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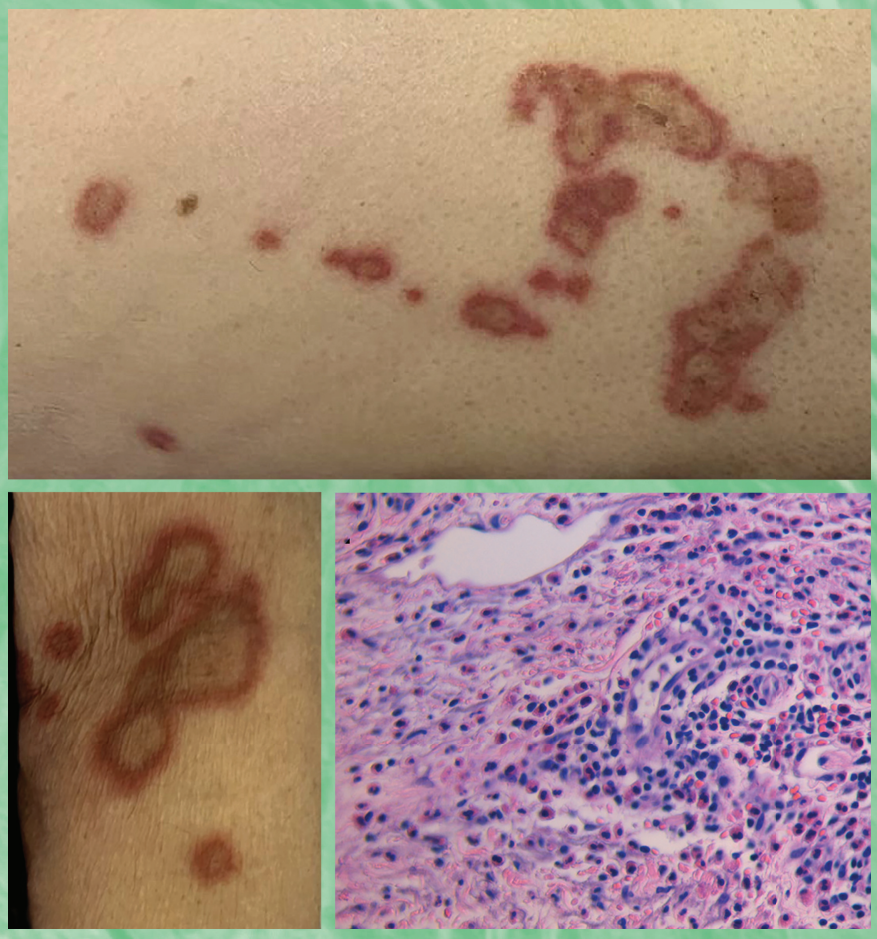

Eosinophilic annular erythema in a patient with hepatitis B-related cirrhosis
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CONTINUING MEDICAL EDUCATION

Varicella-zoster virus infection: a review about varicella and herpes zoster☆

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Abstract The Varicella-zoster virus (VZV) is a prevalent human pathogen that links dermatology, virology, and immunology. Following primary varicella infection, the virus establishes lifelong latency in the sensory ganglia, with reactivation manifesting as herpes zoster. The clinical spectrum ranges from typical dermatomal vesicular eruptions to atypical or disseminated presentations in older adults or immunocompromised patients, often posing diagnostic challenges. Early recognition and prompt initiation of antiviral therapy are essential to limit lesion progression, reduce viral shedding, and prevent complications. Dermatologists are uniquely positioned to identify these manifestations and distinguish VZV infection from its clinical mimics. Advances in molecular diagnostics have improved the detection of atypical cases, while the introduction of the attenuated-virus vaccine for varicella and recombinant glycoprotein E–based vaccine for herpes zoster has transformed prevention, providing durable protection even in older adults and immunosuppressed populations. Beyond therapy, dermatologists play a key role in integrating vaccination assessment and patient education into routine care. Understanding the biological continuum of VZV (from latency to reactivation) enhances diagnostic precision, guides evidence-based treatment, and supports immunization strategies against VZV. As VZV continues to impose a substantial burden of cutaneous and neuropathic morbidity, an integrated dermatological approach that combines early therapeutic intervention with preventive counseling represents the most effective strategy to reduce its clinical and public health impact.

☆ Study conducted at the Postgraduate Program in Gerontology, Universidade Federal de São Carlos; Vigilare Lab, Department of Medicine, Universidade Federal de São Carlos; University Hospital, Universidade Federal do Piauí; and Department of Specialized Medicine, Universidade Federal do Piauí.

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Introduction

The Varicella-zoster virus (VZV, human herpesvirus 3) is a ubiquitous human pathogen of the *Herpesviridae* family responsible for two clinically distinct conditions: primary infection or varicella (chickenpox) and viral reactivation, known as herpes zoster (shingles).[1,2] Both entities are highly relevant in dermatological practice, not only because of their characteristic cutaneous patterns but also because of their potential complications, including chronic pain syndromes, bacterial superinfection, and postherpetic neuralgia.[3,4]

Although vaccination programs have reshaped the epidemiological landscape, VZV remains a substantial health concern, particularly in adults, older patients, and immunocompromised hosts.[3,5] Therefore, understanding its virology, immunopathogenesis, and clinical behavior is essential for dermatologists, who are often the first to recognize the disease and initiate timely antiviral therapy.

This review provides an updated, clinically oriented synthesis of VZV-related skin diseases tailored for dermatology practitioners. It integrates the fundamental aspects of viral biology, epidemiology, and host interactions with practical guidance on diagnosis, management, and prevention. Emphasis is placed on clinical reasoning and decision-making, translating current scientific knowledge into evidence-based dermatologic care practices.

Essential virology and pathogenesis

VZV is an enveloped, double-stranded DNA virus that belongs to the *Alphaherpesvirinae* subfamily.[2,6] Its genome encodes more than 70 proteins, including structural and regulatory components essential for viral replication, latency, and immune evasion.[6,7] Although VZV shares structural similarities with Herpes Simplex Viruses (HSV-1 and HSV-2), it exhibits unique biological behaviors and tissue tropism, with a strong predilection for cutaneous and neuronal cells.[8]

During primary infection, VZV enters the host through the respiratory mucosa or conjunctiva and replicates in the regional lymph nodes.[2] Transient viremia subsequently disseminates the virus to the skin, leading to the formation of characteristic vesicular lesions.[2] Although these lesions contain high viral loads, transmission occurs predominantly via the respiratory route through inhalation of virus-containing aerosols and droplets.[2] Following resolution of the primary infection, VZV establishes lifelong latency in the sensory dorsal root and cranial nerve ganglia, where it persists in a non-replicative state.[9,10] Unlike HSV, which may reactivate repeatedly, VZV typically remains dormant for decades until reactivation is triggered by waning cell-mediated immunity, most often in older adults and immunocompromised patients.[11] The reactivated virus travels centrifugally along the sensory nerves to the skin, giving rise to a localized vesicular eruption of herpes zoster.[8]

The viral genome encodes several glycoproteins critical for infection and immune evasion, among which glycoprotein E (gE) is the most abundant and primary target of neutralizing antibodies.[2] Viral replication predominantly occurs in the nuclei of epithelial and neuronal cells, inducing cytopathic changes that underlie the vesicular morphology of lesions.[2]

The pathogenesis is driven by intricate interactions between the virus and the host. During primary infection, humoral immunity contributes to viral clearance; however, long-term control and latency depend on cellular immunity, particularly VZV-specific CD4+ and CD8+ T-lymphocytes.[2,11] With advancing age or under immunosuppressive conditions, T-cell-mediated surveillance declines, facilitating viral reactivation.[2,11] The ensuing inflammation of the affected ganglia and nerves produces both cutaneous manifestations and neuropathic pain, which define herpes zoster.[9,12]

Latency is maintained through the suppression of lytic gene expression and modulation of neuronal survival pathways, whereas reactivation induces neuronal damage that may persist beyond lesion resolution, manifesting as postherpetic neuralgia.[9,11,12] The clinical diversity of VZV infections (including atypical, multidermatomal, and disseminated forms) stems from the balance between viral replication and host immune competence.[9]

Epidemiology and clinical relevance

VZV infection is nearly universal in unvaccinated populations, with most individuals acquiring primary varicella infections during childhood.[13,14] In temperate climates, varicella typically occurs in early childhood, whereas in tropical regions, the infection may be delayed until adolescence or adulthood.[14] Before the introduction of routine vaccination, varicella caused substantial morbidity, particularly among adults, pregnant women, and immunocompromised patients.[5]

Following widespread immunization with the live-attenuated varicella vaccine, the incidence of primary infection has declined substantially, resulting in reduced circulation of the wild-type virus within the community.[13] This epidemiological shift has been proposed as a contributing factor to changes in herpes zoster incidence, partly due to diminished opportunities for exogenous immune boosting.[15] However, long-term population-based analyses from the United States have not demonstrated the pronounced post-vaccination surge in herpes zoster incidence predicted by early models, suggesting a more complex and context-dependent relationship.[15,16] Despite decreased transmission, VZV remains endemic, sustained through lifelong latency in previously infected individuals.[11] Consequently, herpes zoster continues to represent a significant public health burden, as viral reactivation may occur decades after the initial infection.[4,17,18]

The lifetime risk of developing herpes zoster in immunocompetent individuals is estimated to be approximately one in three, increasing sharply with age.[17,19] This reflects the progressive decline in VZV-specific cell-mediated immunity that accompanies immunosenescence.[20–22] Additional risk factors include immunosuppressive therapy, malignancies, HIV infection, and chronic diseases such as diabetes mellitus and renal failure.[23]

From a dermatological perspective, VZV reactivation is clinically significant, not only for its cutaneous manifestations but also for its systemic impact.[24,25] Complications

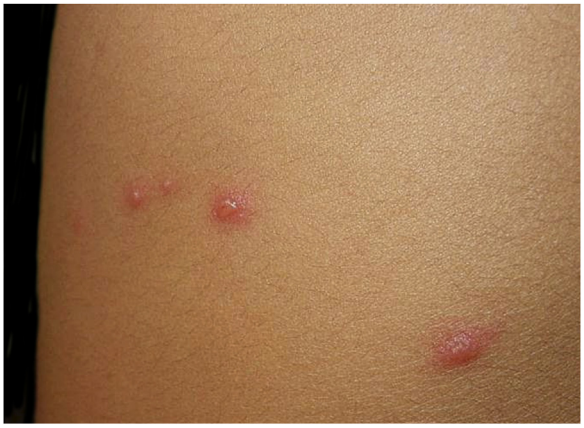

Figure 1 Acute varicella lesion. Courtesy: Lauro Lourival Lopes Filho, MD, Ph.D.

such as bacterial superinfection, postherpetic neuralgia, and ophthalmic or neurological involvement can result in long-term morbidity and a diminished quality of life.[24,26] The introduction of recombinant zoster vaccines has substantially improved prevention in older adults; however, coverage and adherence remain inconsistent worldwide.[27–30] For dermatologists, understanding the epidemiological landscape of VZV is crucial for anticipating disease patterns, identifying at-risk populations, and promoting preventive vaccination.

Clinical manifestations

The dermatological spectrum of VZV infection encompasses two clinically distinct entities: primary varicella and herpes zoster.[2,11] Despite their differing epidemiological profiles, both share the same viral etiology and pathogenic foundation.[1,2,8]

Varicella (primary infection)

Primary infection with VZV results in varicella or chickenpox, a generalized vesicular exanthem typically preceded by a brief prodromal phase characterized by low-grade fever, malaise, and mild respiratory symptoms.[31–33] The eruption classically follows a craniocaudal progression and manifests as successive crops of pruritic vesicles on an erythematous base, often described as a ''dew drop on a rose petal'' (Fig. 1).[31,34] These lesions evolve asynchronously into pustules and crusts, and consequently, lesions at different stages of development commonly coexist within the same anatomical area (Fig. 2).[31,35] The exanthem predominates on the trunk and face, with relative sparing of the extremities.[31] In addition to cutaneous involvement, vesicles or erosions of the oral mucosa are frequent, and conjunctival involvement may also occur, although less commonly.[31,35]

In healthy children, varicella is usually self-limiting.[33,35] However, in adults, pregnant women, and immunocompromised patients, the disease can be severe, with complications such as pneumonia, hepatitis, and encephalitis.[31,33,35] Secondary bacterial infections of

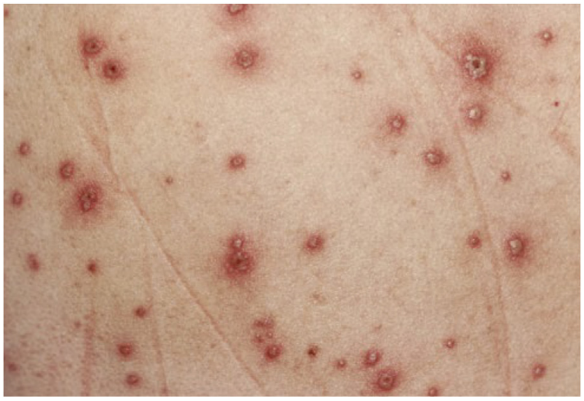

Figure 2 Polymorphic rash of varicella. Courtesy: Silvio Alencar Marques, MD, PhD.

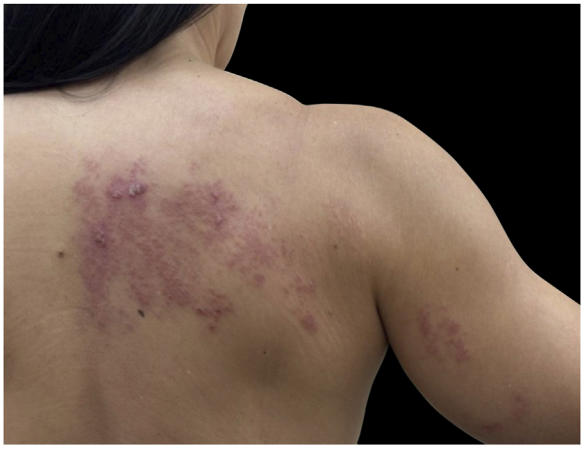

Figure 3 Herpes zoster: typical dermatomal involvement with erythema and vesicles.

excoriated lesions are common, particularly in young children.[31,33,35] Cutaneous scarring may occur in severe or hemorrhagic forms of the disease, which is rare.[31]

Herpes zoster (reactivation)

Herpes zoster, or shingles, represents reactivation of latent VZV from sensory ganglia.[9,36,37] The condition typically begins with localized pain, burning, or paresthesia along a dermatomal distribution, followed by the appearance of grouped vesicles on an erythematous base.[37] The eruption is unilateral and does not cross the midline, providing a key diagnostic clue.[9,37] The thoracic and cranial dermatomes are the most frequently involved (Fig. 3).[9,24,38]

In selected patients (particularly those who are immunocompromised), VZV reactivation may be accompanied by transient viremia, leading to the appearance of vesicular lesions at sites distant from the primary dermatome.[39,40] In such cases, disseminated herpes zoster may partially mimic primary varicella, with scattered varicella-like lesions coexisting with a dominant unilateral dermatomal eruption.[39–41] This atypical presentation can complicate clinical recognition and management, underscoring the importance of careful assessment of lesion distribution and host immune status.

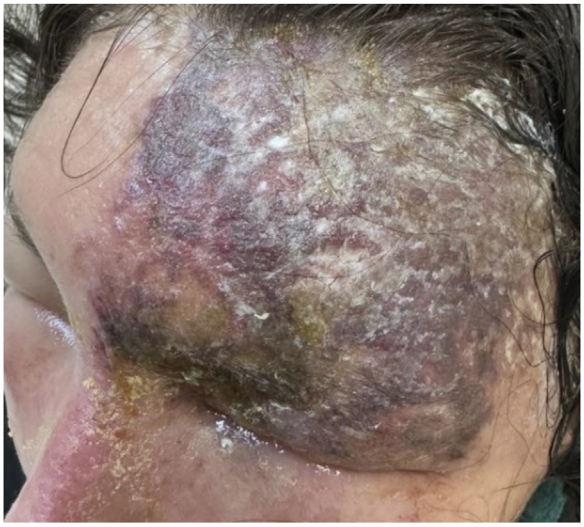

Figure 4 Extensive necrotic herpes zoster in an HIV-infected patient. Severe unilateral dermatomal involvement with extensive vesiculation and necrotic changes. Courtesy: Hiram Larangeira de Almeida Jr., MD, PhD.

Lesions typically evolve through vesicular, pustular, and crusting stages over 7–10 days.[9] New vesicles may continue to emerge for several days, and pain frequently precedes the appearance of the rash or persists beyond its resolution.[9] In a subset of patients (particularly older adults), postherpetic neuralgia may endure for months or even years.[12,42]

Atypical presentations are relatively common and may obscure diagnosis. Herpes zoster *sine herpete* presents as dermatomal pain in the absence of cutaneous lesions, whereas disseminated zoster can mimic primary varicella infection, particularly in immunocompromised individuals.[10,11,43] In this context, herpes zoster may manifest as exuberant and destructive morphologies, including extensive vesiculation with necrotic changes. Fig. 4 illustrates a severe necrotic presentation in an HIV-infected patient, in which, despite marked tissue damage, lesions remained strictly confined to a single dermatomal distribution, reinforcing unilateral involvement as a critical diagnostic feature, even in advanced or atypical cases.[23,44]

The involvement of anatomically complex regions, such as the cervical and facial areas, can complicate diagnosis.[10,45] Cervical and facial herpes zoster may resemble other inflammatory, vesiculobullous, or infectious dermatoses, especially early on (Figs. 5 and 6).[2,9,10,45] In both cases, recognition of a unilateral dermatomal pattern that respects the midline is essential for accurate diagnosis.[36]

Reactivation of the trigeminal ganglion, on the face, may lead to ophthalmic complications, including keratitis, uveitis, and permanent visual impairment.[3,23,45,46] Ramsay Hunt syndrome, resulting from facial nerve involvement, is characterized by vesicular lesions affecting the external ear or oral mucosa and is frequently accompanied by facial paralysis and auditory symptoms.[3,23,45]

In dermatological practice, prompt recognition of early, atypical, and anatomically challenging presentations is essential. Early initiation of antiviral therapy limits viral replication, shortens the duration of acute pain, and reduces the risk of cutaneous and neurological complications.[47–49]

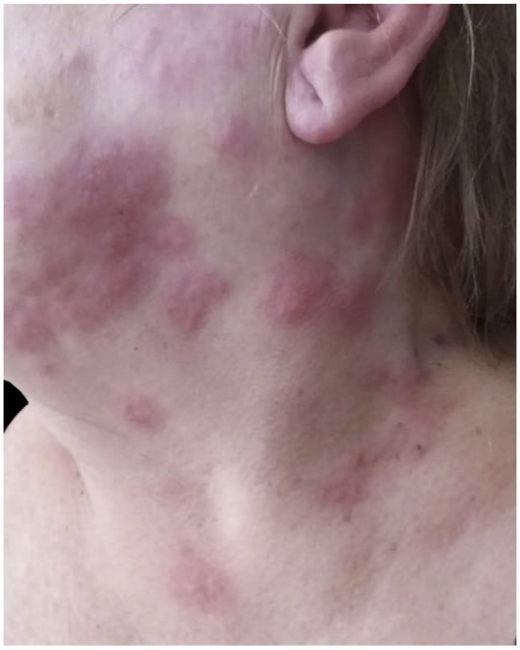

Figure 5 Cervical herpes zoster. Grouped vesicles on an erythematous base were distributed unilaterally along a cervical dermatome, respecting the midline. Courtesy: Hiram Larangeira de Almeida Jr., MD, PhD.

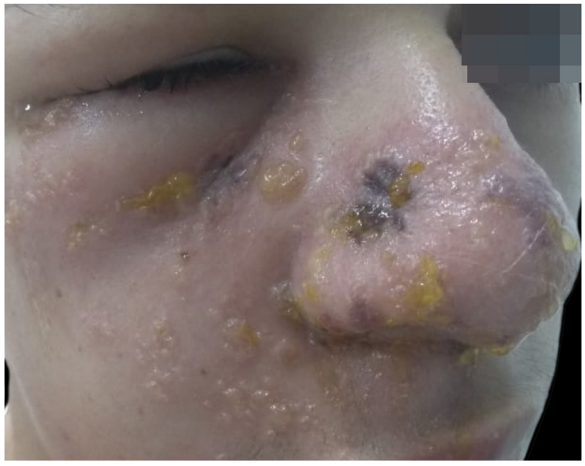

Figure 6 Facial herpes zoster. Unilateral vesicular eruption involving the facial region, consistent with the trigeminal nerve distribution.

Complications

The complications of VZV infection range from mild cutaneous sequelae to severe systemic disease, depending on host immunity and age.[3,45,50] Although most cases resolve uneventfully, the burden of complications (particularly those associated with herpes zoster) remains substantial and clinically relevant for dermatologists.

Cutaneous complications

The most frequent cutaneous complication is a secondary bacterial infection of excoriated or ruptured vesicles, commonly caused by *Staphylococcus aureus* or *Streptococcus pyogenes*.[3,5] Impetiginization can result in scarring or post-inflammatory dyspigmentation.[33,35] In rare instances, necrotizing fasciitis may develop, particularly in immunocompromised patients.[3,5] Chronic or ulcerative lesions are also observed in patients receiving long-term corticosteroid or other immunosuppressant therapy.[3,5,23]

Neurologic complications

Postherpetic Neuralgia (PHN) is the most debilitating sequelae of herpes zoster.[51] It is characterized by persistent neuropathic pain lasting for at least 90-days after rash onset.[52] The incidence and severity of PHN increase with age, reflecting cumulative neuronal injury and reduced regenerative capacity of the nervous system.[53] Pathophysiologically, PHN results from inflammation, demyelination, and necrosis of the affected sensory neurons, leading to altered pain signaling within the dorsal horn.[54–56] Clinically, patients describe burning, shooting, or stabbing pain, often accompanied by allodynia or hyperesthesia.[50,52]

Other rare neurological complications include meningoencephalitis, transverse myelitis, and cranial nerve paralysis.[3,5] VZV vasculopathy, resulting from viral invasion of the cerebral arteries, can manifest as stroke or focal neurological deficits.[3,5,9] In immunocompromised individuals, disseminated infections may involve the central nervous system, with high morbidity.[23,44,57]

Ophthalmic and otologic complications

Herpes zoster *ophthalmicus*, arising from the reactivation of the ophthalmic branch of the trigeminal nerve, can cause keratitis, uveitis, and retinitis, potentially leading to permanent vision loss.[46,58] The presence of vesicular lesions on the tip of the nose (Hutchinson's sign) indicates nasociliary nerve involvement and predicts ocular complications.[46,58] Ramsay Hunt syndrome, caused by involvement of the geniculate ganglion, presents with auricular vesicles, facial paralysis, and sensorineural hearing loss, often requiring multidisciplinary care.[58,59]

Systemic complications

Systemic dissemination of VZV can lead to serious extracutaneous complications, including pneumonitis, hepatitis, and disseminated intravascular coagulation.[33,35,45] These events occur predominantly in immunocompromised individuals and during pregnancy, in whom viral replication is often more extensive and immune control is diminished.[23,60] Varicella pneumonia represents the most severe of these manifestations, carrying a mortality rate of 10%–30% in untreated adults and requiring prompt recognition to avoid rapid respiratory deterioration.[33,35]

Transplacental transmission during pregnancy may result in congenital varicella syndrome, a rare but devastating condition marked by limb hypoplasia, cicatricial skin lesions, ocular abnormalities, and neurodevelopmental impairment.[35,60] Additional risks emerge when aspirin is administered during active varicella infection, given its association with Reye syndrome, characterized by acute encephalopathy and hepatic steatosis.[35]

For dermatologists, maintaining a high index of suspicion regarding these systemic outcomes is essential. Early identification of cutaneous patterns suggestive of severe or disseminated disease supports timely referral, multidisciplinary coordination, and initiation of appropriate antiviral therapy, thereby reducing the likelihood of long-term morbidity.

Diagnosis

The diagnosis of VZV infection is primarily clinical and is supported by the characteristic morphology and distribution of skin lesions. However, atypical presentations, immunocompromised hosts, and early or late disease stages may require laboratory confirmation of diagnosis.

Clinical diagnosis

Pattern recognition remains central to the clinical diagnosis of varicella-zoster virus infections.[2,11] Varicella typically presents with lesions at different stages of evolution (macules, papules, vesicles, and crusts) distributed in a centripetal pattern involving the trunk, face, and scalp.[33,35] In contrast, herpes zoster produces a unilateral dermatomal eruption of grouped vesicles on an erythematous base, frequently preceded or accompanied by neuropathic pain. The lack of lesions crossing the midline is a key diagnostic feature.[2,11,43]

Immunocompromised individuals and patients with disseminated disease may exhibit atypical or ambiguous presentations that resemble other vesiculobullous conditions.[23,44,61] Relevant differential diagnoses include herpes simplex virus infections, impetigo, allergic contact dermatitis, bullous drug reactions, and autoimmune blistering disorders.[2,11,35] A careful evaluation of the lesion distribution, morphology, temporal evolution, and pain characteristics helps delineate VZV from these mimickers.[33,35]

Additional differentials for varicella include Mpox and, historically, smallpox. Although smallpox was eradicated in 1980, this comparison is clinically instructive.[35] Mpox lesions are typically monomorphic and evolve more slowly, whereas varicella lesions are asynchronous at multiple developmental stages.[35] Hand-foot-and-mouth disease may also resemble early varicella; however, its vesicles are confined predominantly to the hands, feet, and oral mucosa, with no tendency toward diffuse involvement.[35]

Other entities that may enter the differential diagnosis (particularly in atypical, severe, or disseminated presentations) include disseminated herpes simplex infection, *pityriasis lichenoides et varioliformis acuta*, rickettsial infections, drug eruptions, arthropod reactions, and scabies.[2,33,35] A systematic approach that integrates morphology, distribution, symptom patterns, and host immune status enhances diagnostic accuracy and guides early therapeutic intervention.

Laboratory and molecular tests

Laboratory confirmation is recommended when the clinical diagnosis is uncertain or in high-risk settings such as pregnancy or immunosuppression.[62,63] Polymerase Chain Reaction (PCR) testing, which detects VZV DNA in vesicular fluid, lesion crusts, or tissue biopsy specimens, is the most sensitive and specific method.[62] PCR can differentiate between wild-type and vaccine strains and has largely replaced viral culture in clinical practice because of its rapid turnaround and higher sensitivity.[63]

Direct Fluorescent Antibody (DFA) testing remains a useful rapid diagnostic option when PCR is unavailable, although with lower sensitivity.[62,64,65] The Tzanck smear, once widely used, can reveal multinucleated giant cells but cannot distinguish VZV from herpes simplex infection and is now of mainly historical interest.[66,67]

Serological testing can demonstrate prior exposure or immune status by detecting VZV-specific IgG; however, it is not useful for diagnosing acute herpes zoster.[62,64,65] Rising IgM titers may indicate recent infection; however, false negatives are frequent in reactivation cases.[62,64,65]

Histopathology

Skin biopsy is rarely required but can be valuable in atypical, severe, and disseminated presentations. Histopathological examination typically demonstrates intraepidermal vesiculation with multinucleated keratinocytes, acantholysis, and eosinophilic nuclear inclusion bodies (Fig. 7).[68] A superficial perivascular lymphocytic infiltrate, sometimes with scattered eosinophils, is also characteristic.[68]

The microscopic appearance of varicella closely mirrors that of herpes simplex virus infection, with both displaying multinucleated keratinocytes with molded nuclei and marginated chromatin.[68] Because routine histology cannot reliably distinguish between the two, confirmatory studies are often necessary when morphology is ambiguous.[68] Immunohistochemistry using VZV-specific antibodies or *in situ* hybridization can accurately identify viral DNA and resolve cases in which clinical or histological overlap complicates the diagnosis.[64,65,68]

Diagnostic pitfalls in immunosuppressed and older adults

In immunocompromised individuals (such as patients with hematologic malignancies, organ transplants, or those undergoing immunomodulatory therapy), VZV infection may present without the classic vesicular eruption.[19,20,44,57] Lesions can be necrotic or hemorrhagic and can mimic bacterial or autoimmune blistering diseases.[35] Disseminated zoster may develop without clear dermatomal limitation, and pain can be absent or minimal, leading to misdiagnosis as a drug reaction or vasculitis.[23,44,57]

Older adults may exhibit similar diagnostic challenges, particularly when neuralgia precedes the rash or when the eruption remains localized and subtle.[12,69] Misattributing this pain to musculoskeletal or neuropathic pain can delay antiviral treatment initiation and increase the risk of postherpetic neuralgia.[12,26,69] Dermatologists should maintain a high suspicion in older adults or immunocompromised patients presenting with localized neuropathic pain or atypical vesiculobullous lesions.

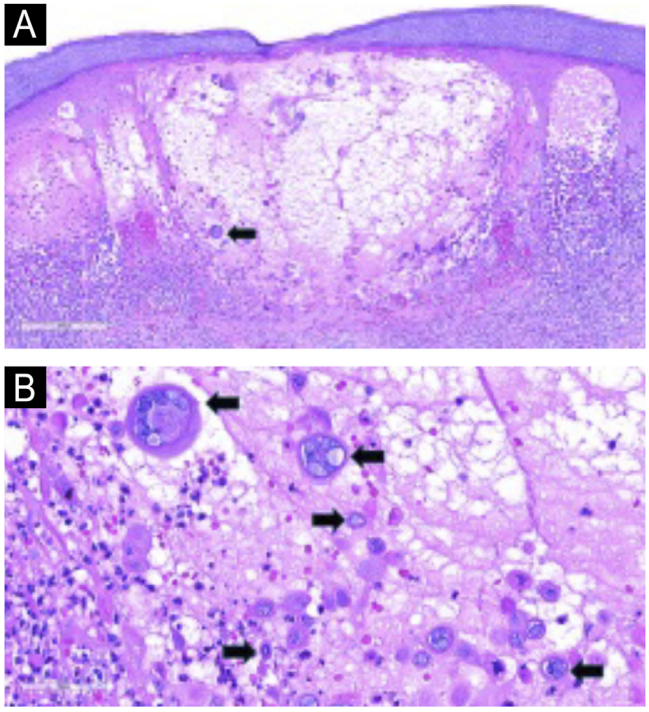

Figure 7 Skin histological section showing an intraepidermal vesicle with acantholysis, ballooning, and reticular degeneration in the epidermis. Note the multinucleated keratinocytes (arrow) and lymphocytic inflammatory infiltrate in the superficial dermis (Hematoxilyn & eosin, ×85) (A) Higher magnification demonstrating viral cytopathic changes. Multinucleated keratinocytes, nuclear molding, and peripheral chromatin margination ('ground glass' appearance) were observed (arrows) (Hematoxilyn & eosin, ×400) (B). Courtesy: Thiago Jeunon, MD.

Early PCR testing of lesion material or biopsy for VZV detection is recommended in ambiguous presentations, as prompt confirmation allows for immediate antiviral therapy and prevents dissemination.[64,65]

Treatment and prevention

Effective management of VZV infection aims to alleviate symptoms, accelerate lesion healing, and prevent complications, such as postherpetic neuralgia and secondary bacterial infection. General care and early antiviral therapy remain the cornerstones of treatment, complemented by appropriate pain control and preventive vaccination.

General care

Supportive care remains essential for both varicella and herpes zoster, complementing antiviral therapy when indicated. Adequate hydration should be encouraged, particularly in patients with high fever, extensive lesions, or oral discomfort that may limit fluid intake.[33,70] Rest during the acute

phase helps reduce systemic symptoms and may lower the risk of complications.[36,49,70]

Acetaminophen or ibuprofen is appropriate for fever and pain control across age groups. Acetylsalicylic acid is contraindicated in children and adolescents because of its association with Reye's syndrome.[33,35] Pruritus can be managed with topical agents such as calamine lotion, oatmeal baths, cold compresses, and regular emollient use, along with oral antihistamines when needed.[70] To minimize excoriation and secondary bacterial infection, patients should be advised to keep their nails short and avoid scratching.[33,35]

Preventing secondary infections is particularly important.[9] Gentle cleansing of the affected area and application of antiseptic solutions, such as povidone-iodine, chlorhexidine, or boric acid, can reduce bacterial colonization.[37,49] When signs of impetiginization arise, topical antibiotics may be used as adjunctive therapy while antiviral treatment proceeds.[9,49,71]

Antiviral therapy

Oral antiviral therapy should be considered for patients with a substantial likelihood of severe disease to shorten the clinical course of varicella, reduce symptom intensity, and limit the risk of complications, oral antiviral therapy should be considered for patients with a substantial likelihood of severe disease.[33,35] This group includes unvaccinated individuals aged ≥13-years, secondary household cases (which often manifest more intense presentations due to higher inoculum), patients with chronic dermatologic or pulmonary conditions, children receiving prolonged oral or inhaled corticosteroids, individuals with long-term acetylsalicylic acid exposure, and pregnancy.[33,35] In contrast, healthy children typically do not benefit from antiviral therapy, as varicella in this population follows a self-limited course, and treatment provides only modest improvements.[33,35]

Intravenous antiviral therapy is recommended for immunocompromised individuals, such as those with malignant neoplasms, HIV infection, or ongoing immunosuppressive regimens.[35,49,63] In varicella, timing is essential: treatment started within the first twenty-four hours after rash onset consistently yields the greatest reduction in viral replication and lesion progression.[33,35]

For herpes zoster, systemic antiviral therapy is recommended for all patients.[9,72,73] Initiation within seventy-two hours of rash onset provides clearer clinical benefits, notably by limiting the formation of new lesions and reducing acute neuritic pain.[63,74] Most patients can be effectively managed with oral agents; intravenous therapy becomes necessary when dissemination, ocular involvement, or significant immunosuppression is present.[47,49,63]

Acyclovir, valacyclovir, and famciclovir remain the principal therapeutic agents (Table 1). Valacyclovir and famciclovir provide superior bioavailability and simpler dosing schedules compared with acyclovir, which often facilitates adherence and supports a more consistent therapeutic response.[58,59,73,75,76]

Adjunctive corticosteroids may be considered for herpes zoster in selected immunocompetent adults with severe pain or extensive rashes, provided that antiviral therapy is administered concomitantly.[49,72] Their use remains controversial because they do not prevent postherpetic neuralgia and may pose risks to older or frail individuals.[47] Topical antivirals have limited efficacy and are not recommended for use.[63]

Pain management

Pain control is central to the management of herpes zoster and often requires a multimodal approach. During the acute phase, nonsteroidal anti-inflammatory drugs, analgesics, or short courses of opioids can be used to treat nociceptive pain.[77] Neuropathic pain agents, such as gabapentin, pregabalin, or tricyclic antidepressants, should be introduced early if neuralgia develops, and even in the acute phase.[24,77,78] Topical lidocaine patches and capsaicin creams may provide additional relief.[9]

Persistent pain lasting beyond 90-days is defined as PHN.[24,77,78] Management may require higher doses of gabapentinoids, combination therapy, or referral to pain specialists.[24,79,80] Preventive strategies, particularly early antiviral therapy and vaccination, are more effective than late-stage treatment.[47]

Vaccination and prevention

Vaccination has transformed the epidemiology of VZV infections, markedly reducing the incidence of varicella and herpes zoster.[81,82]

For the prevention of varicella, routine childhood immunization is based on a two-dose schedule with a live-attenuated varicella vaccine administered at 15-months (as part of the tetravalent formulation) and at 4-years of age, conferring durable protection.[83] Although breakthrough infections may occur, they are typically mild. In a small proportion of vaccinated individuals, the attenuated vaccine strain may later reactivate and manifest as herpes zoster.[31]

Recent updates in immunization policies have refined the recommendations regarding combined formulations. In 2025, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) recommended the suspension of the combined Measles, Mumps, Rubella, and Varicella (MMRV) vaccine due to safety concerns, favoring the separate administration of MMR and varicella vaccines in young children.[84] Divergent positions remain among professional societies, and national schedules may continue to evolve.[85]

In contrast, the prevention of herpes zoster has undergone a definitive shift. Although a live-attenuated zoster vaccine (Zostavax®) was previously available, it is no longer recommended by the CDC and was discontinued in the United States in 2020.[86,87] In Europe, its marketing authorization was formally withdrawn by the European Commission in June 2025 at the request of the manufacturer.[86,87] Consequently, live-attenuated zoster vaccines no longer play a role in current prevention strategies against VZV.

The recombinant subunit vaccine (Shingrix®) is now the global standard of care for herpes zoster prevention.[82] It is composed of VZV glycoprotein E combined with the AS01B adjuvant and induces robust and sustained immune responses, including in older adults and immunocompro-

Table 1 Antiviral therapy for Varicella-Zoster virus.

Drug	Dose (adults)	Dosing Interval	Typical Duration
Acyclovir	800 mg orally	Every 4 hours (5×/day)	7–10 days
	10 mg/kg intravenous	Every 8 hours (3×/day)	7–10 days
Valacyclovir	1,000 mg orally	Every 8 hours (3×/day)	7 days
Famciclovir	500 mg orally	Every 8 hours (3×/day)	7 days

Note: Dose adjustment is required for all nucleoside analogues in patients with impaired renal function.

mised populations.[4,27] The vaccine is administered in two intramuscular doses given 2–6 months apart and is recommended even for individuals with a prior history of herpes zoster.[88] Vaccination may be initiated six months after an acute episode, with earlier administration acceptable when clinically appropriate.[88] Efficacy consistently exceeds 90% against herpes zoster and postherpetic neuralgia.[29,30,88,89] Local reactogenicity is common but transient.[89] In comparison, live-attenuated zoster vaccines confer lower and less durable protection and are contraindicated in immunocompromised individuals.[90,91]

Post-exposure prophylaxis

The administration of varicella-zoster immunoglobulin (125 U/10 kg, up to a maximum of 625 U), given intramuscularly within 96 h of exposure, is recommended for post-exposure prophylaxis in immunocompromised non-immune adults, pregnant women, and high-risk neonates.[33,35] This passive immunization provides temporary protection, with suppression of clinical disease lasting approximately three weeks.[33,35] Intravenous immunoglobulin, administered at doses $\geq$0.4 g/kg and containing high titers of anti-varicella-zoster virus IgG, represents an alternative option in selected settings.[35]

Prophylaxis with oral acyclovir at a standard varicella dose may also be considered for 1-week, starting 7–10 days after exposure.[35] Furthermore, post-exposure vaccination with a live attenuated virus vaccine can prevent or mitigate the clinical picture when administered within 72–120 hours and is indicated for non-immune individuals aged one year or older, provided they are immunocompetent and eligible for immunization.[35]

Practical guidance and conclusions

VZV remains a significant cause of dermatologic morbidity, bridging fundamental virology, immunology, and clinical practice. Its two clinical faces (varicella as a primary infection and herpes zoster as reactivation) represent distinct biological expressions of the same pathogen, each shaped by host immunity and age-related vulnerability. For dermatologists, understanding this continuum provides a conceptual framework for accurate diagnosis and evidence-based therapies.

Advances in molecular diagnostics and antiviral pharmacotherapy have transformed clinical outcomes; however, delayed recognition and underdiagnosis persist, particularly in atypical or immunocompromised presentations. The advent of recombinant subunit vaccination marks a paradigm shift toward prevention through durable immunologic control rather than reactive management. As this preventive model matures, the dermatologist's role expands beyond treatment to encompass patient counseling, vaccine advocacy, and the integration of immunization strategies into everyday practice.

Ultimately, the management of VZV infection exemplifies the convergence of basic science and applied dermatology. Through sustained clinician awareness, rapid therapeutic intervention, and widespread vaccination, the burden of VZV and its complications can be substantially reduced in the future.

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Research data availability

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Authors' contributions

Maria Paula Barbieri D'Elia: Design and planning of the study; collection of data; drafting and editing of the manuscript and critical review of important intellectual content; data collection, analysis, and interpretation of data; effective participation in research orientation; critical review of the literature; approval of the final version of the manuscript.

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Conflicts of interest

Maria Paula Barbieri D'Elia, Carla Riama Lopes de Pádua Moura, Rafael de Deus Moura, and Juliana de Sá Pires Carvalho declare no conflicts of interest. Henrique Pott declares no additional conflicts of interest beyond the aforementioned institutional support. Henrique Pott received funding from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001. The remaining authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

DAPSA scores reflect both articular and cutaneous involvement in psoriatic arthritis☆

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Severity of illness index

Abstract

Background: The Disease Activity Index for Psoriatic Arthritis (DAPSA) is a widely used tool to assess joint involvement in Psoriatic Arthritis (PsA), but its ability to reflect skin disease severity remains unclear.

Objective: This study aimed to investigate the association between DAPSA scores and skin disease severity in patients with PsA.

Methods: This single-center, cross-sectional study included PsA patients meeting the CASPAR classification criteria at Xiangya Hospital from April 2019 to February 2025. Skin disease severity was assessed using the Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI), while disease activity was assessed with the DAPSA. Propensity Score Matching (PSM) was applied to adjust for musculoskeletal disease activity.

Results: Among the 646 PsA patients (median age 46.0 years; 41.0% male), DAPSA scores increased from 12.6 (SD = 13.2) in patients with no skin disease (PASI = 0) to 20.4 (SD = 16.9) in those with severe skin disease (PASI > 10). Patient global assessment, patient pain assessment scores and C-reactive protein levels also rose with PASI severity (all $p < 0.001$). After PSM, patients with PASI $\geq$ 10 had significantly higher DAPSA scores than those with PASI < 10 (25.4 vs. 16.9, $p < 0.001$). A weak but statistically significant positive correlation was observed between DAPSA and PASI scores (Spearman's rho = 0.256, $p = 0.003$).

Study limitations: Cross-sectional design, single-center setting and potential residual confounding limit causal inference and generalizability.

☆ Study conducted at the Department of Dermatology, Xiangya Hospital, Central South University, Changsha, HN, China.

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Conclusion: Although not designed to assess skin disease, DAPSA may partially capture skin-related burden through its inflammatory and patient-reported components. In the absence of dedicated skin assessments, DAPSA could serve as a practical and holistic tool for initial disease activity evaluation in PsA.

Introduction

Psoriatic Arthritis (PsA) is a chronic inflammatory disease that affects approximately 20%–30% of patients with psoriasis.[1] It is characterized by heterogeneous manifestations, including peripheral arthritis, axial involvement, enthesitis, dactylitis, and cutaneous disease.[2] PsA can lead to irreversible joint damage, functional disability, and reduced quality of life.[3] The complexity of PsA poses significant challenges in comprehensively assessing disease activity, necessitating the use of composite measures that integrate multiple clinical domains.

Among the composite indices developed to assess disease activity in PsA, the Disease Activity Index for Psoriatic Arthritis (DAPSA) has emerged and shown high sensitivity and specificity in distinguishing disease states.[4] It incorporates Tender Joint Counts (TJC), Swollen Joint Counts (SJC), Patient Global Assessment (PtGA), Patient Pain Assessment (PtPA), and C-Reactive Protein (CRP), providing a quantitative and clinically feasible assessment of musculoskeletal disease activity.[4,5] Previous studies have demonstrated the strong correlation between DAPSA and ultrasound assessments and their predictive value for radiographic progression.[6] Furthermore, compared with the complex calculation method of Psoriatic Arthritis Disease Activity Score (PASDAS),[7,8] the DAPSA requires only five variables for computation, making it widely applicable in both clinical practice and research settings.[9–11]

Although DAPSA effectively captures articular involvement, its ability to reflect extra-articular manifestations, particularly the severity of skin disease, remains uncertain. Skin disease severity, typically assessed using the Psoriasis Area and Severity Index (PASI) or Dermatology Life Quality Index (DLQI), may influence PtGA Visual Analogue Scale (VAS) scores[12] and CRP,[13–17] which are key components of DAPSA. Nevertheless, the extent to which DAPSA indirectly reflects skin disease activity through its various components warrants further investigation.

Therefore, the present study aimed to evaluate whether DAPSA reflects skin disease severity in PsA patients in a Chinese cohort. Specifically, the authors examined the associations between DAPSA and established measures of skin severity (PASI and DLQI) and assessed whether skin involvement affects patient-reported components of the DAPSA score. Understanding this relationship is crucial for interpreting DAPSA scores in patients with prominent skin disease and may inform future approaches to comprehensive PsA assessment.

Method

Study design and participants

This single-center, cross-sectional study was conducted at the Dermatology Department of Xiangya Hospital, Central South University in China, and included patients with PsA who met the CASPAR classification criteria[18] between April 2019 and February 2025. The diagnosis of PsA was confirmed by an experienced dermatologist and/or rheumatologist. Written informed consent was obtained from all participants. The study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval for this study was granted by the Ethics Committees of Xiangya Hospital of Central South of University (approval number: 2018121106).

Data collection

Baseline demographic and clinical characteristics were obtained from electronic medical records, including age, sex, duration of psoriasis, and duration of PsA. Additionally, the following clinical parameters were collected: PtGA, PtPA, 68 TJC, 66 SJC, enthesitis and dactylitis counts, and CRP levels (mg/L). PtGA and PtPA were measured using a Visual Analog Scale (VAS) ranging from 0 to 10 cm. DAPSA was calculated as: TJC + SJC + PtGA + PtPA + CRP (mg/dL).[4] PASI scores were categorized as none (0), mild (< 3), moderate (3–10), or severe (> 10), while DLQI scores were categorized as having no impact (0–1), small impact (2–5), moderate impact (6–10), large impact (11–20), or extreme impact (21–30). Other covariates collected included the Physical Component Summary score of the 36-Item Short Form Survey (SF-36 PCS) and the Health Assessment Questionnaire (HAQ) score. Due to incomplete clinical assessments (such as joint counts, laboratory tests, or skin evaluations) in some patients, sample sizes varied across different variables. All available data were included in the analysis without imputation of missing values to preserve the authenticity of the findings.

Statistical analysis

For statistical analysis, continuous variables were summarized as median (Interquartile Range, IQR) due to non-normal distributions, while categorical variables were presented as number (%). The association between DAPSA

Table 1 Baseline demographics and clinical characteristics.

