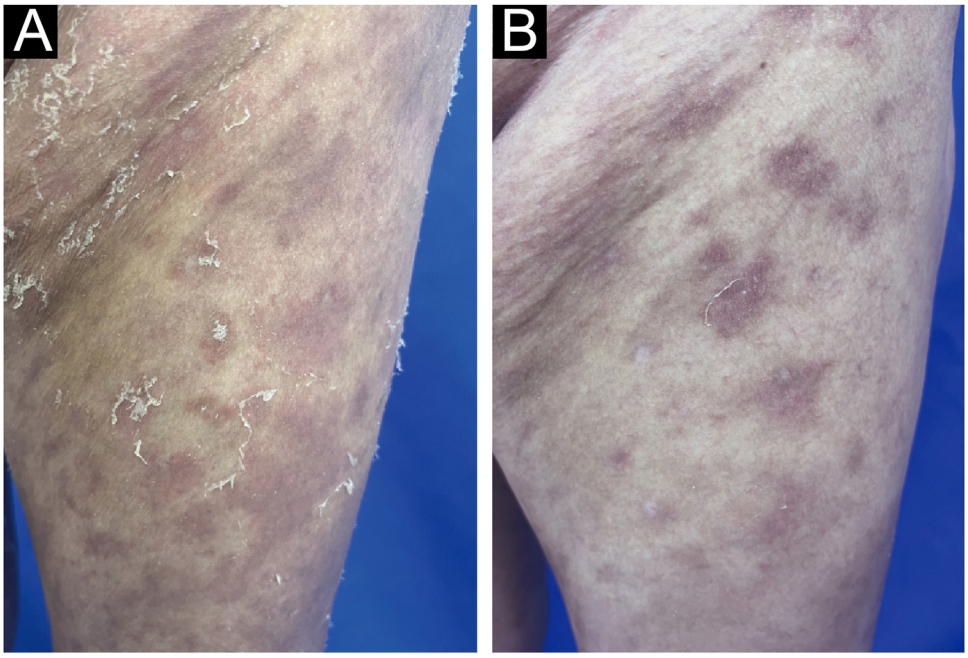

Figure 3 (A) Changes in skin lesions on the left thigh 5-days after Spesolimab treatment; (B) Changes in skin lesions on the left thigh 3-months after Spesolimab treatment.

generalized erythema lightened with minimal desquamation and no new skin lesions observed. Her blood routine, CRP, and albumin returned to normal levels without any signs of new infection (GPPGA: 2, GPPASI: 5) (Fig. 3A). The patient experienced rapid relief of GPP symptoms post-Spesolimab treatment and was discharged after 5-days of treatment. She continued topical corticosteroid cream at the lesion sites post-discharge and remained free of significant erythema and pustules at the 3-month follow-up (Fig. 3B).

Due to the rarity and complexity of GPP, there is currently no globally agreed-upon treatment regimen that can completely control GPP flare-ups. Research has revealed a close immunopathological link between GPP and plaque psoriasis, and some biologics used for treating plaque psoriasis, such as anti-TNF-α antibodies, anti-IL-17A antibodies, and

Table 1 Similar cases successfully treated with Spesolimab.

Authors/Year	Patient characteristics and GPP history	Plaque psoriasis history	Initial biologic agent used	Preliminary outcome	Dosage of Spesolimab used	Final outcome
Jiang et al.[4] 2023	34-years-old, female, 2-years	20-years	Ustekinumab (anti-IL-12/23) 45 mg once; Adalimumab (anti-TNF-α) 80 mg twice	The condition tended to stabilize within 1-week, but new pustules appeared later	A single dose of 900 mg	Complete resolution of skin lesions within 1-week, with no recurrence or adverse reactions during the 5-month follow-up after treatment
Ran et al.[5] 2023	26-years-old, female, 14-years	Negative	Adalimumab (anti-TNF-α)	Ineffective	A single dose of 900 mg	Complete resolution of skin lesions at 16-weeks post-treatment
Müller et al.[6] 2023	63-years-old, male, about 4-years	Negative	Infliximab (anti-TNF-α) 5 mg/kg; Risankizumab (anti-IL-23)	Regular recurrences	Two doses of 900 mg	Complete disappearance of pustules, significant reduction in erythema, no relapse
Our case	52-years-old, female, 2-years	Negative	Ixekizumab (anti-IL-17A) initially 160 mg, followed by 80 mg every 2-weeks for a total duration of 12-weeks	Ineffective	A single dose of 900 mg	Complete disappearance of pustules within 24-hs, a significant reduction in erythema, no relapse after 3-months

anti-IL-12/23 p40 antibodies, have also shown efficacy in treating GPP and have been included in the recommended treatment guidelines for GPP in Japan.[1] However, studies on their efficacy primarily involve small-scale clinical cases, with limited systematic clinical research or randomized controlled trials, resulting in a lower level of evidence. Although patients with GPP often exhibit clinical manifestations similar to plaque psoriasis, growing evidence suggests that GPP, as a separate clinical entity, is an autoinflammatory pustular neutrophilic disease. Unlike plaque psoriasis, the core of GPP development lies in the IL-1 and IL-36 pathways.[2] Our case seems to confirm this distinction. Spesolimab, an IL-36 receptor inhibitor, has demonstrated efficacy and safety in rapidly controlling acute GPP episodes through Phase II clinical trials,[3] making it a promising therapeutic option for GPP management. Additionally, although some evidence suggests that other biologics typically used for plaque psoriasis might also be effective for GPP, several reported cases of GPP had previously attempted treatment with biologics such as ustekinumab, adalimumab, infliximab, and risankizumab (Table 1),[4–6] but the potential efficacy of these biologics in managing GPP was not well demonstrated in these patients. In contrast, these cases achieved rapid and significant relief of skin lesions after spesolimab treatment. Although IL-36 cytokines can induce the expression and interaction of various downstream cytokines like IL-17A, IL-23, and TNF-α, which may also play roles in the pathogenesis of GPP, the role of IL-36 in the clinical treatment targets of GPP may be more crucial and significant. In summary, spesolimab represents a more precise and potent option when other biologics show suboptimal results in treating GPP, and future research may require larger-scale validation to demonstrate its safety and durability.

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Authors' contributions

Wenjie Li: Writing of the manuscript and critical review of important intellectual content.

Fan Cui: Critical review of the literature.

Lixia Zhang: Intellectual participation in the propaedeutic and therapeutic conduct of the studied case.

Ge Yang: Effective participation in the research guidance.

Zhen Rang: Effective participation in the research guidance.

Minyan Xu: Effective participation in the research guidance.

Yangying Liu: Final approval of the final version of the manuscript.

Siyu Wang: Final approval of the final version of the manuscript.

Conflicts of interest

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