	Range	Median (IQR) or number (%)	n
Age		46.0 (36.0–55.0)	646
Female, n (%)		265 (41.0)	646
Duration of psoriasis (y)		8.0 (3.0–15.0)	646
Duration of PsA (y)		2.0 (0.5–4.5)	643
PtGA VAS	0–100	50.0 (20.0–70.0)	641
PtPA VAS	0–100	30.0 (20.0–60.0)	641
SJC	0–66	1.0 (0.0–4.0)	636
TJC	0–68	2.0 (1.0–5.0)	636
Enthesitis	0–6	0 (0–0)	646
Dactylitis	0–20	0 (0–1.0)	616
SF-36 PCS	0–100	70.6 (43.8–82.3)	606
HAQ	0– 3	0 (0–0.1)	604
CRP (mg/L)	0–500	4.3 (1.6–13.1)	600
PASI	0–72	4.3 (1.8–8.9)	607
PASI, n (%)			607
	No psoriasis	55 (9.0)	
	< 3	160 (26.3)	
	3–10	259 (42.5)	
	> 10	135 (22.2)	
DLQI	0–30	5.0 (2.0–9.0)	556
DAPSA		14.4 (8.3–24.0)	590

* Data are median (IQR) or n (%) unless otherwise stated.
IQR, Interquartile Range; PtGA, Patient Global Assessment; PtPA, Patient Pain Assessment; VAS, Visual Analogue Scale (0–100); SJC, Swollen Joint Count; TJC, Tender Joint Count; SF-36 PCS, SF-36 Physical Component Summary score; HAQ, Health Assessment Questionnaire score; CRP, C-Reactive Protein; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; DAPSA, Disease Activity index for PSoriatic Arthritis.

and PASI categories was compared using ANOVA, and Spearman correlation coefficients were calculated to assess the relationships between DAPSA and PASI. To control for confounding by musculoskeletal activity, Propensity Score Matching (PSM) was performed, grouping patients based on PASI $\geq$ 10 (severe skin involvement) versus PASI < 10 (non-severe skin involvement), with 1:1 matching conducted based on TJC, SJC, enthesitis, and dactylitis. The Mann-Whitney *U* test was used to compare outcomes between the matched groups. A sensitivity analysis was also performed by repeating the PSM for patients with moderate skin involvement (PASI 3–10) versus those with mild or no skin involvement (PASI < 3) to validate the consistency of the results. All analyses were conducted using SPSS v27.0, with a two-tailed p-value of less than 0.05 considered statistically significant.

Results

Patient characteristics

The study included 646 patients with PsA. The mean age of the cohort was 46.0 years (IQR: 36.0–55.0), with 41.0% being female. The median duration of psoriasis was 8.0 years (IQR: 3.0–15.0), and the median duration of PsA was 2.0 years (IQR: 0.5–4.5). The median DAPSA score was 14.4 (IQR: 8.3–24.0), indicating moderate disease activity. The median PASI score was 4.3 (IQR: 1.8–8.9), with 9.0% of patients having no psoriasis (PASI = 0), 26.3% having mild disease (PASI < 3), 42.5% having moderate disease (PASI 3–10), and 22.2% having severe disease (PASI > 10). The median DLQI score was 5.0 (IQR: 2.0–9.0), reflecting a moderate impact on quality of life (Table 1).

DAPSA across skin disease activity scores

Table 2 presents the mean DAPSA, PtGA, PtPA scores, and CRP levels across subgroups stratified by skin disease severity, as measured by PASI and DLQI. DAPSA scores showed a significant upward trend with increasing severity of skin involvement. For PASI categories, DAPSA scores ranged from 12.6 (SD = 13.2) in patients with no skin disease (PASI = 0) to 20.4 (SD = 16.9) in those with severe skin disease (PASI > 10). Similarly, for DLQI categories, DAPSA scores ranged from 10.6 (SD = 10.2) in patients with no impact on quality of life (DLQI 0–1) to 29.5 (SD = 14.4) in those with an extreme impact (DLQI 21–30). PtGA, PtPA scores, and CRP levels exhibited an upward trend in parallel with increasing skin disease severity (all p-values < 0.001).

Propensity score matching analysis

To further evaluate the impact of skin disease severity on DAPSA, patients were matched for musculoskeletal disease activity using propensity scores. In the matched cohort (n = 178, patients with severe skin involvement (PASI $\geq$ 10) had significantly higher DAPSA scores (25.4 vs. 16.9, p < 0.001), PtGA (73.4 vs. 49.6, p < 0.001), PtPA (50.4 vs. 37.9, p = 0.002), CRP (28.1 vs. 8.5, p < 0.001) and DLQI scores (9.0

Table 2 DAPSA, PtGA scores, PtPA scores and CRP levels by PASI and DLQI categories.

	DAPSA	PtGA VAS	PtPA VAS	CRP
PASI	**(n = 590)**	**(n = 641)**	**(n = 641)**	**(n = 572)**
0 (none)	12.6 (13.2)	35.7 (30.3)	28.3 (30.3)	8.2 (22.0)
< 3 (mild)	15.9 (12.8)	43.2 (27.6)	36.6 (28.4)	7.7 (14.6)
3-10 (moderate)	18.9 (13.7)	52.8 (25.4)	41.9 (27.0)	13.2 (24.1)
> 10 (severe)	20.4 (16.9)	63.8 (23.9)	40.6 (27.4)	23.3 (34.7)
DLQI				
0–1 (none)	10.6 (10.2)	33.9 (28.8)	25.6 (27.5)	9.8 (17.7)
2–5 (small)	17.3 (13.9)	48.9 (24.4)	36.5 (26.4)	13.8 (28.4)
6–10 (moderate)	20.1 (16.9)	54.5 (26.2)	44.6 (27.5)	12.9 (24.3)
11–20 (large)	23.2 (15.1)	66.5 (23.2)	47.0 (27.6)	19.3 (30.8)
21–30 (extreme)	29.5 (14.4)	72.9 (31.5)	65.7 (27.6)	34.3 (52.9)

DAPSA, Disease Activity index for PSoriatic Arthritis; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; PtGA, Patient Global Assessment; PtPA, Patient Pain Assessment; VAS, Visual Analogue Scale (0–100); CRP, C-Reactive Protein.

Table 3 Comparison of groups matched for severity of musculoskeletal disease.

	PASI ≥ 10 (n = 89)	PASI < 10 (n = 89)	p-value
Age	46.2 (12.3)	45.5 (14.3)	0.753
Psoriasis duration(y)	10.9 (9.7)	10.4 (11.4)	0.732
PsA duration(y)	4.0 (4.8)	3.8 (5.8)	0.890
PtGA VAS	73.4 (15.9)	49.6 (28.5)	<0.001
PtPA VAS	50.4 (23.7)	37.9 (30.1)	0.002
SJC	4.7 (8.0)	3.0 (4.7)	0.080
TJC	5.5 (7.9)	4.3 (7.8)	0.314
Enthesitis	0.2 (0.7)	0.2 (0.9)	0.924
Dactylitis	1.5 (3.6)	1.2 (2.6)	0.508
SF-36 PCS	51.6 (22.0)	62.7 (22.5)	0.002
HAQ	0.3 (0.5)	0.2 (0.5)	0.353
CRP (mg/L)	28.1 (39.0)	8.5 (14.0)	<0.001
DLQI	9.0 (5.0)	5.2 (4.1)	<0.001
DAPSA	25.4 (17.4)	16.9 (13.2)	<0.001

PsA, Psoriatic Arthritis; PtGA, Patient Global Assessment; PtPA, Patient Pain Assessment; VAS, Visual Analogue Scale (0–100); SJC, Swollen Joint Count; TJC, Tender Joint Count; SF-36 PCS, SF-36 Physical Component Summary score; HAQ, Health Assessment Questionnaire score; CRP, C-Reactive Protein; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; DAPSA, Disease Activity index for PSoriatic Arthritis.

vs. 5.2, $p < 0.001$) compared to those with mild to moderate skin involvement (PASI < 10) (Table 3).

A sensitivity analysis comparing patients with moderate skin involvement (PASI 3–10) to those with mild or no involvement (PASI < 3) revealed similar trends, with higher PtGA (55.3 vs. 40.7, $p < 0.001$), PtPA (42.5 vs. 34.2, $p = 0.005$), CRP (15.6 vs. 8.21, $p < 0.001$) and DLQI scores (6.6 vs. 4.7, $p = 0.001$). DAPSA scores remained significantly elevated in the moderate skin involvement group (19.2 vs. 15.7, $p = 0.025$) (Supplementary Table S1).

Correlation between DAPSA and PASI

A scatterplot of DAPSA and PASI scores demonstrated a weak but statistically significant positive correlation (Spearman's rho = 0.256, $p = 0.003$) (Supplementary Fig. S1). ANOVA analysis further confirmed the association, showing a significant difference in DAPSA scores across PASI categories ($F = 4.917$, $p = 0.002$) (Supplementary Fig. S2).

Discussion

Musculoskeletal and cutaneous manifestations in PsA are often thought to progress independently,[19] making comprehensive disease assessment challenging. Existing tools largely focus on isolated disease domains and may overlook the full clinical spectrum of PsA.[10] In the cross-sectional study of 646 Chinese patients with PsA, the authors found that DAPSA, although originally developed for peripheral joint assessment, was significantly associated with skin disease severity. This may be attributed to its inclusion of PtGA, PtPA scores, and CRP levels, which capture elements of systemic inflammation and patient-perceived disease burden. These findings suggest that DAPSA may reflect not only musculoskeletal involvement but also cutaneous manifestations, offering a more holistic measure of PsA disease activity.

The observed increase in PtGA and PtPA scores with worsening PASI supports the hypothesis that skin disease severity contributes to patient-reported outcomes. These

findings are aligned with prior studies reporting significant correlations between patient-reported global assessments and PASI,[20–22] helping to explain why DAPSA, despite lacking a formal skin domain, can indirectly reflect cutaneous involvement. Moreover, even after matching for musculoskeletal disease activity using PSM, patients with more severe skin involvement exhibited higher DAPSA scores. Notably, patients with severe skin involvement (PASI $\geq$ 10) had significantly elevated DAPSA scores, global assessments, and CRP levels compared to those with milder skin disease (PASI < 10). These findings underscore the potential role of systemic inflammation, as reflected by elevated CRP, in linking articular and cutaneous manifestations. This association is further supported by previous studies demonstrating that PsA patients with higher CRP levels tend to have more severe skin disease.[13–17]

Previous studies have demonstrated the validity of DAPSA, showing strong correlations with ACR response and Minimal Disease Activity (MDA), with high sensitivity and specificity (both $\geq$ 90%), including when compared with joint ultrasonography.[5,23–27] The present study is the first to examine the relationship between DAPSA and skin disease severity. The authors observed a weak correlation between DAPSA and PASI, which should be interpreted cautiously. DAPSA should not be considered a substitute for skin assessments, particularly in patients with severe cutaneous involvement. Its practical utility as a holistic screening tool may be best suited for initial global assessment in settings where formal dermatology scoring is unavailable, rather than for precise quantification of skin activity.

Several limitations should be acknowledged. First, the cross-sectional design limits our ability to establish causal relationships between DAPSA and skin disease severity. Second, this study was conducted at a single tertiary center in China, which may limit the generalizability of the present findings to other populations with different genetic, environmental, and clinical characteristics. Thirdly, although the authors applied propensity score matching to adjust for differences in musculoskeletal disease activity, residual confounding due to unmeasured variables – such as psychological burden, treatment adherence, or subclinical inflammation – may still exist. These limitations highlight the need for well-designed prospective studies to clarify the dynamic interplay between skin and joint involvement in PsA and to refine integrated disease activity measures.

Clinically, the present results highlight that DAPSA, although not a substitute for dedicated skin assessments, may serve as a practical and holistic tool for initial disease activity evaluation in PsA, particularly where PASI or DLQI are unavailable. Future research should explore longitudinal relationships between DAPSA and skin severity, and whether integrating PASI into composite indices improves their predictive validity for outcomes like treatment response or radiographic progression.

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IRB approval status

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Authors' contributions

Qianzi Liu: Methodology; formal analysis; writing-original draft.

Minjia Tan: Conceptualization; data curation; writing-review and editing.

Yehong Kuang: Supervision; funding acquisition; writing, review, and editing.

Qianzi Liu and Minjia Tan share the leading authorship of this manuscript because of their equal and significant contributions to this study.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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.2026.501368.

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ORIGINAL ARTICLE

Epiplakin expression in non-melanoma skin cancer: associations with epithelial-mesenchymal transition markers and tumor invasion☆

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Abstract

Background/Objectives: Epiplakin is a member of the plakin family of proteins involved in cytoskeletal organization, yet its role in skin cancers remains poorly understood. This study aimed to evaluate epiplakin expression in cutaneous skin lesions and to investigate its association with epithelial-mesenchymal transition markers and tumor progression.

Methods: The authors retrospectively analyzed skin specimens from squamous cell carcinomas, basal cell carcinomas, and benign intradermal nevi collected between 2021 and 2025. Histopathological features were assessed, and immunohistochemical analysis of Epiplakin, E-cadherin, and N-cadherin was performed. Epiplakin expression was quantified and correlated with cadherin levels and Breslow thickness. Plakin family protein-protein interaction networks were analyzed using KEGG pathway and GO functional enrichment.

Results: Protein-protein interaction network analysis demonstrated that plakin family members are associated with multiple cancer-related pathways, with a prominent enrichment in regulating cell proliferation. Epiplakin expression was significantly higher in squamous cell carcinomas (389.94 ± 70.56) compared with basal cell carcinomas (70.39 ± 15.32) and intradermal nevi, while basal cell carcinomas showed a significant decrease compared with normal skin ($p < 0.05$). In non-melanoma skin cancers, epiplakin expression demonstrated a strong positive correlation with E-cadherin ($r = 0.565$, $p < 0.001$) and a weak positive correlation with N-cadherin ($r = 0.329$, $p < 0.05$). No significant correlation was observed with Breslow thickness ($p > 0.05$).

Study limitations: Retrospective design and the absence of high-grade squamous cell carcinoma cases in the study population.

☆ Study conducted at the Bilecik Şeyh Edebali University Faculty of Medicine and Bilecik Training and Research Hospital, Bilecik, Turkey.

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Conclusions: This is the first study to assess epiplakin expression among epithelial cutaneous cancers. Epiplakin appears to be associated with epithelial–mesenchymal transition and early tumor progression, and its differential expression pattern may provide diagnostic utility.

Introduction

Carcinogenesis is a complex biological process involving cellular proliferation, invasion, and alterations in adhesion, with the cytoskeleton playing a pivotal role in maintaining cell shape, polarity, and mechanical stability. Among the proteins that anchor cytoskeletal elements – such as microfilaments, intermediate filaments, and microtubules – to cell junctions, the plakin family has emerged as essential for both tissue integrity and tumor biology. Members of this family, including Desmoplakin (DSP), Envoplakin (EVPL), Periplakin (PPL), Plectin (PLEC), and Bullous Pemphigoid Antigen-1 (BPAG1), provide structural links between cytoskeletal filaments and junctional complexes such as desmosomes and hemidesmosomes.[1] Alterations in their expression or localization have been associated with various cancers, and some plakins have been proposed as potential biomarkers. For example, elevated serum anti-BPAG1 autoantibodies have been reported in melanoma patients compared with healthy individuals, although these findings have not been consistently replicated across studies.[2,3] Furthermore, studies in breast cancer have shown that decreased levels of plakins accompany early cytoskeletal disorganization. Their reduced expression leads to centrosome mispositioning and weakening of intercellular junctions – changes that reflect loss of epithelial polarity and are characteristic of Epithelial-Mesenchymal Transition (EMT).[4]

Epiplakin (EPPK1) represents a less-characterized member of the plakin family, distinguished by its unique arrangement of tandem plakin repeat domains. Unlike other plakins, EPPK1 lacks spectrin repeats and a clear actin-binding domain, suggesting a divergent structural and functional role. While it is expressed in multiple epithelial tissues, its contribution to tumorigenesis remains incompletely understood, and studies on its involvement in cancer are still limited.[1] Data from GEPIA2 indicate that EPPK1 mRNA levels are reduced in cutaneous melanoma, whereas UALCAN-based proteomic datasets show that protein-level alterations remain unclear.[5,6] Given that melanocytes and keratinocytes are interconnected through cadherin-based junctions, plakin proteins such as EPPK1 may contribute to the stabilization of these adhesion complexes. Clarifying whether EPPK1 expression varies between benign and malignant cutaneous lesions may offer diagnostic value.[7] Despite this potential relevance, systematic studies examining EPPK1 expression across diverse cutaneous malignancies – such as Squamous Cell Carcinoma (SCC) and Basal Cell Carcinoma (BCC) – are currently lacking, and its expression profile in benign lesions like intradermal nevi has not been characterized either.

Previous studies have linked EPPK1 to the development of several cancer types, including hepatocellular, cervical, colorectal, bladder urothelial, and esophageal squamous cell carcinomas.[8–12] Given that plakins contribute to cytoskeletal anchorage and junctional stability, altered EPPK1 expression may influence adhesion-related pathways that are also reflected in cadherin dynamics. Because the balance between E-cadherin and N-cadherin is an important indicator of adhesion loss and invasive potential, evaluating their relationship with EPPK1 expression may help clarify whether this plakin participates in adhesion remodeling in skin tumors. The present study aims to assess the immunohistochemical expression of EPPK1 alongside E-cadherin and N-cadherin in SCC, BCC, intradermal nevi, and normal skin specimens. Expression levels are compared across lesion types, and correlations with Breslow thickness are analyzed to explore associations with tumor invasiveness. Normal skin specimens serve as controls. Findings from this study may provide new insights into the diagnostic significance of EPPK1 and its potential interplay with cadherin-mediated adhesion in cutaneous lesions. In addition to the immunohistochemical evaluation, this study also aims to investigate the molecular interaction network of plakin family proteins and to identify their overlap with SCC-associated protein networks. Furthermore, GO and KEGG enrichment analyses are conducted to identify significantly enriched biological processes and signaling pathways associated with the overlapping proteins.

Materials and methods

Subjects and inclusion/exclusion criteria

This retrospective study analyzed skin tissue samples collected between 2021 and 2025 from the archives of the Pathology Department at Bilecik Education and 83 Research Hospital. A total of 24 intradermal nevi were included to allow comparison with 20 corresponding normal tissue samples in immunohistochemical analyses. In addition, 40 malignant cutaneous lesions were examined, comprising 20 BCCs and 20 SCCs.

Only primary cutaneous malignancies from patients who had not received prior radiotherapy or chemotherapy were included. Benign tissues obtained from patients with malignant lesions were excluded to avoid confounding. To minimize the influence of external factors on the analysis, individuals with known pre-existing dermatologic or pulmonary diseases were excluded, given emerging evidence that alterations in plakin-related proteins may affect keratinocyte adhesion and have been implicated in conditions such as bronchiolitis obliterans.[12–14] To ensure adequate tissue for immunohistochemical assessment, only lesions measuring $\geq$ 0.5 mm were included. Ethical approval for this study was granted by the Ethics Committee of Bilecik University (approval nº 2025/7-12). All procedures were con-

ducted in accordance with institutional guidelines and the principles outlined in the Declaration of Helsinki.

Histopathological examination

Tissue specimens were fixed in 10% neutral buffered formalin to preserve structural integrity. Following fixation, samples underwent standard histopathological processing, including dehydration, clearing, and paraffin embedding. Sections of 4 μm thickness were prepared from paraffin blocks and mounted onto glass slides. Slides were deparaffinized in xylene and rehydrated through a graded ethanol series (100%, 90%, 80%, 70%). The sections were then stained with Hematoxylin and Eosin (H&E) to allow detailed visualization of cellular and tissue morphology. After staining, the slides were cover-slipped using Entellan.

Histopathological evaluation was performed using an Olympus CX23 brightfield microscope equipped with an Olympus EP50 camera (1920 × 1080 pixels). Lesions were categorized according to established diagnostic criteria: intradermal nevi were characterized by melanocytic nests confined to the dermis; BCC by basaloid tumor islands with peripheral palisading and hyperchromatic nuclei; and SCC by keratinocytic atypia, intercellular bridges, and keratinization.[15,16] For BCC subtyping, nodular, superficial, nodulocystic, and adenoid variants were classified as non-aggressive forms, whereas morpheaform and infiltrative subtypes were considered aggressive.[17] Tumor invasion was assessed by measuring Breslow thickness, defined as the perpendicular distance from the granular layer of the epidermis to the deepest point of tumor extension.[18]

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue blocks were sectioned at a thickness of 4 μm. Sections were deparaffinized in xylene and rehydrated through a graded alcohol series. Antigen retrieval was performed in citrate buffer (pH6), followed by blocking of endogenous peroxidase activity using 3% hydrogen peroxide.

The sections were incubated at room temperature with the primary antibodies: EPPK1 (1:100, PA5-64412, Thermo Fisher Scientific, Waltham, MA, USA), E-cadherin (1:250, sc-8426, Santa Cruz Biotechnology, Dallas, TX, USA), and N-cadherin (1:250, sc-59987, Santa Cruz Biotechnology, Dallas, TX, USA). After incubation with the appropriate secondary antibody, immunoreactivity was visualized using a streptavidin–HRP detection system, with 3,3′-Diaminobenzidine (DAB) as the chromogen. Slides were counterstained, dehydrated, and mounted for evaluation under a light microscope.

Quantitative digital image analysis

Immunohistochemical staining intensity was quantified using ImageJ software (v1.53e, National Institutes of Health, USA). For each case, five regions of interest (ROIs) were randomly captured at ×400 magnification using an Olympus CX23 brightfield microscope equipped with an Olympus EP50 camera (1920 × 1080 pixels). Images were processed using ImageJ software (version 1.53e, National Institutes of Health, USA). To separate the chromogen signal from hematoxylin counterstaining, color deconvolution was applied, and the resulting image was converted to 8-bit grayscale for quantification. A fixed threshold limit, determined based on control staining to ensure appropriate discrimination of positive signal, was applied to all images to maintain consistency across samples. Immunoreactivity was quantified in terms of Integrated Optical Density (IOD), calculated as area × optical density.[19] Mean IOD values obtained from each ROI were averaged and normalized (divided by 10^6) prior to statistical analysis.

Protein–protein interaction network analysis

A Protein–Protein Interaction (PPI) network was constructed for plakin family members, including EPPK1, DSP, EVPL, PPL, PLEC, BPAG1, and Microtubule Actin Crosslinking Factor-1 (MACF1), using a minimum confidence score of 0.4 and incorporating 100 additional interactors. Similarly, a disease-associated network related to SCC (DOID:1749) was generated using the same 0.4 confidence cutoff and 200 additional interactors. Both networks were generated and processed in Cytoscape v3.10 (Cytoscape Consortium, San Diego, CA, USA), where the Merge/Intersect tool was used to identify shared interactors. The resulting intersected protein set was subjected to KEGG pathway and GO functional enrichment analysis using the STRING v12 online platform. The top ten significantly enriched pathways (FDR < 0.05) were visualized as box plots, indicating both statistical significance and enrichment magnitude.[20]

Statistical analysis

All statistical analyses were performed using SPSS Statistics v26 (IBM, Armonk, NY, USA). Data distribution was assessed for normality using the Shapiro-Wilk test. Differences in continuous immunohistochemical expression levels among groups were analyzed using the Kruskal-Wallis test, followed by Bonferroni-adjusted post hoc pairwise comparisons. Categorical variables were evaluated using the Chi-Square test. Correlations between protein expression levels and Breslow thickness were assessed with Spearman's rank correlation analysis. A p-value < 0.05 was considered statistically significant.

Results

Clinico-pathological characteristics of the study samples

Histopathological evaluation of intradermal nevi demonstrated nests of round to oval nevus cells dispersed throughout the dermis. BCC specimens exhibited basaloid cell nests extending into the dermis with prominent peripheral palisading. In SCC samples, infiltrative nests of squamous cells were observed, showing variable degrees of keratinization and occasional formation of keratin pearls (Fig. 1).

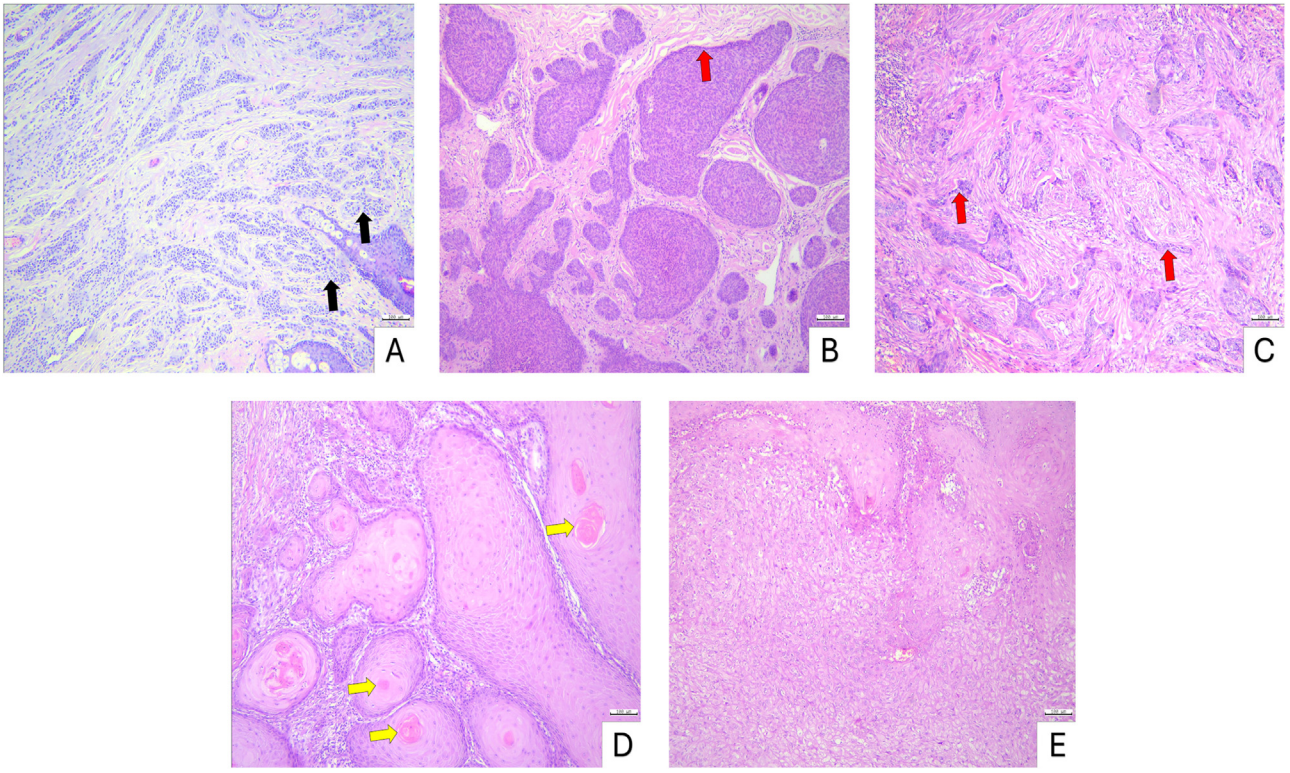

Figure 1 Histopathology of non-melanoma skin lesions (Hematoxylin & eosin stain) (A) Intradermal nevus, nests of round to oval nevus cells (black arrow) within the dermis. (B) Nodular BCC, basaloid nests with peripheral palisading (red arrow). (C) Infiltrative BCC, strands and cords of basaloid cells (red arrow) infiltrating the dermis. (D) Well-differentiated SCC, squamous nests with prominent keratinization and keratin pearls (yellow arrow). (E) Moderately differentiated SCC, squamous nests with intermediate keratinization. Scale bars: 100 μm.

Table 1 Clinico-pathological parameters of intradermal nevi and non-melanoma skin cancers.

	Intradermal nevi	SCC	BCC	p-value
Age (years)	41.33 ± 10.33	69.05 ± 12.32	70.40 ± 14.22	**0.000**[a,c]
Gender				
Male (n)	8 (33.3%)	10 (50%)	15 (75%)	**0.022**[b,c]
Female (n)	16 (66.7%)	10 (50%)	5 (25%)	
Total %	24 (100%)	20 (100%)	20 (100%)	
Localization				
Head, Neck (n)	21 (59.4%)	18 (75%)	18 (75%)	0.953[b]
Trunk, Extremities (n)	3 (40.6%)	2 (25%)	2 (25%)	
Total (%)	24 (100%)	184 (100%)	184 (100%)	
Grade				
Low (n)		10 (50%)		
Mid (n)		10 (50%)		
Total %		20 (100%)		
Types				
Non-Aggressive (n)			15 (75%)	
Aggressive (n)			5 (25%)	
Total %			20 (100%)	
Breslow (μm)		4186.13 ± 2512.96	3534.26 ± 2652.04	0.372[a]

Data are shown as mean ± SD or number and percentage (%).
[a] Kruskal-Wallis test; [b] Chi-Square test.
SCC, Squamous Cell Carcinoma; BCC, Basal Cell Carcinoma; SD, Standart deviation. Statistical significance ([c] $p < 0.05$).

Clinico-pathological characteristics of the study samples are summarized in Table 1. The mean age differed significantly among the groups, with patients in the intradermal nevus group being younger (41.33 ± 10.33 years) compared to those in the SCC (69.05 ± 12.32 years) and BCC (70.40 ± 14.22 years) groups ($p < 0.05$). Gender distribution also varied significantly ($\chi^2 = 7.612$, $p < 0.05$), with a female predominance in the intradermal nevus group (66.7%) and a male predominance in the BCC group (75%). Tumor localization did not differ significantly among groups ($p > 0.05$), with the majority of lesions located on the head and neck in all groups. In SCC samples, histopathological grading was evenly distributed between low-grade (50%) and moderately differentiated (50%) tumors. In BCC, most cases were classified as non-aggressive (75%), while a smaller proportion were considered aggressive (25%). Breslow thickness did not differ significantly between SCC and BCC groups (4186.13 ± 2512.96 μm vs. 3534.26 ± 2652.04 μm, $p > 0.05$) (Table 1).

EPPK1 expression across benign and malignant skin lesions

EPPK1 expression levels differed significantly among the groups. The intradermal nevus group (27.08 ± 3.82) exhibited markedly lower expression compared with normal skin (147.85 ± 17.58, $p < 0.05$) and the SCC group (392.66 ± 55.24, $p < 0.05$). In normal skin, EPPK1 immunoreactivity was predominantly cytoplasmic in cells of the stratum granulosum, with mild expression observed in the stratum spinosum. No significant difference in EPPK1 expression was noted between the nevus and BCC groups (70.39 ± 15.32, $p > 0.05$). Compared with normal tissue, BCC samples showed significantly lower EPPK1 expression ($p < 0.05$). In contrast, SCC specimens demonstrated significantly higher EPPK1 expression relative to both nevus and BCC samples ($p < 0.05$), while expression levels in SCC were not significantly different from the normal group ($p > 0.05$) (Fig. 2).

Cadherin expression in non-melanoma skin cancer

E-cadherin expression differed significantly between the BCC and SCC groups. In normal skin, E-cadherin showed strong localization at intercellular junctions, with mild cytoplasmic staining in the squamous layer. The BCC group exhibited a mean E-cadherin optical density of 147.54 ± 38.26, whereas the SCC group showed markedly higher expression at 389.94 ± 70.56 ($p < 0.05$), with some cells exhibiting increased cytoplasmic staining. In contrast, N-cadherin expression was generally low in both BCC (139.61 ± 45.47) and SCC (216.37 ± 59.83) groups, with no statistically significant difference between them ($p > 0.05$) (Fig. 3).

In well-differentiated SCC samples, E-cadherin immunoreactivity remained largely at intercellular junctions, whereas EPPK1 showed intense cytoplasmic expression. In areas where some tumor cells exhibited increased cytoplasmic E-cadherin, the corresponding sections displayed widespread cytoplasmic upregulation of EPPK1 (Fig. 4).

Correlation of EPPK1 expression with cadherins and breslow thickness

Spearman correlation analysis demonstrated significant positive associations between EPPK1 expression and cadherin levels in non-melanoma skin cancers. EPPK1 exhibited a strong positive correlation with E-cadherin ($r = 0.565$, $p < 0.001$) and a moderate positive correlation with N-cadherin ($r = 0.329$, $p < 0.05$) (Table 2, Fig. 5). When tumor subtypes were analyzed separately, EPPK1 showed significant positive correlations with both E-cadherin and N-cadherin in BCC. In SCC, EPPK1 remained positively correlated with E-cadherin and additionally demonstrated a moderate positive correlation with Breslow thickness ($p < 0.05$), whereas no significant association was observed with N-cadherin (Table 2).

Protein–protein interaction network analysis

PPI network associated with SCC (DOID:1749) was constructed using a minimum confidence score of 0.4 and including 200 additional interactors. The resulting network consisted of 246 nodes and 8258 edges, with an average node degree of 67.1 and an average local clustering coefficient of 0.692. In comparison, a random network of the same size was expected to contain 3172 edges, highlighting a significantly higher connectivity in the observed network (PPI enrichment p-value < 1.0e-16).

Intersection of the plakin family protein network with the SCC-associated network identified a subset of shared interactors. KEGG pathway enrichment analysis of these overlapped proteins showed significant enrichment (FDR < 0.05) across multiple pathways. The top ten enriched pathways were: MicroRNAs in cancer, Pancreatic cancer, Bladder cancer, Melanoma, Endocrine resistance, Proteoglycans in cancer, Prostate cancer, EGFR tyrosine kinase inhibitor resistance, Kaposi sarcoma-associated herpesvirus infection, and Non-small cell lung cancer (Table 3).

GO enrichment analysis identified significant overrepresentation of several biological processes. The most enriched terms included regulation of epithelial cell proliferation (FDR = 2.49E−21, 39 genes) and positive regulation of cell population proliferation (FDR = 1.91E−34, 75 genes). Additional proliferation-related processes were also highlighted, such as regulation of fibroblast proliferation (FDR = 7.42E−14, 18 genes) and positive regulation of epithelial cell proliferation (FDR = 1.32E−16, 27 genes). Cytoskeletal organization pathways were enriched, including intermediate filament cytoskeleton organization (FDR = 6.36E−14, 18 genes). Adhesion-associated processes showed significant enrichment, including regulation of cell adhesion (FDR = 1.65E−30, 65 genes) and negative regulation of cell–cell adhesion (FDR = 3.15E−16, 26 genes). Additional enriched terms included negative regulation of apoptotic signaling (FDR = 1.71E−17, 29 genes), regulation of T-cell activation (FDR = 5.95E−21, 39 genes), and positive regulation of cell migration (FDR = 9.71E−24, 48 genes) (Fig. 6).

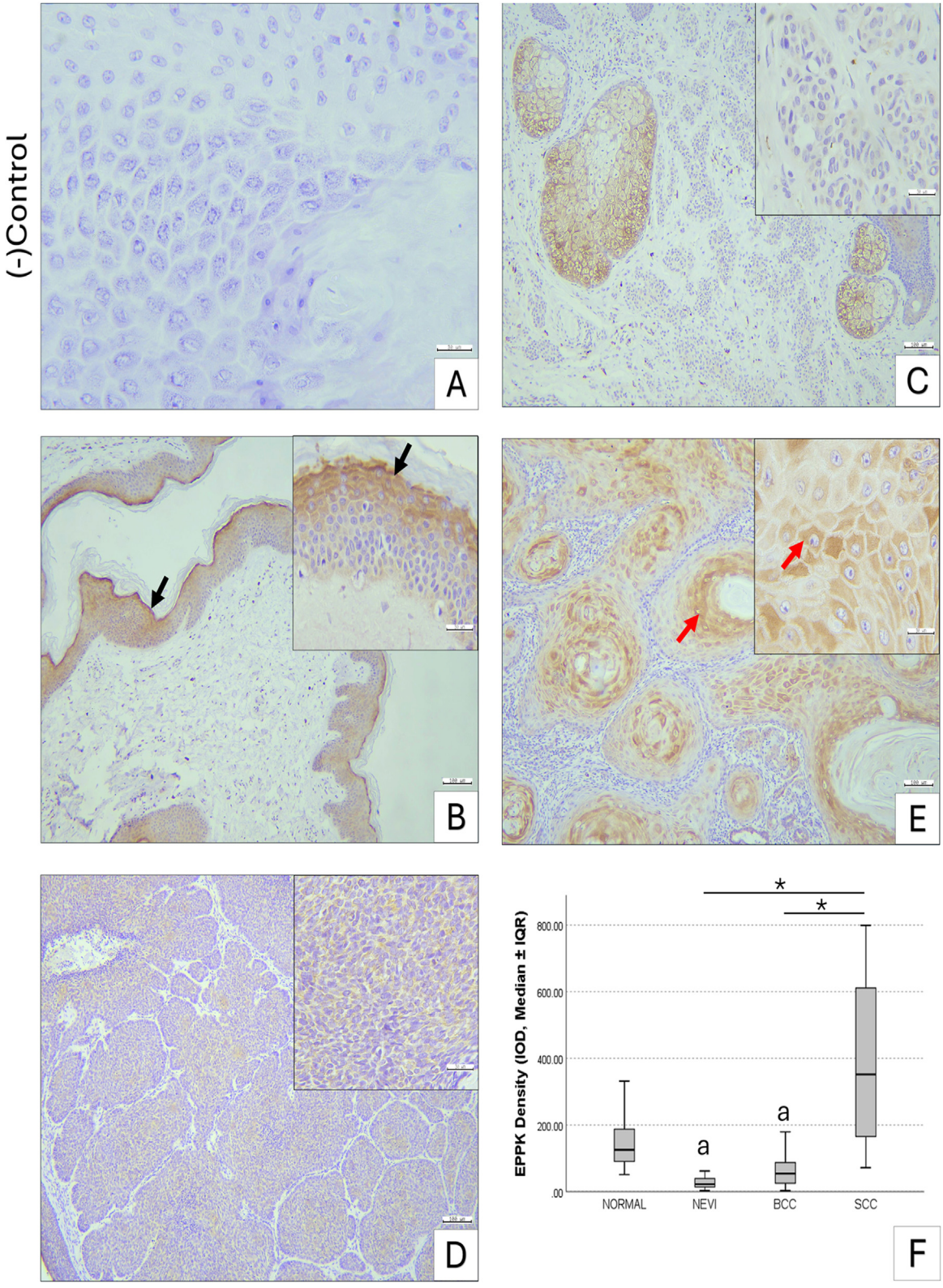

Figure 2 Immunohistochemical staining of EPPK1 in skin samples. (A) Negative control. (B) Normal skin, intense cytoplasmic EPPK1 expression in stratum granulosum (black arrow) and mild in stratum spinosum. (C) Intradermal nevus, very low cytoplasmic EPPK1 expression. (D) Basal cell carcinoma, moderate cytoplasmic EPPK1 expression. (E) Squamous cell carcinoma, strong cytoplasmic EPPK1 expression, especially in cells surrounding keratin pearls (red arrow). Scale bars: A, insets 30 μm, B–E 100 μm. (F) Boxplot showing EPPK1 optical density as median ± IQR; whiskers indicate minimum–maximum. Kruskal-Wallis test, * $p < 0.05$, a, Significantly different from normal skin and SCC. BCC, Basal Cell Carcinoma; SCC, Squamous Cell Carcinoma; IQR, Interquartile Range.

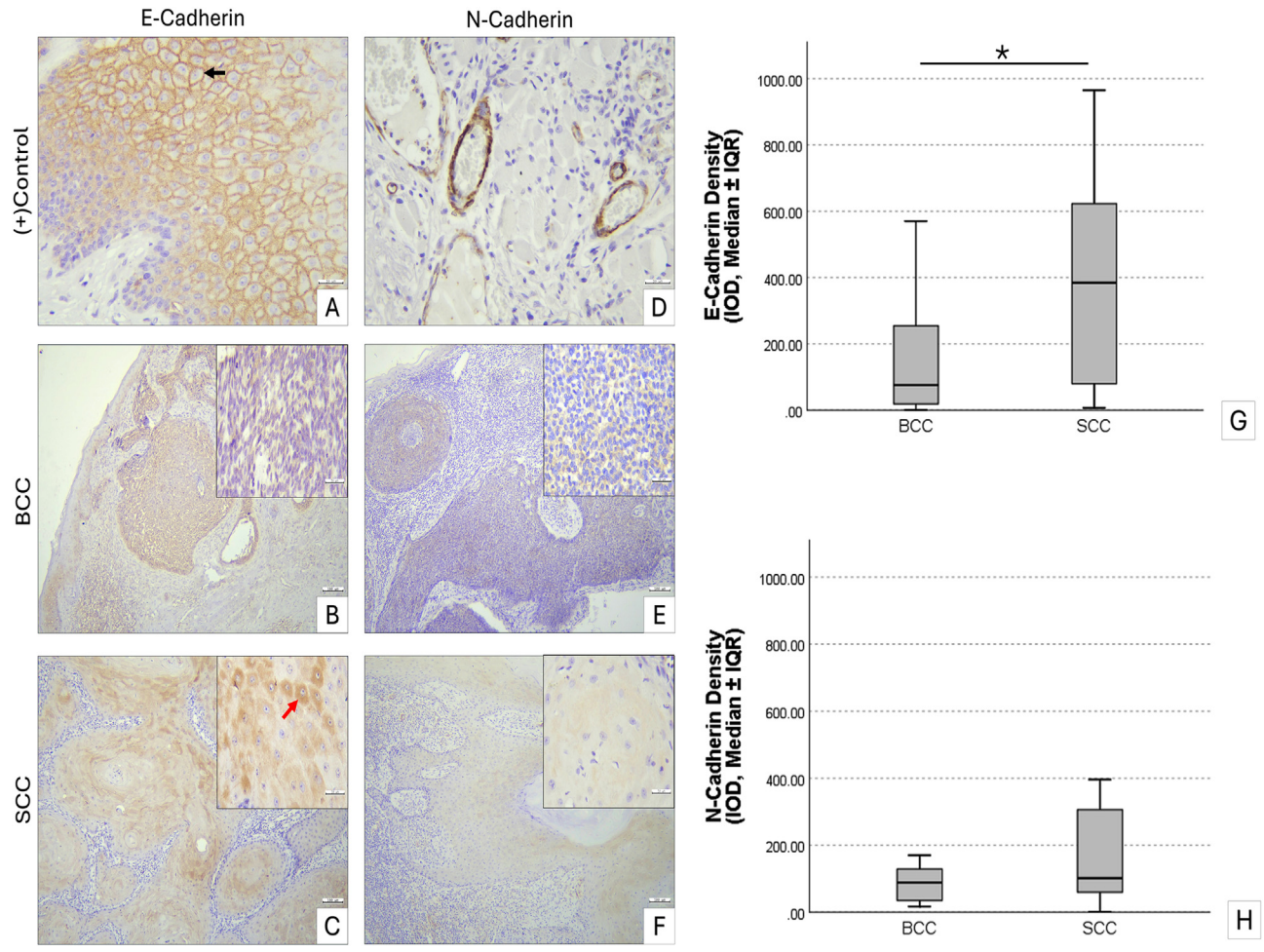

Figure 3 Immunohistochemical staining of E-cadherin and N-cadherin in skin samples. (A) Normal skin, E-cadherin predominantly at intercellular junctions with lower cytoplasmic expression. (B) BCC, E-cadherin cytoplasmic expression. (C) SCC, E-cadherin cytoplasmic expression, with increased intensity in some cells. (D) Normal skin, intense N-cadherin in vascular walls. (E) BCC, N-cadherin cytoplasmic expression. (F) SCC, low N-cadherin expression. Scale bars: A, D, insets 30 μm; B, C, E, F 100 μm. (G) Boxplot of E-cadherin optical density (median ± IQR), SCC significantly higher than BCC. (H) Boxplot of N-cadherin optical density (median ± IQR). Whiskers indicate minimum – maximum. Kruskal-Wallis test, * $p < 0.05$. BCC, Basal Cell Carcinoma; SCC, Squamous Cell Carcinoma; IQR, Interquartile Range.

Table 2 Correlation analysis of EPPK1 expression with cadherins and Breslow thickness.

		Non-melanoma Skin Cancers EPPK1	BCC EPPK1	SCC EPPK1
E-Cadherin	*r*	**0.565**	**0.375**	**0.327**
	p	**0.0002**[a]	**0.011**[a]	**0.020**[a]
N-Cadherin	*r*	**0.329**	**0.350**	0.015
	p	**0.044**[a]	**0.018**[a]	0.917
Breslow	*r*	0.134	-0.224	**0.338**
Thickness	p	0.409	0.145	**0.015**[a]

Spearman's correlation test. BCC, Basal Cell Carcinoma; SCC, Squamous Cell Carcinoma; *r*, Correlation coefficient. [a] $p < 0.05$.

Discussion

The cytoskeleton and its associated junctional complexes play a central role in maintaining epithelial tissue integrity by regulating cell adhesion, polarity, and mechanotransduction – processes that are profoundly altered during carcinogenesis. Plakin family proteins serve as critical structural bridges linking intermediate filaments to desmosomes and hemidesmosomes, thereby stabilizing epithelial architecture under physiological conditions.[1] Accumulating evidence indicates that disruption of plakin-mediated

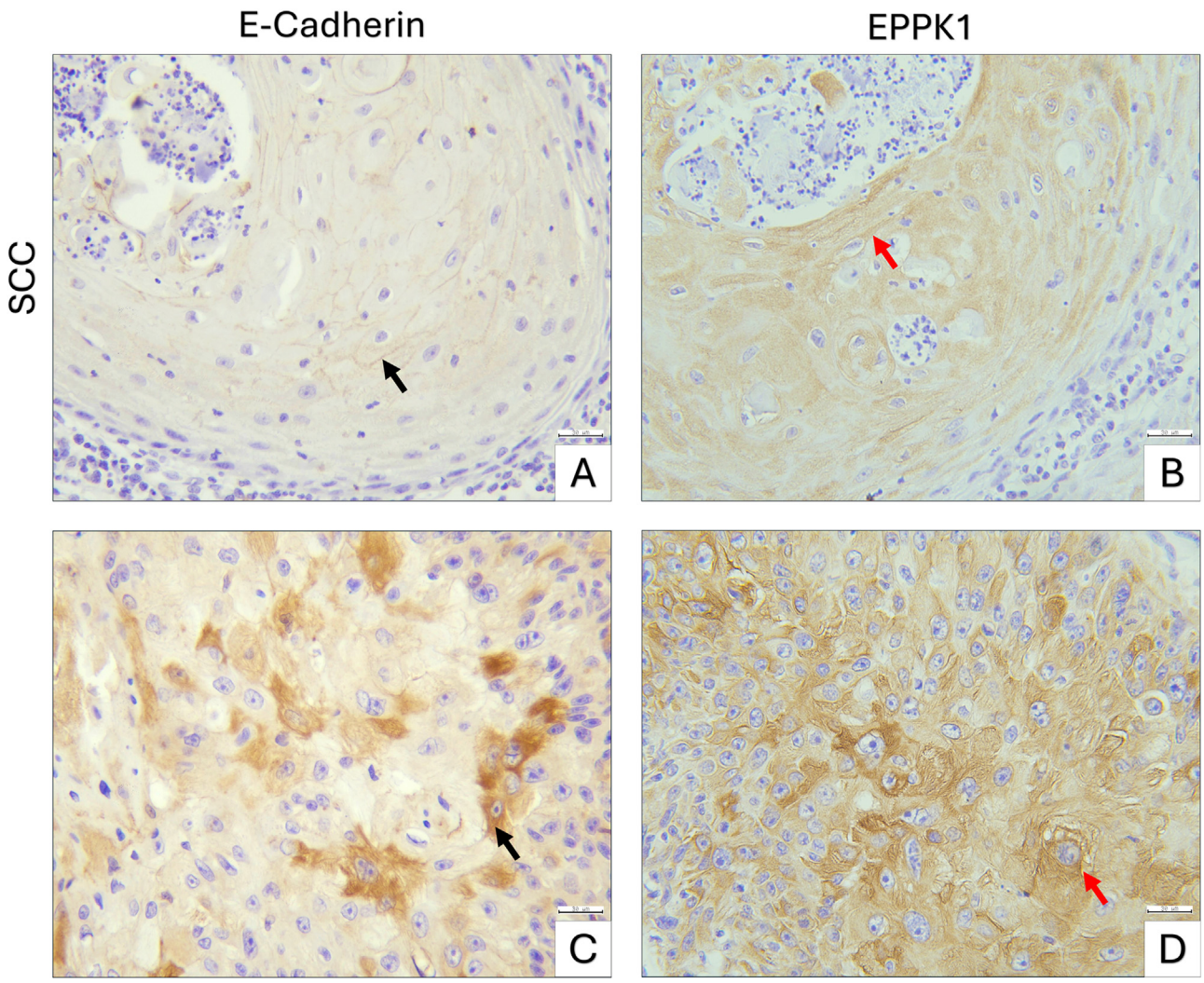

Figure 4 Immunohistochemical staining of E-cadherin and EPPK1 in SCC. (A–B) Well-differentiated SCC, E-cadherin predominantly at intercellular junctions (black arrow) and corresponding region showing intense cytoplasmic EPPK1 expression (red arrow). (C–D) Another area of the same SCC tumor, showing regionally increased cytoplasmic E-cadherin in some tumor cells (black arrow) and widespread cytoplasmic upregulation of EPPK1 across the same region (red arrow). Scale bars: 30 μm.

cytoskeletal anchoring enhances cellular plasticity, promotes migratory capacity, and contributes to tumor progression across various malignancies. For instance, studies in ovarian cancer have shown that decreased PLEC and PPL expression in high-grade tumors coincides with reduced structural stability and a shift toward a more permissive state for invasion, even in the absence of overt EMT marker changes. These observations suggest that plakin loss may represent an early structural destabilization, priming tumor cells for migration by weakening epithelial anchorage.[21] PPI network analysis of plakin family members in SCC revealed a highly interconnected network comprising 246 nodes and 8258 edges, with an average node degree of 67.1 and a clustering coefficient of 0.692 (PPI enrichment $p < 1.0e16$), highlighting a biologically meaningful organization. KEGG pathway enrichment of the overlapping proteins highlighted significant associations with multiple cancer-related pathways, including proteoglycans (FDR < 0.05). These results suggest that plakins function not only as structural components but may also participate in SCC signaling cascades that regulate tumor cell behavior, adhesion, and migration. Experimental evidence from HeLa cells shows that EPPK1 knockdown accelerates keratinocyte motility and induces cytoskeletal rearrangements, whereas overexpression suppresses motility.[22]

Among plakins, EPPK1 is distinctive in that it lacks spectrin repeats and a clear actin-binding domain, and its role in cancer remains poorly understood.[1,23] Research on EPPK1 is still limited, and its involvement in cutaneous malignancies has yet to be fully elucidated. Previous studies in esophageal SCC have reported markedly elevated EPPK1 expression compared with normal controls, whereas in colorectal adenocarcinomas, EPPK1 expression was decreased, suggesting a context-dependent role for this protein.[10,12] A recent review on head and neck cancers highlighted that desmosomal components, including plakin proteins, can paradoxically act, as their expression, localization, and interactions dynamically change

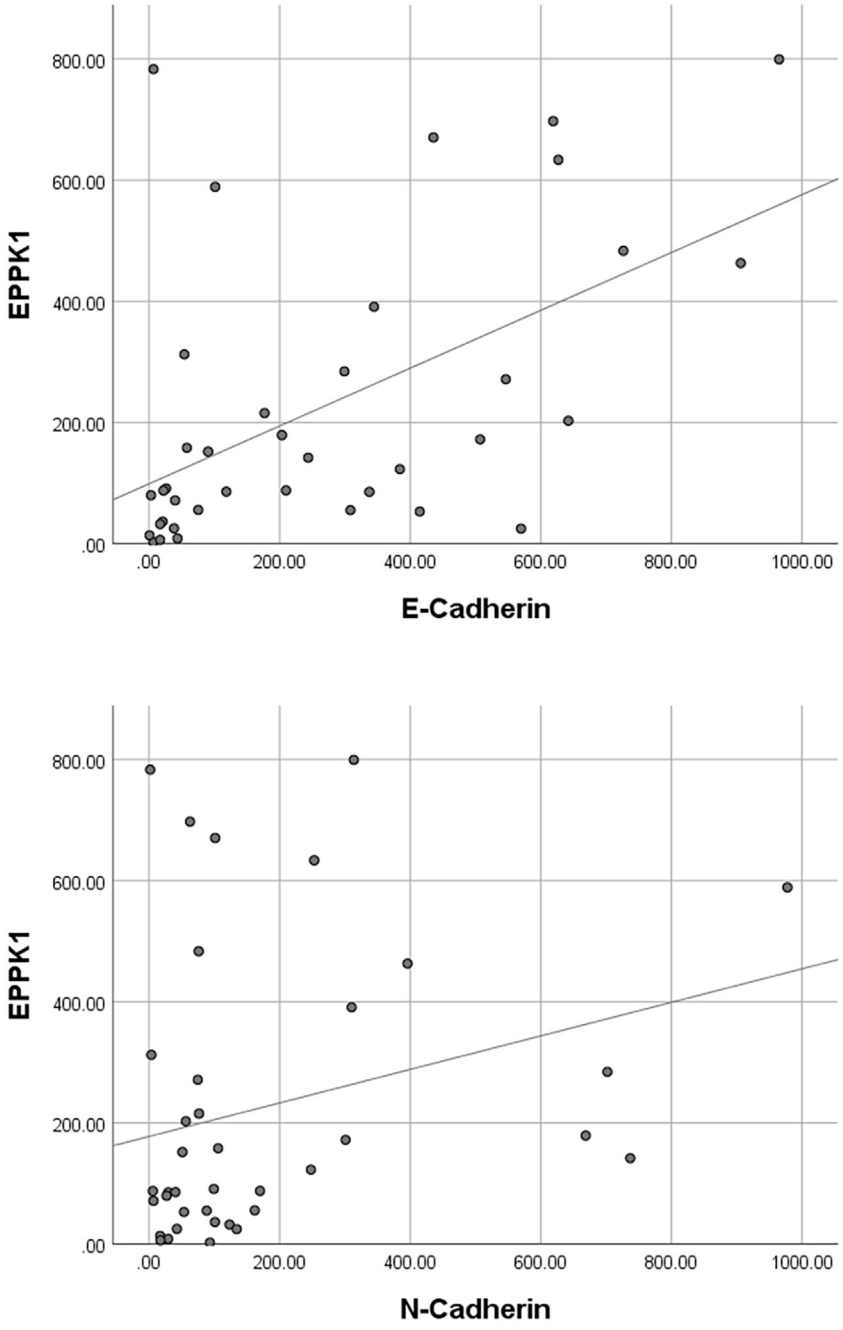

Figure 5 Scatter/dot graph of EPPK1 optical density versus E-cadherin and N-Cadherin optical density. Spearman's correlation test, $p < 0.05$.

during cancer progression.[24] Likewise, although plectin is frequently upregulated in many tumor types, its downregulation has been reported in certain malignancies, emphasizing a dual expression pattern and underscoring the pivotal role of plakins in regulating tumor progression depending on cellular and tissue context.[25] These observations suggest that the functional consequences of EPPK1 expression may vary according to tissue context and tumor type, highlighting the need for further investigation, particularly in cutaneous tumors. In cutaneous cancers, elevated serum anti-BPAG1 autoantibodies have been reported in melanoma patients compared with healthy individuals, indicating a potential, yet still uncertain, role of plakins as biomarkers.[2,3] In the present study, the authors aimed to systematically evaluate the immunohistochemical expression of EPPK1 in benign intradermal nevi, BCC, and SCC to clarify its potential role in skin tumor biology. The present findings demonstrated significantly higher EPPK1 expression in cutaneous SCC (392.66 ± 55.24) compared with BCC (70.39 ± 15.32) and benign intradermal nevi (27.08 ± 3.82) ($p < 0.05$). This variation likely reflects intrinsic cell type-dependent differences, as keratinocytic SCC cells possess distinct cytoskeletal architecture and keratinization-related features compared with BCC and benign melanocytic lesions,

Table 3 KEGG enrichment analysis of the proteins shared between the plakin-family network and the Squamous Cell Carcinoma (SCC, DOID:1749) – associated network. Plakin family proteins (EPPK1, DSP, EVPL, PPL, PLEC, BPAG1, and MACF1) were merged with the SCC-associated PPI network, and overlapping proteins were subjected to KEGG pathway enrichment analysis using STRING v12. The table lists the top 10 most significantly enriched pathways. Each pathway entry also includes the number of associated genes (nGenes) and the specific pathway gene set identified. False Discovery Rate (FDR) < 0.05.

Enrichment FDR	nGenes	Pathway Genes	Signal	Pathways
2.20e-37	42	159	5.54	MicroRNAs in cancer
1.19e-27	27	71	5.25	Pancreatic cancer
4.14e-24	21	40	5.13	Bladder cancer
2.76e-26	26	72	4.98	Melanoma
1.26e-27	29	94	4.9	Endocrine resistance
1.81e-34	42	194	4.82	Proteoglycans in cancer
2.44e-27	29	97	4.81	Prostate cancer
9.41e-26	26	77	4.81	EGFR tyrosine kinase inhibitor resistance
1.10e-32	40	187	4.66	Kaposi sarcoma-associated herpesvirus infection
3.04e-24	24	68	4.66	Non-small cell lung cancer

EPPK1, Epiplakin; DSP, Desmoplakin; EVPL, Envoplakin; PPL, Periplakin; PLEC, Plectin; BPAG1, Bullous Pemphigoid Antigen-1; MACF1, Microtubule Actin Crosslinking Factor 1.

potentially contributing to their higher EPPK1 expression. Given this differential expression pattern, EPPK1 may have potential diagnostic utility in cutaneous malignancies. Routinely used markers, such as E-cadherin, p53, and certain metalloproteinases, have been suggested to aid in differentiating SCC from pseudocarcinomatous hyperplasia. However, a limitation of these studies was that marker expression was not analyzed according to tumor grade, and the differentiation of well-differentiated SCC from pseudocarcinomatous hyperplasia remained challenging.[26] In this study, EPPK1 demonstrated a distinct expression pattern in low- to mid-grade SCC, suggesting that it may provide additional diagnostic value. Notably, in well-differentiated SCC regions, E-cadherin immunoreactivity remained largely at intercellular junctions, while EPPK1 showed intense cytoplasmic expression. In areas where some tumor cells exhibited increased cytoplasmic E-cadherin, EPPK1 expression was already widespread, indicating that changes in EPPK1 may precede detectable alterations in E-cadherin localization.

In normal skin, EPPK1 expression was predominantly observed in the suprabasal layers of the epidermis, with the most intense immunoreactivity localized near the granular layer, suggesting a role in late keratinocyte differentiation and epidermal barrier organization. In SCC samples, EPPK1 expression was particularly prominent in tumor nests and was most intense in squamous cells surrounding keratin pearls. This distinct spatial distribution may indicate that EPPK1 expression in SCC is associated with areas of keratinization and squamous differentiation. Such spatial patterns align with findings from epithelial models showing that keratin intermediate filaments and plakin family cytolinkers cooperatively stabilize keratin-rich surface structures, supporting the idea that plakins may influence keratinization dynamics in human epidermal lesions.[27] Beyond malignancy, EPPK1 has also been implicated in epithelial barrier regulation. In psoriasis, EPPK1 is specifically downregulated in an interferon-γ–dependent manner, and its deficiency has been associated with impaired epithelial adhesion and barrier-related gene expression, supporting a role for EPPK1 in maintaining epithelial stability.[28] Consistent with this concept, in the non-melanoma skin cancer group, EPPK1 expression showed a significant positive correlation with E-cadherin, suggesting that EPPK1 may be functionally linked to cadherin-mediated adhesion dynamics in cutaneous epithelial lesions.

Plakin family members can exert distinct and sometimes opposing effects in tumor biology. Notably, DSP displays a consistent tumor-suppressive pattern, with marked reductions observed across oral and lung carcinomas. This loss has been linked to poorer clinical outcomes, and experimental data demonstrate that DSP depletion enhances keratinocyte proliferation and activates prosurvival ERK/Akt signaling, whereas its overexpression suppresses lung cancer cell growth via modulation of Wnt pathway mediators. In contrast, the plakin-related protein MACF1 exhibits a more oncogenic profile, being highly expressed in glioblastoma; its knockdown reduces proliferation and migration while downregulating Wnt pathway components.[23] Regarding EPPK1, previous studies in esophageal SCC reported functional knockdown experiments revealing reductions in cell proliferation, colony formation, migration, and invasion.[10] Similarly, in adenocarcinomas such as colorectal cancer, EPPK1 expression was positively correlated with Ki67, suggesting a role in cellular proliferation.[12] In line with these findings, the GO functional enrichment analyses demonstrated that the shared protein network formed by plakin family members in SCC was predominantly associated with cell proliferation–related processes, including ''regulation of epithelial cell proliferation'', ''positive regulation of cell population proliferation'', and ''regulation of fibroblast proliferation'', all enriched with highly significant FDR values (FDR < 0.05). Beyond proliferative signaling, the network also showed strong associations with cytoskeletal organization, especially ''intermediate filament cytoskeleton organization'', consistent with the canonical structural roles of plakins. Interestingly, reflecting the known dual and sometimes opposing functions of plakin proteins, the GO analysis revealed that the overlapping proteins were enriched in both positive and negative regulation of cell

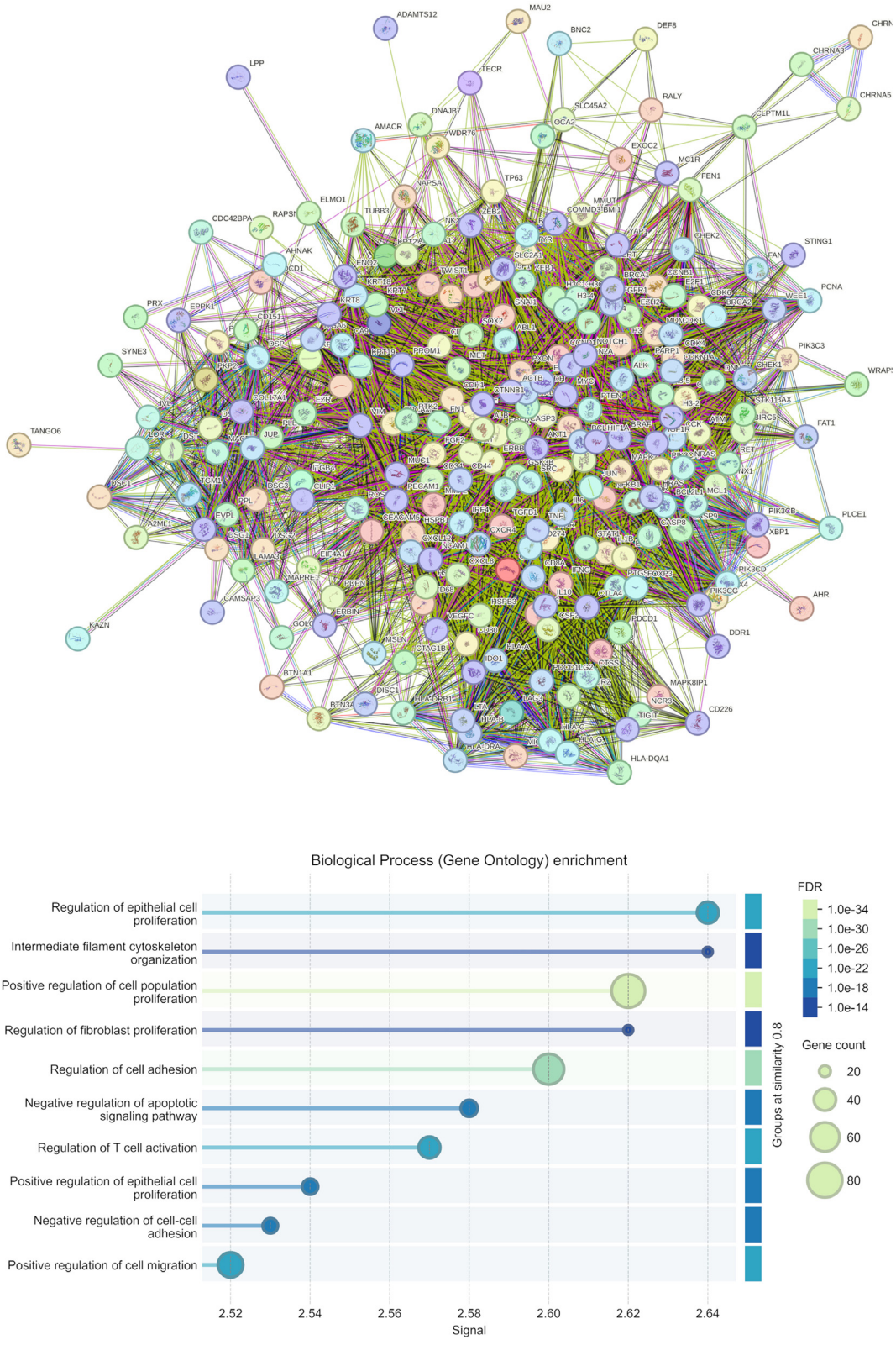

Figure 6 GO functional analysis of overlapped proteins from the intersection of plakin family proteins and squamous cell carcinoma associated networks. Plakin family proteins (EPPK1, DSP, EVPL, PPL, PLEC, BPAG1, and MACF1) were intersected with SCC-associated networks, and the shared proteins were subjected to KEGG pathway enrichment analysis. The box plot displays the ten most significantly enriched biological processes (FDR < 0.05). The color gradient from dark blue to pale green indicates decreasing FDR values, while the size of each box reflects the number of genes contributing to the enrichment, representing the weight of that pathway within the intersected dataset. EPPK1, Epiplakin; DSP, Desmoplakin; EVPL, Envoplakin; PPL, Periplakin; PLEC, Plectin; BPAG1, Bullous Pemphigoid Antigen-1; MACF1, Microtubule Actin Crosslinking Factor-1.

adhesion, highlighting their context-dependent contribution to junctional stability or loosening. Furthermore, enrichment in ''positive regulation of cell migration'' and processes linked to apoptotic signaling underscores a potential involvement of plakins in pathways that facilitate tumor cell motility and survival during carcinogenesis. In the context of the present study, these functional signatures guided the investigation of EPPK1 expression in cutaneous malignancies, prompting us to examine its associations with EMT markers and Breslow thickness to better understand its potential contribution to tumor progression.

EMT involves the loss of cell–cell junctions and epithelial polarity, including adherens junctions. Cadherins, as adhesion molecules, can also act as signaling mediators, influencing cellular behaviors such as migration, proliferation, apoptosis, and differentiation.[29] Pogorzelska-Dyrbuś et al. reported significantly higher E-cadherin and N-cadherin expressions in SCC, with N-cadherin levels being significantly elevated compared with BCC, which was associated with a relatively higher metastatic potential.[30] Similarly, Kim et al. observed increased vimentin expression in SCC.[31] In the present study, although SCC samples exhibited higher N-cadherin levels (216.37 ± 59.83), the difference compared with BCC (139.61 ± 45.47) was not statistically significant ($p > 0.05$), likely due to the predominance of low- and mid-grade SCCs in the studied cohort. Suiqing et al. reported that E-cadherin expression is markedly lower in poorly differentiated SCC compared with well-differentiated tumors.[32] Consistently, in the present study, E-cadherin showed intense cytoplasmic immunoreactivity in SCC cases (389.94 ± 70.56, $p < 0.05$). In the literature, this shift of cadherins from the cell membrane to the cytoplasm is often interpreted as a functional loss of these adhesion molecules, potentially compromising cell integrity and facilitating malignant transformation and metastasis during EMT.[29] Interestingly, EPPK1, which exhibited a positive correlation with E-cadherin in the non-melanoma skin cancer samples, may similarly be involved in EMT-related or other cellular processes, including proliferation. Its immunoreactive localization with enhanced cytoplasmic expression was observed particularly in nests of squamous cells surrounding keratin pearls. The positive moderate correlation between EPPK1 expression and Breslow thickness in SCC may partly reflect increased keratinization and the more prominent formation of keratin pearls in thicker tumors, given the structural association of EPPK1 with the cytoskeletal network.

In lung adenocarcinoma, EPPK1 knockdown led to increased E-cadherin expression and a concomitant decrease in vimentin levels, suggesting a role in modulating epithelial–mesenchymal characteristics.[33] In corneal epithelial wound healing models, EPPK1 deficiency was associated with decreased expression of E-cadherin, keratin-6, and vimentin, indicating a role in cytoskeletal regulation and potentially facilitating cell migration during tissue repair.[34] In the present study, EPPK1 expression in non-melanoma skin cancers showed a strong positive correlation with E-cadherin ($r = 0.565$, $p < 0.001$) and a modest positive correlation with N-cadherin ($r = 0.329$, $p < 0.05$). Lopes et al. reported a positive correlation between N-cadherin and E-cadherin in melanoma, interpreted as a partial EMT state with a hybrid cadherin expression profile.[35] Venza et al. found that reduced E-cadherin in cutaneous melanoma did not significantly correlate with clinical stage or Breslow thickness, and they suggested that its downregulation may be more closely associated with regulating melanoma cell proliferation.[36] In the non-melanoma skin cancer samples, the low correlation between EPPK1 and N-cadherin, along with the absence of a significant correlation with Breslow thickness, indicates that EPPK1 alone may not serve as a reliable invasion marker, although it could play a role in the early stages of EMT.

Epidemiologically, intradermal nevi are predominantly observed in female patients, with 80.46% of cases reported in women.[37] A retrospective analysis of cases diagnosed between 2010 and 2018 similarly confirmed this female predominance, with 1973 women and 667 men affected.[38] In contrast, BCC and SCC primarily affect older adults, with the most frequent age of onset around 70–85 years.[39] Specifically, cutaneous SCC generally presents around 70-years of age, with over 80% of cases occurring in individuals aged 60 or older.[40] Consistently, in the present study, SCC and BCC groups exhibited a higher proportion of males and an increased mean age compared with the intradermal nevus group, reflecting known epidemiological trends.

The present study represents the first systematic evaluation of EPPK1 expression in the context of cutaneous malignancy progression. Although limited by its retrospective design, the findings provide valuable insights into the potential role of EPPK1, particularly in relation to EMT processes. Notably, EPPK1 expression was significantly higher in well-differentiated SCC compared with BCC and benign intradermal nevi, and it demonstrated a positive correlation with E-cadherin, suggesting a role in EMT dynamics and potentially other early tumor-related processes.

In conclusion, EPPK1 appears to act as a context-dependent molecule associated with EMT, showing elevated expression in keratinocytic SCC. Its differential expression pattern and correlation with key adhesion markers highlight its potential utility as a diagnostic biomarker for cutaneous malignancies. Future studies with larger cohorts, including high-grade SCCs, are warranted to further clarify the prognostic significance of EPPK1.

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Institutional review board statement

Ethical approval was obtained from the Ethics Committee of Bilecik University (approval number: 2025/7-12, Date: August 04, 2025). All methods were conducted in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki.

Research data availability

The entire dataset supporting the results of this study was published in this article.

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Authors' contributions

Damla Gül Fındık: Study conception and planning; data collection, analysis and interpretation; statistical analysis; preparation and writing of the manuscript; approval of the final version of the manuscript.

Özlem Türelik: Data collection, analysis and interpretation; preparation and writing of the manuscript; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Histopathological evaluation of facial melasma treated with oral tranexamic acid alone and in combination with ketotifen☆

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Abstract
Background: Tranexamic Acid (TA) has demonstrated effectiveness on melasma treatment, and Ketotifen (KET) may inhibit mast cell-mediated melanogenesis. The histologic basis of their depigmenting effects remains unclear.
Objectives: To evaluate histopathological changes from TA with KET over a 3-month treatment.
Methods: In this randomized, double-blind trial, 50 women with facial melasma were assigned to KET 1 mg plus TA 250 mg (TA/KET group) or TA 250 mg (TA group), every 12 h for 3-months, with broad-spectrum sunscreen. Skin biopsies were performed at baseline and day-90. Primary outcome was epidermal melanin density reduction; secondary outcomes included stratum corneum compaction, solar elastosis, basement membrane disruptions, and counts of mast cells, melanocytes (including pendulum melanocytes), and upper dermal VEGF density.
Results: Groups were comparable at baseline. Both showed reduced epidermal melanin without intergroup difference, with unchanged VEGF expression, mast cell and melanocyte count, and stratum corneum parameters. The TA/KET-group presented an increase in epidermal thickness, reduction in solar elastosis, pendulum melanocytes counting, and basal membrane disruptions.

☆ Study conducted at the Department of Dermatology, Universidade Federal de São Paulo, São Paulo, SP, Brazil

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Study limitations: The short treatment and follow-up may have limited detection of histologic progression. Toluidine blue, while effective in detecting abundant mast cell populations, may lack sensitivity for precise quantification. PAS staining of the basement membrane may occasionally produce artifactual discontinuities, even when the membrane is structurally intact. Ketotifen was not tested alone.
Conclusion: Both interventions led to epidermal melanin reduction. The combination TA/KET induced greater dermal and epidermal remodeling changes that surpassed those with TA alone, showing features associated with photoaging reversal and skin homeostasis restoration.

Introduction

Melasma is a chronic, acquired pigmentary disorder characterized by symmetrical hyperpigmentation in sun-exposed areas. It predominantly affects women of childbearing age with intermediate and dark skin phototypes.[1] In a Brazilian prevalence study, melasma was observed in 36.3% of adult women.[2] Given its frequent facial distribution, melasma often has a significant impact on quality of life.[3]

Chronic exposure to ultraviolet (UV) and visible light is the primary extrinsic trigger of persistent epidermal hypermelanosis in melasma. This exposure promotes the upregulation of the melanocortin-1 receptor and α-MSH, and induces a senescent phenotype in dermal fibroblasts.[4–6] Sex hormones also contribute to the pathogenesis, as pregnancy is a commonly associated risk factor, alongside a genetic predisposition.[1] Melanocytes in melasma are hypertrophic and contain an increased number of melanosomes. These cells undergo paracrine stimulation via cytokines and mediators such as IL-17, iNOS, endothelin, prostaglandin E2, and growth factors (e.g., α-MSH, SCF, and β-FGF), as well as by the overexpression of the estrogen receptor-β.[7]

In addition to epidermal hyperpigmentation, structural alterations resembling photoaging, such as solar elastosis, basement membrane disruption, increased vascularization, and mast cell infiltration in the upper dermis, are also observed in melasma, partly due to impaired autophagy.[8]

According to current evidence-based clinical guidelines, the first-line treatment for melasma continues to rely on the use of broad-spectrum sunscreens in combination with topical depigmenting agents.[8,9] However, the limited response in many patients has stimulated interest in adjuvant therapies, including systemic agents.

Oral Tranexamic Acid (TA), a synthetic derivative of lysine, inhibits the conversion of plasminogen to plasmin, thereby disrupting the interaction between melanocytes and keratinocytes and reducing melanin synthesis.[10] It also suppresses the production of prostaglandins and arachidonic acid by keratinocytes, molecules known to stimulate melanogenesis. TA may further exert effects by indirectly reducing circulating α-MSH levels and acting as a competitive inhibitor of tyrosinase. Additionally, it is proposed to suppress UV-induced plasmin activity, reduce mast cell activation, and downregulate β-FGF, leading to decreased dermal vascularization and mast cell infiltration.[11]

Among the various bioactive mediators released by mast cells, histamine has been shown to promote melanogenesis primarily through H2 receptor activation.[12] Stem Cell Factor (SCF), which is overexpressed in melasma, supports mast cell survival, proliferation, migration, and activation via binding to the c-KIT receptor. Tryptase, another mast cell-derived protease, activates Matrix Metalloproteinases (MMP-1 and MMP-9), which degrade types I and IV collagen, contributing to extracellular matrix degradation and basement membrane disruption. Mast cells also stimulate angiogenesis by releasing VEGF, FGF-2, and TGF-β.[13,14]

Ketotifen Fumarate (KET) is a mast cell stabilizer commonly used in the treatment of asthma with allergic components. One proposed mechanism of action is the blockade of IgE-activated Ca^{2+} channels, which prevents the release of histamine and other mediators.[15] In a clinical trial involving 74 women with melasma, a combination of KET and famotidine (an H2-receptor antagonist) resulted in a modest improvement in skin lightening.[16]

While the efficacy of tranexamic acid in melasma treatment is well established, the role of antihistamines remains less defined. As the histopathological basis of improvement from these agents remains poorly understood, investigating the tissue-level changes associated with KET and TA is essential for supporting the development of new treatment strategies for melasma.

Methods

This was a prospective, randomized (1:1), comparative, parallel-group, double-blind, superiority clinical trial conducted from September to December 2022. Fifty women (aged 18–65 years) with untreated facial melasma, except for the use of sunscreen for at least one month, were enrolled. Exclusion criteria included the presence of other facial dermatoses, pregnancy or lactation, immunosuppression, and risk factors for thromboembolism (e.g., use of hormonal contraceptives or hormone replacement therapy, smoking, obesity, sedentary lifestyle, or a personal or family history of thromboembolic events).

The study was conducted at the outpatient clinic of a public hospital in Brazil. The protocol was approved by the Institutional Research Ethics Committee (approval nº 0333/2022), and all participants provided written informed consent. The study was registered in the Brazilian Registry of Clinical Trials (ReBEC: RBR-10jn7f39). Clinical, quality-of-life, and colorimetric efficacy data from this trial were published previously.[17]

Fifty eligible participants were randomized using a computer-generated sequence into two groups. The control group (TA) received 250 mg of oral tranexamic acid plus a placebo every 12 h, while the intervention group (TA/KET) received 250 mg of oral tranexamic acid plus 1 mg of ketotifen every 12 h. All components were compounded into identical capsules, and both participants and evaluators were blinded to treatment allocation. The blinding code was maintained by the compounding pharmacy and was only broken after statistical analyses were completed. Systemic treatment lasted 90-days.[18] All participants received a tinted broad-spectrum sunscreen (Photoaging Control SPF 50, Eucerin™) and were instructed to reapply it every 3-hs during the day throughout the study period.

Skin biopsies were obtained using a 3-mm punch at baseline (D0) and on day-90 (D90), from the same anatomical site, with a maximum variation of 1 cm. Samples were fixed in formalin, paraffin-embedded, and stained with Hematoxylin-Eosin (HE), Fontana-Masson, Periodic Acid-Schiff (PAS), and toluidine blue. Immunohistochemistry was performed using anti-Melan-A (Dako, undiluted, A103 clone, RTU) and anti-vascular endothelial growth factor (VEGF; Dako, 1:50 dilution, VG1 clone) antibodies.

Slides were photographed in triplicate at 40× magnification using a digital scanner (3DHistech, Budapest, Hungary), selecting representative interfollicular areas free of artifacts. Images were saved in TIFF format. Quantitative analyses were conducted using ImageJ software (version 1.51e; NIH, USA) by a trained dermatologist who was blinded to both the biopsy time point (D0 or D90) and the treatment allocation. The only exception was the Toluidine Blue staining, which was evaluated by two trained pathologists due to the complexity of its assessment.[19]

The primary outcome was the change in epidermal melanin content between D0 and D90, assessed by Fontana-Masson staining using split-channel analysis and image binarization. Staining intensity was quantified as the mean pixel intensity in the color histogram, ranging from 0 (black) to 255 (white). Secondary outcomes included: stratum corneum compaction and solar elastosis (evaluated on HE); basement membrane disruptions (PAS); mast cell density in the upper dermis (toluidine blue); melanocyte density and presence of pendulum melanocytes (Melan-A); and VEGF staining intensity (color deconvolution analysis in ImageJ). Due to the algorithm used for deconvolution in ImageJ, intensity values are not restricted to the standard 8-bit scale (0–255), but reflect summed optical density, yielding higher raw pixel values proportional to stain deposition.[20] Solar elastosis was qualitatively graded as: 0 = absent, 1 = mild/focal to moderate, and 2 = intense. Stratum corneum compaction was scored as: 0 = absent, 1 = partial, and 2 = diffuse.[21]

Sample size was calculated using G*Power software to detect a between-group difference greater than 20%, assuming a standard deviation of a similar magnitude. A 10% dropout rate was anticipated. With a one-tailed alpha of 0.05 and 80% statistical power, the required sample was 25 participants per group.

Normality was assessed using the Shapiro-Wilk test.[22] Statistical analyses were performed using IBM SPSS version 25. Between-group comparisons were conducted using a generalized linear mixed-effects model with Sidak adjustment for multiple comparisons.[23] Analyses followed the intention-to-treat principle, and missing data were handled via mixed model imputation. Statistical significance was set at $p \leq 0.05$ (one-tailed).[24]

Results

A total of 71 participants were initially screened, of whom 21 (29.5%) were excluded based on eligibility criteria. The trial ultimately enrolled 50 participants, equally allocated to the TA group (n = 25) and the TA/KET group (n = 25). Six participants discontinued the study (5 from the TA group and 1 from the TA/KET group) due to reasons unrelated to treatment-related adverse effects: two were lost to follow-up, and four declined to undergo the second biopsy (Fig. 1).

The groups were demographically comparable: the mean age (SD) was 48 (6) years in the TA/KET group and 45 (7) years in the TA group, and most participants in both groups had high phototypes (IV, V, or VI) (Table 1). Both groups showed clinical improvement in all evaluated parameters (mMASI, MelasQoL, and colorimetry) from baseline (D0) to post-treatment (D90), with no differences between them (Fig. 2). At day 90 (D90), for example, the mean reduction in mMASI was 47% (36–58%) in the TA group and 52% (44%–59%) in the KETO group ($p > 0.25$, 95% CI). During follow-up without treatment (D120), recurrence was observed in both groups, with no significant difference between them ($p = 0.36$).[17]

Histological and immunohistochemical findings are summarized in Table 2. An overall reduction in epidermal melanin content was observed in both groups after 90-days of treatment (−12.7; 95% CI: −18.0 to −7.4; $p < 0.001$), with no difference between the groups (Fig. 3).

The melanocyte count, assessed via Melan-A staining, remained unchanged in both groups. However, a reduction in melanocyte area was observed across groups after treatment (−89; 95% CI: −167 to −11; $p = 0.025$), again with no between-group difference. Notably, melanocyte area decreased significantly in the TA/KET group (−132; 95% CI: −254 to −10; $p = 0.034$). In addition, the number of pendulum melanocytes was reduced in the TA/KET group (−0.66; 95% CI: −1.18 to −0.13; $p = 0.015$) (Fig. 4).

An increase in epidermal thickness was observed exclusively in the TA/KET group at day-90 (14.3; 95% CI: 7.1 to 21.4; $p < 0.001$). This group also showed a significant reduction in solar elastosis (-0.20; 95% CI: −0.41 to −0.36; $p = 0.014$), suggesting a favorable remodeling effect in the dermal compartment (Fig. 5). Furthermore, the number of basal membrane disruptions decreased significantly only in the TA/KET group after treatment (−0.73; 95% CI: −1.04 to −0.4; $p < 0.001$) (Fig. 6).

No significant changes were observed between groups or over time in mast cell count (evaluated using toluidine blue staining), stratum corneum thickness and compaction (assessed via H&E), or VEGF expression (evaluated by immunostaining).

Discussion

Although no clinical differences were observed between groups after treatment, and a relapse occurred in both groups 30-days after treatment suspension,[17] this study

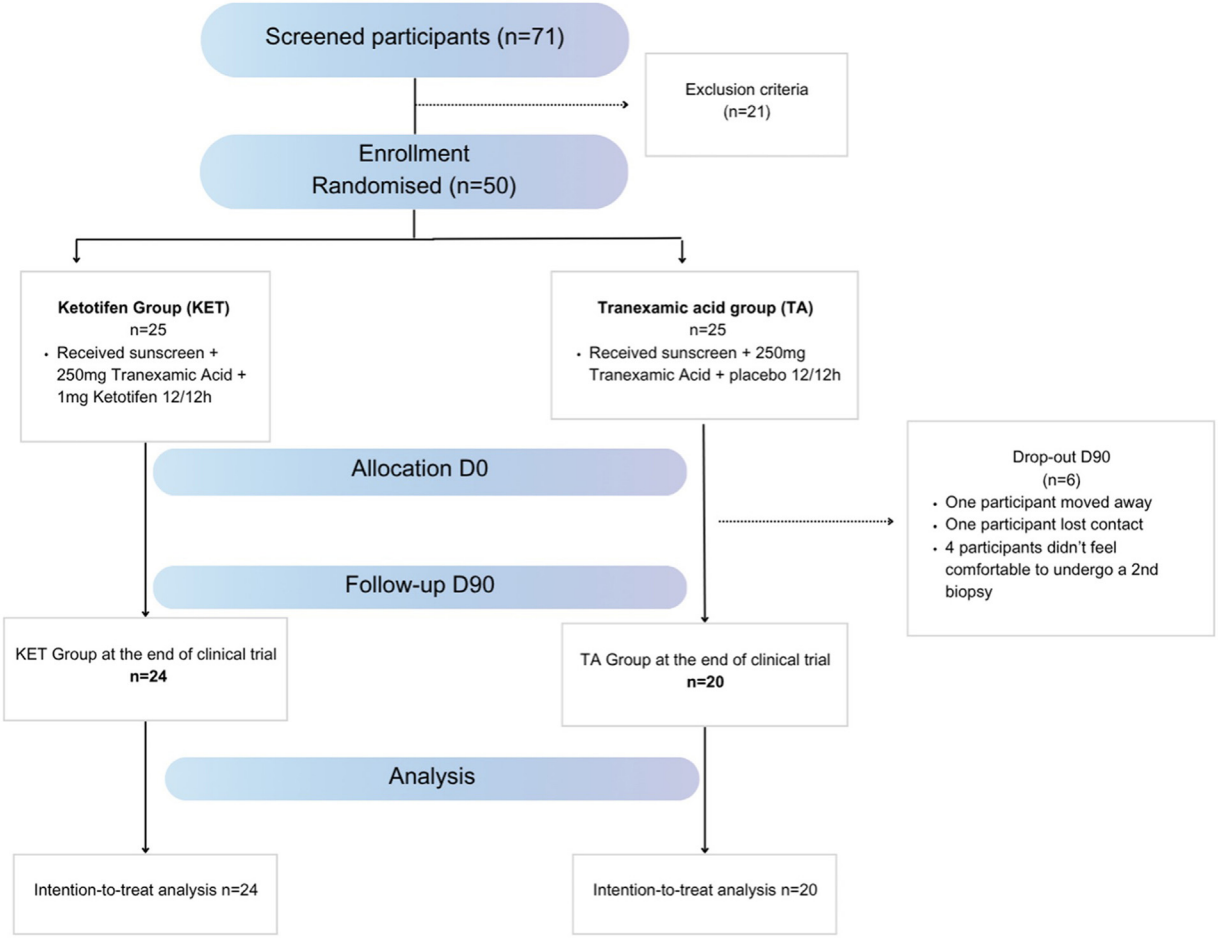

Fig. 1 CONSORT flow diagram of the study.

Table 1 Main clinical and demographic variables of the participants at inclusion.

Variables		TA/KET group	TA group
n		25	25
Age (years), mean (SD)		48 (6)	45 (7)
Phototype,	II and III	4 (16)	9 (36)
n	IV	11 (44)	9 (36)
(%)	V and VI	10 (40)	7 (28)
Pregnancies, median (P_{25}–P_{75})		2 (1–2)	2 (1–3)
Daily exposition to the sun (min), mean (SD)		95 (79)	73 (68)
Family history of melasma, n (%)		18 (72)	17 (68)
Age of melasma onset (years), mean (SD)		33 (11)	29 (9)
mMASI, mean (SD)		8 (2)	8 (2)
MELASQoL, mean (SD)		47 (12)	53 (12)
Dif-*L, mean (SD)		4 (2)	4 (2)

Group TA/KET: Combination therapy of oral 1 mg of ketotifen plus 250 mg of tranexamic acid 12/12 h. Group TA: Oral therapy of 250 mg of tranexamic acid plus placebo 12/12 h. mMASI, Modified Melasma Area and Severity Index; MELASQoL, Melasma Quality of Life questionnaire; Dif-*L, Colorimetric difference of the lightness (*L) between melasma and adjacent skin.

revealed distinct histopathological changes following the interventions, suggesting a potential role of mast cell stabilizers and antihistamines in the treatment of melasma.

The pathogenesis of melasma involves multiple mechanisms beyond melanocyte hypertrophy. Alterations in different skin compartments, such as the epidermis, dermis, basement membrane, and cutaneous barrier, are involved in the disease process.[7] Histological features such as solar elastosis, increased perivascular mast cells and sebaceous glands, basement membrane disruption, and enhanced vascularization have been consistently demonstrated in melasma-affected skin.[25–28] Additionally, a transcriptional

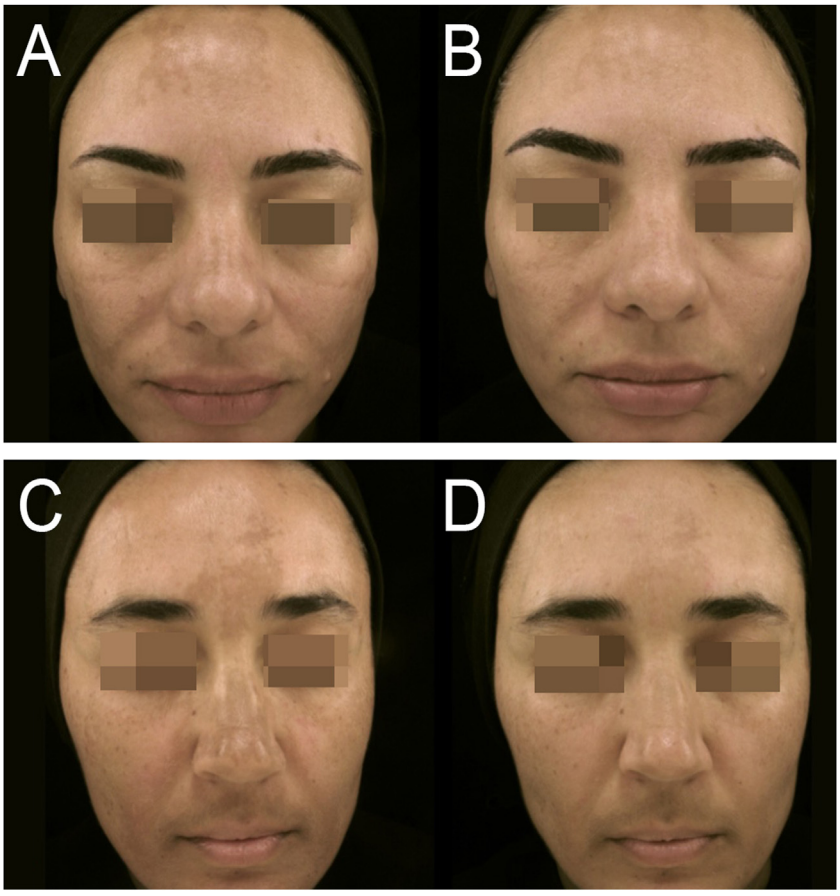

Fig. 2 Photographic records are presented at baseline (DO), at the conclusion of systemic treatment (D90). TA group (A–B); KET group (C–D).

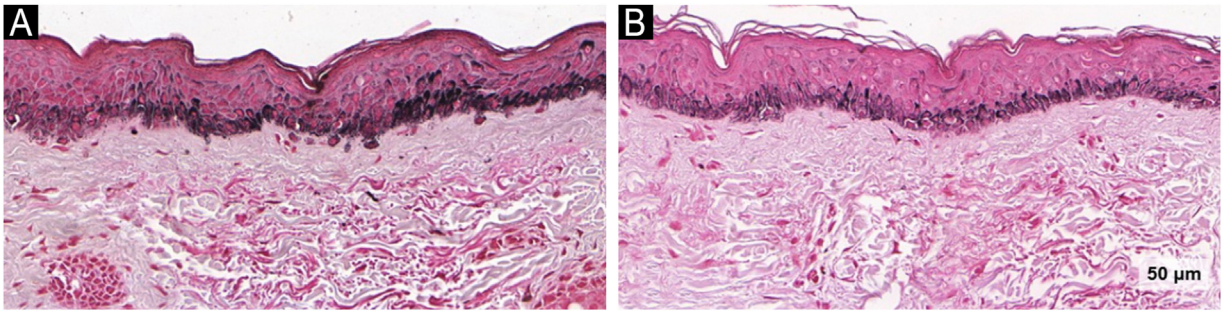

Fig. 3 Fontana-Masson images of TA group evidencing epidermal melanin reduction: (A) baseline and (B) post-treatment (Fontana-Masson, ×40).

analysis of melasma lesions reported the involvement of nearly 300 genes, underscoring the complexity of its pathophysiology, which extends beyond melanocytes to include dermal components as well.[29]

The reduction in epidermal melanin observed in both the TA and TA/KET groups is consistent with previous evidence supporting the depigmenting effects of TA, even when used without topical lightening agents.[10,11] However, the addition of ketotifen did not yield a significantly greater reduction in melanin, possibly due to the dominant effect of TA masking any additional impact. Notably, although between-group differences in melanocyte volume were not statistically significant, the TA/KET group showed a more pronounced reduction after treatment.

While melanophages are commonly increased in hyperpigmented skin,[30,31] their exact role in melasma remains uncertain. Given their absolutely low density compared to epidermal melanin,[32] their contribution may be more indicative of chronic photodamage than a primary driver of pigmentation. Nevertheless, melanophages are recognized markers of photoaging and are more prevalent in individuals with darker phototypes.[30,31]

Although total melanocyte counts remained stable in both groups, a significant reduction in pendulum

Table 2 Histological and immunohistochemical variables according to group (n = 44).

Variables	TA			TA/KET			p (time × group)
	D0 Mean (SD)	D90	p (time)	D0 Mean (SD)	D90	p (time)	
Epidermal melanin (intensity)[a]	84 (13)	67 (16)	<0.001	83 (13)	75 (17)	0.005	0.103
Dermal melanin (intensity)[a]	21 (14)	13 (7)	0.013	19 (14)	18 (12)	0.74	0.183
Mast cells[b]	1.7 (1.9)	2.8 (2.9)	0.154	2.7 (2.2)	2.2 (1.5)	0.253	0.424
Basal layer melanocytes[c]	16 (5)	14 (5)	0.131	17 (6)	15 (4)	0.085	0.480
Pendulum melanocytes[c]	1 (0.8)	0.8 (1.3)	0.219	1.5 (1.3)	1 (1.2)	0.015	0.54
Melanocytes area (×10)[d]	68 (19)	63 (12)	0.344	71 (24)	57 (14)	0.034	0.179
BMZ discontinuities[c]	0.9 (0.8)	0.8 (0.8)	0.776	1.3 (0.9)	0.6 (0.6)	<0.001	0.608
Thickness of the stratum corneum [μm]	40 (12)	43 (16)	0.18	44 (16)	47(13)	0.5	0.335
Thickness of the epidermis [μm]	97 (26)	261 (35)	0.156	282 (30)	264 (33)	<0.001	0.191
Compaction of the stratum corneum[e]	**n (%)**			**n (%)**			
0 (absent)	10 (40)	10 (47)	0.387	12 (48)	16 (66)	0.257	0.323
1 (partial)	11 (44)	9 (42)		11 (44)	6 (25)		
2 (diffuse)	4 (16)	2 (9)		2 (8)	2 (8)		
Solar elastosis[f]	**n (%)**			**n (%)**			
0 (absent)	3 (12)	4 (19)	0.166	4 (16)	5 (20)	0.014	0.636
1 (mild to moderate)	13 (52)	11 (52)		12 (48)	14 (58)		
2 (moderate to severe)	9 (36)	6 (28)		9 (36)	5 (20)		
VEGF ×103 intensity[g]	79 (69)	77 (13)	0.465	73 (68)	76(11)	0.276	0.683

[a] Mean pixel intensity, as shown in the color histogram, varies between 0 and 255.
[b] Number of mast cells (calculated as the mean count across five zones at 40× magnification).
[c] Absolute number of cells at 40× magnification.
[d] Melanocytes mean area at 40× magnification.
[e] Visual qualitative scale: 0 (compactation absent, ''basket-weave'' pattern), 1 (partial corneum compaction, intermixed areas of compact and non-compact stratum corneum) and 2 (diffuse compaction of the stratum corneum).
[f] Visual qualitative scale for solar elastosis in the upper dermis: 0 (absent), 1 (mild to moderate) and 2 (moderate to intense).
[g] Vascular Endothelial Growth Factor (VEGF, Dako, 1:50): mean pixel intensity in the upper dermis. Due to the output scale of the deconvolution algorithm, values were no longer restricted to the standard 8-bit range (0–255) and instead ranged between 73,000 and 7.

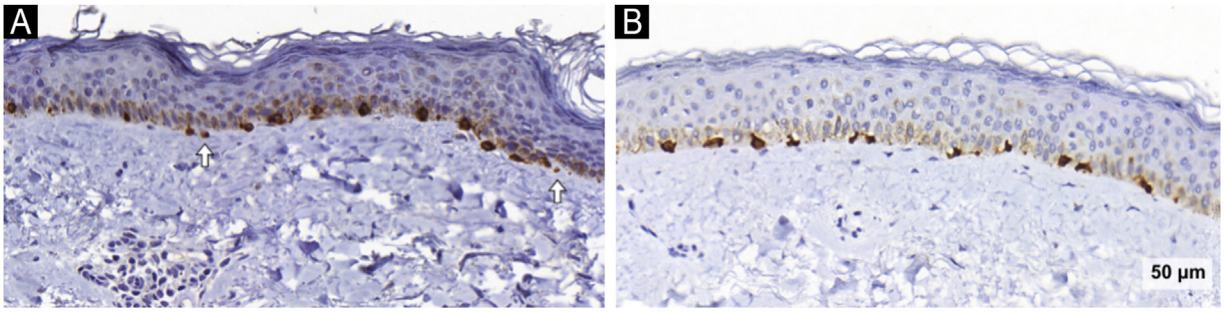

Fig. 4 Melan-A images of the TA/KET group. Arrows indicate pendulous melanocytes before (A) and reduced after treatment (B) (Melan-A, ×40).

melanocytes was observed in the TA/KET group. These cells are more prevalent in melasma lesions compared to perilesional skin[33] and are supposed to represent inactive dendritic melanocytes, as demonstrated by confocal microscopy.[26] Lacking epidermal connectivity, they are unlikely to contribute directly to melanogenesis but can be induced by UVA radiation.[34] While the precise mechanisms underlying their formation are unclear, evidence suggests that chronic sun exposure may increase MMP-2 expression, promoting basement membrane disruption and pendulum melanocyte formation.[35]

Mast cell density is typically higher in chronically sun-exposed areas compared to non-exposed regions,[36] and they induce melanogenesis via bioactive mediators acting on histamine H2 receptors.[12] The role of mast cells in photoaging is further supported by experimental studies in UV-irradiated mice, in which ketotifen treatment reduced wrinkle formation, epidermal thinning, mast cell accumulation, and matrix degradation.[15] Although mast cell counts did not change in the present study, several histological markers of photoaging improved only in the TA/KET group, including reduced solar elastosis, restoration of basement membrane

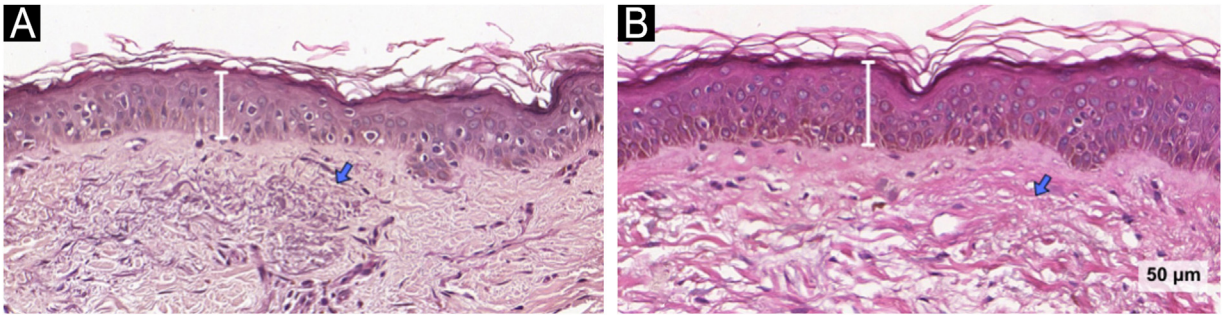

Fig. 5 Hematoxylin & eosin images of the TA/KET group: (A) before, (B) after. Bars indicate the increased epidermal thickness; arrows show reduced solar elastosis (Hematoxylin & eosin, ×40).

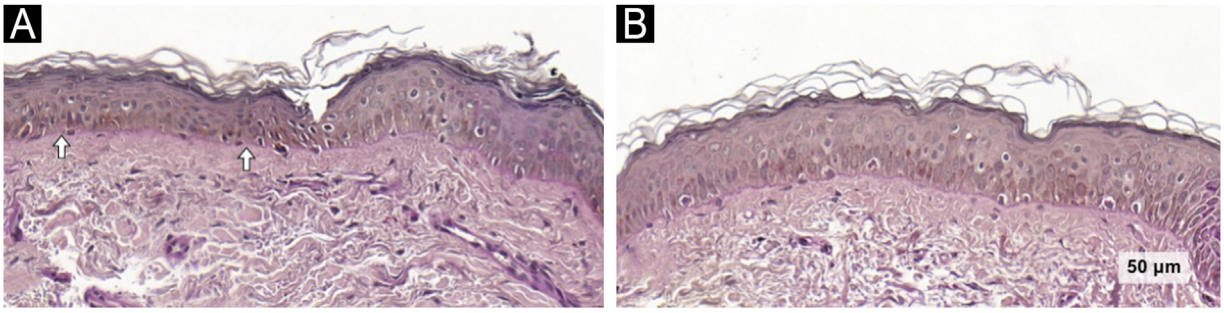

Fig. 6 PAS images of the TA/KET group: (A) before, (B) after. Arrows highlight areas of basement membrane discontinuity restored after treatment (40× magnification).

integrity, decreased pendulum melanocyte presence, and increased epidermal thickness.

The maintenance of dermal and epidermal homeostasis is critically dependent on the integrity of the basement membrane. In melasma, this structure is often disrupted, facilitating the diffusion of dermal cytokines into the epidermis, which enhances melanogenesis and supports melanocyte protrusion into the dermis. In addition, fibroblasts in the melasma dermis exhibit a senescent phenotype with impaired capacity for basement membrane repair.[37] In the present study, treatment with TA/KET led to a significant reduction in basement membrane disruptions, an effect not observed in the TA group.

In a cross-sectional study of 50 patients with facial melasma, epidermal atrophy was observed in 90% of lesions versus 28% of perilesional skin samples.[32] Similarly, the authors observed increased epidermal thickness after treatment in the TA/KET group. A recent study proposed that a thicker epidermis may enable a more uniform distribution of melanin, improving the absorption of solar radiation by photochromophores and reducing direct UV impact on melanocytes, thereby attenuating melanogenesis.[6]

Solar elastosis, a hallmark of chronic UV exposure, is more prevalent in melasma-affected skin compared to adjacent areas, reinforcing the hypothesis that photoaging contributes to melasma pathogenesis. UVB exposure stimulates keratinocytes to promote melanocyte proliferation via secretion of SCF, βFGF, and α-MSH.[5] In this trial, the reduction in solar elastosis observed in the TA/KET group suggests that ketotifen may exert a beneficial remodeling effect on the dermal matrix.

Melasma is associated with increased vascularity, which is not merely a consequence of UV damage but appears to play a central role in disease pathogenesis. VEGF, known to influence melanocyte activity through its receptor, is upregulated in melasma lesions.[38] In this study, however, VEGF expression did not decrease in either group, indicating that TA is ineffective to act in this aspect.

The stratum corneum in melasma is typically more compact, and improving its integrity can enhance protection against UV radiation. Treatments such as triple combination creams and procedures like chemical peels or lasers have demonstrated efficacy in reducing stratum corneum compaction.[4,34] In the present study, no significant changes in the stratum corneum were observed in either group, potentially due to the absence of adjunctive topical therapies or resurfacing interventions.

Finally, as melasma is a multifactorial condition involving multiple skin compartments and pathogenic pathways, the most effective interventions should target multiple fronts to restore skin homeostasis and promote long-lasting results. Mast cells can stimulate melanogenesis through the release of bioactive mediators acting on histamine H2 receptors. Ketotifen, a mast cell stabilizer, has demonstrated potential skin-rejuvenating effects, including increased epidermal thickness and reductions in solar elastosis, pendulum melanocytes, and basement membrane disruption. These results are consistent with previous studies showing ketotifen's ability to prevent UV-induced wrinkle formation in murine models and further support its potential to improve photoaging-related parameters in melasma-affected skin.[15]

Since the combination of oral TA/KET was not superior to oral TA alone in terms of clinimetric parameters,[17] this

association should be tested in clinical trials with different regimens before it can be recommended in clinical practice. Notably, the topical application of ketotifen remains largely unexplored, highlighting the need for future studies integrating it into combination treatment strategies.

Limitations

The use of 3 mm biopsies may not represent the whole melasma across the face. The relatively short duration of the trial may also have limited the observation of robust dermal remodulation despite the histopathological changes found. Ketotifen was not assessed without its combination with TA. Toluidine blue, while effective in detecting abundant mast cell populations, may compromise the sensitivity for precise quantification of sparse cells. PAS staining of the basement membrane may occasionally produce artifactual discontinuities, even when the membrane is structurally intact; however, it did not hinder the detection of changes.

Conclusion

In this trial, both interventions led to a reduction of epidermal melanin. The combination of KET with TA produced histopathological changes indicative of dermal and epidermal remodeling that surpassed those observed with TA alone, including increased epidermal thickness, reduced solar elastosis, fewer pendulum melanocytes, and improved basement membrane integrity, features associated with photoaging reversal and restoration of skin homeostasis. These findings suggest that targeting mast cell-mediated pathways may offer structural benefits beyond pigment reduction, potentially addressing deeper pathogenic components of melasma.

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Registration

This trial was registered on Plataforma Brazil (https://plataformabrasil.saude.gov.br) under the number CAAE 57773122.9.0000.5505.

This protocol was registered by the ReBEC platform (Brazilian registry of Clinical Trials) under the number ReBEC: RBR-10jn7f39.

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Authors' contributions

Ana Clara Ladeira Cruz: Participant recruitment and clinical assessment; analysis and interpretation of clinical and histopathological data; funding acquisition; manuscript drafting and critical revision; final approval of the manuscript.

Daniel Pinho Cassiano: Co-supervision; study conception and design; analysis and interpretation of clinical and histopathological data; funding acquisition; critical revision of the manuscript; final approval of the manuscript.

Hélio Amante Miot: Co-supervision; statistical analysis; critical revision of the manuscript; final approval of the manuscript.

Ana Cláudia Cavalcante Espósito: Critical revision of the manuscript; final approval of the manuscript.

Karime Hassun: Funding acquisition; Critical revision of the manuscript; final approval of the manuscript.

Mackerley Bleixuvehl de Brito: Clinical assessment of participants; final approval of the manuscript.

Milvia Maria Simões e Silva Enokihara: Histopathological analysis; final approval of the manuscript.

Maria Carolina Cavalcanti Lima Constantino: Histopathological processing; final approval of the manuscript.

Heitor Raia Bottura: Histopathological analysis; final approval of the manuscript.

Joaquim Soares de Almeida: Histopathological processing; final approval of the manuscript.

Ediléia Bagatin: Supervision; Critical revision of the manuscript; final approval of the manuscript.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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REVIEW

Complementary strategies in psoriasis – Non-pharmacological approaches for comprehensive management

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KEYWORDS
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Complementary therapies;
Diet, Mediterranean;
Exercise;
Psoriasis;
Vitamins

Abstract

Background: Psoriasis is a chronic immune-mediated inflammatory disease linked to systemic comorbidities such as obesity, diabetes, cardiovascular disease, and inflammatory bowel disease. Non-pharmacological interventions, such as dietary modifications, nutritional supplementation, exercise, and psychological interventions, have emerged as complementary therapies in the management of psoriasis.

Objectives: Review the current and recent evidence and the role of trace elements, vitamins, diet, exercise, and psychological interventions as complementary approaches in the management of patients with psoriasis.

Materials and methods: A narrative review was conducted, analyzing clinical trials, meta-analyses, and cohort studies from major databases.

Results: Trace elements such as zinc, copper, and selenium, and vitamins including D, E, B-complex, and A, play roles in oxidative stress modulation, immune regulation, and keratinocyte biology. However, the clinical efficacy of micronutrient supplementation remains uncertain due to inconsistent and conflicting findings. Dietary interventions, particularly Mediterranean diet adherence and weight loss through caloric restriction or bariatric surgery, have been associated with reductions in psoriasis severity, although clear clinical protocols are lacking. Aerobic exercise appears beneficial but is underutilized, partially due to psychological and disease-related barriers. Furthermore, psoriasis is associated with a high prevalence of psychological disorders, with the necessity to integrate psychological interventions to optimize disease management.

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Study limitations: The available evidence is limited and with heterogeneity in study design, with small sample sizes, observational methodologies, and inconsistent intervention protocols, restricting causal inference and generalizability.
Conclusion: While non-pharmacological strategies show promise as complementary interventions in psoriasis management, they cannot replace conventional therapy. Further studies are required to confirm their clinical impact. These approaches should be considered as complementary strategies, with individualized patient assessments and continuous follow-up being essential.

Introduction

Psoriasis is a chronic inflammatory disease of immunological origin, characterized by excessive activation of the Tumor Necrosis Factor-alpha (TNF-α)/Interleukin (IL)-23/IL-17 axis, leading to hyperproliferation and abnormal differentiation of epidermal keratinocytes. This condition is frequently associated with various comorbidities, including obesity, diabetes mellitus, dyslipidemia, cardiovascular diseases, and inflammatory bowel disease.[1] Patients with psoriasis often exhibit unbalanced dietary habits, with high-fat intake and low fiber consumption. In recent years, nutrition has been shown to play a key role in the development and progression of psoriatic disease, as well as in its associated comorbidities. This has led to a growing interest in the scientific literature regarding the use of nutritional supplements, such as trace elements and vitamins, in the treatment of psoriasis.[2] On the other hand, exercise also influences chronic inflammatory diseases, including psoriasis. Likewise, the presence of this disease can impact patients' physical activity levels. Regular moderate to vigorous exercise has been found to be an independent preventive factor in reducing the risk of developing psoriasis. Moreover, in overweight patients, physical activity aimed at weight loss may improve disease severity. However, this population tends to be more sedentary and faces multiple barriers to engaging in exercise.[3] Psoriasis is not merely a dermatological condition; it significantly impacts patients' quality of life and mental health. Patients with psoriasis are 1.5 times more likely to present a mental illness, also a 12.7% can have suicidal ideations.[4] Integrating cognitive-behavioral therapy, support groups, or other psychological interventions is also essential for a comprehensive disease management approach. In this study, the authors explore the impact of some of the most relevant nutrients in psoriasis, as well as the role of diet, exercise, and the evaluation of psychiatric conditions in its management and progression.

Materials and methods

This study is a narrative review evaluating the role of trace elements, vitamins, diet, exercise, and psychological interventions in psoriasis pathophysiology and management. A systematic search was conducted in PubMed, Scopus, Web of Science, and Google Scholar databases, between March and April of 2025. Search terms included ''Psoriasis AND trace elements (Zinc, Copper, Selenium)''; ''Psoriasis AND vitamins (Vitamin D, Vitamin E, Vitamin A, Vitamin B complex)''; ''Psoriasis AND diet (Mediterranean diet, Caloric restriction, Micronutrient deficiencies)''; ''Psoriasis AND exercise (Physical activity, Weight loss, Obesity, Inflammation)''; ''Psoriasis AND bariatric surgery''; ''Psoriasis AND psychological disorders (Depression, Anxiety, Quality of life)''. Only studies published in English and Spanish were included.

Results

Psoriasis and trace elements

Zinc and copper

Zinc (Zn) is an essential cofactor in the catalytic activity of over 200 enzymes, playing a crucial role in immune function, wound healing, protein synthesis, DNA synthesis, and cell division.[5] It acts as a coenzyme for DNA and RNA polymerases and is important in the hyperproliferation of keratinocytes observed in psoriasis skin, resulting in higher Zn consumption secondary to this accelerated cellular turnover in psoriasis, which may lead to a reduction in serum levels.[6] Conversely, Zn deficiency can lead to decreased enzymatic activity of key antioxidants and immune cell dysfunction, thereby increasing susceptibility to viral and bacterial infections that can exacerbate skin inflammation and trigger psoriatic lesions.[7] Copper (Cu) is another essential trace element with redox properties that make it both physiologically beneficial and potentially cytotoxic.[8] In serum, Cu primarily binds to α2-globulin to form ceruloplasmin, a major antioxidant protein involved in scavenging excess free radicals.[7] Elevated serum Cu levels observed in patients with psoriasis may reflect an upregulation of ceruloplasmin in response to the OS caused by the chronic inflammation in psoriasis. However, free Cu can catalyze the formation of Reactive Oxygen Species (ROS), such as superoxide anions (O_2-), Hydrogen peroxide (H_2O_2), and Hydroxyl radicals (OH-) through the Fenton reaction, and contribute to cellular damage and inflammation.[9] A 2021 case-control study involving 72 patients with psoriasis, categorized by Psoriasis Area and Severity Index (PASI) score (Group T1: PASI < 10, mild psoriasis; Group T2: PASI > 10, severe psoriasis), reported that serum Cu levels and the Cu/Zn ratio in psoriatic patients compared to healthy controls were significantly higher.[10] The serum Zn levels were not significantly different between the two groups, suggesting that the increase in the Cu/Zn ratio may be attributable to the increase in Cu rather than decreased Zn levels. A meta-analysis conducted between 1988 and 2016 supports these findings, with studies comparing serum Cu and Zn

levels between psoriasis patients and healthy controls, and they observed elevated serum Cu levels and reduced serum Zn levels in patients with psoriasis.[7] Moreover, research in patients with psoriatic arthritis has indicated that elevated Cu and reduced Zn levels may contribute to disease pathogenesis. Interestingly, one proposed mechanism underlying the therapeutic efficacy of methotrexate in psoriatic arthritis is its ability to increase serum Zn and reduce serum Cu concentrations.[11] In summary, although alterations in Zn and Cu levels are consistently observed in psoriatic and psoriatic arthritis, the clinical relevance of these findings and their potential utility as therapeutic targets remain unclear and require further investigation.

Selenium

Selenium (Se) is an essential element with antiproliferative and immunoregulatory properties. It has been proposed that Se contributes to psoriasis improvement by mitigating the OS, potentially through the upregulation of catalase and superoxide dismutase activity via its antioxidant effects.[12] Another hypothesis suggests that Se regulates immune processes in psoriasis, modulating cytokine expression, expressing inhibitory effects on TNF-α levels and promoting an increase in CD4+ T-cells populations in the reticular dermis of psoriatic lesions.[13–16] Several studies have investigated the relationship between Se levels and psoriasis severity. A 2002 study reported an inverse correlation between serum Se levels and psoriasis severity.[14] A double-blind, placebo-controlled clinical trial comparing the effects of a combination therapy of Se aspartate, coenzyme Q10, and vitamin E versus placebo demonstrated significant improvement in PASI and Severity Score (SS) in patients with severe erythrodermic and arthropathic psoriasis.[15] Consistent with these findings, other studies have observed that serum Se levels in patients with psoriasis tend to be lower compared to healthy controls, suggesting a possible link between Se deficiency, OS, and altered immune responses in the disease's pathogenesis.[16,17] However, evidence regarding the therapeutic efficacy of Se supplementation remains inconsistent. In a double-blind parallel-group study no added benefit of Se supplementation when its combined with narrowband UVB (NB-UVB) phototherapy compared to NB-UVB with placebo.[18] Additionally, a case-control study conducted on hospitalized patients between January and June 2002, reported that selenomethionine supplementation was ineffective as an adjunct treatment for plaque psoriasis, and Se supplementation might contribute to sustained elevations in soluble TNF-α type 1 receptor in psoriasis patients, even after lesion remission.[19] A 2012 meta-analysis reinforced these mixed findings, with no statistically significant differences in serum Se levels between psoriasis patients and controls.[20] In summary, the role of Se in psoriasis appears to be multifactorial, involving potential contributions to OS regulation, cytokine modulation, and immune system balance. Despite evidence supporting an association between low Se levels and disease severity, current data on its therapeutic application remain inconclusive. Further high-quality, controlled studies are necessary to clarify the mechanistic and clinical significance of Se in psoriasis management.

Psoriasis and vitamins

Vitamin D

Vitamin D (VD) plays a critical role in calcium-phosphorus homeostasis. Its prolonged deficiency leads to rickets in children and osteomalacia in adults. Beyond its skeletal effects, VD presents immunomodulatory functions, influencing both innate and adaptive immune responses.[21] Given its role in immune regulation and skin homeostasis, the association between VD status and psoriasis has been extensively investigated.[22–26] Multiple studies have reported that patients with psoriasis present lower serum concentration of 25-Hydroxyvitamin D (25(OH)D) compared to healthy controls, suggesting a potential contributory role of VD deficiency in psoriasis pathogenesis.[23] However, interventional trials have yielded mixed results. Some randomized clinical trials evaluating oral VD supplementation have not demonstrated significant improvements in PASI scores, indicating that VD supplementation alone may not suffice to induce clinical remission.[24] Similarly, a study examining seasonal VD supplementation during winter failed to show significant changes in disease severity between treated and placebo groups.[25] An interventional cohort study evaluating NB-UVB therapy provides evidence that NB-UVB therapy can reduce VD-Binding Protein (DBP) and high-sensitivity C-Reactive Protein (hs-CRP) levels while increasing serum VD levels in psoriasis patients.[26] This suggests a potential systemic anti-inflammatory effect of phototherapy, particularly in VD-deficient patients. It has also been proposed that VD derivatives may enhance phototherapy efficacy in psoriasis without causing adverse side effects.[22,26] Additionally, a Mendelian randomization analysis has suggested a potential protective effect of higher VD levels against psoriasis development, although further studies are needed to confirm this relationship.[27] In summary, while VD appears to play a role in the pathogenesis and treatment response of psoriasis, current evidence does not support its routine use as a monotherapy. Regular monitoring of VD levels in psoriasis patients is advisable, and supplementation should be considered in individuals with confirmed deficiency.

Vitamin E

Vitamin E (VE) is a lipophilic antioxidant that protects cellular membranes from oxidative damage, which has been implicated in the pathogenesis of inflammatory skin diseases, including psoriasis.[28] The relationship between VE and psoriasis has been explored in multiple studies. A meta-analysis demonstrated that serum VE levels are lower in psoriasis patients compared to healthy controls, suggesting that VE deficiency may predispose individuals to developing this immune-mediated disease.[29] Supporting this finding, a cross-sectional study based on data from the National Health and Nutrition Examination Survey (NHANES) found that higher dietary intakes of VE were inversely associated with the risk of psoriasis.[30] It has also been found that VE supplementation, in combination with other antioxidants such as coenzyme Q10 and Se, has improved clinical conditions in patients with severe forms of psoriasis, such as psoriatic arthritis and erythrodermic psoriasis.[31] In conclusion, although current evidence indicates a potentially beneficial role of VE in psoriasis prevention and symptom modulation,

additional high-quality clinical trials are required to establish its efficacy and determine optimal dosing strategies. At present, VE may be considered as part of a comprehensive dietary and lifestyle approach to psoriasis management, rather than as a standalone therapeutic intervention.

Vitamin B

Cobalamin (vitamin B12) and folic acid (vitamin B9) have been implicated in the pathophysiology of psoriasis through their role in homocysteine metabolism. Hyperhomocysteinemia in these patients has been related to VB9 and VB12 deficiency,[32,33] and with immunoinflammatory processes by activation of Th1 and Th17 lymphocytes and suppressing T-reg cells.[34] A meta-analysis found that psoriasis patients exhibit higher homocysteine levels and a greater prevalence of hyperhomocysteinemia compared to controls; however, no significant differences in serum levels of VB12 were detected between the two groups.[32] In contrast, another study reports a direct correlation between homocysteine levels and psoriasis severity, and an inverse relationship with folic acid levels.[35] In a study of 98 psoriasis patients and 98 controls, which found that 57% of psoriasis patients had elevated homocysteine levels compared to 25% in controls ($p < 0.0001$). These patients also had significantly lower serum vitamin B12 levels, though no direct association with PASI was observed.[36] Regarding vitamin B6, alterations in its metabolism have been suggested to influence skin inflammation, though further studies are required to confirm these findings.[37] In summary, there is growing evidence supporting a connection between altered homocysteine metabolism and psoriasis, possibly mediated by deficiencies in VB9 and VB12. These alterations may contribute to both disease pathogenesis and its associated cardiovascular risks. While current findings highlight the potential value of assessing homocysteine and B-vitamin levels in psoriasis patients, more robust clinical trials are necessary before clear supplementation guidelines can be established.

Vitamin A

Vitamin A (VA) and its metabolites – such as retinoic acid and synthetic retinoid derivatives – have been used in the management of psoriasis with variable therapeutic outcomes. Retinoids influence keratinocyte proliferation, differentiation, and keratinization, processes that are dysregulated in psoriasis[38]; VA is critical for maintaining epithelial integrity and modulating immune responses. The metabolism of VA is correlated to the CYP1A1 gene. A study comparing 45 psoriasis patients and 45 healthy controls analyzed the CYP1A1 polymorphism (rs1048943) and serum VA levels. The AG genotype was found exclusively in psoriasis patients (22.2%, $p = 0.001$) and was associated with lower VA concentrations. Additionally, psoriasis patients had significantly reduced VA levels compared to controls ($p < 0.001$), suggesting that the CYP1A1 gene and VA deficiency may contribute to disease susceptibility and severity.[39] Controversy a NHANES analysis in the United States found that psoriasis patients had higher serum VA levels compared to healthy controls, suggesting a possible association between elevated VA levels and psoriasis.[40] However, these findings are inconsistent and require further investigation to determine the direction and implications of this association. Retinoic acid has anti-inflammatory and immunoregulatory properties, which could improve clinical psoriasis lesions. And it exhibits fungistatic effects, which are particularly relevant for psoriasis patients undergoing IL-17 inhibitor therapy, as such biologics may increase the risk of fungal infections.[41] Topical formulations may offer a more favorable safety profile when combined with corticosteroids. Systemic retinoids, such as acitretin, have shown benefits in erythrodermic or pustular psoriasis, and have been used as an adjuvant treatment for generalized psoriasis to enhance the effects of anthralin, PUVA, or UVB therapy.[38] In summary, although vitamin A derivatives have shown therapeutic potential in psoriasis by targeting keratinocyte function and inflammation, their clinical application is constrained by dose-dependent toxicity and variable patient response. The relationship between vitamin A levels, genetic polymorphisms, and psoriasis pathogenesis remains incompletely understood and warrants further research. Currently, VA supplementation is not recommended as a standalone treatment, but retinoids may have a role in select clinical scenarios.

Psoriasis and exercise

Physical activity plays a crucial role in the prevention and management of chronic diseases, including inflammatory disorders, cardiovascular diseases, obesity, and metabolic syndrome.[42] Psoriasis is associated with these comorbidities, and both obesity and physical inactivity are recognized as significant risk factors for its development. Therefore, moderate-intensity exercise has been proposed as a complementary treatment for psoriasis patients.[43] The American Heart Association (AHA) recommend in all adults aged 18–65 years take part in moderate-intensity aerobic physical activity for a minimum of 30 minutes on 5-days each week, or vigorous-intensity aerobic physical activity a minimum of 20-minutes on 3-days each week.[44] The HUNT study evaluated the relationship between the Body Mass Index (BMI), waist circumference, waist-to-hip ratio, and 10-year weight changes on psoriasis risk. The study found a significant association between an increase in body weight and psoriasis risk, particularly in individuals who gained 10 kg or more during the follow-up period. These findings highlight weight control as a potential preventive strategy for psoriasis.[45] It has been demonstrated that increased adipose tissue affects levels of inflammatory cytokines involved in psoriasis, such as TNF-α and IL-17. Since obesity is a risk factor for developing or worsening psoriasis, physical activity may have a protective role against the disease.[46] A randomized clinical trial by Naldi et al. evaluated the impact of exercise in psoriasis patients with PASI > 10 and overweight or obesity. The study included 303 patients who performed aerobic exercise for at least 40-minutes, three times per week, for 20-weeks, aiming for a 5% weight reduction. The exercise group experienced a 48% PASI reduction, while the control group showed a 25.5% PASI reduction ($p = 0.02$).[47] A recent systematic review examined the role of physical activity in preventing and treating patients with psoriasis. The findings suggest that engaging in moderate intensity exercise can lead to improved antioxidant gene expression, reduced oxidative stress, higher levels of sex hormone-binding globulin, and lower levels of Insulin-like Growth Factor 1 (IGF-1),

along with a decrease in adipose tissue mass. These changes in metabolism and hormones help lower insulin and leptin levels, boost adiponectin levels, and ultimately reduce systemic inflammation.[48] A 2022 systematic review suggested that the beneficial effects of exercise on psoriasis may be mediated, in part, through adipose tissue reduction. However, psoriasis patients often report reduced physical activity levels, attributed to disease-related limitations such as skin discomfort, pain, or social stigma.[45] In another study that evaluated the barriers to physical activity in patients with chronic psoriasis, found that 53% of patients aged 18–65, and 66% of those over 65, did not meet recommended physical activity levels for cardiovascular health, the main key barriers were skin sensitivity and discomfort during exercise, embarrassment about the appearance of their skin, limitations in clothing choices (such as avoiding sportswear that exposes affected areas), and the impact of treatments interfering with exercise routines. The study also showed that greater disease severity and poorer dermatology-related quality of life (measured by the DLQI) were linked to lower physical activity levels, particularly in women aged 18–65.[49] In summary, physical activity may play a dual role in both psoriasis prevention and symptom improvement, particularly among overweight or obese individuals. It should be considered as a complementary, non-pharmacological strategy within a multidisciplinary treatment approach. Also, healthcare professionals need to recognize and address the specific barriers that can restrict psoriasis patients from engaging in physical activity. Tailored interventions that accommodate the unique challenges faced by individuals with psoriasis are recommended to promote healthier, more active lifestyles.

Psoriasis and diet

The role of diet as a treatment for psoriasis has been evaluated in several studies, showing that a dietary intervention can reduce systemic inflammation through the intake of antioxidant and anti-inflammatory nutrients.[50] The current Western diet is considered pro-inflammatory, being rich in omega-6 fatty acids, high-calorie intake, and trans fats, and it may exacerbate immune dysregulation in psoriasis.[51] In contrast, nutritional strategies that promote immune homeostasis, particularly the Mediterranean diet, rich in vegetables, fruits, whole grains, and healthy fats, have been associated with reduced incidence of metabolic and inflammatory disease and may offer a protective effect in psoriasis.[52] Calorie-restricted diets have been shown to slightly reduce PASI scores and improve the quality of life in affected individuals.[53] Furthermore, diets high in fiber, vitamins, and polyphenols have demonstrated anti-inflammatory properties and may positively influence the gut microbiota, a factor increasingly recognized in psoriasis pathophysiology.[53–55] A comparative study of 45 psoriasis patients with 43 controls, revealing that psoriasis patients had higher BMI, LDL cholesterol, and total cholesterol levels, but lower HDL cholesterol levels. Additionally, they consumed more carbohydrates and fats, but less fiber, folate, and VE. These findings suggest that nutritional imbalances and dyslipidemia may contribute to disease severity, reinforcing the importance of targeted dietary counseling in psoriasis management.[56] A meta-analysis found that weight loss through lifestyle interventions significantly improved psoriasis compared to control group interventions. Consequently, it has been suggested that, in combination with conventional therapy, an appropriate diet should be implemented to enhance clinical responses in psoriasis and reduce comorbidities.[57]

Psoriasis and bariatric surgery

Bariatric surgeries, including procedures such as sleeve gastrectomy and gastric bypass, have emerged as a potential complementary therapy in obese psoriasis patients. A recent observational study of 32 patients undergoing bariatric surgery reported a significant reduction in PASI score after the surgical intervention.[58] In another study involving 10 obese psoriasis patients, 70% remained in remission for at least six months following surgery, and three out of four patients on systemic therapy discontinued medication due to significant improvement. Improvements in quality of life and reduction in cardiovascular risk factors were also observed.[59] However, bariatric surgery is associated with an increased risk of micronutrient deficiencies, including VD, VB12, iron, calcium, Se, Zn, among others, due to altered nutrient absorption post-surgery.[60–63] These deficiencies can lead to anemia, osteoporosis, neurological complications, and potentially exacerbate psoriasis symptoms. For example, selenium deficiency has been linked to muscle weakness, cardiomyopathy, and psoriasis flares.[63,64] Despite the widespread use of multivitamin and mineral supplements, nutrient deficiencies persist in a considerable percentage of patients, highlighting the need for continuous evaluation.[63,65] In conclusion, weight reduction strategies, including diet and bariatric surgery, may offer substantial benefits in psoriasis – particularly among obese patients. Nevertheless, these interventions require careful patient selection and a comprehensive risk-benefit evaluation, given the potential for long-term metabolic and nutritional complications.

Psoriasis and mental health

It's clear that psoriasis is associated impacts in patients' quality of life and mental health. The presence of depression, anxiety, and social stigma is well-documented in psoriasis patients. In a systematic review of anxiety disorders in patients with psoriasis was 7%–48%.[66] In the case of depression, the prevalence is estimated to 20%–30%.[67] The association with other psychiatric conditions has been described, such as schizophrenia, bipolar disorder, and post-traumatic stress disorder.[4] The suicidal ideation in patients with psoriasis has been reported in a 12.7% of the patients.[68] The higher presence of proinflammatory markers has been correlated with elevated risk of depression, anxiety, and schizophrenia in patients with psoriasis, suggesting a nexus with the neuroinflammatory pathways and the severity of lesions in the skin.[69] In the other hand, social stigma affects patients with psoriasis, potentially leading to worsened symptoms or difficulty engaging in physical activity.[70,71] In patients with psoriasis, a screening for depression, anxiety, and suicidality should be made, and the evaluation of

other psychiatric conditions. Addressing stress, depression, or anxiety can improve the overall health and quality of life of patients, reducing the severity of skin lesion, the consideration of behavioral interventions or Cognitive-Behavioral Therapy (CBT) might aid in improving adherence to dietary changes and exercise programs.

Discussion

Psoriasis is an immune-mediated inflammatory chronic disease caused by a complex interplay of genetic, environmental, and lifestyle factors.[1] Emerging evidence highlights the role of nutrition, physical activity, and specific micronutrients in modulating the disease course and associated comorbidities.[31]

For instance, Se shows potential due to its antioxidant and immunoregulatory functions; studies report inconsistent outcomes, with some suggesting clinical improvements and others finding no significant effect.[20] VD deficiency is frequent in psoriasis patients, yet supplementation alone has not consistently translated into clinical improvement, possibly due to differences in baseline levels, dosing, or concurrent therapies.[27] Similar ambiguities surround VE, with a lack of definitive evidence for its use as a monotherapy. The relationship between elevated homocysteine and psoriasis implicates deficiencies in vitamin B12 and folic acid. Although some studies demonstrate correlations with disease severity and cardiovascular risk, direct benefits from supplementation remain uncertain.[32,33] Vitamin A and its derivatives have shown efficacy in certain psoriasis subtypes but are limited by their toxicity profiles. Genetic polymorphisms influencing VA metabolism may further affect individual responses.[39] Exercise and dietary interventions offer promising adjunctive benefits. Structured aerobic exercise has demonstrated improvements in PASI scores and metabolic parameters,[47] yet patient adherence may be hindered by disease-related physical or psychological barriers.[49] Similarly, while anti-inflammatory diets – particularly the Mediterranean diet – are associated with symptom improvement, adherence and long-term outcomes require further validation.[52] Caloric restriction and nutrient-rich diets improve quality of life and inflammation, but need standardization in clinical recommendations. Bariatric surgery provides significant benefits for obese psoriasis patients, including symptom remission and medication reduction. However, the procedure is associated with long-term micronutrient deficiencies (e.g., VD, Se, B12), necessitating careful post-operative monitoring.[62,63] The limited sample sizes and observational nature of current studies also limit the strength of conclusions. Psoriasis significantly impacts mental health, with a high prevalence of anxiety, depression, and even suicidal ideation.[4] It is also associated with other psychiatric disorders and inflammatory processes.[69] Additionally, social stigma can worsen symptoms. Therefore, psychological support and interventions like cognitive-behavioral therapy are essential.

Despite promising associations, several limitations constrain the current body of research. Firstly, many studies cited are observational or cross-sectional, which limits causal inference. Randomized controlled trials remain scarce or yield mixed results, particularly for micronutrient supplementation. Variability in study design, sample sizes, disease severity, and intervention protocols further complicates data interpretation. Additionally, heterogeneity in patient populations, such as age, BMI, comorbidities, and baseline nutrient levels, affects generalizability. Confounding factors such as medication use, dietary patterns, and lifestyle behaviors are often inadequately controlled. Future research should prioritize randomized controlled trials, standardized protocols for dietary, exercise, and psychological interventions, and integration of psychosocial support into psoriasis management strategies.

In summary, while the role of nutrition and lifestyle in psoriasis management is gaining recognition, the current evidence is insufficient to establish universal clinical guidelines. Individualized strategies focusing on weight management, balanced nutrition, and regular moderate-intensity physical activity hold promise in enhancing treatment outcomes and quality of life for patients with psoriasis.

Conclusion

There is evidence suggesting an interaction between trace elements, vitamins, diet, exercise, and psychological support with psoriasis. This information offers promising complementary strategies for psoriasis management. However, given the variability and inconsistency of the current evidence, these approaches should not substitute for established treatments. Further studies and research are needed to clarify these relationships and aim to develop clear clinical guidelines and integrate psychological considerations to optimize outcomes in psoriasis patients.

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Authors' contributions

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Conflicts of interest

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REVIEW

How to minimize pain with local anesthesia and improve patient experiences: a review

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Abstract
Background: Local anesthesia is essential in common procedures in dermatology, but injection and infiltration of anesthetic often cause significant pain, reducing patient comfort and satisfaction.
Objective: To review evidence-based techniques to reduce pain associated with local anesthetic injection and infiltration.
Methods and materials: A narrative review of the literature was performed, and techniques were summarized for clinicians to reference.
Results: Technical methods to reduce pain include using smaller-gauge needles (30–33G), smaller syringes (1–3 mL), buffering lidocaine with sodium bicarbonate, inserting the needle at 90 degrees, slow infusion, subcutaneous delivery, and pore-guided injection. Adjuncts such as warming anesthetic, vibration, ice, music, and verbal distraction (''talkesthesia'') also reduce patient perception of pain.
Study limitations: Limitations include heterogeneity in study designs, outcomes measures, and clinical contexts across the included literature, precluding quantitative synthesis or direct comparison of individual techniques. Additionally, several recommendations are based on expert opinion or limited evidence.

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Conclusion: A multimodal approach using both technical refinements and adjunctive measures can make local anesthetic administration less painful. Dermatologists may routinely implement these strategies to improve patient experience and satisfaction.

Introduction

Local anesthesia is ubiquitous in medical practice, commonly used for a wide range of procedures, including biopsies, cauterization, excision, and surgical wound reconstruction.[1] The injection of local anesthetic is often considered the most painful aspect of these procedures and optimizing injection technique is essential for surgeons to ensure patient comfort and safety.[2] Moreover, minimizing patient discomfort during the injection of local anesthesia has been shown in the literature to deliver positive patient-reported outcomes.[3]

Patients are often warned about the two sources of discomfort associated with local anesthetic infiltration. The first source of discomfort is caused by a needle penetrating the skin, which provokes a sharp, brief pain. The second source of discomfort is through infiltration of the solution, which activates cutaneous nociceptors through both mechanical stretching of the tissues and exposure to the anesthetic's acidic pH.

Fortunately, there are proven strategies to make local anesthesia nearly painless. The purpose of this article is to gather, discuss, and illustrate techniques in reducing pain with local anesthesia and to encourage their routine adoption with a focus on patient comfort and excellence in care.

Preparation for injection

Needle gauge

Smaller needles (larger gauges) are associated with significantly decreased intensity of pain during insertion.[4] This has been confirmed by several studies in the literature as these smaller needles require less force to penetrate the skin, come into contact with fewer nociceptors, and decrease the rate of anesthetic injection.[5,6] Additionally, the smaller diameter also allows for easier penetration in areas of increased skin thickness, such as the palm of the hand or the sole of the foot.[3] These findings are consistent with clinical practice, where smaller-gauge needles are preferred for procedures requiring superficial injections, such as those on the face, due to the decreased pain. A recommendation from the authors for anesthesia on the face includes the use of a 30G or 33G needle due to greater precision and less discomfort during application, especially in more sensitive areas.

Syringe size

The intensity of pain during the injection of local anesthetic is also influenced by syringe size, even when needle sizes remain constant.[7,8] It is hypothesized that smaller syringes (1 mL) are associated with less pain, likely because they require less mechanical force to inject the anesthetic and allow for a smoother, controlled infiltration of fluid into the tissues. This is exemplified by a ''split-scalp'' study of 20 patients undergoing hair restoration surgery. Lidocaine with epinephrine (1:100,000) was delivered using a 30G needle with either a 1 mL or 3 mL syringe. The results showed that 1 mL syringes caused significantly less pain than the 3 mL syringes.[7] A recommendation from the authors is to start with 1 mL syringe and transition to a 3 mL syringe to optimize efficiency without compromising patient comfort. If more control is required in the hands of the injector, consider filling the 1 mL syringe halfway. In anatomically sensitive regions, including the nasal tip and perioral area of patients, the 1 mL syringe can be used alone.

Buffering

Buffering of lidocaine with sodium bicarbonate has been shown to reduce the burning pain associated with infiltration through increasing the pH of the acidic anesthetic formulations. Studies have shown that a 1:10 ratio of 8.4% sodium bicarbonate to 1% lidocaine with 1:100,000 epinephrine effectively minimizes discomfort without compromising anesthetic efficacy.[6,9] As stated in the joint position statement by the American Academy of Dermatology (AAD), American College of Mohs Surgery, American Society For Dermatologic Surgery, and American Society For Mohs Surgery it is recommended that physicians and their clinic staff meet or exceed the safety standards of the U.S. Pharmacopeial Convention and the FDA Insanitary Conditions Guidance as buffering is subject to compounding regulations at the federal level and possibly the state level.[10] Furthermore, buffered lidocaine begins to lose its vasoconstrictive efficacy after seven days and should be administered by then, with appropriate labelling with expiration dates.[11,12]

Injection technique

Needle insertion angle

When the needle is inserted into the skin, nociceptors in the dermis are directly activated.[5,6] By penetrating the skin at a 90-degree angle as compared to a 45-degree angle, the needle passes through fewer nociceptors and thus causes less pain.[13] In a clinical trial comparing pain during application of infiltrative local anesthesia using lidocaine, there was a statistically significant difference in pain levels between needle insertion angles. Injections performed at 90-degrees had a median pain level of 2.0 (IQR 2.0–3.0) vs. injections performed at 45-degrees had a median pain level of 3.0 (IQR 2.0–4.0, $p = 0.002$). Furthermore, patients independently

reported that the 45-degree injection was more painful than the 90-degree injection. These results indicate that the 90-degree insertion angle provides a less painful experience to patients.[14] It is important to note that once the needle has been inserted and a small amount of local anesthesia has been injected, the needle can be ''reangulated'' so that the local anesthesia can be better dispersed throughout the surrounding area or ''walked''. The authors recommend that when inserting at 90 degrees is not feasible or is suboptimal, such as in the case of eyelid skin, fine motor control with counter tension applied with the opposite hand and injection at an angle would be appropriate. Injection at an angle may allow better support and stability in these specific cases due to better hand positioning, and allows clinicians to ''walk'' the anesthesia in the direction they wish.

Rate of anesthetic infusion

Another factor influencing pain during infiltration of an anesthetic is the activation of nociceptors responding to rapid tissue stretch and distention.[3] By reducing the rate of injection, an anesthetic has the ability to diffuse and block nerve transduction of stimulated fibers, functionally eliminating ''the burn'' classically associated with local anesthesia.[3,6,8,15–18] Furthermore, rapid injection has been associated with increased levels of pain with injection and consequently decreased patient satisfaction with their procedure.[19,20] A recommendation from the authors is that slow infusion of anesthetic is a major contributor to reducing pain when injecting local anesthesia. Furthermore, a recommendation from the authors is to meticulously clear the syringe and syringe of any air and depress the plunger while advancing the needle into the skin, as the local anesthetic would then be injected the instant the entire opening of the needle is below the skin surface.

Injection plane

When considering injection depth, subcutaneous injections cause less pain than intradermal injections while achieving the same end-goal analgesic effect.[6] However, intradermal injections induce anesthesia more quickly than subcutaneous injections. As such, it may be appropriate to raise an intradermal wheal, withdraw, then reintroduce the needle at the numbed site toward the subcutaneous plane (Fig. 1). By withdrawing and reintroducing the needle through the intradermal wheal, it is possible to substantially reduce a patient's burden of pain from needle sticks.[3,13] Furthermore, subcutaneous injections also treat the nerve roots supplying the dermis, providing analgesia without having to anesthetize the dermal layer specifically, which would cause a patient much more pain.[6] It is notable that these larger nerve roots take a longer time to numb.

Injection volume

Anesthetic should be administered with an endpoint of forming visible edema in the procedural area. No robust comparative studies between volumes of anesthetics have been published so far in the literature. Larger volumes have been observed to virtually eliminate the risk of pain during interventions and studies observing peak serum concentrations of lidocaine during Mohs micrographic surgery show safety and efficacy in large volumes during the procedure.[18] Furthermore, increased volumes in the procedural area contribute to mechanical vasoconstriction, which helps control bleeding (Fig. 2). It is paramount to highlight that anesthetic should be applied to areas that also extend beyond incision

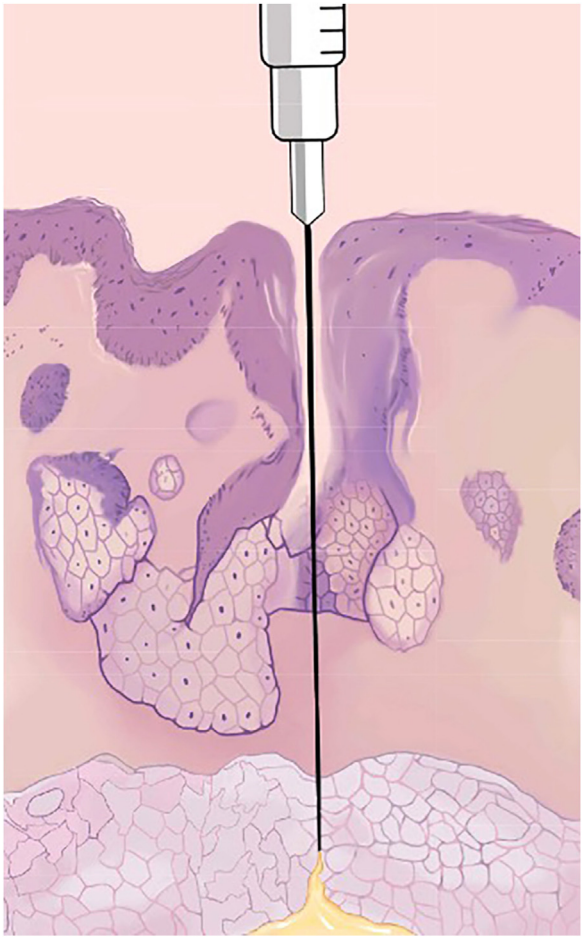

Figure 1 Injection plane and pore-guided injection.

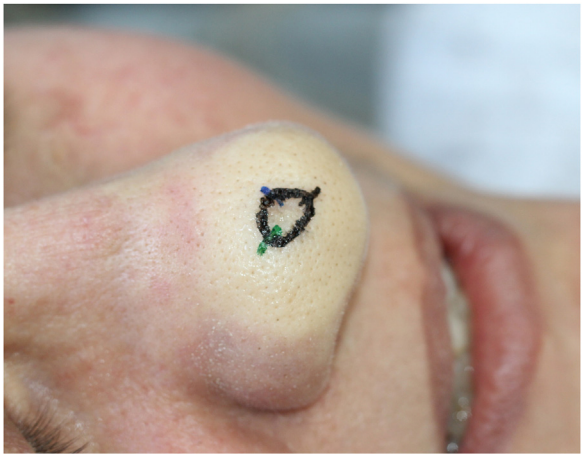

Figure 2 Edema endpoint.

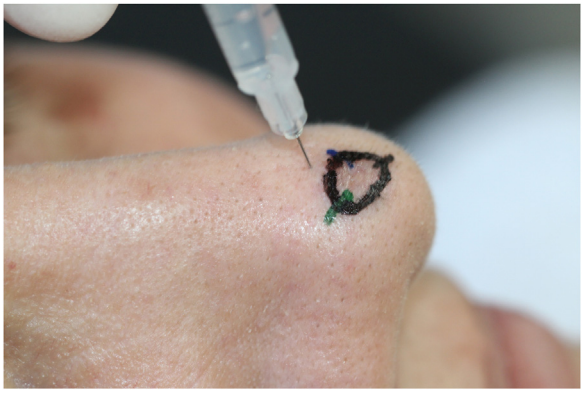

Figure 3 Needle Insertion Angle. It is recommended to first inject the proximal part of the nasal tip because it will ''block'' the distal portion.

margins, since undermining, sutures, and the use of thermal cautery can cause pain in adjacent regions.

Use of warmed solution

A systematic review and meta-analysis demonstrated that solutions warmed to 37 °C have been shown to reduce pain levels during the administration of local anesthesia compared to non-warmed solutions.[21–23] Furthermore, studies using warmed tumescent solutions have also shown a significant reduction in pain compared to room-temperature solutions.[24,25]

''Pore-guided'' injection

A recommendation from the authors is to consider introducing the needle through a pore, which acts as an isolated tunnel or portal ''shortcut'' for the needle (Fig. 3).[41] By doing this, it is possible to reach deeper planes with less trauma in the dermal layers, especially in the reticular dermis, which hosts more sensitive structures. However, systematic reviews and further studies to robustly prove the efficacy of this technique are lacking.

''Walking''

The authors recommend that when numbing a larger area, after the initial syringe is used, insert subsequent needles at the margin of the already numbed area so the patient does not feel each poke. Furthermore, angling the needle toward the margin and allowing the fluid wave to move forward advances the anesthetized area while causing less discomfort to the patient. Examples of utility for this technique include numbing the tarsal plate or the palmar surface of the fingertip. For the tarsal plate, inject the eyelid and allow the fluid wave to infiltrate and numb the tarsus. Similarly, start with the thinner skin on the lateral or dorsal finger and ''walk'' the anesthetic to the palmar surface. In the experience of the authors, on the nose, areas with subcutaneous adiposity are easier to start with and less painful for patients. Therefore, if the surgical site is near an area with subcutaneous adiposity, start within the adiposity and ''walk'' the anesthesia to the target site.

Adjunct tools

Background music

Various articles in the literature have studied background music and its beneficial effects on pain associated with local anesthesia. Evidence is varied and depends on the specific clinical context, but most notably, a clinical trial studying the intervention of classical music vs silence during anesthetic injection showed significantly decreased pain and anxiety scores after exposure to classical music.[26] This study is limited in its subjectivity, but as pain is a subjective measure, this study points to music as a simple, safe, and effective intervention in surgical practice.

Cooling the skin

Cooling the skin prior to infiltration of local anesthetic has been shown to significantly reduce pain related to the procedure.[27] A randomized controlled study evaluated the application of ice before local anesthesia injections for simple laceration repair and found a significant reduction in pain perceived by patients.[28] Another study compared the use of ice vs topical anesthetics during botulinum toxin injections and concluded that ice provided pain relief comparable to the topical anesthetic, suggesting that ice may be a convenient option due to its shorter application time.[29] However, the guidelines of the American Academy of Dermatology (AAD) indicate that, although ice is safe, data on its effectiveness in reducing infiltration pain from local anesthesia are limited and contradictory.[1]

Local vibration

Evidence suggests that stimulation of Meissner's and Pacinian corpuscles through the use of a vibratory device substantially reduces the sensation of pain during the injection of local anesthesia.[30,31] The reduction of pain can be explained by neurophysiologic mechanisms, including gate control theory and other complex interactions within the nervous system that mask pain with injection and subsequent infiltration. Gate control theory suggests that the activation of nerve fibers that conduct non-noxious stimuli, such as Aβ fibers, can inhibit the transmission of pain signals to the central nervous system, thus reducing the perception of pain.[32–34] Furthermore, vibration has been shown to induce kinesthetic illusions that also contribute to analgesia.[35] In a clinical trial evaluating the use of a vibratory device to mitigate pain during local anesthesia, the use of the device resulted in a 40% significant reduction in pain during injection and infiltration.[36] Therefore, the low side effect profile and ease of use for this technique warrant consideration for its inclusion in daily practice. A recommendation from the authors, in consideration of efficiency, is manual vibration performed with the practitioner's own fingers. Although this may provide less intense vibration compared to a device, this technique helps modulate the

Table 1 Summary of recommendations for minimizing pain with injection and infiltration of local anesthesia.

Technique	Recommendation
Small Needle Gauge	Consider a 30G or 33G needle.
Small Initial Syringe Size	Consider starting with a 1 mL syringe, then transition to a 3 mL syringe.
Buffering	Consider buffering lidocaine with sodium bicarbonate at a 1:10 ratio of 8.4% sodium bicarbonate to 1% lidocaine with 1:100,000 epinephrine.
90-degree Needle Insertion Angle	Consider penetrating the skin at a 90-degree angle instead of a 45-degree angle. When inserting at 90-degree is not feasible, fine motor control with counter tension applied with the opposite hand and injection at an angle would be appropriate
Rate of Anesthetic Infusion	Consider slow infusion of anesthetic during infiltration. Clear any air from the syringe and needle, and depress the plunger while inserting the needle into the skin
Subcutaneous Injection Plane	Consider aiming to inject subcutaneously rather than intradermally. Consider raising a wheal, withdrawing the needle, then re-introducing the needle at the site of the wheal
Large Injection Volume	Consider forming visible edema in procedural area during infiltration. Apply to surrounding areas, beyond incision margins.
Use of Warmed Solution	Consider warming solutions to 37 °C.
''Pore-guided'' injection	Consider introducing the needle through a pore.
''Walking''	After initial infiltration, consider inserting subsequent needles at the site of the already numbed area. Consider angling the needle toward the margin and allowing the fluid wave to advance the anesthetized area.

patient's sensory perception and reduce discomfort without the need for an additional device. Mechanical stimulation prior to injection by physicians has been studied previously and has been shown to have a significantly reduced patient's perception of pain.[37,38]

''Talkesthesia''

Guidelines set forth by the AAD state that verbal distraction is a recommended technique to reduce pain during local anesthetic infiltration.[1] This recommendation was based on expert opinion, and the authors encourage engaging patients by discussing topics that generally appeal to most people, such as hobbies, cooking, grandchildren (for elderly patients), movies, books, music, etc. One study demonstrated that the use of engaging, kind, and reassuring words during the administration of local anesthetics can improve the perception of pain and increase comfort compared to the use of negative words.[39] It is important to consider this technique as part of a broader set of strategies to minimize pain with anesthetic infiltration.

Topical anesthetics

Studies evaluating the use of topical anesthetics prior to injection of local anesthetic show that they may be effective in some patient cases, but the long period required for them to remain on the skin for their effect to take place is a significant disadvantage to efficiency. Furthermore, a recent randomized controlled trial found no significant difference in pain reduction during administration of local anesthesia on the head and neck region when comparing the use of a 2.5% lidocaine and 2.5% prilocaine emulsion, ethyl chloride ''cold spray'', and a topical control.[40]

Asking patients to close their eyes

The authors recommend that clinicians either cover their patients' eyes or ask their patients to close their eyes during local anesthetic administration. In the authors' experience, patients become more nervous when watching. Furthermore, this provides added protection to patients as local anesthetics can squirt out of a pore, or the needle may separate from the syringe in some cases.

Conclusion

Several techniques described in this review have been clinically proven to reduce pain during the injection and infiltration of local anesthesia. Specifically, smaller needle gauges and syringes, buffering of acidic solution, 90-degree injection angle, slow infusion, subcutaneous and larger volume infiltration, and warmed solution have been proven in the literature. Adjuncts to injection and infiltration that have also been clinically proven include background music, cooling of the skin, local vibration, ''talkesthesia'', and topical anesthetics. By implementing a combination of these techniques, it may be entirely possible to make the process of local anesthesia virtually painless to the patient (Supplementary Video 1). Surgeons are commonly assessed by patient-reported outcomes such as mitigation of pain during procedures and as such, surgeons should make all efforts

Table 2 Adjunct tools summary.

Technique	Recommendation
Background music	Consider playing music that the patient enjoys.
Cooling the Skin	Consider application of ice prior to injection.
Local vibration	Consider manual vibration performed by the practitioner's own fingers during infiltration.
''Talkesthesia''	Consider engaging patients by discussing topics that generally appeal to most people such as hobbies, cooking, grandchildren (for elderly patients), movies, books, music, etc.
Topical Anesthetics	Consider combining other options.
Asking patients to close their eyes	Consider covering the patient's eyes or ask patients to close their eyes.

to ensure a patient's experience is as painless as possible. Furthermore, in many clinics, a local anesthetic is administered by ancillary staff. It may be beneficial to formally instruct those administering local anesthetics or consider developing training materials on the concepts and techniques mentioned in this manuscript. The authors provide several recommendations commonly used by colleagues in addition to those proven in the literature (Tables 1 and 2). These include the use of a 30G or 33G needle on areas of the face, starting with a 1 mL syringe, introducing the needle through a pore, manual vibration with the practitioner's own fingers, ''walking'' anesthetic towards target sites, engaging patients by discussing topics that generally appeal to most people, and covering/closing patients' eyes. It is important to prioritize many factors when implementing these recommendations, including the anecdotal nature of some recommendations, differences in clinic operations, regulations, the procedure being performed, and anatomic location. Future research should focus on comparing these techniques in randomized controlled trials to ascertain the optimal course of local anesthesia for these patients.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

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Authors' contributions

Umer Nadir: Contributed to study conception, data acquisition, analysis, and interpretation, and drafted substantial portions of the manuscript, reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

Isadora Rinaldo Scaburi: Contributed to data interpretation and drafted the original version of the manuscript, reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

Felipe Bochnia Cerci: Contributed to the conceptual framework and provided critical intellectual input to the study design and content, reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

George Michael Jeha: Contributed to critical revision of the manuscript for important intellectual content, reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

Stanislav Nickolaevich Tolkachjov: Supervised the study, contributed to study design and interpretation of data, provided critical revision and final approval of the manuscript, reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

Conflicts of interest

Stanislav Nickolaevich Tolkachjov is an investigator/speaker for Bioventus, Kerecis, Boehringer Ingelheim, CASTLE, and Regeneron. Other authors have no relevant conflict of interest to declare.

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.2026.501366.

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REVIEW

Thin and in situ melanoma: an update for the dermatologist☆

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Abstract

Background: Thin melanoma (TM, ≤1.0 mm Breslow thickness) and Melanoma In Situ (MIS) constitute the majority of melanoma diagnoses worldwide and are responsible for melanoma-related deaths in these early-stage tumors. Despite their favorable prognosis, MIS and TM represent an opportunity for improving patient outcomes through early detection, accurate risk stratification, and long-term surveillance for metastasis and new skin neoplasms.
Objective: Provide an update of current evidence regarding epidemiology, risk factors, prognostic indicators, genetic background, and clinical management of MIS and TM.
Methods: A comprehensive review of the literature and international guidelines was conducted, integrating epidemiologic data, clinical prognostic parameters, and molecular insights relevant to MIS and TM.
Results: MIS and TM account for over 80% of all melanomas, with increasing incidence and relatively stable mortality rates. Prognosis is primarily determined by Breslow depth and ulceration, while factors such as mitotic rate, anatomic site, and age further refine risk assessment. Genetic alterations contribute to tumorigenesis but are not yet integrated into routine management. Long-term dermatological surveillance is needed, as new neoplasms, recurrence, and metastasis can develop during follow-up.
Conclusions: MIS and TM are increasingly diagnosed, and dermatologists need to be a part of early detection, multidisciplinary management, and lifelong surveillance, which remain the cornerstone of reducing melanoma-related mortality.
Study limitations: The substantial heterogeneity among the included studies limits direct comparison and quantitative synthesis of the available data.

☆ Study conducted at the Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.

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Introduction

In recent years, advances in the genetic characterization of melanomas, early diagnosis, and new treatments have changed the perspective and knowledge of this tumor. Even in the absence of a defined model of melanoma evolution, the clinical and epidemiological importance of Melanoma In Situ (MIS) and Thin Melanoma (TM) (Breslow thickness $\leq$1.0 mm), which comprises the vast majority of cases, is well established.

Increased use of dermoscopy, translation of novel technologies into clinical practice, improved melanoma awareness in clinical practice and public health campaigns all contribute to earlier diagnosis of skin tumors, leading to an increasing number of patients with MIS and TM being diagnosed and managed by dermatologists.

Progression of melanoma to invasive and metastatic disease has a substantial impact on public health, as these stages account for most new diagnoses and are responsible for approximately one-third of melanoma-related deaths. Moreover, MIS and TM are important risk factors for the development of subsequent primary melanomas and other cutaneous neoplasms, underscoring the necessity of long-term dermatologic surveillance.

Epidemiology

Unlike most other tumors, the overall global incidence of cutaneous melanoma has been steadily increasing in recent decades, with mortality stabilizing over the years.[1] Despite being a less frequent skin tumor, its lethality is responsible for almost 73% of all deaths from skin cancers.[2,3]

There is debate about the cause of increased melanoma incidence and its reliability, since the increase is only observed in cutaneous melanomas and is not accompanied by increased mortality (Fig. 1).[4–6] Some authors hypothesize that the increase in incidence is primarily driven by an increased tendency for pathologists to diagnose melanoma in lesions that were previously considered to be only atypical or benign.[7] Overdiagnosis of undoubted melanoma patients that died from other pathologies and were exempt from autopsy is also a confounding factor, since their mortality is often attributed to melanoma. However, it is more likely that this rise in incidence is multifactorial, including greater exposure to Ultraviolet (UV) radiation, population aging, improvement of surveillance services that record tumors, definition and standardization of histopathological criteria, early detection campaigns, and the use of diagnostic tools such as dermoscopy, which has refined the diagnostic accuracy of melanoma.[5]

This discrepancy between rising melanoma incidence and relatively stable or declining mortality rates should not deter individualized medical decision-making regarding patient treatment and follow-up. Similarly, patient education and early detection efforts should not be deprioritized, as they can significantly influence disease awareness, facilitate earlier diagnosis, and ultimately improve prognosis.

The Surveillance, Epidemiology, and End Results (SEER) registry reports that in 2020 in the USA, the age-adjusted incidence rates for MIS were 18.39/100,000 and 11.32/100,000 for TM.[8,9] The *Instituto Nacional do Câncer* (INCA) estimated 8,980 new cases of melanoma in Brazil for 2023–2025. Following a worldwide trend, the incidence of melanoma is higher in men, with 4640 new cases and 4340 in women, with a national incidence (across all stages) of 4.13 cases per 100,000 persons and a higher incidence in the south of the country. In 2020, there were 1923 melanoma-related deaths in Brazil, comprising 1120 deaths among men and 803 among women.[10]

Currently, most of the melanomas diagnosed are MIS and TM, globally and in the USA, accounting for 83% of all cases.[9] Although they usually have a good prognosis, a small percentage of these patients will have disease progression, and since they are very numerous, MIS and TM melanomas are responsible for 30% of all melanoma deaths.[11]

Recently, global and national databases have improved the registration process substantially, including the implementation of automatic reporting and staging verification. Identification of late-stage melanomas is more reliable due to the use of hospital, regional pathology lab, and death records, whereas early-stage melanomas are likely to be relatively more difficult for the registry to document. This

Fig. 1 Rate of new melanoma cases and deaths per 100,000 persons in the United States of America over the years. Reprinted with permission from Cancer Stat Facts: Melanoma of the Skin. Surveillance, Epidemiology, and End Results (SEER) program.

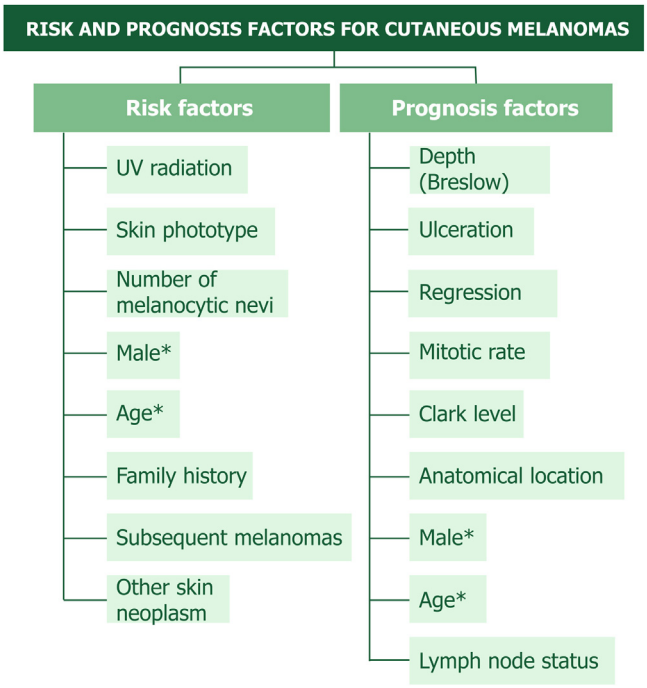

Fig. 2 Well stablished risk and prognostic factor in patients with cutaneous melanoma. * Some features such as age and sex are mutual factors. Pigmentation phenotype includes lightly pigmented skin, hair, eyes, red hair and freckles as risk factors.

is likely responsible for some of the observed increasing incidence of melanoma and possibly contributes to the disparity between incidence and mortality increases. There is a significant possibility that melanoma cases may still be underreported, leading to errors in large databases, which could result in the underrepresentation of these tumors.

Risk and prognostic factors

New insights into melanoma risk and prognostic factors have been published in recent years. This is important so that patient awareness and better risk stratification can be achieved. Prognostic factors are related to disease progression and are constantly being assessed and updated by the American Joint Committee on Cancer (AJCC) and the National Comprehensive Cancer Network (NCCN).

Few studies have established specific MIS and TM risk factors. Fig. 2 provides a schematic view of these factors so they can be easily addressed during patient consultation and counseling.

UV radiation, skin phototype and melanocytic nevi

Exposure to UV radiation is the most common environmental risk factor for skin tumors. The mutations caused by UV radiation can be considered a pathogenic factor, acting from neogenesis to advanced stages of melanoma. Individuals' phenotypes are controlled by the ratio of eumelanin and pheomelanin. Eumelanin provides protection against UV-induced DNA damage and is almost not present in red-haired and Caucasian individuals, who have more pheomelanin and have a greater tendency to develop skin cancers.[12]

Risk of melanoma is correlated with the number of sunburns that a patient has suffered, which are more common in individuals with lightly pigmented phototypes. Individuals with dark skin phototypes are not exempt from melanomas, which occur preferentially in acral topography, with a worse prognosis, often with advanced disease. Recent mutational data have shown that acral melanomas have a low mutational burden, suggesting that it is not a UV-induced malignancy.[13] The risk of individuals with lightly pigmented phototypes developing melanoma is 10 times higher when compared to individuals with dark skin.[14]

Evidence suggests that the number of Melanocytic Nevi (MN) is more important as an individual risk marker for the development of melanoma than as precursor lesions. About one-third of melanomas originate from pre-existing nevi, occurring most commonly on the trunk of young patients, while 70% are *de novo*.[15] These data indicate that most melanomas do not originate from the malignant transformation of nevus cells. A challenge in the MN approach is the differential diagnosis with MIS, especially in dysplastic nevi with severe atypia.

Anatomical location, sex and age

Melanomas located on the head and neck deserve particular care due to their worse prognosis. They occur in the elderly, and their frequency is considered high (up to 26.7%) for an area that corresponds to only 9% of the body surface.[16–18]

The trunk is the most affected site in men (41.5%) and the lower limbs (32.7%) in women.[19] Previous studies reveal that a worse prognosis is expected in male patients, increased age, and sites such as the head and neck or trunk.[20–22] Men generally have a higher mean age (56-years) at the time of diagnosis than women (52-years).[19]

Family history, subsequent melanomas and other skin neoplasms

Family History (FH) of melanoma is a well-defined risk factor. Wei et al. followed 216,115 individuals, finding a 74% increased risk of melanoma (Hazard Ratio [HR = 1.74]) when compared with those without FH. Hereditary melanomas have an increased risk of cancers in other organs, such as the breast, pancreas, or central nervous system.[23,24]

A prior history of any melanoma should be considered a high-risk factor for cutaneous melanoma, with 1% to 8% of these patients developing multiple melanomas.[14] On follow-up, 18.7% of MIS and TM patients developed a second melanoma.[25] The subsequent tumor is usually thinner than the first, and its risk is higher in patients with fair skin and hair and an increased number of nevi.[19]

Individuals with a FH also have a 22% increased risk (HR = 1.22) of Squamous Cell Carcinoma (SCC), 27% (HR = 1.27) for Basal Cell Carcinoma (BCC), and an increased risk of melanomas on the trunk in both sexes and SCC on the extremities in women.[26]

In a meta-analysis, the lifetime risk of developing secondary skin tumors, after a primary melanoma, was 3.8% for a new melanoma, 2.8% for BCC and 1% for SCC. The

calculated 20-year cumulative risk was 5.4% for a second melanoma, 14% for BCC, and 4% for SCC. Although the analyses by subgroups and continents show substantial differences, the previous history of melanoma is a strong predictive factor for the development of a subsequent melanoma (approximately 10-fold increase in RR).[27]

As the lifespan of patients with melanoma has increased with new treatments, the likelihood of new melanomas and SCC/BCC also increases, and greater surveillance is needed in this group.[25,28]

Breslow

Breslow thickness (depth or index) represents the measurement in millimeters from the granulosa layer of the epidermis to the maximum depth of tumor invasion. This measurement is the most important prognostic factor for metastasis used by the AJCC for staging.[29,30]

New data indicate a ''breakpoint'' in 0.7 to 0.8 mm for the survival of T1 patients; this subgroup of TM should be assessed for their high risk of disease progression and Lymph Node Biopsy (LNB) should be considered in the multidisciplinary tumor board.[31] Invasive melanomas with Breslow depth $\geq$0.8 mm have a 1.7 hazard ratio of worse survival than patients with <0.8 mm.[30] TM patients with Breslow thickness between 0.8 and 1 mm also have a six-fold risk for progression to death, and the same six-fold risk for head and neck localization, when compared to tumors <0.8 mm. Melanomas with higher Breslow thickness should be monitored more frequently, especially if other associated risk factors are present.[25,32,33]

Ulceration

Besides Breslow depth, the presence of ulceration in the primary tumor is the most important pathological prognostic indicator in melanoma, being associated with aggressive disease and risk of Lymph Node (LN) metastasis.[30,34–36] This is reflected by upstaging these patients in the AJCC when ulceration is present. MIS does not have any ulceration, and it is rare in T1 patients.

Regression

Patients with invasive tumors may present with partial regression on pathology, a phenomenon that may represent an immunological response to the melanoma. Macroscopically, this may present as pink, grayish, hypopigmented or depigmented areas.[37,38] The influence of regression on prognosis remains unknown, with some studies considering it to be a negative prognostic factor, because of the difficulty in accurately assessing Breslow thickness in regressed areas.[39] This phenomenon was associated in some studies with a better prognosis, since effective activation of the host immune system against melanoma cells is likely its basis.[40] Regression is usually measured based on changes that are present in the dermis, which makes this factor inappropriate for MIS.[38]

Mitotic rate

Despite being removed from the last AJCC 8th staging edition, this index remains an important prognostic factor in most studies. It is considered an independent prognostic factor for LN positivity in TM, along with Breslow thickness in several studies.[29,35,41,42] However, the reproducibility of this risk factor, including interobserver variability and conflicting data on the number of mitoses that would be considered the threshold to become a factor of worse prognosis, makes it harder to standardize.

Clark level

For decades, Clark's levels of invasion have been used in conjunction with Breslow thickness for staging and classification in past AJCC editions. The challenge associated with reproducibility in measurements of Clark's levels among observers has precipitated the abandonment of this parameter in recent years.[43]

Although it is not used for staging in the AJCC 8th edition, the Clark level is a well-established prognostic factor and correlates with increased mortality in most studies.[33,35,39] Clark level is important for TM evaluation and risk stratification and is a part of a complete pathological report.

Genetic aspects

Genetic profiling of melanomas will most likely provide missing information on tumor progression, therapeutic targets and personal staging in the upcoming years. It is important for the classification and identification of mutations in different populations, stages, and anatomical sites in an academic scenario (Table 1).[24,44–46]

Somatic genetic mutations in early melanomas are distinct and necessary for tumorigenesis and disease progression. The most common oncogenic mutations are *BRAF* (commonly *V600E*), *NRAS*, *Kit*, especially in acral and mucosal subtypes.[46–48]

BRAF-V600E can be found in 28% of lethal TM patients, as this could be a potential marker, probably associated with other mutations and a treatment target in the future.[49] They are also found in primary, metastatic, and melanoma cell linages, suggesting that they occur before tumor progression and spread and remain at a constant incidence during progression.[12] *BRAF* mutation can occur early and be found in more than 80% of patients with common acquired MN and dysplastic nevus, and is considered a benign feature of nevi formation. Since these pigmented lesions rarely progress to melanoma, it can be concluded that other mutations and additional genetic changes are required for tumor progression.[12,49,50]

Germline mutations predispose individuals to melanoma due to hereditary predisposition and syndromes. Multiple genes such as *CDKN2A*, *CDK4*, *BAP1*, *POT1* and *MITF* are correlated to melanoma-dominant syndromes. Subordinate syndromes are associated with *BRCA1/2*, *PTEN* and *TP53* mutations and contribute to an increased melanoma risk and other cancers (e.g., pancreatic, astrocytoma, breast, colon, ovarian, prostate, BAP1 syndrome) in an individual context.[21,24,46]

Table 1 Mutations related to cutaneous melanomas, syndrome types, and associated cancers.

Gene mutation	Syndrome type	Syndrome name	Associated cancers
CDKN2A	Dominant	FAMMM, FMPC	Cutaneous melanoma, pancreatic cancer, CNS tumors (astrocytoma)
CDK4	Dominant	Familial Melanoma Syndrome	Cutaneous melanoma
BAP1	Dominant	BAP1 Tumor Predisposition Syndrome	Uveal melanoma, cutaneous melanoma, mesothelioma, renal cell carcinoma, atypical Spitz tumors
MITF (E318K)	Dominant	Familial Melanoma	Cutaneous melanoma, renal cell carcinoma
POT1	Dominant	Familial Melanoma	Cutaneous melanoma, glioma, angiosarcoma, leukemia
TERT	Dominant	Familial Melanoma (emerging)	Cutaneous melanoma, various cancers
NF1	Subordinate	Neurofibromatosis Type 1	Nerve sheath tumors, glioma, breast cancer, pheochromocytoma, melanoma risk increased
BRCA1/2	Subordinate	Hereditary Breast and Ovarian Cancer Syndrome	Breast, ovarian, prostate, pancreatic, melanoma risk increased
PTEN	Subordinate	Cowden Syndrome	Breast, thyroid, endometrial, colon, melanoma risk increased
TP53	Subordinate	Li-Fraumeni Syndrome	Breast, sarcoma, brain tumors, adrenocortical carcinoma, melanoma risk increased
ATM	Subordinate	ATM-associated Hereditary Cancer Syndrome	Breast, pancreatic, melanoma risk increased
CHEK2	Subordinate	CHEK2-associated Hereditary Cancer Syndrome	Breast, colon, prostate, melanoma risk increased
MLH1, MSH2, MSH6, PMS2	Subordinate	Lynch Syndrome	Colorectal, endometrial, ovarian, stomach, hepatobiliary, urinary tract, melanoma risk increased
PALB2	Subordinate	PALB2-associated Hereditary Cancer Syndrome	Breast, pancreatic, melanoma risk increased
APC	Subordinate	Familial Adenomatous Polyposis (FAP)	Colorectal, hepatoblastoma, medulloblastoma, thyroid, melanoma risk increased
TERF2IP, ACD	Dominant	Emerging familial melanoma syndromes	Cutaneous melanoma, limited data
NBN	Subordinate	NBN-associated Cancer Syndrome	Breast, prostate, melanoma risk increased
RAD50	Subordinate	RAD50-associated Cancer Syndrome	Breast, ovarian, melanoma risk increased
SMARCA4	Subordinate	SCCOHT	Ovarian, melanoma risk suggested

Dominant syndromes – melanoma is the major type of cancer in this syndrome. Subordinate syndromes – melanoma risk is elevated, however it is not the dominant cancer type. CNS, Central Nervous System; FAMMM, Familial Atypical Multiple Mole Melanoma syndrome; FMPC, Familial Melanoma and Pancreatic Cancer syndrome; SCCOHT, Small Cell Carcinoma of the Ovary Hypercalcemic Type.

About 10% of melanomas are associated with germline mutations, and these can increase the risk of melanoma by four to 100-times.[23] Progression to metastatic disease is probably due to a combination of mutations and the individual immune system. It has been associated with mutations in the gene *PTEN* or *TP53*, there is a lack of studies in MIS and TM patients.[50,51] Genetic testing in high-risk individuals with multiple primary melanomas or FH of melanoma and other cancers is available for genetic counseling.

Environmental risk factors such as UV radiation from early and intermittent sun exposure, and individual factors (lightly pigmented skin, hair, eyes, red hair and freckles) tend to result in a high mutational burden (>10 mutations per megabase), with a high number of mutations typical of UV damage.[50] This environmental exposure predisposes to *BRAF*-driven melanomas, usually in younger patients, on non-sun damage on the skin (e.g., trunk) and melanoma of the superficial extensive type.[50,52] Chronic sun exposure,

on the other hand, is associated with mutations in *NRAS*, unrelated to the MN number.[50]

Gene Expression Profiling (GEP) represents an emerging adjunctive tool for the diagnostic and prognostic evaluation of cutaneous melanoma, though its integration into routine clinical practice remains under active investigation. They can aid the diagnosis of challenging melanocytic, however, GEP results should not supersede established histopathological criteria in guiding critical management decisions such as LNB or imaging surveillance strategies.[45,46]

Current knowledge about the genetic alterations that participate in the development of initial MIS and TM is insufficient, and genetic testing should not be performed routinely. Different combinations of mutations have been found, and new genes discovery increases the number of possible genetic combinations. Mutations in high-penetrance genes, such as *CDKN2A*, *CDK4,* and *BAP1*, confer a 60% to 90% lifetime risk of melanoma.[23] The future use of mutation biomarkers for risk stratification, choice of imaging, LNB, and adjuvant therapy is promising, but there is still no consensus for its use, requiring further studies.[53,54]

Melanoma Prevention Working Group guidelines state that genetic testing should be analyzed as continuous variables to avoid low- and high-risk dichotomous interpretations that may have no biological significance. Results of these genetic profiles should always be evaluated and compared with established prognostic factors and by the risk stratification of the AJCC, and there are not yet sufficient data for their routine use.[54]

Currently, commercial use of genetic testing on different platforms can aid pathologists in challenging melanocytic lesions.[44] There are no specific guidelines for genetic analysis in MIS or TM for risk stratification, treatment, or follow-up. It is the authors' opinion that genetic profiling of these initial tumors could contribute to the future, so treatment and follow-up can be tailored to each patient.

Diagnosis and treatment

Diagnosis should be made by clinical and dermoscopic evaluation, followed by anatomopathological examination. Dermoscopy allows the magnification of structures not visible to the naked eye, in the superficial epidermis and dermis, and is mandatory for dermatologists and health professionals caring for patients with melanocytic lesions and tumors.

The ABCD rule for the clinical diagnosis of melanoma, described in the 1980s, was a milestone for its earlier detection, especially considering that until then, large and ulcerated tumors were common.[55] Later, the addition of the letter ''E'' to the ABCD acronym – indicating ''evolution'' or ''change'' – further refined melanoma diagnosis.[56]

This dynamic behavior of the lesion may occasionally be the only indication of the tumor, facilitating even earlier diagnoses, particularly in initial melanomas that may not exhibit a striking ABCD criteria. In the 1990s, dermoscopy improved the accuracy of melanoma diagnosis by more than 30%, revolutionizing the approach to these cutaneous tumors.[57] This technique has allowed the identification of increasingly early melanomas, including melanomas that do not resemble typical ones.[58]

The main dermoscopic findings in MIS and TM (Fig. 3), include an irregular pigmented network, negative network, irregular globules and dots, radial streaks, irregular pigmentation, structureless areas, and dermoscopic islands (well-circumscribed areas showing a uniform dermoscopic pattern that differs from the rest of the pigmented lesion).

Photographic follow-up with total body mapping and digital dermoscopy has also contributed to earlier melanoma diagnoses while avoiding unnecessary removal of MN. It is plausible that this trend toward earlier diagnoses will continue to grow, especially with the implementation of artificial intelligence in dermatology.[59]

Initial biopsy should be, whenever possible, excisional, with minimal margins (1 to 3 mm), for complete pathological evaluation of the lesion and removing the least amount of unaffected skin, to avoid alteration in the local lymphatic drainage, with the longest axis in the same direction/parallel to lymphatic vessels.[46]

Special sites with aesthetic or functional impact, such as the face, extremities, and genitalia, where initial complete resection may lead to mutilation, incisional or punch biopsy may be performed and guided by dermoscopy. Confocal microscopy can aid in diagnosing challenging lesions and in guiding biopsies, especially in the face.[60]

Diagnostic challenges in MIS may arise from heterogeneity across histologic sections and overlap with severely atypical dysplastic nevi, which can promote inter-observer variability when dermatopathologists rely only on Hematoxylin-Eosin (HE) staining. This is relevant in melanocytic lesions with architectural disorder and cytologic atypia, where the differentiation between MIS and dysplastic nevi is uncertain even for experienced dermatopathologists.[15,38] Current diagnostic guidelines emphasize that Immunohistochemical (IHC) stains are not essential for the microscopic diagnosis of melanoma and should be reserved for selected cases in which morphology on HE is insufficient for the diagnosis; IHC should be used to support, rather than supplant, the primary histopathologic assessment.[24,45,46,61,62]

IHC can be helpful in challenging MIS and TM cases where standard HE examination is uncertain or when dermoepidermal junction architecture and cytologic features overlap with benign or atypical melanocytic proliferations. IHC panels include markers such as S-100, SOX10, Melan-A/MART-1, and HMB-45 that enhance melanocytic lineage identification and can identify deeper dermal invasion that may be underestimated on HE. IHC markers can have false positives or complicate interpretation in heavily pigmented lesions.[63]

Molecular diagnostic platforms, such as gene-expression-based assays, DNA-based sequencing, cytogenetic analyses, and copy-number assessment, can aid in selected cases of diagnostically challenging melanocytic tumors. Gene-expression assays evaluate the transcriptional profile of tumor cells to distinguish benign from malignant melanocytic proliferations and estimate metastatic risk in specific settings. DNA-based sequencing techniques identify somatic mutations in oncogenic pathways (e.g., *BRAF*, *NRAS*, *KIT*), providing insight into tumor genesis and potential therapeutic targets. Cytogenetic and copy-number techniques detect chromosomal gains, losses, or structural rearrangements that are more frequently associated with melanoma

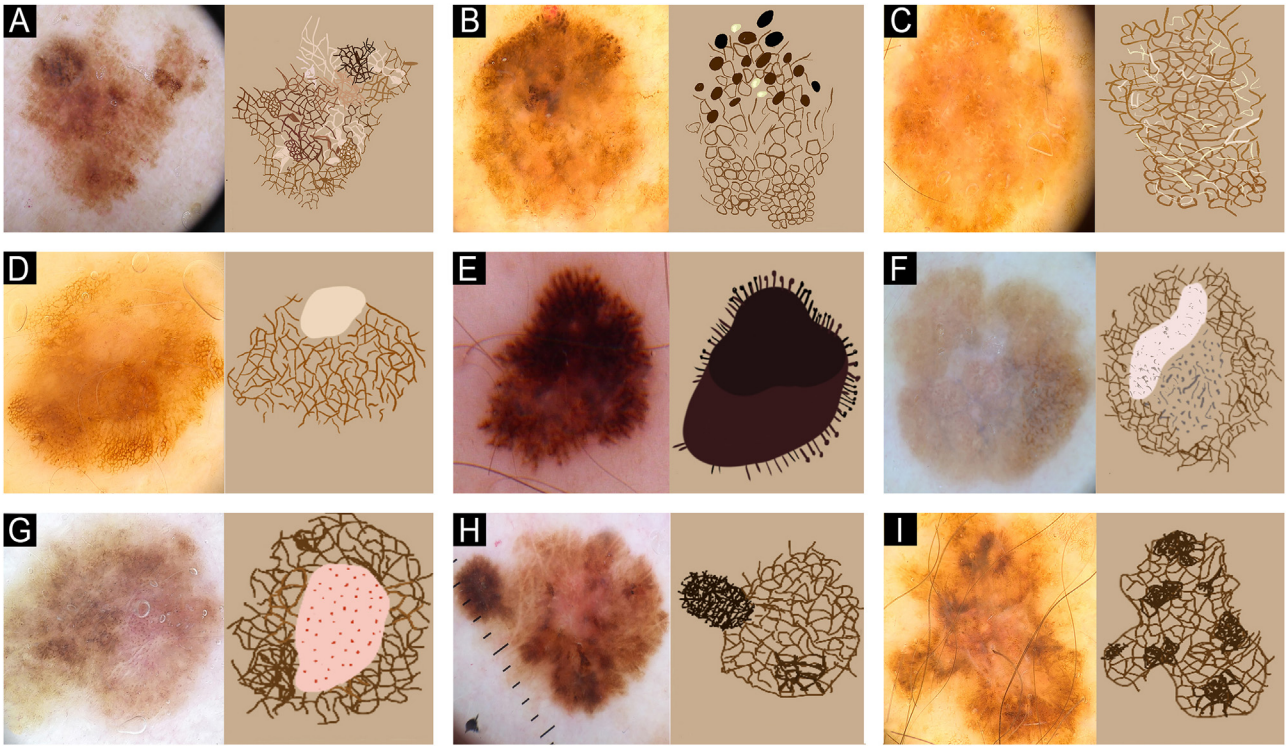

Fig. 3 Dermoscopy features and their schematic features in MIS and TM. (A) Atypical, pigmented network. (B) Irregular globules and dots. (C) Negative pigmented network. (D) Peripheral tan and structureless areas. (E) Irregular radial streaks. (F) Regression. (G) Dotted vessels. (H) Dermoscopic islands. (I) Irregular pigmentation.

Table 2 Recommended margins for the surgical treatment of melanomas.

Tumor thickness	Surgical margin
In situ	0.5 – 1cm
≤1.00 mm	1 cm
>1.00 to 2.00 mm	1 – 2 cm
>2.00 – 4.0 mm	2 cm

than with benign nevi.[45,50,54,64] These techniques also should not supersede established histopathologic criteria for diagnosis, management, and staging. Such methods have not yet been incorporated into routine clinical practice, they require further validation before their application in risk stratification and melanoma management.[24,44,45]

Cutaneous melanomas are classified according to their growth pattern, clinical and histopathological characteristics into four subtypes of invasive melanomas: Superficial Spreading (SS), Nodular Melanoma (NM), Acral Lentiginous (AL) and Lentigo Maligna Melanoma (LMM).[37,65] Lentigo Maligna (LM) is a subtype of MIS, which is slow growing and can evolve into an invasive component (LMM). These subtypes are not included as prognostic factors by the AJCC.[65]

After histological confirmation of melanoma, definitive surgical excision of scar tissue or residual lesion, along with adjacent tissue, should be planned and performed. NCCN 2025 guidelines for surgical margins of this definitive excision should be based on Breslow thickness (Table 2), and margins greater than 2 cm had no impact on Local Recurrence (LR) and survival.[46] Whenever possible, the largest margin according to the Breslow thickness of the tumor should be performed, respecting the maximum value of 2 cm.[62,66]

Surgery with intraoperative margin control (e.g., modified Mohs) associated with the use of IHC markers has been used in some countries with similar survival rates to standard surgery.[67] Regular frozen sections without IHC can undergo artifact alterations, making the correct assessment of melanocytic lesions challenging, and should not be performed according to NCCN guidelines.[46]

LNB should not be performed in MIS. T1b melanoma (Breslow depth < 0.8 mm with ulceration or 0.8–1 mm with or without ulceration) should be assessed for LNB as a shared decision and discussed in multidisciplinary tumor boards.[46,68]

LNB remains a crucial factor in the staging of patients and an important prognostic factor and predictor of survival.[69] It remains the most sensitive and specific test to identify occult metastasis in LN, but it should not be routinely performed in TM.[70] Complete LN dissection should not be performed since it does not impact patient survival.[71]

For greater uniformity, most studies use the AJCC system, staging tumors as in situ, according to Breslow thickness, LN involvement, and presence of metastasis (Table 3). MIS, by definition, do not exceed the basal layer and do not have Breslow depth, being staged as Tis. Accurate staging of patients by a dermatologist is mandatory so they can receive proper treatment, follow-up, and imaging when necessary.

The term TM is historically used in the literature and in research and comprises tumors that have an IB ≤ 1.0 mm. Until 2002, the AJCC defined TM as lesions ≤0.76 mm, and

Table 3 American Joint Committee on Cancer staging system for stage I and II patients.

T	Definition of the primary tumor	N	M	Clinical stage	Pathological stage
Tis	Melanoma *in situ*	0	0	0	0
T1a	< 0.8 mm without ulceration	0	0	IA	IA
T1b	< 0.8 mm with ulceration	0	0	IB	IB
T1b	0.8–1.0 mm with OR without ulceration	0	0	IB	IB
T2a	> 1.0–2.0 mm without ulceration	0	0	IB	IB
T2b	> 1.0–2.0 mm with ulceration	0	0	IIA	IIA
T3a	> 2.0–4.0 mm without ulceration	0	0	IIA	IIA
T3b	> 2.0–4.0 mm with ulceration	0	0	IIB	IIB
T4a	> 4.0 mm without ulceration	0	0	IIB	IIB
T4b	> 4.0 mm with ulceration	0	0	IIC	IIC

T, Definition of the primary tumor; N, Characteristics of regional lymph nodes; M, Distant metastasis. Reprinted with permission and adapted from Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA, A Cancer Journal for Clinicians. 2017;67:472-92.[30]

the changes in this definition and in the staging over the years make it difficult for meta-analysis studies and often cannot be compared with present data.[72]

Currently, there is no recommendation for using neoadjuvant or adjuvant treatment for MIS and TM. If these patients progress to metastatic/advanced stages, they can benefit from anti PD-1 (pembrolizumab and nivolumab), anti CTLA-4 (ipilimumab); and/or mutation-directed therapies (dabrafenib/trametinib, vemurafenib/cobimetinib encorafenib/binimetinib), with well-established results, according to their staging.[46]

Radiotherapy remains indicated for palliative treatments or in inoperable cases, for local control of the disease. Use of topical medications should be restricted to exceptional situations and/or palliative cases in whom resection is not feasible or desirable. Topical Imiquimod (IMQ) has been used for MIS, particularly LM, as a first-line, second-line, or adjuvant therapy, with high rates of clinical and histopathological clearance. Patient response to topical medication can vary, and there is a need for long-term studies to further validate its efficacy. Therefore, the decision to use IMQ should be made collaboratively with the patient and discussed in tumor boards, in cases where surgery is not viable.[46]

A thorough history and clinical examination, including not only the area of the melanoma scar for the detection of LR, but also the entire body surface, with dermoscopy performed on all pigmented and non-pigmented lesions, is required. Total body digital dermoscopy can aid patient surveillance for new skin neoplasms.[73]

LN palpation is mandatory. Imaging should be performed based on specific patient signs and symptoms.[46] LN Doppler ultrasound can assist dermatologists in assessing patients with challenging physical examinations (e.g., obesity, inguinal folds) when performed by a trained and experienced specialist. Performing a high-quality clinical examination is paramount, highlighting the dermatologist's role in the follow-up of melanoma patients, since they are at a higher risk of developing new melanomas than metastases.[46,62,65,66]

There is no need for baseline/follow-up laboratory tests or imaging in MIS and TM; they should be considered in patients with a Breslow >0.8 mm. Clinical follow-up aims at early detection of recurrence, subsequent primary melanomas, and education.[46]

Patient education regarding SCC, BCC and new melanomas can aid early diagnosis and modify personal risk factors (Fig. 2). This should be tailored to the patient's educational level in simple language and focused on patient counseling. MIS and TM patients should not be discharged since they have an increased risk of new neoplasms and of LR and metastasis.

There are some global discrepancies on how often MIS and TM patients should be followed. Usually, a dermatological consultation every 4-months in the first year of diagnosis, followed by every 6-months in the second year and annually after is sufficient for most patients. The number of visitations can be modified due to patient risk and prognosis factors or due to public health-specific guidelines in each country.[62,65,66,74,75]

The first five years of follow-up are important because about 90% of metastases occur during this period, with almost two-thirds occurring in the first two years.[65,76] The risk of late metastasis and recurrence should be kept in mind, so that if they occur, appropriate treatment is not delayed.

Despite advances in recent years, treatment is still challenging in patients with metastatic disease, having a high mortality rate when diagnosed in advanced stages. Thus, the measure with the greatest impact to reduce mortality is based on early detection of initial tumors, maximizing survival rates.[5,60]

Local recurrence and metastasis

Early diagnosis and appropriate surgical treatment for MIS and TM are the most important factors in patient survival. Despite their good prognosis, since this is the largest number of melanoma patients, a significant number of patients will have LR or metastasis, and this should be promptly diagnosed by dermatologists.

There is a lack of uniformity in the definition of LR in the literature. Most authors consider LR to be the reappearance of the tumor in the scar or adjacent to the initial surgical procedure. Some studies use the nomenclature, distant recurrence, for LN involvement or metastasis.[76–79]

Table 4 Studies that evaluated local recurrence and metastasis in early melanomas.

Author	Time period	Number of individuals – n (staging included)	Recurrence rate	Metastasis rate	Average follow-up time	Survival
Gontijo et al.[25]	1997–2020	1122 (580 MIS and 542 T M)	2.4% MIS; 1.3% TM	0.3% MIS; 2.2% TM	79.5 months MIS; 77.1 months TM	
Gimotty et al.[88]	1988–2002	26736 (TM)		1.,60%	97 months	89.1% to 99% (20 years)
Leiter et al.[92]	1976–2007	23842 (stage I)	7.1%		53 months	89% (no recurrence at 10 years)
Lamb et al.[93]	1980–2015	10928 (TM)		4.5% (LN only)		
Claeson et al.[32]	1995 - 2014	1613 (TM)		1,5%		
Kunishige et al.[82]	1982–2008	1072 (MIS)	0.30%	0.2%	56 months	
Durham et al.[89]	2005–2015	512 (0.75 to 0.99 mm)		6.8%	48 months (average)	
Hou et al.[94]	1995–2005	407 (LM)	4.49%	0		7.9 years
Joyce et al.[81]	2008–2014	410 (MIS)	2.20%	0.24%	26 months	
Bricca et al.[87]	1980–2002	331 (MIS) and 294 (invasive)	0	0.7% MIS and 1.9% TM	58 months	99.2% for MIS and 100% TM (5 years)
Akhtar et al.[84]	2001–2009	192 (MIS)	2.9%	0	31 months	
Bene et al.[83]	12 years	167 (MIS)	1.8%	0	63 months	
Huilgol et al.[80]	1993–2002	165 (TM and MIS)	2%		38 months	
Murali et al.[95]	1983–2003	178 (with metastasis) and 178 control	3.20%		79 months	
Moura et al.[85]	2009–2014	155	9%	1.8%	36 months	
Nosrati et al.[86]	1978–2015	662	4.07%			92%–94% (5 years)

LN, Lymph Node; LM, Lentigo Maligna; TM, Thin Melanoma; MIS, Melanoma in situ.

The rate of LR in MIS is variable, ranging from 0.3 to 9%, with most studies having a small number of individuals. In TM, the LR rate ranges from 2% to 11.3%, depending on the study design and follow-up time. Table 4 summarizes the findings of LR and metastasis in MIS and TM in the literature.[25,80–86]

Metastases are defined as invasion of the tumor into an organ or tissue, with melanoma being a neoplasm with lymphatic and hematogenous dissemination (Fig. 4). It is estimated that in up to two-thirds of cases, they are locoregional, affecting the skin or adjacent lymphatic system.[76] In almost half of metastatic melanomas, only one organ is affected, with the skin accounting for about 20% of cases and the lungs, liver, and brain for 50%.[37]

These regional metastases can be classified as satellitosis, in transit, or nodal (LN involvement), according to the distance from the primary tumor.[37] Satellitoses are metastatic papules/nodules that appear within 2 cm of the primary tumor. They may be adjacent to the surgical scar, and their differential clinical diagnosis with LR may be difficult, and it is necessary to highlight their dermal component on histology. In-transit metastases represent invasion of the tumor into the skin or subcutaneous tissue and are located 2 cm beyond the primary site and the LN drainage.[37] Nodal metastases are more common at the nodal draining site of the primary tumor; nevertheless, they can also be found in discordant and unexpected LN drainages. In about 3% of patients with metastases, the primary site is not found.[65]

Presence of metastasis during follow-up of MIS patients raises the question about primary tumor depth missed by the pathologist and possible presence of another thick or unknown melanoma that may be the origin of metastatic disease. Studies reporting metastasis in this group are scarce, with rates ranging from 0.24% to 1.8%.[25,81,85,87]

The rate of metastasis in patients with TM is rarely reported; if the authors exclude studies of LN involvement, being from 1.6% to 6.8%, according to Breslow thickness and study design.[25,77,88,89]

Late recurrence is generally defined by most studies as the recrudescence of the disease after 10-years (some authors consider it to be late after 5-years) and early recurrence when it occurs before this period. Late recurrence incidence can reach up to 6.9%, varying according to the population studied.[78,79] These data show that patients with melanoma have a rate of LR even after long follow-up periods.

Some authors state that melanomas may possibly remain quiescent for decades in individuals until the development of LR or metastasis. In an analysis of 2,766 melanomas staged I–IV, from 1960 to 1996, Tsao et al. found a 18.1-years period for regional recurrence and 19-years for distant metastasis, showing that ultra-late recurrence (more than 15-years after diagnosis) can occur and without identifiable risk factors in the study.[79]

Progression rate from MIS to invasive melanoma is not known, but the rarity of LR and the exceptional deaths

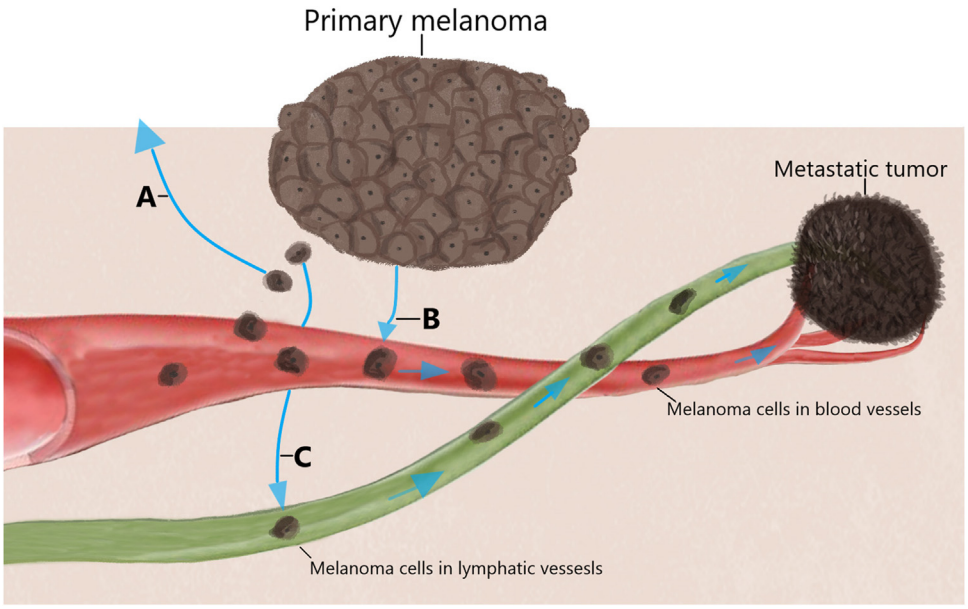

Fig. 4 Melanoma dissemination pathways. Tumor cells can spread through adjacent skin (A), blood vessels (B) and lymphatic vessels (C). Its dissemination can occur either simultaneously or individually and lead to local recurrence, satellitosis and distant metastasis.

of these patients due to metastases suggest that not all MIS lesions would be precursors of invasive tumors and may remain without vertical or invasive growth. MIS can be considered a risk factor for the development of a second melanoma, which may present aggressive and invasive behavior.[7]

A limitation of long-term studies is that patients who died from causes other than melanoma may have died from occult metastasis and are not accounted. The incidence of occult metastasis can only be verified through autopsy, a procedure that is difficult to access and in some countries is subject to strict legal requirements.

Another possible bias when interpreting LR and metastasis is the lack of uniformity in large databases. A study of SEER data revealed that in one data center, a quarter of TM had Breslow depth errors. These tumors were reclassified as Breslow >1.0 mm, including 96% of the deaths associated with TM.[90]

When diagnosed in early stages (T1a), patients have a five-year survival rate of 99% and a 10-year survival rate of 98%. As these tumors progress, 5-year survival drops to 82% and 10-year survival to 75% in T4b N0 patients.

Since MIS and TM represent up to 83% of new melanoma diagnoses, even a 2% lethality rate represents a massive number of patients dying from early-stage disease, currently representing more than 30% of all melanoma deaths.[9] In Australia, there are currently more deaths related to TM than to thick melanomas; these tumors comprise a substantial fraction of the overall burden of lethal melanomas in this high-incidence population.[91]

Careful consideration must be taken when advising MIS and TM patients on their diagnosis, follow-up and risk factors. One should not state that MIS or TM patients are disease-free (''cured'') and do not require follow-up. Strong current data prove that these patients have a risk of LR and metastasis and will most likely develop a secondary melanoma, BCC, or SCC. Current prognostic tools do not allow us to stratify which patients are at higher risk for a worse outcome. Since initial melanomas are the majority of melanoma diagnoses, this gives dermatology an opportunity for patient education, screening, and facilitating secondary prevention. Aggressive behavior towards MIS and TM with expensive imaging and exams might also not be the correct approach for a vast number of patients, placing an economic and psychological burden on patients.

Conclusion

MIS and TM have a growing incidence and importance, representing a substantial part of dermatological practice. Individual risk stratification, early diagnosis, and patient information about prevention are essential to reducing incidence and mortality. Strict clinical follow-up will facilitate timely diagnosis of recurrences, metastases, secondary melanomas, and other skin neoplasms, reinforcing the need for continuous long-term follow-up of these patients. New treatments and diagnostic tools will possibly be incorporated into the future management of these patients by dermatologists, making it essential to update them.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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SPECIAL ARTICLE

Psoriasis in skin of color: clinical presentation, diagnostic challenges, and therapeutic considerations☆

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Abstract Psoriasis in individuals with Skin of Color (SOC) shows distinctive clinical features and particularities that require careful consideration for accurate recognition and care. Erythema is often less apparent, and plaques may appear violaceous or dark brown. These features, together with limited discussion of these nuances in textbooks and articles, contribute to delayed diagnosis, greater reliance on skin biopsy, and reduced diagnostic accuracy. Although overall prevalence may be lower than in White populations, SOC patients frequently present with greater body-surface involvement, thicker scale, and a disproportionate impact on quality of life. Early, effective control is critical not only to limit systemic comorbidities and quality of life impairment but also to prevent post-inflammatory dyspigmentation, which can persist for years after clinical resolution and substantially affect psychosocial well-being. Despite major advances in psoriasis research, important gaps remain regarding genetic drivers, immunopathogenesis, and the comparative effectiveness and safety of therapies across diverse populations, gaps compounded by the persistent underrepresentation of SOC in clinical trials. This review synthesizes current evidence on epidemiology, clinical presentation, diagnostic pitfalls, pigmentary sequelae, psychosocial dimensions, and therapeutic options so as to support equitable, patient-centred outcomes for SOC patients living with psoriasis.

Introduction

Psoriasis is a chronic, immune-mediated systemic inflammatory disease that affects the skin and joints and is associated with multiple comorbidities.[1] It carries a substantial quality-of-life and psychological burden, particularly among people with Skin of Color (SOC), where the disease may be more severe and stigmatizing.[2]

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Although prevalence varies across ethnic groups and regions, most epidemiologic data come from White populations, leaving important gaps for SOC.[3,4] Emerging evidence suggests that while plaque psoriasis may be less prevalent in SOC, it often involves greater body-surface area and yields a higher quality-of-life impact.[4]

Clinical presentation also differs in SOC: plaques are frequently violaceous or hyperpigmented, erythema may be subtle, and resolution commonly leaves persistent post-inflammatory dyschromias, which many patients find more distressing than active lesions.[5]

Despite therapeutic advances, important disparities persist in the diagnosis, treatment access, and outcomes of psoriasis in SOC populations. Structural and socioeconomic barriers, implicit bias in healthcare delivery, underrepresentation in clinical trials, and the lack of culturally sensitive approaches all contribute to suboptimal care.[6] Recognizing these differences is essential to deliver equitable and effective care.

Methods

This narrative review was conducted through a comprehensive literature search of the PubMed/MEDLINE, Embase, and Cochrane Library databases, covering articles published between 2000 and 2025. The search strategy utilized MeSH terms and keywords including ''Psoriasis'', ''Skin of Color'', ''Black Skin'', ''darker skin phototypes'', ''Fitzpatrick types IV–VI'', ''ethnic skin'', ''pigmented skin'', ''African'', ''Asian'', ''Hispanic'', combined with terms related to clinical presentation, diagnosis, treatment, biologics, and health disparities.

Articles were selected based on clinical relevance, focusing on studies that included diverse racial and ethnic populations to synthesize current evidence on diagnostic and therapeutic nuances in SOC (Table 1).

Terminology: Why use the term ''skin of color''

In the global dermatology literature, the term SOC has gained prominence to describe populations with richly pigmented skin. However, in Brazil, there is no universally accepted term to refer to the non-White population within medical or dermatological contexts. Expressions such as *ethnic skin* have appeared in texts but are increasingly viewed as problematic due to their Eurocentric bias.[7]

The use of the term *ethnic skin* often implicitly positions White skin as the default, thereby marginalizing the broad phenotypic diversity of global populations.[8] Consequently, several authors and international guidelines recommend abandoning terms such as *ethnic skin*, *Hispanic skin*, and *Asian skin* in favor of SOC – a term that more accurately captures biologically relevant characteristics in dermatological care while avoiding cultural reductionism.[9]

In this article, the authors have opted to adopt the term SOC, as it aligns with current international discourse, facilitates communication with the global scientific community, and acknowledges the heterogeneity of the Brazilian population. Nevertheless, the authors recognize that this terminology is not without limitations and should be continuously refined to better reflect the specific dermatological needs of diverse populations.

Skin of color in the Brazilian context

Brazil is one of the most genetically diverse countries in the world, a consequence of centuries of admixture between Indigenous peoples, enslaved Africans, and European settlers, along with more recent immigration from various global regions.[10] This complex genetic mosaic has led to a wide spectrum of skin tones across the population, which

Table 1 Summary of key points – psoriasis in SOC.

Unmet Needs in Care	Diagnostic Challenges	Treatment Challenges
Lower healthcare utilization rates, fewer physician visits, and higher hospitalization rates due to economic burdens and lack of culturally competent care	Diagnostic delays in SOC patients are 3× longer compared to lighter-skinned populations	Underrepresentation in clinical trials: Only 15.7% of psoriasis clinical trial participants are non-white
Psoriasis has a greater negative impact on quality of life in SOC populations compared to white populations	Up to 4× more biopsies required for diagnosis due to lower accuracy of visual diagnosis alone	Cultural preferences and aversion to tanning limit acceptance and adherence to phototherapy among Asian patients
Significant underrepresentation in dermatology educational resources: only 4.5% of images in dermatology textbooks depict darker skin types	Difficulty recognizing erythema leading to underestimated severity and artificially low PASI scores; greater initial body surface area involvement	Preference for topical therapies that minimize risk of hypopigmentation and are compatible with hair-care practices in African American patients
Delay in initial presentation to dermatologists due to reliance on traditional treatments before medical consultation	Frequent confusion with other skin conditions (e.g., lichen planus, lupus), leading to misdiagnosis and inappropriate treatments	Genetic polymorphisms influencing Methotrexate metabolism; higher risk of hypertension and renal complications with Cyclosporine in African American patients

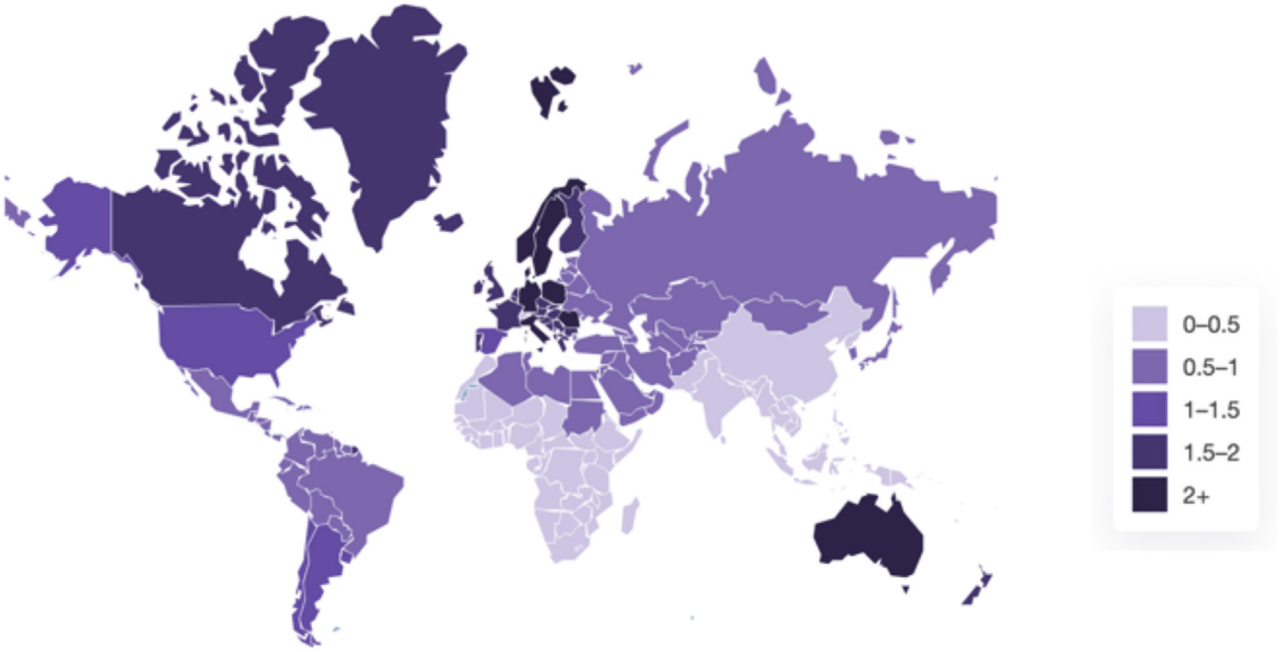

Figure 1 Global prevalence of psoriasis – Global Psoriasis Atlas. Global Psoriasis Atlas. Global prevalence of psoriasis – heatmap [Internet]. Manchester: International Psoriasis Council; c2025 [cited 2025 Jun 19]. Available from: https://www.globalpsoriasisatlas.org/en/explore/prevalence-heatmap.

presents both diagnostic and therapeutic challenges in dermatological practice (Fig. 1).

The Brazilian Institute of Geography and Statistics (IBGE) classifies the population into five self-reported racial/ethnic categories: *branca* (White), *preta* (Black), *parda* (mixed-race), *indígena* (Indigenous), and *amarela* (East Asian). This classification system is based on self-identification and reflects the country's sociocultural and historical dynamics.[11] In academic and policy contexts, the term ''negro'' is commonly used to collectively refer to individuals who identify as *preto* or *pardo*, acknowledging shared experiences and the structural disadvantages historically faced by Afro-descendant populations.

According to the 2022 Census, 20.7 million Brazilians (10.2%) identified as *preto* and 89.2 million (43.5%) as *pardo*. Combined, these groups form a population of 109.9 million people, representing over 50% of the total population.[12] This demographic reality marked the first time in Brazilian census history that the *negra* population became the majority.

This underscores the need to recognize and address disparities in dermatological care. Clinical manifestations of skin diseases – such as psoriasis – can vary significantly according to skin tone, and failure to account for these differences may lead to underdiagnosis or delayed treatment.[4] Tailored diagnostic strategies and inclusive therapeutic approaches are essential to ensure equitable and effective care for all population groups.

Epidemiology

Psoriasis affects men and women equally, with a mean age of onset around 33-years.[13] Its prevalence varies significantly across geographic regions and ethnic groups. Globally, approximately 125 million individuals are estimated to live with the disease (Fig. 2).[1]

The condition is notably more prevalent among individuals of European ancestry, particularly in northern European countries such as those in Scandinavia, where prevalence rates can reach up to 5%.[13] In contrast, psoriasis appears to be rare or even absent among some Indigenous populations. A dermatologic survey involving 25,000 individuals from Andean communities reported no cases of psoriasis, reinforcing this observation.[14,15]

Similarly, a population-based clinical survey conducted in an isolated indigenous community in the Yanomami Territory in Northern Brazil found no documented cases of psoriasis among 555 individuals,[16] suggesting the potential influence of protective environmental or genetic factors. In Asia, prevalence also shows considerable variability. While Malaysia reports higher rates (4%–5%), countries like China, Japan, and Sri Lanka exhibit much lower prevalence, ranging between 0.05% and 0.47%.[4]

In the United States, recent population-based studies have reported psoriasis prevalence rates of 3.6% among White individuals, 1.9% among African Americans, and 1.6% among Hispanic/Latino populations.[15] Data from the NHANES 2009–2010 survey corroborate this ethnic gradient, with African Americans estimated to have a 52% lower prevalence than White Americans, depending on the methodology used, with reported rates ranging from 0.7% to 1.9%, depending on study methodology.[17]

Interestingly, the prevalence in African Americans mirrors that seen in several West African countries, including Nigeria, Mali, and Senegal, where estimates range from 0.3% to 0.8%.[14] This similarity is hypothesized to reflect shared ancestral origins, as the majority of African Americans trace their lineage to West Africa.[18]

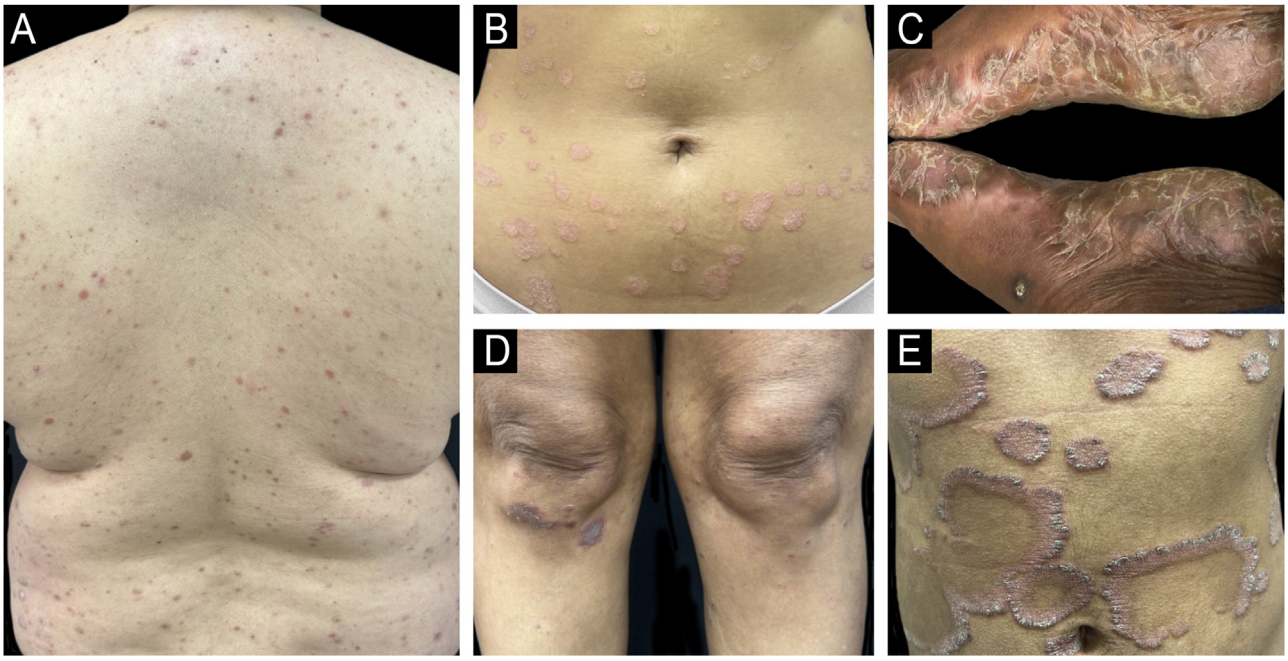

Figure 2 Clinical variability of psoriasis across different skin phototypes. (A) Small-plaque psoriasis in a patient with phototype III – a variant more frequently observed in Asian populations, characterized by numerous small lesions rather than classic large plaques. (B) Classic plaque psoriasis in a patient with skin phototype III, showing well-demarcated erythematous plaques with silvery-white scale. (C) Palmoplantar psoriasis in a patient with skin phototype VI. Marked hyperkeratosis and yellowish scale on the soles may mimic chronic eczema or tinea. (D) Psoriasis in a patient with skin phototype V. Violaceous papules and plaques with gray scaling are observed on typical extensor surfaces. (E) Annular psoriasis in a patient with skin phototype IV, with well-defined arcuate and serpiginous plaques exhibiting central clearing.

In Brazil, the overall prevalence of psoriasis is estimated at 1.31%, based on a population-based telephone survey conducted in all 26 state capitals between October 2015 and January 2016.[19] Regional differences were statistically significant ($p = 0.02$), with higher prevalence in the South and Southeast, and lower rates in the North and Northeast. Although there are no national epidemiological data stratified by race or skin color, this geographic gradient appears to reflect Brazil's ethnic distribution: the North and Northeast regions have a greater proportion of individuals of African and Indigenous ancestry. In contrast, the South and Southeast regions, with the highest reported psoriasis prevalence, have larger proportions of individuals of European ancestry.[12]

In addition to possible genetic factors, other explanations for this disparity include differences in Ultraviolet (UV) exposure – given the higher solar irradiance in northern Brazil, which may exert a protective effect – and unequal access to dermatologic care.[19] Interestingly, these findings echo U.S. data showing lower psoriasis prevalence among African Americans compared to White individuals and may suggest that individuals with African ancestry have a lower genetic predisposition to develop psoriasis, although further studies are needed to confirm this hypothesis.[15,18]

Globally, a critical barrier to understanding psoriasis epidemiology in SOC populations is the lack of population-based data. A recent analysis highlighted that only 19% of countries worldwide currently have published epidemiological data on psoriasis.[20] This data gap is particularly prominent in Africa, Asia, and Latin America, where many studies are limited to small hospital-based cohorts with variable diagnostic criteria.[3]

Recognizing this need, the Global Psoriasis Atlas (https://www.globalpsoriasisatlas.org), a collaborative initiative involving the International Federation of Psoriasis Associations, the International League of Dermatological Societies, and the International Psoriasis Council, has been working to address these disparities and improve the understanding of psoriasis epidemiology in underrepresented populations.

Genetic insights

Psoriasis is a complex, immune-mediated disease with significant genetic involvement, with heritability estimates exceeding 60% across various populations.[21] Twin and family-based studies underscore this genetic component, showing higher concordance rates among monozygotic twins compared to dizygotic twins.[22] Genome-Wide Association Studies (GWAS) have significantly advanced our understanding of psoriasis genetics, identifying over 80 susceptibility loci across diverse ethnicities.[13]

The PSORS1 locus, located within the Major Histocompatibility Complex (MHC) on chromosome 6p21, remains the primary genetic risk factor,[15] within this region, the HLA-C06:02 allele is strongly linked to early-onset and guttate psoriasis.[4] Nevertheless, HLA-C06:02 frequency varies significantly across ethnicities, being most common among

Europeans (up to 70% of psoriasis cases) and notably lower in Asian and African populations.[4]

In contrast, HLA-C01:02 (Cw1) is more prevalent in certain Asian populations, including Southern Chinese, Thai, and Japanese patients, and associates predominantly with severe forms like erythrodermic and pustular psoriasis, later disease onset, and poorer response to conventional treatments. Additional alleles such as HLA-B46 and HLA-A02:07 have also been implicated specifically within Asian cohorts, further highlighting genetic diversity among populations.[23]

Beyond the HLA region, numerous non-HLA genes linked to innate and adaptive immunity are also implicated in psoriasis. Notably, the IL-23/Th17 axis genes, including IL23R, IL12B, TYK2, STAT3, and TRAF3IP2, exhibit strong associations across various ethnic groups.[13,21] Moreover, variants in NF-κB signaling genes like CARD14 and TNFAIP3 have particular relevance for Asian and Middle Eastern populations.[21]

African populations display genetic heterogeneity, with paradoxically low psoriasis prevalence despite higher frequencies of some susceptibility alleles, suggesting protective genetic or environmental modifiers.[4]

In the Brazilian context, genetic admixture creates a unique genomic landscape that could impact psoriasis susceptibility, clinical presentation, and therapeutic responses. Recent genomic studies highlight significant regional variations in ancestry across Brazil, underscoring the need for tailored genetic research and healthcare strategies that reflect this diversity.[10]

Pathophysiology

Psoriasis is characterized by complex interactions between genetic susceptibility, environmental triggers, and immune dysregulation.[1] The pathogenesis of plaque psoriasis, the most common clinical variant, is primarily driven by a feed-forward inflammatory loop centered on the TNF-α/IL-23/IL-17 axis.[24]

This cascade begins with activation of innate immune cells such as plasmacytoid dendritic cells and macrophages. These cells produce proinflammatory cytokines, including Interferon-Alpha (IFN-α), Interleukin-1 Beta (IL-1β), and Tumor Necrosis Factor-Alpha (TNF-α), which together promote the activation and maturation of myeloid dendritic cells. IL-12 promotes Th1 differentiation, while IL-23 plays a critical role in the survival and expansion of Th17 and Th22 cells.[1] The Th17 pathway is now recognized as the principal driver of psoriatic inflammation, with IL-17 and IL-22 being key cytokines leading to keratinocyte hyperproliferation, impaired differentiation, and the recruitment of additional immune cells to the skin.[24]

Keratinocytes are not passive bystanders but active participants in psoriasis pathogenesis. They respond to inflammatory cytokines by producing chemokines, antimicrobial peptides, and further inflammatory mediators, thereby amplifying the immune response. In addition, dysregulation of skin barrier function, with alterations in genes like those from the Late Cornified Envelope (LCE) cluster, may further exacerbate the inflammatory loop.[1,13]

Although data on the pathophysiological mechanisms of psoriasis in SOC populations are still limited,[5] some studies suggest possible differences in skin barrier function and immune response across racial and ethnic groups.[6] In an experimental model using 3D human skin equivalents from African American and White Non-Hispanic keratinocytes, African American cells showed higher baseline pro-inflammatory gene expression and an amplified response to TNF-α stimulation.[25] However, these findings have yet to be directly correlated with clinical differences in disease severity or treatment outcomes.

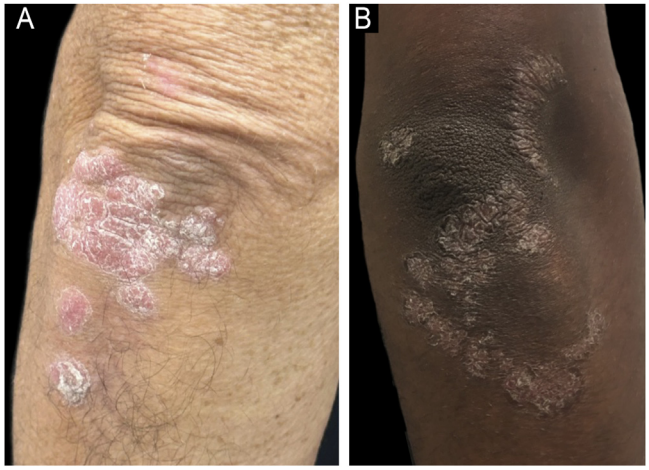

Figure 3 Clinical presentation of psoriasis plaques demonstrating the challenges of erythema recognition in SOC. (A) A typical erythematous plaque of psoriasis clearly seen on lighter skin. (B) A psoriasis plaque presenting with violaceous, hyperchromic, and grayish tones on darker skin, illustrating the variability in visual appearance. Such differences underscore the importance of recognizing non-traditional signs of inflammation to accurately diagnose and assess psoriasis severity in SOC patients.

Clinically, patients with SOC often exhibit distinctive psoriatic lesion morphology and a greater tendency toward post-inflammatory pigmentary changes, which may reflect underlying pathophysiological differences.[4] However, current evidence does not support the presence of fundamentally distinct immunopathogenic pathways when compared to White populations.[6]

Clinical presentation in SOC and diagnostic challenges

The clinical presentation of psoriasis varies considerably depending on the patient's skin phototype, posing particular diagnostic challenges in individuals with SOC. While plaque psoriasis is classically described in fair-skinned populations (Fitzpatrick phototypes I–III) as erythematous plaques covered by silvery-white scales, these typical presentations are often substantially modified in patients with darker skin tones (phototypes IV–VI), leading to diagnostic delays and errors (Fig. 3).[2,4]

One major challenge in diagnosing psoriasis in SOC populations is the reduced visibility of erythema. Rather than presenting with classic red or salmon-colored plaques, lesions in darker skin tones often manifest as violaceous, dark brown, hyperpigmented, or grayish tan-colored patches due to masking of underlying inflammation by melanin.[26]

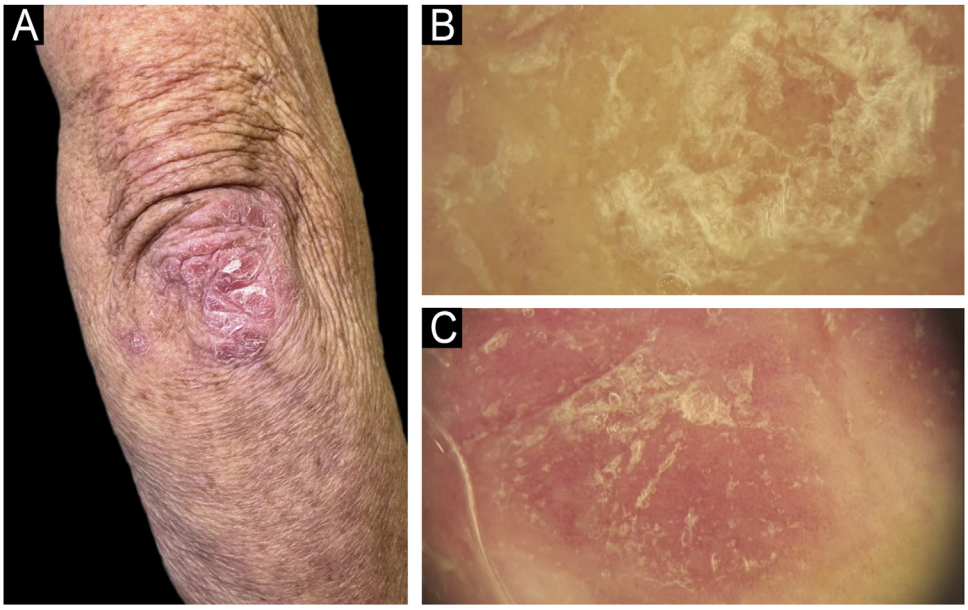

Figure 4 Dermoscopy of plaque psoriasis. (A) Clinical image of a psoriatic plaque on the elbow, showing well-demarcated erythematous plaque with silvery scale. (B) Dermoscopic image highlighting white scales and dotted vessels. (C) Dermoscopy in a lighter phototype showing prominent regular dotted vessels on a homogeneously erythematous background with white scaling – classic findings in psoriasis.

This altered appearance significantly decreases visual diagnostic accuracy, contributing to frequent misdiagnosis or delayed diagnosis.[2]

A large-scale visual diagnostic challenge found diagnostic accuracy to be significantly lower in darker skin compared to lighter skin tones, confirming the impact of underrepresentation and inadequate training in dermatologic education.[27,28] The use of the term ''erythema'' itself has been recently challenged, given its limited applicability and imprecise nature in describing inflammation in darker skin phototypes, and experts have recommended reevaluating or replacing this descriptor to improve clinical accuracy and inclusivity.[29]

As a consequence, patients with darker skin experience notably longer diagnostic delays, often triple the time[2] taken for lighter-skinned counterparts, and require significantly more diagnostic biopsies. Indeed, studies have demonstrated that the probability of biopsy utilization to confirm a psoriasis diagnosis is four times greater in SOC individuals.[2]

Diagnostic tests such as Brocq's methodical curettage, Auspitz sign, and the candle wax sign remain particularly useful in SOC, as these physical findings do not depend on the visibility of erythema and therefore help confirm the diagnosis.

In addition, patients with SOC commonly present with thicker plaques, more pronounced scaling, and a higher degree of body surface area involvement. Specifically, palmoplantar psoriasis and severe plaque psoriasis involving more than 10% of body surface area are disproportionately prevalent among Black and Hispanic populations compared to White populations.[2,4]

Dermoscopy is increasingly recognized as a valuable adjunctive diagnostic tool, especially important in SOC populations. Typical dermoscopic features of psoriasis: regular dotted vessels, homogeneous background erythema (when visible), and scales remain consistent irrespective of skin tone. Dermoscopy significantly enhances diagnostic accuracy by enabling visualization of subtle vascular changes and distinguishing psoriasis from other papulosquamous diseases, thereby reducing unnecessary invasive procedures (Fig. 4).[30]

A further diagnostic consideration in SOC patients is the spectrum of differential diagnoses, which notably includes conditions such as lichen planus, sarcoidosis, cutaneous lupus erythematosus, tinea corporis, secondary syphilis, eczema, and mycosis fungoides. These conditions frequently exhibit morphological overlap with psoriasis in darker skin, complicating clinical differentiation (Fig. 5).[2,4]

Asian populations frequently present a particular variant termed small plaque psoriasis, characterized by stable, chronic lesions typically smaller than 2 cm, contrasting with the larger plaques more common in Western populations. Despite their smaller size and milder clinical appearance, molecular studies have demonstrated a similar activation of the IL-17 pathway in these small plaques.[31]

Given these clinical complexities, it is essential to recognize the profound diagnostic challenges faced by dermatologists treating SOC patients. Educational resources, clinical guidelines, and research studies remain insufficiently representative of darker skin types, directly influencing clinicians' diagnostic accuracy and management strategies.

A recent analysis of dermatology textbooks revealed that psoriasis images in SOC accounted for only 7.3%[32] of all psoriasis-related photographs, despite darker-skinned populations constituting a significant and growing proportion of global demographics.

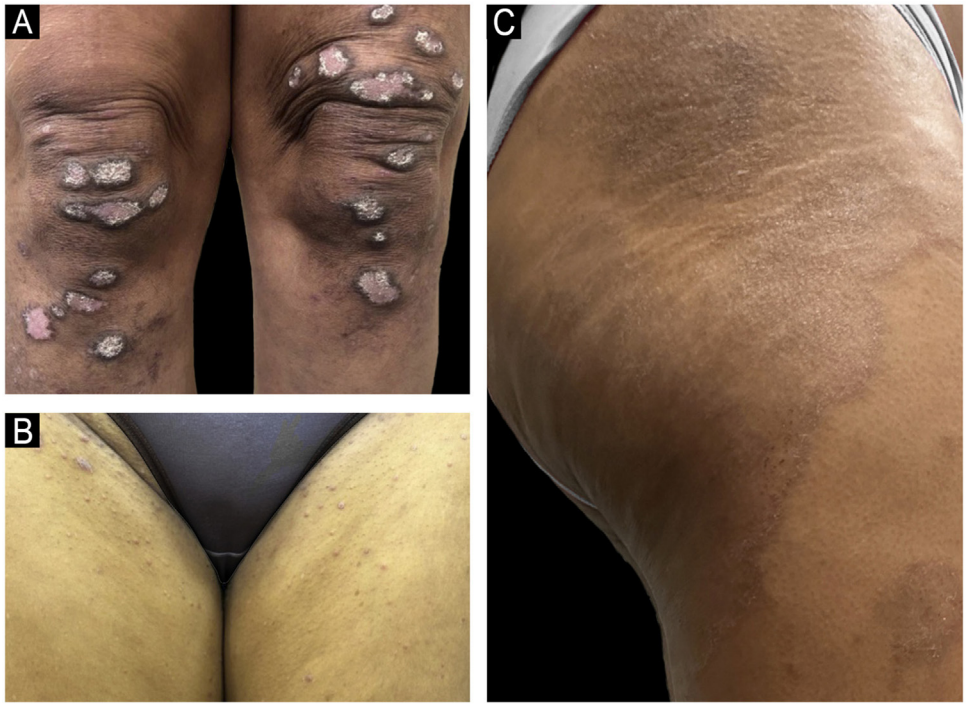

Figure 5 Diagnostic challenges in SOC. (A) Patient with chronic cutaneous lupus erythematosus presenting with discoid lesions. (B) Patient with psoriasis previously misdiagnosed as lichen planus for several years. (C) Patient with atopic dermatitis without visible erythema, a common presentation in darker skin tones.

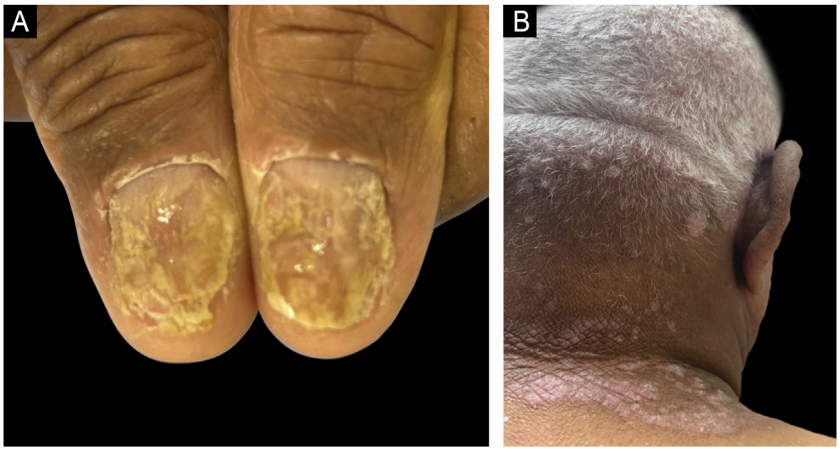

Figure 6 Psoriasis manifestations in hard-to-treat areas. (A) Nail involvement in a patient with Fitzpatrick phototype VI, showing subungual hyperkeratosis, onycholysis, and oil drop sign. (B) Scalp involvement in the same patient, a site commonly affected in patients with skin of color and often associated with increased disease burden.

Enhancing dermatologic training, updating clinical resources, and improving representation in research are imperative to reduce existing racial and ethnic disparities and significantly improve patient outcomes in SOC populations (Fig. 6).

Dyschromias in psoriasis in skin of color

Post-inflammatory dyschromias, encompassing both hyperpigmentation and hypopigmentation, represent a prominent clinical challenge in managing psoriasis in patients with SOC. These pigmentary changes frequently persist after inflammatory lesions resolve and often impact patient quality of life more profoundly than active psoriasis itself, due to their highly visible and long-lasting nature, affecting patient self-esteem and social interactions (Fig. 7).[4,26]

Post-inflammatory Hyperpigmentation (PIH) is particularly common in patients with darker skin phototypes. It arises secondary to inflammatory mediators such as IL-1, IL-6, IL-18, and prostaglandins (notably PGE2 and PGF2α), which directly stimulate melanogenesis. These mediators upregulate the expression of tyrosinase and

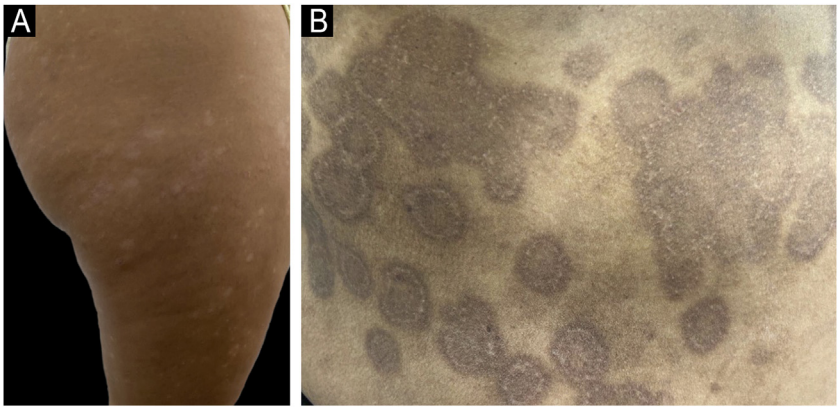

Figure 7 Post-inflammatory dyschromias. (A) Hypopigmented macules on the thigh of a phototype IV patient. (B) Hyperpigmented macules with annular configuration on the trunk of a phototype V patient. Persistent dyschromias represent a significant concern for SOC patients, often impacting quality of life more severely than the initial inflammatory lesions themselves.

other melanogenic enzymes, enhancing melanin synthesis and subsequent epidermal pigmentation following inflammation.[33]

Hypopigmentation also occurs as a distinct post-inflammatory sequela of psoriasis. The most classic and specific manifestation of hypopigmentation associated with psoriasis is the Woronoff ring, a pale annular zone appearing around healing psoriasis plaques.[34] Described over a century ago, the Woronoff ring results from cytokine-mediated disruption of melanogenesis during inflammation.

Recent studies have clarified the underlying mechanism, implicating IL-17 and TNF-α in simultaneously suppressing melanin production while paradoxically increasing melanocyte proliferation within these lesions. This imbalance leads to visibly decreased pigmentation despite an increased density of melanocytes, forming the characteristic depigmented halo around regressing plaques.[34]

In addition to the Woronoff ring, post-inflammatory hypopigmentation areas following psoriasis can occur, often exacerbated by therapeutic interventions such as phototherapy and topical corticosteroids. These treatment modalities, while effective for psoriasis management, may further disrupt melanocyte function or melanin distribution, compounding hypopigmentation issues and highlighting the careful balance needed in therapeutic decisions.[34]

Depth of pigment also matters clinically: epidermal PIH typically appears tan-to-brown and can persist for months, whereas dermal PIH shows a blue-gray hue and may be long-lasting or permanent.[35] Because ultraviolet exposure and ongoing inflammation aggravate PIH, rigorous photoprotection and early control of cutaneous inflammation are foundational. In fact, contemporary PIH care frameworks emphasize that the first step is to treat the underlying inflammatory disease promptly; although that algorithm is often illustrated with acne,[36] the same principle should be applied in psoriasis to minimize deeper, harder-to-treat pigment deposition.[37]

Therapeutic options for PIH are limited and include topical retinoids, azelaic acid, hydroquinone, and – more recently – thiamidol, a selective inhibitor of human tyrosinase, as well as other available lightening agents and chemical peels. Energy-based devices (e.g., 1064-nm Q-switched Nd:YAG) can be useful in expert hands but warrant caution in richly pigmented skin. A practical barrier for extensive body involvement is that most depigmenting topicals are sold in small volumes and may be cost-prohibitive for large surface areas. This limitation should be discussed during shared decision-making, prioritizing sites that most affect patient well-being.[37]

Tranexamic Acid (TXA) is an increasingly discussed adjunct for PIH. Mechanistically, TXA can reduce UV-induced melanogenesis and dampen pro-pigmentary signaling (e.g., via effects on arachidonic-acid metabolites and autophagy). Small, randomized studies around laser procedures show mixed results for prevention but suggest faster PIH resolution when TXA is continued post-procedure. Safety data in nonsurgical patients without thrombotic risk factors are reassuring, though standard contraindications and risk counseling remain essential.[38] Beyond pigment specifically, preclinical work suggests topical TXA may also attenuate psoriasis-like inflammation by blunting IL-17-driven NF-κB signaling and inflammasome activation – raising the possibility that TXA could, in carefully selected cases, both improve pigmentary outcomes and assist in controlling psoriatic inflammation.[39]

Despite the recognized significance of these pigmentary changes, they remain understudied, and current dermatological literature inadequately addresses therapeutic management specifically tailored for SOC populations. Expanding clinical studies and refining management strategies focused on pigmentary sequelae are, therefore, critical steps toward improving outcomes and quality of life for patients with psoriasis.

Psoriatic arthritis

Psoriatic Arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis, affecting up to 30% of psoriasis patients, typically developing within 7- to 10-years after the onset of cutaneous symptoms. However, joint involvement may precede skin lesions in approximately 15% of patients or occur simultaneously.[1]

PsA presents heterogeneously, characterized by peripheral arthritis, axial involvement, dactylitis, enthesitis, and nail disease, significantly affecting quality of life and leading

to functional impairment if untreated. Diagnosis is clinical, supported by imaging and classification criteria such as the CASPAR (Classification Criteria for Psoriatic Arthritis). Common presenting symptoms include joint pain, swelling, stiffness, fatigue, and functional limitation, typically worsened in the morning or after prolonged rest.[1,13]

Despite the broad epidemiological knowledge regarding PsA, data specifically examining the clinical presentation and epidemiology among SOC populations remain limited. Recent studies indicate significant racial and ethnic disparities in PsA phenotypes, disease activity, and clinical outcomes. Specifically, Hispanic and non-white individuals with PsA are more likely to exhibit higher tender joint counts, elevated patient-reported disease activity scores (e.g., RAPID3), and increased prevalence of moderate to severe cutaneous psoriasis despite similar usage of systemic therapies. Radiographic axial involvement, traditionally associated predominantly with Caucasian populations due to the association with HLA-B27, has been increasingly documented among non-white individuals, highlighting the phenotypic diversity of PsA across different ethnicities.[40]

Furthermore, PsA patients from SOC populations frequently experience diagnostic delays and increased morbidity, partially attributable to underrecognition and underrepresentation in clinical studies and medical education resources. These patients often present with higher disease burden and worse patient-reported outcomes at initial clinical visits, reflecting potential disparities in healthcare access and socioeconomic barriers.[4]

Additionally, studies reveal that Asian populations, particularly South Asians, may exhibit distinct PsA phenotypes characterized by a younger age of onset, more severe joint symptoms, and increased frequency of enthesitis and dactylitis compared to their Caucasian counterparts. These clinical differences underscore the necessity for increased clinician awareness, culturally competent healthcare strategies, and inclusion of diverse populations in clinical trials.[15,40]

Comorbidities in psoriasis patients with skin of color

Psoriasis is recognized as a systemic inflammatory disease, frequently associated with various comorbidities beyond joint involvement. Commonly reported comorbidities among psoriasis patients include cardiovascular diseases, metabolic syndrome, obesity, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, and psychiatric disorders such as depression and anxiety. The presence of these conditions significantly influences patient management strategies and long-term prognosis, underscoring the importance of comprehensive clinical assessment beyond cutaneous manifestations.[1]

Although these comorbidities are well-established in psoriasis populations generally, research specifically examining the comorbidity burden in SOC patients remains relatively limited. Recent studies utilizing large-scale, population-based databases, such as the National Ambulatory Medical Care Survey (NAMCS), have provided valuable insights into racial and ethnic differences. Interestingly, a recent comprehensive analysis comparing the comorbidity burden in SOC psoriasis patients to White psoriasis patients, measured by the Charlson Comorbidity Index (CCI), found no statistically significant differences among racial groups. Hypertension, arthritis, hyperlipidemia, and diabetes were among the most frequently reported conditions across all races, suggesting commonalities rather than differences driven by biological or genetic factors associated with race alone.[41]

However, disparities in health outcomes, treatment access, and quality of life persist among SOC patients, largely attributable to socioeconomic status, healthcare access, and potential underrepresentation in clinical guidelines and research. Despite similar comorbidity burdens between SOC and White populations, SOC patients frequently experience worse disease outcomes due to delayed diagnosis, misdiagnosis, and inadequate management arising from systemic inequities. Therefore, addressing these disparities requires targeted interventions focused on improving healthcare accessibility.[41]

Special considerations in the treatment of psoriasis in skin of color

Topical therapies

Topical therapies remain first-line treatments for mild psoriasis across all skin types. However, treatment of psoriasis in SOC populations demands careful consideration due to increased risk of post-inflammatory hypo- and hyperpigmentation. The prolonged use of potent topical corticosteroids is often discouraged among patients with darker skin due to their potential for causing significant hypopigmentation, atrophy, and striae, which negatively impact patient adherence.[42]

Non-bleaching alternatives, such as vitamin D analogs (e.g., calcipotriene) and calcineurin inhibitors (e.g., tacrolimus and pimecrolimus), are often preferred, particularly for facial and intertriginous areas.[4] A recent analysis highlighted the efficacy and safety of calcipotriene/betamethasone dipropionate foam in SOC patients, demonstrating good clinical outcomes with an acceptable pigmentary safety profile.[43]

When managing scalp psoriasis in SOC patients, particularly those of African descent, clinicians should tailor topical regimens to accommodate cultural hair care practices and styling preferences. Daily washing with medicated shampoos, often recommended in standard protocols, may not be feasible for many African American women due to concerns over hair dryness, breakage, and disruption of protective hairstyles such as braids, weaves, and locks.[15]

Instead, a more suitable approach involves weekly use of medicated shampoos combined with once- or twice-daily application of corticosteroids in vehicles compatible with the patient's hair texture and styling habits. Oil-based preparations, lotions, and emollient foams are often better accepted. Engaging in a brief discussion about vehicle preferences, hair care routines, and potential use of traditional scalp treatments is essential to optimize adherence and treatment satisfaction in this population.[15]

Phototherapy

Phototherapy remains a cornerstone in the management of moderate-to-severe psoriasis, particularly in patients with more than 10% body surface area involvement or in those refractory to topical therapies. Common phototherapeutic modalities include broadband Ultraviolet B (BB-UVB), Narrowband UVB (NB-UVB), and Psoralen Plus UVA (PUVA), each with unique efficacy and safety profiles.

BB-UVB, which utilizes the entire UVB spectrum (254–313 nm), has demonstrated efficacy but has largely been supplanted by NB-UVB (311–313 nm) due to superior clearance rates and a better safety profile in head-to-head trials. PUVA therapy, combining UVA (320–400 nm) with psoralens, has shown high efficacy, with clearance rates approaching 89% in some studies.[44] However, concerns about long-term carcinogenic risks, especially squamous cell carcinoma, have limited its use.[45] Additionally, in SOC populations, PUVA is associated with a higher risk of dyschromias, making NB-UVB generally the preferred modality.[44]

An important consideration in SOC patients is the impact of increased melanin content on UV dose calculation and treatment tolerability. Traditionally, clinicians have escalated NB-UVB doses in darker-skinned individuals to achieve mild erythema (erythemogenic threshold), assuming it correlates with treatment efficacy. However, emerging evidence challenges this approach. A bilateral, split-body, prospective study compared suberythemogenic (70% of Minimal Erythema Dose – MED) and erythemogenic (100% MED) NB-UVB regimens in dark-skinned Egyptian patients with chronic plaque psoriasis (Fitzpatrick skin types III–V). After treatment, both dosing regimens resulted in statistically similar PASI reductions and clearance rates, but the suberythemogenic side received significantly lower cumulative UVB doses (42.73 vs. 62.36 J/cm^2, $p < 0.001$).[46] These findings suggest that suberythemogenic NB-UVB protocols may offer equivalent efficacy with reduced cumulative phototoxic burden in SOC patients.

Cultural attitudes also play a critical role in phototherapy adherence. In some Asian populations, darker skin is culturally associated with manual labor and lower socioeconomic status, leading to a cultural aversion to tanning. Studies report that some Asian patients undergoing phototherapy express dissatisfaction with unwanted tanning, directly affecting adherence. These cultural nuances should inform shared decision-making during treatment planning.[44,47]

In clinical practice, these findings advocate for personalized phototherapy dosing strategies in SOC patients, balancing efficacy with the minimization of adverse effects like PIH and patient-reported cosmetic concerns. Suberythemogenic NB-UVB protocols now represent an evidence-based option to optimize outcomes while minimizing pigmentary side effects in these populations.[46]

Classical systemic therapy

Classical systemic therapies, including methotrexate, acitretin, and cyclosporine, remain foundational options for the management of moderate-to-severe psoriasis worldwide, particularly in regions where access to biologic agents is limited.

Methotrexate, a folate antagonist with immunomodulatory and anti-inflammatory effects, is widely used as a first-line systemic option due to its affordability and long-standing clinical experience. Although its efficacy appears comparable across racial and ethnic groups, there is limited representation of SOC populations in clinical trials.[6] Hepatic safety remains a key concern, particularly in areas with higher prevalence of viral hepatitis (e.g., parts of Asia and sub-Saharan Africa), reinforcing the need for baseline screening and regular liver function monitoring.

Notably, genetic polymorphisms in the MTHFR gene (e.g., C677 T and A1298C) – which affect folate metabolism and thus methotrexate pharmacokinetics – occur with varying frequency across populations. Asian and Hispanic individuals, for instance, exhibit a higher prevalence of the C677T variant, which has been associated with increased toxicity risk, while African populations tend to have a lower frequency of this allele.[48]

Acitretin, a systemic retinoid, is typically reserved for patients with pustular, erythrodermic, or palmoplantar psoriasis or as a maintenance agent. It is not immunosuppressive, making it useful in patients with contraindications to immunosuppressants. However, the teratogenicity and mucocutaneous side effects can be more noticeable and distressing in SOC, particularly due to the impact on lip and facial pigmentation and potential for PIH.[14]

Cyclosporine, a calcineurin inhibitor, is fast-acting and effective in acute flares. It is commonly used for short-term control of severe disease; long-term use is limited by nephrotoxicity and hypertension, both of which may disproportionately affect certain ethnic groups. For instance, African American patients have a higher baseline risk of hypertension and may require closer monitoring when using cyclosporine.[49] Cyclosporine's favorable impact on disease control must be weighed against its side effect profile, especially in populations already at increased cardiovascular risk.

Importantly, there is a lack of clinical trial data specifically evaluating these therapies in SOC populations, making it difficult to draw firm conclusions about optimal dosing, efficacy, and adverse event profiles. Cultural factors may also influence treatment choice and adherence. In some cultures, there may be hesitation regarding the long-term use of systemic drugs due to fears of ''chemical'' medications, organ damage, or infertility – factors that may not be explicitly addressed in standard consultations.[14]

Biologic therapies for psoriasis in skin of color: current evidence and unmet needs

Biologic therapies targeting TNF-α, IL-12/23, IL-17 and IL-23 pathways have transformed the treatment landscape for moderate-to-severe psoriasis, offering high levels of skin clearance with favorable safety profiles. However, despite their widespread use, data on treatment efficacy and safety in SOC populations remain scarce and fragmented. Historically, non-white patients have been grossly underrepresented in pivotal psoriasis trials, with a recent systematic review showing that 84.3% of participants in psoriasis biologic trials were White, leaving less than 16% from all other racial and ethnic groups combined.[50]

Recent systematic reviews have tried to address this knowledge gap by pooling available data. A 2024 review, analyzing 11 phase 3 trials, included 1,393 SOC psoriasis patients, with the majority being Asian (64.3%), but Black and Hispanic patients remained strikingly underrepresented.[50] Another review included 24 studies, again demonstrating a predominance of Asian (n = 2,740) and White (n = 8,735) participants, while only 138 Black and 728 Latino patients were enrolled across all studies.[51]

Some subgroup analyses have attempted to compare biologic responses across ethnicities, but results remain inconclusive due to low patient numbers and heterogeneity in study designs. In the review by Ferguson et al., ixekizumab showed numerically higher PASI75 response rates in Asian (98.8%) and Latino (96.6%) patients, while guselkumab appeared more effective among Black (74.2%) and White (86.8%) participants.[51] Similarly, bimekizumab demonstrated high PASI90 and PASI100 response rates in SOC patients (85.5% and 52.6%, respectively) in Rijal et al.'s review, but again with small sample sizes (only 62 SOC patients receiving bimekizumab).[50] Importantly, these findings are exploratory and should not yet guide clinical decision-making, given the limitations of retrospective and underpowered analyses.

Fortunately, the landscape is beginning to shift. In 2025, the publication of the VISIBLE trial (NCT05272150) marked a major milestone. This was the first large, prospective, randomized, placebo-controlled trial specifically designed to evaluate the safety and efficacy of a biologic agent (guselkumab) in SOC patients with psoriasis. The study enrolled 211 patients, all self-identifying as a race/ethnicity other than White, with over 50% having Fitzpatrick skin types IV–VI.[52]

VISIBLE had two cohorts: one focusing on moderate-to-severe body psoriasis (Cohort A) and another on scalp psoriasis, an area of particular concern in SOC patients due to its psychological and cultural relevance (Cohort B). By week 16, 59.5% of SOC patients treated with guselkumab achieved PASI90, and 41.7% reached complete clearance (PASI100). Regarding scalp involvement, 78% achieved a 90% improvement in the Psoriasis Scalp Severity Index (PSSI90), showing robust efficacy even in this challenging site.[52]

In clinical practice, the implications of the still-limited data for SOC populations suggest that, while no definitive guidelines or studies currently exist to direct the choice of a specific biologic agent based on ethnicity,[50] intervention should not be postponed. On the contrary, establishing early and effective treatment is essential, as patients with SOC often experience a disproportionately greater impact on quality of life.[4] Such an agile therapeutic approach is fundamental to promptly interrupt the inflammatory cascade and, consequently, mitigate the risk of post-inflammatory dyschromias, which represent a significant morbidity and a central concern for these patients.[5]

Psoriasis management in the Brazilian Health System

In Brazil, psoriasis care is delivered through the public Unified Health System (SUS) and the private sector. According to the 2024 Brazilian Psoriasis Consensus, treat-to-target principles remain aligned with the ''rule of tens'' (PASI > 10, BSA > 10, or DLQI > 10) and are embedded in public and private access frameworks, helping standardize eligibility for systemic therapy and biologics nationwide.[53]

In practice, access is generally broad via SUS and regulated private coverage; however, limited specialist availability and financial constraints still impede uptake. Treatments for dyschromia, procedures and topical depigmenting agents are not routinely available in SUS and are often costly out of pocket, disproportionately affecting people in worse financial circumstances, among whom patients with higher Fitzpatrick phototypes are frequently overrepresented.

Pustular psoriasis in skin of color

Pustular psoriasis represents a rare but severe clinical subtype of psoriasis, characterized by the presence of sterile pustules on an erythematous or inflamed background. Its most serious form, Generalized Pustular Psoriasis (GPP), is considered a dermatologic emergency, often requiring hospitalization and associated with a mortality rate of approximately 3 deaths per 100 patient-years.[54]

Epidemiological data on pustular psoriasis in SOC populations remain scarce, but existing studies suggest potential ethnic variability. A cross-sectional analysis from the University of California-San Francisco found that Asian and Hispanic/Latino patients had significantly higher odds of having pustular psoriasis compared to Caucasians (OR = 4.36 [95% CI: 1.24–17.62] for Asians; OR = 5.94 [95% CI: 1.03–31.03] for Hispanics/Latinos).[55] Although African descent populations were underrepresented in that study, these findings suggest that non-White patients may have a relatively higher risk of pustular forms.

From a pathophysiological perspective, GPP is now recognized as an autoinflammatory condition predominantly driven by dysregulation of the IL-36 pathway, with monogenic forms linked to IL36RN mutations, especially prevalent in Asian cohorts.[54,56]

Regarding treatment, historically, systemic therapies such as cyclosporine, methotrexate, and acitretin have been the mainstays for controlling acute GPP flares.[54] Cyclosporine is often preferred for rapid control, especially in unstable cases, while acitretin plays a role in maintenance and chronic pustular variants like palmoplantar pustulosis.

Recent advances in IL-36-pathway inhibition have reshaped the management of GPP. Spesolimab, an anti-IL-36 receptor monoclonal antibody, became the first FDA-approved biologic, and is also approved by ANVISA in Brazil, specifically indicated for treating acute GPP flares in adults, based on the Effisayil-1 trial, which showed significantly faster pustule clearance and broader clinical improvement versus placebo.[56]

Importantly, most clinical trials evaluating therapies for pustular psoriasis have included very few SOC patients, limiting the ability to draw definitive conclusions about treatment efficacy and safety in these groups.

Conclusion

Managing psoriasis in SOC presents unique challenges that extend beyond clinical features and reflect broader issues of equity, representation, and cultural competence: socioeconomic and structural barriers (including limited access to dermatologic specialists and financial constraints) disproportionately affect SOC communities and delay diagnosis and initiation of effective therapy.[15] At the same time, implicit bias within health systems contributes to underrecognition or misdiagnosis because presentations often differ from those in lighter phototypes,[6] and these inequities are compounded by the persistent underrepresentation of SOC individuals in clinical trials, which constrains the evidence base needed to inform guidelines and to validate the efficacy and safety of therapies across diverse populations.[57]

In Brazil, socioeconomic and structural barriers, including limited access to dermatologic specialists and financial constraints, disproportionately affect vulnerable populations, where Black and mixed-race individuals are overrepresented. These barriers, compounded by regional disparities, can delay diagnosis and initiation of effective therapy, perpetuating worse outcomes for these patients.[58]

Addressing these inequities requires culturally competent, patient-centered care with shared decision-making.[15] Clinicians must recognize subtler SOC presentations: hyperpigmented or violaceous plaques, minimal erythema, and frequent post-inflammatory pigmentary changes.[2]

Conventional severity scoring tools like the PASI heavily weight erythema, which can be challenging to detect in darker skin tones. This reliance on erythema visualization potentially leads to the underestimation of disease severity in these patients.[5] Therefore, there is a pressing need to develop validated, SOC-specific scoring instruments that account for differences in lesion morphology and pigmentary alterations.

Although no severity instrument has been specifically validated for SOC populations, recent studies have increasingly incorporated multimodal approaches combining clinician-reported measures, such as Investigator's Global Assessment (IGA) and BSA, with patient-reported outcomes, including the DLQI and the Psoriasis Symptoms and Signs Diary (PSSD). In addition, tools such as the Skin Discoloration Impact Evaluation Questionnaire (SDIEQ) allow assessment of the psychosocial burden of post-inflammatory dyschromias. Together, these measures provide a more comprehensive and patient-centered evaluation of disease burden, independent of erythema visualization.[59]

Emerging technologies, including dermoscopy and artificial intelligence-based image analysis trained on diverse datasets, offer promise for future objective assessment tools,[3,4] though validation studies in SOC populations remain limited and represent a critical research priority.

Photographic documentation of psoriasis in dark skin requires refinement: standard lighting and imaging techniques often fail to capture lesion contrast in richly pigmented skin, complicating clinical monitoring and research documentation.[60] Future tools should also incorporate assessment of residual dyspigmentation, as these sequelae are often of great concern to SOC patients and can significantly impair quality of life.[5]

Looking ahead, greater inclusion of SOC populations in clinical trials is essential to ensure that treatment recommendations are broadly applicable. Research efforts should also prioritize real-world studies and long-term outcome data reflecting diverse racial and ethnic backgrounds. Ultimately, a comprehensive, equity-focused approach is essential to deliver optimal care for all patients with psoriasis, regardless of skin color.

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Authors' contributions

Anderson Costa: Article writing; Data acquisition, analysis, and interpretation; critical review of the literature.

Ricardo Romiti: Study conception and design; critical review of the intellectual content; active participation in guiding the research; approval of the final version of the manuscript.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

Anderson Costa: Consulting fees from Eli Lilly, Janssen, Novartis and Pfizer; served as a paid speaker for AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi and UCB Pharma. Ricardo Romiti: Consulting fees from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB Pharma; research grants to his institution from AbbVie and has served as a paid speaker for AbbVie, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, SunPharma and UCB Pharma.

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LETTER – RESEARCH

Differential melanoma outcomes in men and women: longitudinal findings from a ten-year study☆

Dear Editor,

Cutaneous melanoma is an aggressive neoplasm arising from melanocytes and is responsible for the majority of skin cancer-related deaths. Although it represents only 4% of skin tumors, it accounts for up to 75% of skin cancer mortality due to its high metastatic potential.[1] Global incidence has increased steadily, with 331,647 new cases estimated in 2022, reflecting 1.7% of all cancers.[2] While early-stage melanomas have a favorable prognosis, advanced cases with greater Breslow thickness and ulceration are associated with poor outcomes.[3]

Several risk factors influence melanoma development, including UV exposure, fair skin, and genetic predisposition.[4] Another well-established risk factor is the number of melanocytic nevi, which is independently associated with melanoma risk.[4] Gender differences in melanoma outcomes have been noted, with women presenting at earlier stages and having better survival rates than men.[5,6] However, these disparities remain underexplored in Latin American populations. This study aimed to investigate gender-related differences in clinical presentation and survival among melanoma patients treated at a reference center in Southeast Brazil over a ten-year period.

In this study, we retrospectively collected data on the epidemiological, clinical, and histopathological data from patients diagnosed with Cutaneous Melanoma (CM) at a cancer reference hospital in southeast Brazil. The research commenced following approval from the local Research Ethics Committee (CAAE #55961622.6.0000.5105).

Our analysis included patients diagnosed between January 2010 and December 2020. Clinical data, including age, gender, socioeconomic status, tumor location, staging, and tumor histological subtype, were extracted from electronic medical records. Information regarding patient mortality was obtained through an active search, which involved families and federal databases. Among the 317 diagnosed cases, 46 were excluded due to incomplete records or inability to contact patients or families for follow-up.

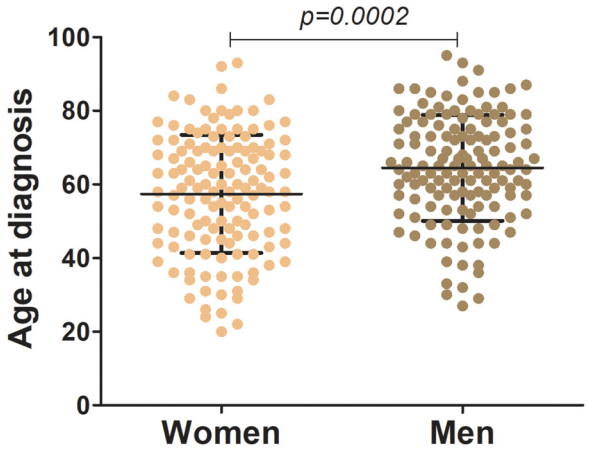

Fig. 1 Age at diagnosis of men and women with melanoma. The figure illustrates the distribution of age at diagnosis by sex, as women were diagnosed at a younger age (57.41-years, SE = 1.38) compared to men (64.47-years, SE = 1.23; p = 0.0002).

Data were analyzed using descriptive statistics, with results presented as absolute and relative frequencies (%). Quantitative variables were summarized using the median and interquartile range. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate, with a significance level set at 5% ($p < 0.05$). ANOVA assessed differences between groups, followed by Tukey's post hoc. The *t*-test evaluated mean age differences between sexes. All analyses were performed using *R* software version 4.2.2 (R CORE TEAM, 2022).

We identified 317 cases of cutaneous melanoma in Southeast Brazil between 2010 and 2020, of which 46 were excluded from the analysis due to incomplete medical records. The cohort comprised 136 men and 135 women (n = 271), with a mean age of 63-years. Women were diagnosed significantly younger than men (57.4 vs. 64.5 years; p = 0.0002) (Fig. 1).

Regarding disease staging, women were more frequently diagnosed at early stages (0–II), while men had a higher prevalence of advanced disease (III–IV) (p = 0.044). Histolog-

☆ Study conducted at the Hospital do Câncer de Muriaé, Fundação Cristiano Varella, Muriaé, MG, Brazil.

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Table 1 Clinical characteristics of cutaneous melanoma in men and women from Southeast Brazil.

Variable	Men (%)	Women (%)	Total (%)	p-value
Staging				0.044*
0	10 (7.4%)	18 (13.3%)	28 (10.3%)	
I	17 (12.5%)	35 (25.9%)	52 (19.2%)	
II	33 (24.3%)	26 (19.3%)	59 (21.8%)	
III	28 (20.6%)	25 (18.5%)	53 (19.6%)	
IV	30 (22.1%)	24 (17.8%)	54 (19.9%)	
Unknown*	18 (13.2%)	07 (5.2%)	25 (9.2%)	
Primary location				0.411
Limbs	54 (39.7%)	52 (38.5%)	106 (39.1%)	
Trunk	35 (25.7%)	45 (33.3%)	80 (29.5%)	
Face	30 (22.0%)	22 (16.3%)	52 (19.2%)	
Neck and sculp	10 (7.3%)	13 (9.6%)	23 (8.4%)	
Other	7 (5.1%)	3 (2.2%)	10 (3.6%)	
Alcohol use				<0.001*
Former user	21 (15.4%)	6 (4.4%)	27 (10.0%)	
Current user	32 (23.5%)	8 (5.9%)	40 (14.8%)	
No	50 (36.8%)	76 (56.3%)	126 (46.5%)	
Unknown	33 (24.3%)	45 (33.3%)	78 (28.8%)	
Tobacco use				<0.001*
Former user	34 (25.0%)	6 (4.4%)	40 (14.8%)	
Current user	16 (11.8%)	11 (8.1%)	27 (10.0%)	
No	62 (45.6%)	76 (56.3%)	138 (50.9%)	
Unknown	24 (17.6%)	42 (31.1%)	66 (24.4%)	
Family history				0.253
Yes	46 (33.8%)	43 (31.9%)	89 (32.8%)	
No	44 (32.4%)	27 (20.0%)	71 (26.2%)	
Unknown	46 (33.8%)	65 (48.1%)	111 (41.0%)	
Treatment				0.238
Surgery only	77 (28.4 %)	89 (32.8%)	166 (61.3%)	
Chemotherapy only	06 (2.2%)	06 (2.2 %)	12 (4.4%)	
Radiotherapy only	02 (0.7%)	02 (0.7%)	04 (1.5 %)	
Immunotherapy	01 (0.4%)	03 (1.1%)	04 (1.5%)	
Combination treatment	28 (10.3 %)	14 (5.2%)	42 (15.5%)	
No treatment (palliative)	22 (8.1 %)	21 (7.8%)	43 (15.9 %)	

ical subtype was unspecified in most cases (54.2%), followed by superficial spreading melanoma (21.8%), with no significant sex-based differences. The most common anatomical sites were the limbs (39.1%), followed by the trunk (29.5%) and face (19.2%), also without differences between sexes ($p = 0.411$).

Significant differences were observed in lifestyle habits: men reported higher rates of tobacco use (36.8% vs. 12.5%) and alcohol consumption (38.9% vs. 10.3%) compared to women ($p < 0.001$ for both). There were no significant differences in family history of cancer between sexes ($p = 0.253$). The greater Breslow thickness observed in men in our cohort reinforces this trend, suggesting both biological and behavioral components influence these outcomes.

Women were more frequently diagnosed under age 50 and at earlier stages, possibly due to greater health-seeking behavior and engagement in skin self-examinations, as described in the literature.[7] In contrast, men reported higher rates of alcohol and tobacco use – factors linked to impaired immune function and worse progression.[8]

In terms of treatment, most patients underwent surgery only (61.3%), while 15.5% received combined modalities such as surgery plus chemotherapy or immunotherapy. A smaller proportion received chemotherapy alone (4.4%), radiotherapy (1.5%), or immunotherapy alone (1.5%). No treatment – usually palliative – was recorded in 15.9% of patients. There were no significant differences in treatment type between men and women ($p = 0.238$) (Table 1).

In survival analysis (mean follow-up: 36-months), worse outcomes were observed in patients with Breslow thickness ≥ 2 mm, Clark level > III, and advanced disease stages ($p < 0.001$). Five-year survival was higher among women (75%) compared to men (50%) ($p < 0.001$) (Fig. 2). This finding is consistent with previous reports showing that men are diagnosed later and have poorer prognosis, even when controlling for tumor stage.[5,6]

Despite no significant sex differences in tumor location or treatment, survival remained lower among men, indicating that anatomical or therapeutic factors alone do not explain this disparity. As supported by previous studies, biological differences in immune response or hormonal influence may contribute to sex-specific disease behavior.[5]

Our study also reinforces the relevance of regional context. Many patients in our cohort came from rural areas,

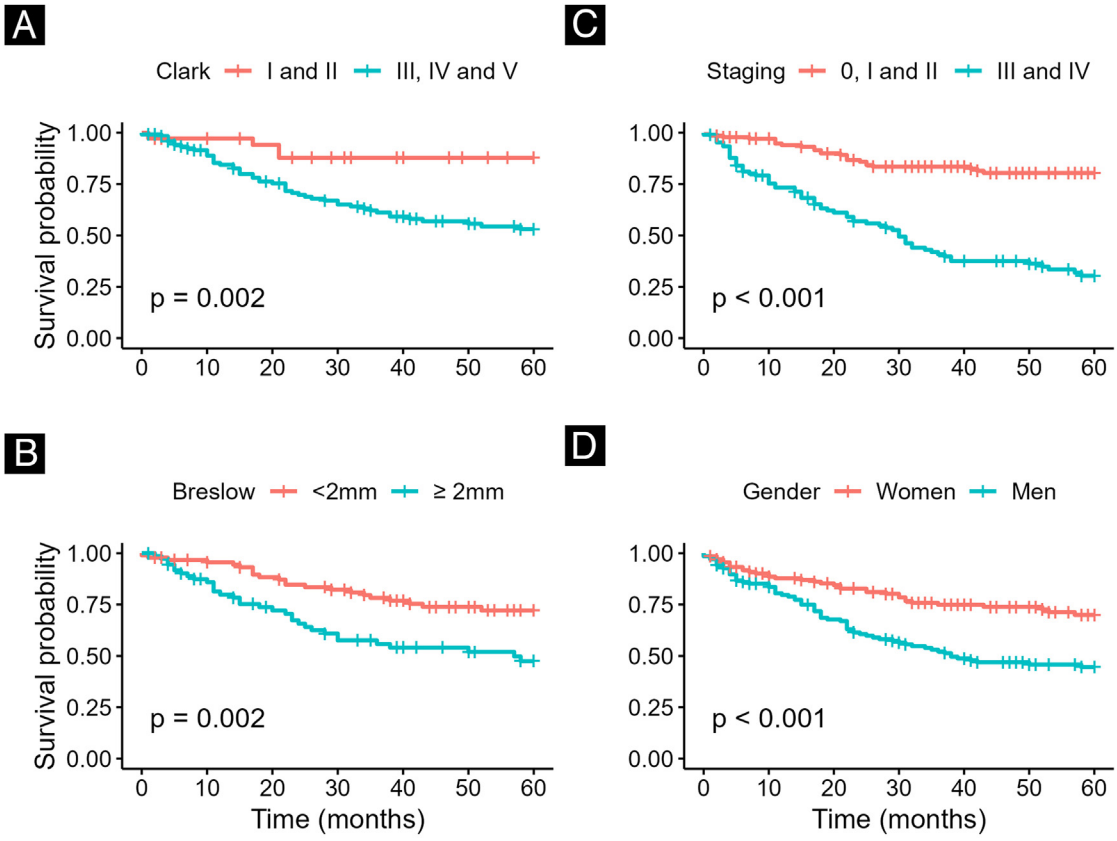

Fig. 2 Survival analysis of patients with melanoma in Southeast Brazil according to (A) Clark level, (B) Breslow depth, (C) disease staging, and (D) gender.

where access to dermatologic care is limited, and sun exposure is chronic, particularly among agricultural workers.[9] These conditions may contribute to delayed diagnoses and worse prognoses, especially in men. Tailored awareness campaigns focusing on rural male populations may help close this gap.

While most patients underwent surgical treatment, advanced therapies such as immunotherapy were rarely used. During the study period (2010–2020), the use of immunotherapy was still incipient in Brazil, which explains its rare application in this cohort. Moreover, the majority of patients were treated within the Brazilian public healthcare system (SUS), where access to high-cost medications remains restricted. Although combinations like nivolumab and ipilimumab have shown survival benefits in metastatic disease,[10] socioeconomic barriers likely limit access in public healthcare settings, underscoring the importance of prevention and early detection.

Our study has limitations. Its retrospective design may introduce bias, and the relatively short follow-up period (median 36-months) limits evaluation of long-term survival. Incomplete medical records also led to the exclusion of cases, which may also have influenced results. Our dataset did not include information on self-care behaviors, such as skin self-examination or healthcare-seeking patterns, that could help explain the differences in stage diagnosis between sexes.

Another limitation of this study is the high proportion of cases without a specified histological subtype, which may have underestimated the prevalence of lentigo maligna melanoma. Also, the grouping of early (I–II) and advanced (III–IV) stages for analysis may have masked distinct prognostic behaviors across individual stages.

Our findings demonstrate significant gender disparities in melanoma outcomes, with men presenting at older ages, with thicker tumors and more advanced disease, leading to worse survival. Taken together, our data support a multifactorial understanding of sex disparities in melanoma, shaped by biological traits, behavioral patterns, healthcare access, and socioeconomic context. Interventions must therefore combine public health efforts, clinical innovation, and equitable healthcare delivery to reduce outcome gaps and improve prognosis for all patients.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

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Conflicts of interest

None declared.

Editor

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LETTER - RESEARCH

IL18 gene variants rs187238 and rs360717 and their associations with psoriasis susceptibility and severity in a Brazilian case-control study☆

Dear Editor,

Psoriasis (PsO) is a chronic inflammatory skin disease of immune-mediated origin, with an estimated prevalence between 1.0% and 3.0% in Western populations, and its pathophysiology involves a complex interaction between keratinocytes and components of the innate and adaptive immune systems.[1] Several hypotheses have been formulated to elucidate the mechanisms underlying the pathogenesis of PsO; however, the prevailing theory proposes that an initial triggering event is followed by a sustained chronic inflammatory phase, regulated by a positive feedback loop, in which keratinocyte activation and proliferation is mediated by cytokines.[2]

Several studies have highlighted the relevance of Interleukin-18 (*IL-18*) in the pathophysiology of PsO. Patients with PsO have significantly elevated levels of *IL-18* in both skin lesions and serum, compared to healthy individuals.[3] Previous investigations have demonstrated a correlation between plasma *IL-18* levels and disease severity, measured by the Psoriasis Area and Severity Index (PASI), suggesting that *IL-18* may act as a potential biomarker for PsO.[4]

Variations in genes encoding cytokines relevant to PsO may be associated with different biological processes and influence disease susceptibility. Single Nucleotide Variants (SNVs) in the *IL17A* and *IL17F*[5] and *IL36G*[6] genes have already been associated with predisposition to PsO. However, data on genetic variants of *IL18* in patients with PsO are scarce in the medical literature.

Thus, aiming to investigate the genetic variants of *IL18* and possible relationships with PsO susceptibility and severity, a case-control study was conducted that included, by convenience sampling, 256 individuals of both sexes, aged between 18 and 70 years, of which 128 patients were diagnosed with PsO recruited from the Dermatology Service of the Specialty Outpatient Clinic of Hospital Universitário (AEHU), Universidade Estadual de Londrina (UEL), Paraná, Brazil. The control group consisted of 128 healthy blood donors from the Regional Blood Center of Londrina, Paraná, Brazil.

Exclusion criteria included thyroid, renal, adrenal, hepatic, gastrointestinal, infectious, oncological diseases, as well as other autoimmune diseases. PsO severity was determined using the PASI at the initial diagnosis, prior to the start of topical and/or systemic treatments. The study was approved by the Research Ethics Committee on Human Beings of UEL under CAAE N. 37420820.0.0000.5231. All participants signed an Informed Consent Form.

Genomic DNA was extracted from the leukocyte layer of peripheral blood using a resin column procedure. Two SNVs of the *IL18* gene were genotyped: rs187238 C > G and IL18 rs360717 G > A. Genotyping of the variants was performed by quantitative real-time Polymerase Chain Reaction (qPCR), using the TaqMan™ method.

Hardy-Weinberg equilibrium was assessed and the frequencies and associations of *IL18* gene variants were analyzed according to allelic, dominant, codominant, recessive, and overdominant genetic models,[7] using the online tool SNPStats (https://www.snpstats.net/start.htm).

To assess the effect of SNVs in the studied groups, binary logistic regression was performed, with the results expressed as Odds Ratio (OR) and 95% Confidence Interval (95% CI). The p-values were adjusted for possible confounding variables, with statistical significance considered when $p < 0.05$.

The distribution of the genotypes of the *IL18* rs187238 C > G and *IL18* rs3607171 G > A variants was in Hardy-Weinberg equilibrium in both study groups (*IL18* rs187238 C > G: $x^2 = 0.7958$, $p = 0.3724$ (control group) and $x^2 = 0.000$, $p = 1.000$ (PsO group); *IL18* rs3607171 G > A: $x^2 = 0.0517$, $p = 0.8201$ (control group) and $x^2 = 0.3178$, $p = 0.5729$ (PsO group). As shown in Table 1, no statistically significant differences were observed in allelic or genotypic frequencies between patients with PsO and healthy controls in the different genetic models.

Additionally, the PsO group was divided according to disease severity, according to PASI (≤ 10 or > 10). No significant differences were identified between the different genotypes and alleles regarding this parameter (Table 2).

☆ Study conducted at the Universidade Estadual de Londrina, Londrina, PR, Brazil.

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Table 1 Frequency distribution of *IL18* rs187238 C > G and *IL18* rs360717 G > A variant genotypes in healthy individuals and in individuals with psoriasis.

Model	Genotype	Control	Psoriasis	OR (95% CI)	p-value
rs187238 C > G					
Allelic	C	188 (73.4%)	192 (75%)	Reference	
	G	68 (26.6%)	64 (25%)	1.02 (0.61 – 1.35)	0.837
Codominant	CC	71 (55.5%)	72 (56.3%)	Reference	
	CG	46 (35.9%)	48 (37.5%)	1.01 (0.59 – 1.72)	0.981
	GG	11 (8.6%)	8 (6.3%)	0.77 (0.29 – 2.06)	0.604
Dominant	CC	71 (55.5%)	72 (56.3%)	Reference	
	CG + GG	57 (44.5%)	56 (43.8%)	0.96 (0.57 – 1.58)	0.882
Recessive	GG	11 (8.6%)	8 (6.3%)	Reference	
	CG + CC	117 (91.4%)	120 (93.8%)	1.29 (0.49 – 3.44)	0.591
Overdominant	CC + GG	82 (64.1%)	80 (62.5%)	Reference	
	CG	46 (35.9%)	48 (37.5%)	1.04 (0.62 – 1.75)	0.886
rs360717 (G > A)					
Allelic	G	190 (74.2%)	191 (74.6%)	Reference	
	A	66 (25.8%)	65 (25.4%)	1.04 (0.65 – 1.43)	0.879
Codominant	GG	71 (55.5%)	71 (55.5%)	Reference	
	GA	48 (37.5%)	47 (36.7%)	0.92 (0.54 – 1.57)	0.767
	AA	9 (7.0%)	10 (7.8%)	1.20 (0.45 – 3.17)	0.717
Dominant	GG	71 (55.5%)	71 (55.5%)	Reference	
	GA + AA	57 (44.5%)	57 (44.5%)	0.96 (0.57 – 1.58)	0.887
Recessive	AA	9 (7.0%)	10 (7.8%)	Reference	
	GA + GG	119 (93.0%)	118 (92.2%)	0.80 (0.31 – 2.08)	0.661
Overdominant	GG + AA	80 (62.5%)	81 (63.3%)	Reference	
	GA	48 (37.5%)	47 (36.7%)	0.90 (0.54 – 1.52)	0.699

Note: Data expressed as absolute numbers and percentages. Analyses adjusted for sex, age, and ethnicity.
OR, Odds Ratio; 95% CI, 95% Confidence Interval.

Table 2 Association between *IL18* rs187238 C > G and *IL18* rs360717 G > A variants and psoriasis activity, assessed by PASI $\leq$ 10 and PASI > 10.

Model	Genotype	PASI $\leq$ 10	PASI > 10	OR (95% CI)	p-value
rs187238 C > G					
Allelic	C	136 (73.1%)	56 (80%)	Reference	0.259
	G	50 (26.9%)	15 (20%)	0.68 (0.35 – 1.33)	
Codominant	CC	50 (53.8%)	22 (62.9%)	Reference	
	CG	36 (38.7%)	12 (34.3%)	0.77 (0.33 – 1.79)	0.546
	GG	7 (7.5%)	1 (2.9%)	0.29 (0.33 – 2.52)	0.261
Dominant	CC	50 (53.8%)	22 (62.9%)	Reference	0.360
	CG + GG	43 (46.2%)	13 (37.1%)	0.68 (0.30 – 1.53)	
Recessive	GG	7 (7.5%)	1 (2.9%)	Reference	0.296
	CG + CC	86 (92.5%)	34 (97.1%)	3.10 (0.36 – 25.00)	
Overdominant	CC + GG	57 (61.3%)	23 (65.7%)	Reference	0.706
	CG	36 (38.7%)	12 (34.3%)	0.71 (0.85 – 1.96)	
rs360717 G > A					
Allelic	G	136 (73.1%)	53 (75.7%)	Reference	
	A	50 (26.9%)	17 (24.3%)	0.87 (0.46 – 1.65)	0.674
Codominant	GG	51 (54.8%)	20 (57.1%)	Reference	
	GA	34 (36.6%)	13 (37.1%)	1.05 (0.45 – 2.43)	0.913
	AA	8 (8.6%)	2 (5.7%)	0.57 (0.11 – 3.00)	0.511
Dominant	GG	51 (54.8%)	20 (57.1%)	Reference	
	GA + AA	42 (45.2%)	15 (42.9%)	0.94 (0.42 – 2.12)	0.892
Recessive	AA	8 (8.6%)	2 (5.7%)	Reference	
	GA + GG	85 (91.4%)	33 (94.3%)	1.78 (0.35 – 9.09)	0.489
Overdominant	GG + AA	59 (63.4%)	22 (62.9%)	Reference	
	GA	34 (36.6%)	13 (37.1%)	1.12 (0.49 – 2.55)	0.793

Data expressed as absolute numbers and percentages. Analyses adjusted for sex, age, and ethnicity.
OR, Odds Ratio; 95% CI, 95% Confidence Interval.

IL-18 has been shown to favor the differentiation and maintenance of T-helper (Th)-17 cells and that the use of neutralizing antibody against IL-18 was able to inhibit the Th17 immune response in a murine model of PsO.[8] These findings indicate that the IL-18-mediated immune response may play a relevant role in PsO pathogenesis, and its inhibition is considered a potential therapeutic strategy.

The present study found no significant differences between *IL18* gene variants and PsO susceptibility or severity. Conversely, a study conducted in the Japanese population identified a significantly higher frequency of the G genotype of the rs187238 variant in individuals with PsO, suggesting that this genotype may be associated with greater functional activity in inducing IL-18 production.[9] From what is known in the medical literature to date, no studies have been described that explore the association between the *IL18* variant rs360717 and PsO.

Similar investigations have been conducted in other dermatological diseases. A meta-analysis with quantitative data suggested that the genetic variant rs187238 of the *IL18* gene may influence the risk of developing atopic dermatitis in the general population.[10]

In conclusion, this is the first Brazilian study to investigate the possible association between the variants rs187238 and rs360717 of the *IL18* gene and PsO. Although the results did not demonstrate a significant association between these genetic variants and disease susceptibility or severity, the data contribute in an unprecedented way to the understanding of the genetic basis of PsO in the Brazilian population. These findings reinforce the importance of further studies to better clarify the role of IL-18 in the pathophysiology of PsO and its potential as a biomarker.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

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Authors' contributions

Cássio Rafael Moreira: Design and planning of the study; collection; analysis and interpretation of data; drafting and editing of the manuscript; critical review of the manuscript; approval of the final version of the manuscript.

Edna Maria Vissoci Reiche: Design and planning of the study; statistical analysis; analysis and interpretation of data; drafting and editing of the manuscript; critical review of the manuscript; approval of the final version of the manuscript.

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Andréa Name Colado Simão: Design and planning of the study; laboratory analysis; statistical analysis; analysis and interpretation of data; drafting and editing of the manuscript; critical review of the manuscript; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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LETTER - RESEARCH

Immunohistochemical analysis of MMP-1 and 2 in patients with lichen planopilaris and frontal fibrosing alopecia☆

Dear Editor,

Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are primary lymphocytic scarring alopecias. Clinically, classic LPP shows an area of irregular alopecia that is more common in the vertex region, while FFA causes hair loss that occurs slowly in the frontotemporal implantation hairline, commonly associated with eyebrow alopecia.[1]

According to Doche et al.,[2] approximately 65% of the scalp biopsy specimens from ''normal-appearing'' areas of LPP and FFA showed perifollicular inflammation around the isthmus/infundibulum region. These findings suggest that both diseases may be more generalized processes affecting the scalp. The lack of relationship between the degree of histopathological inflammation and clinical signs of inflammation supports the idea that some scalp areas could possibly be more prone to develop a cicatricial alopecia.

These disorders are mediated by lymphocytes and result in disruption of the basement membrane cells, destruction of the hair follicle and replacement by fibrosis. They have a chronic course, unpredictable development and, probably, autoimmune pathogenesis. Drugs, infections, genetic factors and immunological abnormalities are possible triggering factors.[3]

Matrix metalloproteinases (MMPs) are involved in cell proliferation and differentiation, inflammation, degeneration, tumor metastasis, and growth. The production and activation of MMPs is rapidly induced when active tissue remodeling is needed. MMP-2, the most widely distributed of all MMPs, along with MMP-9, is said to digest type IV, V and XI collagens; laminin and aggrecan core protein, and singly digests collagens I, II and III.[4]

MMP-1 is capable of degrading type I and III fibrillar collagens.[5]

MMP-4 (or MMP-17) is involved in different pathological processes such as arthritis, cardiovascular disease, and cancer progression.[6]

Our objective was to evaluate the presence of MMP-1 and MMP-2 in LPP and FFA and to assess their role in the pathogenesis of these diseases.

The patients were collected from Renata Zac Dermatological Clinic, Belo Horizonte, MG, Brazil, from 2019 to 2023.

A university ethical committee approval was obtained prior to carrying out this study. Participants taking part gave written informed consent.

Inclusion criteria were patients with clinically and histopathologically proven disease. Patients with lesions not confirmed by biopsy or on treatment at the time of biopsy were excluded from this study.

In this study, 60 patients (48 females and 12 males) aged from 23 to 71 years were included.

To be included in the classical LPP group, the patient should have an irregular involvement of the scalp in the form of plaques presenting with hyperkeratosis, follicular plugs and perifollicular erythema or atrophic scars, mainly in the apex and in the parietal region. Trichoscopy could evidence perifollicular and interfollicular erythema associated with tubular perifollicular scales. Complaints of pruritus and burning sensation were common, as well as the association with the skin, nail and mucosal LP lesions.[3]

To be included in the FFA group, the participants should fulfill the diagnostic criteria for FFA proposed by Vañó-Galván et al.[7] The major criteria are scarring alopecia of the scalp in the frontotemporal region (in the absence of keratotic follicular papules on the body) and bilateral diffuse alopecia of the eyebrows. The minor criteria include trichoscopy with peripilar erythema, peripilar desquamation, or both; histopathological characteristics of scarring alopecia with FFA or LPP pattern; involvement of occipital region, face, sideburns, body hair and presence of non-inflammatory facial papules. The diagnosis requires two major criteria or one major and two minor criteria.

All patients had undergone a scalp biopsy with a 4-mm punch biopsy, with one sample submitted for vertical sections and the other for cross-sectional sections. Diagnosis was confirmed by one pathologist and one dermatologist using hematoxylin and eosin-stained sections. The histopathological alterations found in LPP and FFA are a perifollicular lymphohistiocytic infiltrate, sometimes with

☆ Study conducted at the Clínica Renata Zac, Belo Horizonte, MG, Brazil and Instituto de Assistência Médica do Servidor Público Estadual de São Paulo, São Paulo, SP, Brazil.

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Table 1 Calculation of the Klein score.

% of positive cells (A)	Intensity (B)	Final score
0 = 0%	0 = No reaction	A × B
1 = 1% - 29%	1 = Weak reaction	
2 = 30% - 60%	2 = Moderate reaction	
3 = 61% - 100%	3 = Strong reaction	

a lichenoid pattern, more prominent in the isthmus and infundibulum regions; vacuolar degeneration of basal cells; necrotic keratinocytes; artifactual clefts between the follicle and the perifollicular fibrous band; and perifollicular fibrosis separating the inflammatory infiltrate from the follicle. Over time, there is a reduction and loss of sebaceous glands and destruction of the entire hair follicle.[1]

Twenty apparently normal scalp tissues, age and sex matched, were obtained at the time of facial plastic surgery and used as controls.

This laboratory-based study involved the use of sixty buffered, formalin-fixed, paraffin-embedded tissue blocks of histologically proven cases of LLP, FFA and controls.

The primary antibodies for immunohistochemistry staining included polyclonal antibodies against MMP1 [EP1247Y] (ab52631, Abcam, Cambridge, UK) and MMP2 [6E3F8] (ab86607, Abcam, Cambridge, UK).

The expression of MMP-1 and MMP-2 in LPP, FFA, and control groups was evaluated in the sebaceous glands (SG), all segments of the hair follicles (HF), and the epidermal keratinocytes (KT).

The Klein score is a semiquantitative method used to evaluate the expression of immunohistochemical markers by multiplying the percentage of positive cells by the staining intensity to obtain the final score (Klein et al., 2001).

The Klein score was obtained through the calculation described in Table 1.

Qualitative variables were presented as absolute and relative frequencies, and quantitative variables as minimum, maximum, mean, standard deviation, median, first (Q1) and third (Q3) quartiles. The number of available information (valid n) was presented for each variable.

The association between qualitative variables was assessed using Fisher's exact test. The comparison of quantitative variables between the three comparison groups was performed using the Kruskal-Wallis test.

The analyses were carried out in the R Studio program version 2024.04.2 using the *R* language version 4.4.0, and $p < 0.05$ was considered significant.

There was no difference between the three groups evaluated in the MMP-1 and MMP-2 antibody markers (Figs. 1 and 2 and Tables 2 and 3).

LPP and FFA are primary lymphocytic scarring alopecias in which the lower infundibular and isthmic areas of the hair follicle are primarily affected, the region where follicular stem cells are located.[2]

It has been observed that many patients being followed for LPP and FFA, without inflammatory symptoms

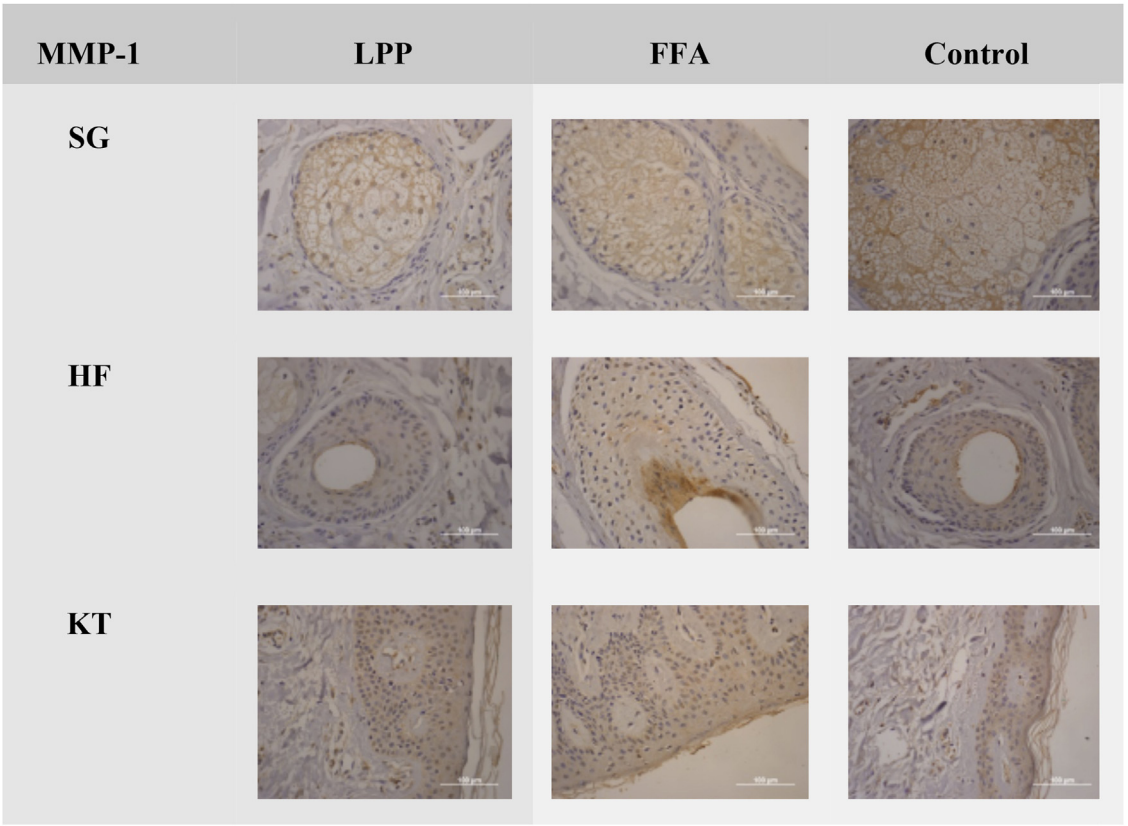

Figure 1 Negative expression of MMP-1 in LPP, FFA, and control groups in the sebaceous glands (SG), hair follicles (HF) and keratinocytes (KT) ×100. Source: research original data.

Table 2 MMP1 antibody data according to the groups evaluated.

Variables	Control	FFA	LPP	p-value
Sebaceous glands				
% Positive cells				–
Min/Max	100.0/100.0	100.0/100.0	100.0/100.0	
Median [Q1; Q3]	100.0 [100.0; 100.0]	100.0 [100.0; 100.0]	100.0 [100.0; 100.0]	
Standard deviation	100.0 (0)	100.0 (0)	100.0 (0)	
N	19	15	15	
Dominant intensity				0.057[a]
No reaction	0 (−)	0 (−)	0 (−)	
Weak reaction	3 (15.8%)	7 (46.7%)	9 (60.0%)	
Moderate reaction	14 (73.7%)	6 (40.0%)	5 (33.3%)	
Strong reaction	2 (10.5%)	2 (13.3%)	1 (6.7%)	
N	19	15	15	
Localization				
Bulb	5 (26.3%)	5 (33.3%)	1 (6.7%)	0.207[a]
Loney hair	0 (-)	1 (6.7%)	2 (13.3%)	0.273[a]
Transversal hair	9 (47.4%)	5 (33.3%)	5 (33.3%)	0.617[a]
Upper portion	6 (31.6%)	3 (20.0%)	7 (46.7%)	0.326[a]
N	19	15	15	
Klein score				0.061[b]
Min/Max	3.0/9.0	3.0/9.0	3.0/9.0	
Median [Q1; Q3]	6.0 [6.0; 6.0]	6.0 [3.0; 6.0]	3.0 [3.0; 6.0]	
Standard deviation	5.8 (1.6)	5.0 (2.2)	4.4 (1.9)	
N	19	15	15	
Hair follicle				
% Positive cells				0.922[b]
Min/Max	0/100.0	0/100.0	0/100.0	
Median [Q1; Q3]	75.0 [57.5; 90.0]	70.0 [30.0; 100.0]	80.0 [20.0; 97.5]	
Standard deviation	69.5 (27.8)	61.1 (39.6)	58.6 (41.9)	
N	20	19	18	
Dominant intensity				0.551[a]
No reaction	1 (5.0%)	4 (21.1%)	4 (22.2%)	
Weak reaction	15 (75.0%)	12 (63.2%)	10 (55.6%)	
Moderate reaction	4 (20.0%)	3 (15.8%)	3 (16.7%)	
Strong reaction	0 (-)	0 (-)	1 (5.6%)	
N	20	19	18	
Klein score				0.620[b]
Min/Max	0/6.0	0/6.0	0/9.0	
Median [Q1; Q3]	3.0 [2.0; 3.0]	3.0 [2.0; 3.0]	3.0 [1.0; 3.0]	
Standard deviation	3.1 (1.6)	2.6 (1.9)	2.8 (2.4)	
N	20	19	18	
Keratinocyte				
% Positive cells				0.780[b]
Min/Max	0/100.0	0/100.0	0/100.0	
Mediana [Q1; Q3]	100.0 [25.0; 100.0]	92.5 [7.5; 100.0]	90.0 [20.0; 100.0]	
Média (dp)	71.1 (40.0)	63.2 (44.7)	62.6 (41.1)	
N válido	19	20	19	
Dominant intensity				0.505[a]
No reaction	2 (10.5%)	5 (25.0%)	1 (5.3%)	
Weak reaction	13 (68.4%)	10 (50.0%)	13 (68.4%)	
Moderate reaction	4 (21.1%)	5 (25.0%)	4 (21.1%)	
Strong reaction	0 (-)	0 (-)	1 (5.3%)	
N	19	20	19	
Klein score				0.971[b]
Min/Max	0/6.0	0/6.0	0/9.0	
Median [Q1; Q3]	3.0 [1.5; 3.0]	3.0 [0.8; 3.8]	3.0 [1.0; 4.5]	
Standard deviation	2.9 (1.9)	2.8 (2.2)	3.1 (2.4)	
N	19	20	19	

Table 2 (*Continued*)

Variables	Control	FFA	LPP	p-value
Layer				0.100[a]
Basal	0 (–)	0 (–)	3 (16.7%)	
Basal and Parabasal	17 (100.0%)	15 (100.0%)	15 (83.3%)	
N	17	15	18	
Limphocytes				
Presence				–
Negative	0 (–)	0 (–)	0 (–)	
Positive	14 (100.0%)	19 (100.0%)	15 (100.0%)	
N válido	14	19	15	
Dominant intensity				0.731[a]
No reaction	5 (35.7%)	3 (15.8%)	2 (13.3%)	
Weak reaction	4 (28.6%)	10 (52.6%)	8 (53.3%)	
Moderate reaction	4 (28.6%)	4 (21.1%)	4 (26.7%)	
Strong reaction	1 (7.1%)	2 (10.5%)	1 (6.7%)	
N	14	19	15	

[a] Teste Exato de Fisher.
[b] Teste de Kruskal-Wallis.

Table 3 MMP2 antibody data according to the groups evaluated.

Variables	Control	FFA	LPP	p-value
Sebaceous glands				
% Positive cells				–
Min/Max	100.0/100.0	100.0/100.0	100.0/100.0	
Median [Q1; Q3]	100.0 [100.0; 100.0]	100.0 [100.0; 100.0]	100.0 [100.0; 100.0]	
Standard deviation	100.0 (0)	100.0 (0)	100.0 (0)	
N	19	13	16	
Dominant intensity				0.602[a]
No reaction	0 (–)	0 (–)	0 (–)	
Weak reaction	0 (–)	0 (–)	0 (–)	
Moderate reaction	1 (5.3%)	2 (15.4%)	2 (12.5%)	
Strong reaction	18 (94.7%)	11 (84.6%)	14 (87.5%)	
N	19	13	16	
Localization				
Bulb	3 (15.8%)	5 (38.5%)	1 (6.2%)	0.103[a]
Loney hair	0 (–)	0 (–)	2 (12.5%)	0.176[a]
Transversal hair	10 (52.6%)	7 (53.8%)	4 (25.0%)	0.203[a]
Upper portion	8 (42.1%)	3 (23.1%)	8 (50.0%)	0.323[a]
N	19	13	16	
Klein score				0.625[b]
Min/Max	6.0/9.0	6.0/9.0	6.0/9.0	
Median [Q1; Q3]	9.0 [9.0; 9.0]	9.0 [9.0; 9.0]	9.0 [9.0; 9.0]	
Standard deviation	8.8 (0.7)	8.5 (1.1)	8.6 (1.0)	
N	19	13	16	
Hair follicle				
% Positive cells				0.360[b]
Min/Max	100.0/100.0	70.0/100.0	90.0/100.0	
Median [Q1; Q3]	100.0 [100.0; 100.0]	100.0 [100.0; 100.0]	100.0 [100.0; 100.0]	
Standard deviation	100.0 (0)	98.0 (7.0)	99.4 (2.4)	
N	20	20	18	
Dominant intensity				0.883[a]
No reaction	0 (–)	0 (–)	0 (–)	
Weak reaction	2 (10.0%)	3 (15.0%)	3 (16.7%)	
Moderate reaction	12 (60.0%)	9 (45.0%)	9 (50.0%)	
Strong reaction	6 (30.0%)	8 (40.0%)	6 (33.3%)	

Table 3 (*Continued*)

Variables	Control	FFA	LPP	p-value
N	20	20	18	
Klein score				0.914[b]
Min/Max	3.0/9.0	3.0/9.0	3.0/9.0	
Median [Q1; Q3]	6.0 [6.0; 9.0]	6.0 [6.0; 9.0]	6.0 [6.0; 9.0]	
Standard deviation	6.6 (1.8)	6.8 (2.1)	6.5 (2.1)	
N	20	20	18	
Keratinocyte				
% Positive cells				0.387[b]
Min/Max	100.0/100.0	100.0/100.0	10.0/100.0	
Mediana [Q1; Q3]	100.0 [100.0; 100.0]	100.0 [100.0; 100.0]	100.0 [100.0; 100.0]	
Média (dp)	100.0 (0)	100.0 (0)	95.5 (20.1)	
N válido	18	20	20	
Dominant intensity				0.933[a]
No reaction	0 (−)	0 (−)	0 (−)	
Weak reaction	3 (16.7%)	4 (20.0%)	5 (25.0%)	
Moderate reaction	9 (50.0%)	10 (50.0%)	11 (55.0%)	
Strong reaction	6 (33.3%)	6 (30.0%)	4 (20.0%)	
N	18	20	20	
Klein score				0.575[b]
Min/Max	3.0/9.0	3.0/9.0	1.0/9.0	
Median [Q1; Q3]	6.0 [6.0; 9.0]	6.0 [6.0; 9.0]	6.0 [5.2; 6.0]	
Standard deviation	6.5 (2.1)	6.3 (2.2)	5.8 (2.2)	
N	18	20	20	
Layer				–
Basal	0 (−)	0 (−)	0 (−)	
Basal and Parabasal	18 (100.0%)	20 (100.0%)	20 (100.0%)	
N	18	20	20	
Limphocytes				
Presence				–
Negative	0 (−)	0 (−)	0 (−)	
Positive	13 (100.0%)	19 (100.0%)	13 (100.0%)	
N válido	13	19	13	
Dominant intensity				0.086[a]
No reaction	0 (−)	0 (−)	0 (−)	
Weak reaction	0 (−)	1 (5.3%)	3 (23.1%)	
Moderate reaction	1 (7.7%)	3 (15.8%)	4 (30.8%)	
Strong reaction	12 (92.3%)	15 (78.9%)	6 (46.2%)	
N	13	19	13	

[a] Teste Exato de Fisher.
[b] Teste de Kruskal-Wallis.

or signs, continue with the progression of the area of alopecia.[1]

Wong and Goldberg,[8] found statistically significant differences between the extent of the inflammatory infiltrate below the isthmus in FFA when compared with LPP (92% vs. 63%; p = 0.02) but found no differences between the inflammatory infiltrate intensity in the two diseases.

Although the pathophysiology of both diseases remains unknown, an autoimmune aetiology is favoured. However, the dramatic increase in the incidence of FFA over the past decade has caused investigators to also postulate a strong potential environmental aetiology for this disease.[2]

We recommend that patients with FFA/LPP avoid daily use of chemical sunscreens and/or sunscreens containing titanium dioxide. Furthermore. General allergen avoidance is important in controlling scalp symptoms.[9]

In oral squamous cell carcinoma, there is an increased expression of MMPs that play an important role in tumor progression. MMP-2 and MMP-9 play an important role in the cleavage of type IV collagen, facilitating the disruption of the basement membrane and migration of dysplastic cells.[4]

Despite the expression of MMP-2 observed mainly in the lymphocytic band in the lamina propria in oral lichen planus,[4] it was not noticed in the patients with LPP or FFA in our study.

MMP-1 positively affects the wound-healing process and reduces unwanted scar formation. Therefore, MMP-1 can potentially be used for preventing or treating hypertrophic scars.[10]

We believe that MMPs increase in situations where there is collagen breakdown and disruption of the basal membrane zone, but in cicatricial alopecias, there is mainly

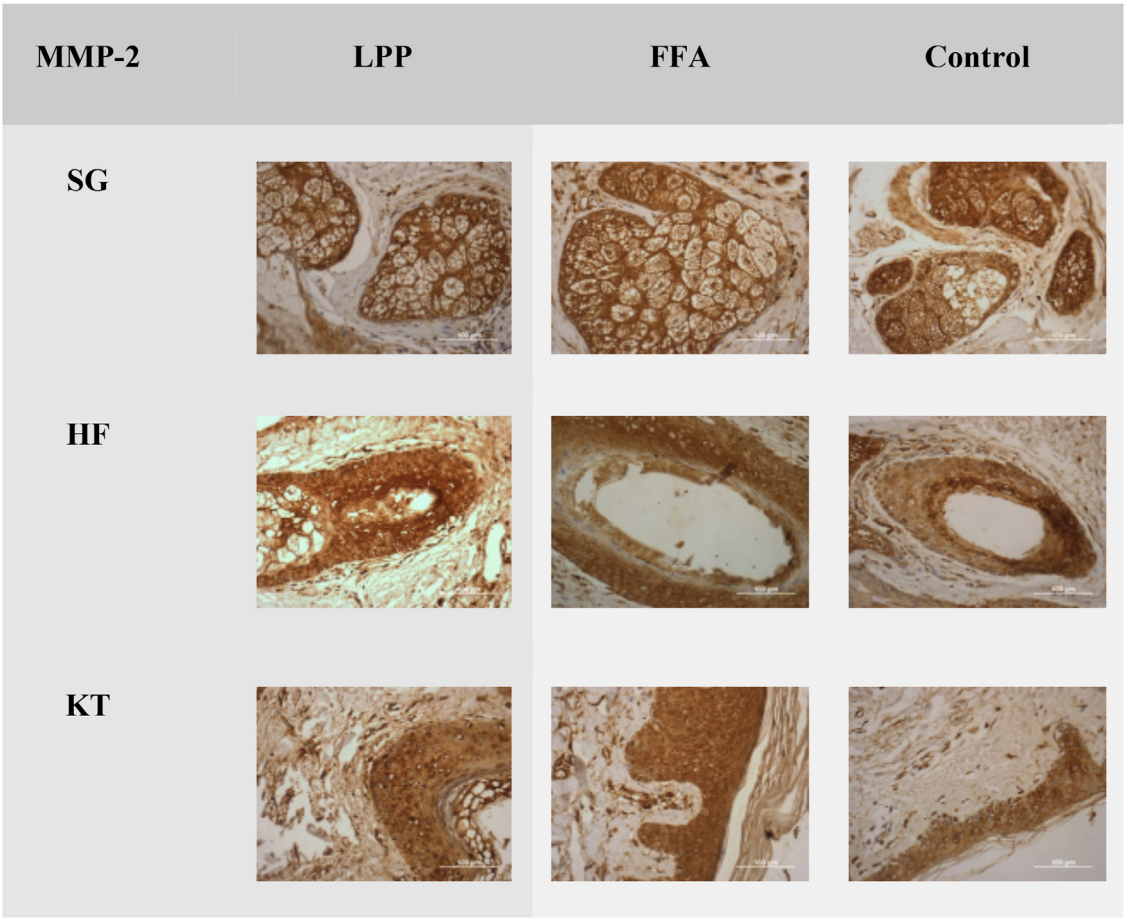

Figure 2 Same expression of MMP-2 in LPP, FFA, and control groups in the sebaceous glands (SG), hair follicles (HF) and keratinocytes (KT) ×100. Source: research original data.

accumulation of this substance in the perifollicular zone and fibrosis.

A key limitation of standard immunohistochemistry when studying matrix metalloproteinases (MMPs) is that it detects the presence and location of the protein (total amount, active and inactive), but it does not provide information on its enzymatic activity, which zymography does measure.

MMP-1 and 2 aren't probably not mediators in the pathogenesis of FFA and LPP.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

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The study received financial support from Fundo de Apoio a Dermatologia (FUNADERM) of the Brazilian Society of Dermatology.

Authors' contributions

Renata Indelicato Zac: The study concept and design; data collection, or analysis and interpretation of data; statistical analysis; writing of the manuscript or critical review of important intellectual content; data collection, analysis and interpretation; 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.

Adilson da Costa: The study concept and design; data collection, or analysis and interpretation of data; statistical analysis; writing of the manuscript or critical review of important intellectual content; data collection, analysis and interpretation; 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.

Emily Ferreira Salles Pilar: Data collection, or analysis and interpretation of data; data collection, analysis and interpretation.

Julio Cesar Moraes: Data collection, or analysis and interpretation of data; data collection, analysis and interpretation.

Isabel Cristina Gomes Moura: Statistical analysis.

Moisés Salgado Pedrosa: Data collection, or analysis and interpretation of data; data collection, analysis and interpretation.

Conflicts of interest

None declared.

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LETTER - RESEARCH

Incidence and mortality of cutaneous melanoma stratified by sex, age, and age group – An analysis of the Brazilian population from 2013 to 2023☆

Dear Editor,

Cutaneous melanoma accounts for nearly 90% of all skin cancer-related deaths worldwide.[1] When detected at early stages, prognosis is significantly better, underscoring the importance of population-level screening. Globally, both incidence and mortality have shown a sustained upward trend, with the greatest burden concentrated in high-income regions.[2] Among these, Australia remains a global reference due to the exceptionally high incidence of melanoma and the early implementation of nationwide screening and education campaigns, initiated in the 1980s. These efforts likely contributed to the observed peak in incidence in 2005, followed by a gradual decline.[3] In contrast, other socioeconomically developed nations, including the United States, have not yet achieved similar reductions in incidence.[4]

In Brazil, the Brazilian Society of Dermatology launched national skin cancer awareness and early detection campaigns beginning in 1999. Despite these initiatives, morbidity and mortality related to melanoma remain substantially high.[5] Genetic susceptibility, chronic ultraviolet exposure, and the country's vast territorial and climatic heterogeneity all contribute to melanoma risk. Meanwhile, access to genetic risk testing and advanced diagnostic technologies remains limited across Brazilian territory, reflecting broader structural inequalities in the healthcare system.[6]

Given this scenario, understanding sociodemographic determinants of melanoma risk is essential to support targeted screening, equitable resource allocation, and the design of cost-effective public health strategies – particularly in large and unequal countries such as Brazil. High-income nations, such as Australia, have already demonstrated that structured policies can lead to stabilization or reduction in melanoma mortality.[3] This reinforces the urgency of implementing scalable and accessible early-detection strategies in Brazil.

Previous studies examining melanoma trends in Brazil have suggested that population growth and aging may be outpacing improvements in diagnostic capacity, potentially contributing to underdiagnosis or delayed detection in certain regions.[5,7,8] To contribute to this discussion, we conducted an ecological study using secondary data from DATASUS, which is the public database of the Brazilian Ministry of Health. Case counts were extracted from the Hospital Information System (SIH/SUS), deaths from the Mortality Information System (SIM/SUS), and annual population estimates from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística – IBGE). Melanoma cases were identified using the ICD-10 code C43, and rates were calculated per 100,000 inhabitants.

Between 2013 and 2023, a total of 20,087 melanoma cases were reported in Brazil. A slight male predominance was observed, with men accounting for 57.5% of cases and women 42.5%. This sex distribution remained stable over the decade. Annual case counts increased gradually from 1,547 in 2013 to 2,047 in 2023 – an overall increase of approximately 32% (Table 1).

Mortality rates also demonstrated consistent sex disparities. Age-adjusted mortality was higher among men throughout the study period, ranging from 0.93 to 1.14 deaths per 100,000 inhabitants, whereas female mortality ranged from 0.63 to 0.80. Although small year-to-year oscillations were observed, the persistent difference suggests a systematically elevated risk of melanoma-related death among men in Brazil (Table 2).

Age was strongly associated with mortality. Individuals younger than 30-years accounted for fewer than 2% of deaths. Mortality increased markedly after age 50, with progressive escalation across older age groups. Adults aged 80-years and older represented the highest mortality burden, accounting for 22.9% of all deaths between 2013 and 2023. Additionally, the relative contribution of the ≥80-year-old group increased over time – from 19.3% of deaths in 2013 to 24.9% in 2023 – highlighting the growing influence of population aging on melanoma mortality in Brazil (Table 3 and 4).

Ethnicity also played an important role. Self-declared White individuals consistently exhibited the highest mortal-

☆ Study conducted at the University Center FMABC, Santo André, Brazil.

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Table 1 Melanoma cases per sex, 2013–2023*.

Sex	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	Total
Male	903 (58.37)	916 (56.93)	1012 (56.41)	1036 (58.43)	1031 (56.19)	1038 (57.99)	1159 (58.59)	1120 (58.24)	1057 (57.70)	1102 (56.25)	1176 (57.45)	11,550 (57.5)
Female	644 (41.63)	693 (43.07)	782 (43.59)	737 (41.57)	804 (43.81)	752 (42.01)	819 (41.41)	803 (41.76)	775 (42.30)	857 (43.75)	871 (42.55)	8,537 (42.5)
Total	1547 (100)	1609 (100)	1794 (100)	1773 (100)	1835 (100)	1790 (100)	1978 (100)	1923 (100)	1832 (100)	1959 (100)	2047 (100)	20,087 (100)

* Values presented in Absolute and relative frequency.

Table 2 Melanoma incidence per 100 000 inhabitants, by sex, from 2013 to 2023.

Sex	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Male	0.78	0.77	0.79	0.79	0.76	1.84	2.82	2.42	2.41	2.72	2.89
Female	0.60	0.59	0.58	0.57	0.55	1.75	2.83	2.37	2.33	2.73	3.01

Table 3 Melanoma incidence per 100,000 inhabitants by age group, 2013–2023.

Age group (years)	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
0–19	0.03	0.02	0.03	0.02	0.02	0.07	0.14	0.10	0.11	0.10	0.14
20–24	0.10	0.11	0.09	0.07	0.07	0.30	0.38	0.29	0.24	0.30	0.32
25–29	0.19	0.16	0.17	0.20	0.14	0.41	0.57	0.57	0.47	0.46	0.47
30–34	0.25	0.34	0.26	0.26	0.24	0.57	0.98	0.70	0.67	0.66	0.72
35–39	0.43	0.46	0.46	0.39	0.39	0.89	1.34	1.05	1.08	1.06	1.14
40–44	0.81	0.63	0.66	0.62	0.57	1.36	2.03	1.72	1.47	1.55	1.79
45–49	1.09	0.80	1.15	0.94	0.80	1.91	2.95	2.36	2.53	2.53	2.78
50–54	1.38	1.39	1.28	1.21	1.10	2.83	4.40	3.61	3.21	3.78	4.04
55–59	2.01	1.86	1.71	1.69	1.61	3.93	6.01	5.03	4.63	5.48	5.38
60–64	2.27	2.24	2.11	2.12	2.14	4.96	7.98	6.98	6.96	7.32	7.95
65–69	2.92	2.52	2.98	2.79	2.64	6.83	10.18	8.60	8.48	9.73	10.16
70–74	2.55	3.23	2.63	3.06	3.12	8.27	12.71	11.00	10.56	13.19	13.35
75–79	3.75	3.55	3.28	3.38	2.78	10.35	15.82	12.44	12.59	14.47	16.28
80 and older	1.93	2.47	2.33	2.17	2.79	10.45	16.23	13.58	13.98	16.55	17.08

Table 4 Melanoma mortality per 100,000 inhabitants by age group, 2013–2023.

Age group (years)	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
0–19	0.01	0.01	0.02	0.02	0.01	0.01	0.01	0.01	0.02	0.01	0.01
20–24	0.06	0.07	0.04	0.09	0.07	0.04	0.05	0.07	0.04	0.04	0.06
25–29	0.11	0.12	0.12	0.13	0.12	0.09	0.10	0.10	0.10	0.12	0.10
30–34	0.27	0.22	0.23	0.25	0.23	0.19	0.21	0.16	0.19	0.23	0.20
35–39	0.41	0.40	0.40	0.42	0.35	0.36	0.28	0.31	0.31	0.31	0.31
40–44	0.51	0.63	0.61	0.59	0.51	0.49	0.48	0.43	0.40	0.43	0.40
45–49	0.72	0.87	0.91	0.81	0.84	0.80	0.79	0.69	0.70	0.86	0.75
50–54	1.07	0.98	1.29	1.45	1.21	1.15	1.13	1.07	0.93	1.02	1.10
55–59	1.72	1.63	1.76	1.61	1.51	1.37	1.54	1.64	1.53	1.42	1.40
60–64	2.37	2.23	2.49	2.23	2.38	2.18	2.42	2.09	2.08	2.07	2.32
65–69	3.10	3.39	3.26	2.87	3.05	2.80	3.37	2.96	2.75	2.66	2.83
70–74	4.12	3.74	4.87	3.89	3.93	4.04	4.57	4.24	3.73	4.58	4.14
75–79	5.42	5.30	5.52	6.08	5.66	6.02	5.58	6.17	4.86	5.30	5.54
80 and older	8.98	9.60	10.67	10.31	10.89	10.53	11.42	10.89	10.51	10.63	11.13

Table 5 Melanoma deaths by ethnicity, 2013–2023.

Ethnicity	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	Total
White	1,262 (81.58)	1,305 (81.11)	1,439 (80.65)	1,430 (80.65)	1,464 (79.78)	1,418 (79.17)	1,563 (79.02)	1,485 (77.22)	1,424 (77.73)	1,576 (80.45)	1,599 (78.11)	15,965 (79.48)
Black	38 (2.46)	34 (2.11)	42 (2.34)	41 (2.31)	50 (2.72)	32 (1.79)	62 (3.13)	47 (2.44)	42 (2.29)	45 (2.30)	49 (2.39)	482 (2.40)
Asian	8 (0.52)	2 (0.12)	5 (0.28)	1 (0.06)	7 (0.38)	3 (0.17)	4 (0.21)	7 (0.36)	5 (0.27)	6 (0.31)	7 (0.34)	55 (0.27)
Brown	172 (11.12)	189 (11.75)	243 (13.71)	243 (13.71)	257 (14.01)	267 (14.94)	307 (15.52)	303 (17.58)	316 (17.25)	307 (15.67)	359 (17.54)	3,030 (14.95)
Indigenous	1 (0.06)	2 (0.12)	1 (0.06)	0 (0)	4 (0.22)	1 (0.06)	2 (0.10)	3 (0.16)	0 (0)	1 (0.05)	1 (0.05)	15 (0.07)
Unreported	66 (4.27)	77 (4.79)	59 (3.29)	58 (3.27)	53 (2.89)	70 (3.91)	40 (2.02)	43 (2.24)	45 (2.46)	25 (1.28)	32 (1.56)	568 (2.83)
Total	1,547 **(100)**	1,609 **(100)**	1,794 **(100)**	1,773 **(100)**	1,835 **(100)**	1,791 **(100)**	1,978 **(100)**	1,923 **(100)**	1,832 **(100)**	1,959 **(100)**	2,047 **(100)**	**20,088** **(100)**

Data are expressed as absolute numbers and percentages of melanoma-related deaths by ethnicity between 2013 and 2023.

ity rates, representing 77%–81% of deaths across all years analyzed (Table 5).

Brazil's heterogeneous ethnic distribution helps contextualize this pattern. The South and Southeast regions – historically shaped by extensive European immigration – concentrate the majority of White individuals in the country and consequently report the highest melanoma incidence and mortality.[9] This demographic pattern aligns with findings from our national dataset and helps explain regional differences in melanoma burden.

Our findings are consistent with the long-standing epidemiological profile described in a large population-based cohort from Blumenau, Santa Catarina, which followed melanoma incidence over nearly four decades. That study demonstrated a persistent predominance of melanoma among White men older than 54-years, with incidence increasing steadily throughout the observation period.[9] The similarity between our national findings and the Blumenau cohort reinforces the hypothesis that demographic composition – particularly the high concentration of individuals of European descent in southern Brazil – plays a substantial role in shaping the distribution of melanoma in the country.

In addition to environmental and demographic factors, sex-specific behavioral and biological determinants may contribute to the disproportionate burden among men. International studies have shown that men tend to engage less frequently in photoprotection, delay dermatological evaluation, and have lower adherence to preventive measures.[10] Biological susceptibility has also been proposed: differences in immune response, DNA repair capacity, and UV-radiation-induced carcinogenesis may predispose men to more aggressive tumor behavior, regardless of geographic or socioeconomic context.[9,10] Together, these factors may help explain the higher mortality observed among Brazilian men.

Taken as a whole, our findings illustrate a multifactorial scenario in which demographic, behavioral, biological, and structural healthcare determinants converge to shape melanoma burden in Brazil. If current global patterns are maintained, Brazil may follow the trajectory of high-income countries, with potential stabilization or gradual decline in incidence among younger individuals, but a continued rise in cases among adults older than 55-years due to population aging. With improved public awareness and expanded screening strategies, however, a reduction in mortality is possible, as demonstrated in other national experiences.[1–3]

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Authors' contributions

Débora Terra Cardial: Conception and study design; data collection, analysis, and interpretation; statistical analysis; manuscript drafting or critical revision for important intellectual content; data acquisition, analysis, and interpretation; active participation in research supervision; intellectual contribution to the diagnostic and/or therapeutic management of the studied cases; critical literature review; final approval of the submitted version of the manuscript.

Francisco Macedo Paschoal: Conception and study design; active participation in research supervision; intellectual contribution to the diagnostic and/or therapeutic management of the studied cases; final approval of the submitted version of the manuscript.

Luiz Vinicius de Alcantara Sousa: Conception and study design; data collection, analysis, and interpretation; statistical analysis; data acquisition, analysis, and interpretation;

active participation in research supervision; critical literature review; final approval of the submitted version of the manuscript.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

Editor

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LETTER – RESEARCH

Predictors of early high-level response to bimekizumab in patients with moderate-to-severe plaque psoriasis: a real-world cohort study☆

Dear Editor,

Bimekizumab is a highly effective therapeutic option in the management of psoriasis; however, treatment response remains heterogeneous in real-world practice, and baseline predictors of high-level response have not been well characterized in routine clinical settings.[1–3] Accordingly, this study aimed to identify baseline characteristics predictive of achieving a Psoriasis Area and Severity Index (PASI) -90 response at week-16 in patients with moderate-to-severe psoriasis receiving bimekizumab.

Advances in the management of moderate-to-severe psoriasis have been driven by biologic therapies targeting the IL-23/IL-17 axis, a pathway central to the disease's immunopathogenesis.[4] Bimekizumab, a humanized monoclonal antibody designed for the dual neutralization of IL-17A and IL-17F, has demonstrated superior efficacy in phase 3 trials over selective IL-17A or TNF-α inhibitors.[1–3] The dual-inhibition strategy is to achieve a more comprehensive suppression of psoriatic inflammation by targeting the distinct pathogenic roles of both IL-17 isoforms.[5]

The expanding therapeutic landscape for psoriasis presents a critical challenge in selecting the optimal biologic for individual patients. This challenge is compounded by the substantial response heterogeneity observed in real-world practice. Identifying baseline factors predictive of therapeutic success is therefore crucial for advancing personalized medicine. Although factors such as baseline disease severity, body weight, and prior biologic exposure have been implicated in the response to various biologics,[6] robust predictors for bimekizumab in routine clinical care have yet to be defined. Accordingly, this study aimed to identify baseline characteristics predictive of achieving a PASI-90 response at week-16 in patients with moderate-to-severe psoriasis receiving bimekizumab.

Table 1 Baseline characteristics of study population (n = 102).

Characteristic	Value
Demographics	
Age, mean ± SD, years	47.2 ± 13.8
Male sex, n (%)	65 (63.7)
Body mass index, mean ± SD, kg/m^2	28.1 ± 5.4
Current smoking, n (%)	48 (47.1)
Disease Characteristics	
Disease duration, mean ± SD, years	14.6 ± 9.2
Age of disease onset, mean ± SD, years	32.6 ± 12.1
Baseline PASI score, mean ± SD	16.8 ± 8.7
PASI 0–20 (mild-moderate), n (%)	68 (66.7)
PASI > 20 (severe), n (%)	34 (33.3)
Family history of psoriasis, n (%)	43 (42.2)
Psoriatic arthritis, n (%)	31 (30.4)
Special Area Involvement, n (%)	
Scalp	53 (52.0)
Nail	44 (43.1)
Palmoplantar	29 (28.4)
Genital	22 (21.6)
Face	24 (23.5)
Prior Treatment History	
Biologic-naive, n (%)	46 (45.1)
1 prior biologic, n (%)	32 (31.4)
≥ 2 prior biologics, n (%)	24 (23.5)
Prior Biologic Classes (n = 56), n (%)	
Anti-TNF	25 (44.6)
Anti-IL-17	19 (33.9)
Anti-IL-23	25 (44.6)
Anti-IL-12/23	10 (17.9)
Comorbidities, n (%)	
Any comorbidity	77 (75.5)
Hypertension	36 (35.3)
Diabetes mellitus	19 (18.6)
Dyslipidemia	17 (16.7)
Psychiatric disorders	24 (23.5)
Respiratory diseases	17 (16.7)

☆ Study conducted at the Department of Dermatology and Venereology, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey.

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Table 2 Baseline characteristics by PASI-90 response status at week-16.

Characteristic	PASI90 Responders (n = 80)	Non-responders (n = 22)	p-value
Demographics			
Age, mean ± SD, years	44.2 ± 12.1	52.8 ± 14.6	**0.006**
Male sex, n (%)	52 (65.0)	13 (59.1)	0.61
BMI, mean ± SD, kg/m^2	28.0 ± 5.5	28.4 ± 5.2	0.76
Disease Characteristics			
Disease duration, mean ± SD, years	14.3 ± 9.3	15.7 ± 8.9	0.53
Age of disease onset, mean ± SD, years	29.9 ± 11.2	37.1 ± 13.5	**0.012**
Baseline PASI, mean ± SD	13.4 ± 6.8	18.9 ± 9.2	**0.003**
Special Area Involvement, n (%)			
Scalp	41 (51.2)	12 (54.5)	0.78
Nail	23 (28.8)	12 (54.5)	**0.01**
Palmoplantar	22 (27.5)	7 (31.8)	0.69
Genital	17 (21.2)	5 (22.7)	0.88
Face	18 (22.5)	6 (27.3)	0.64
Treatment History			
Biologic-naive, n (%)	41 (51.2)	6 (27.3)	**0.03**
1 prior biologic, n (%)	24 (30.0)	8 (36.4)	0.56
≥2 prior biologics, n (%)	15 (18.8)	8 (36.4)	0.08
Comorbidities, n (%)			
Any comorbidity	58 (72.5)	19 (86.4)	0.17
Hypertension	25 (31.2)	11 (50.0)	0.10
Diabetes mellitus	13 (16.2)	6 (27.3)	0.24
Psychiatric disorders	17 (21.2)	7 (31.8)	0.30
Psoriatic arthritis	23 (28.8)	8 (36.4)	0.48

Continuous variables compared using Student's *t*-test or Mann-Whitney *U*-test.
Categorical variables compared using χ^2 or Fisher's exact test.

We conducted a retrospective cohort study of adults with moderate-to-severe chronic plaque psoriasis who initiated bimekizumab between December 2024 and June 2025 at a single tertiary center. The primary endpoint was PASI-90 response at week-16. We extracted baseline demographics, disease characteristics, difficult-to-treat site involvement, and prior treatment history from electronic medical records. The severity of the disease was categorised according to the patient's PASI score at the beginning of the study. This was consistent with the severity thresholds established for clinical practice and therapeutic guidelines: moderate psoriasis (PASI 10–20) and severe psoriasis (PASI > 20).

All statistical analyses were conducted using *R* version 4.3.0. Baseline characteristics were compared between patients who achieved a PASI-90 response (responders) and those who did not (non-responders). Variables with a potential association in the univariate analysis ($p < 0.20$) were included in a multivariate logistic regression model. A final, parsimonious model was then derived via a backward elimination procedure, retaining only independent predictors with a significance level of $p < 0.05$.

The final analysis included a cohort of 102 patients. Baseline clinical and demographic characteristics are presented in Table 1, while characteristics of responders and non-responders are presented in Table 2. The cohort was predominantly male (63.7%) with a mean age of 47.2-years. Patients presented with established, moderate-to-severe disease, as reflected by a mean disease duration of 14.6-years and a mean baseline PASI score of 16.8 (range: 10.2–38.4). The majority of patients had mild-to-moderate disease severity (baseline PASI 0–20: n = 68, 66.7%), while 34 patients (33.3%) had severe disease (baseline PASI > 20). A majority of patients (54.9%) were biologic-experienced. At the primary endpoint of week-16, a PASI-90 response was achieved by 80 of 102 patients (78.4%).

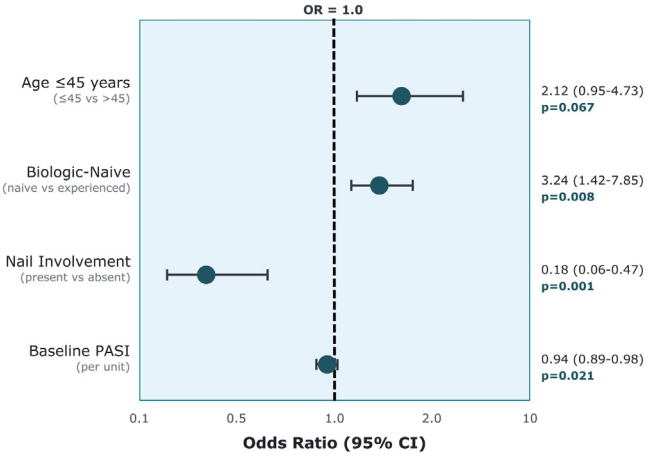

Fig. 1 Forest plot showing multivariate predictors of PASI-90 response at week-16. OR > 1 indicates favorable factor; OR < 1 indicates unfavorable factor.

Multivariate logistic regression analysis identified three independent baseline predictors of a PASI-90 response at week-16 (Table 3, Fig. 1). A biologic-naive status was positively associated with the outcome (Odds Ratio [OR = 3.24]; p = 0.008), whereas both a higher baseline PASI score

Table 3 Univariate and multivariate logistic regression analysis for PASI-90 response at week-16.

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Demographics				
Age ≤ 45-years (vs. > 45)	2.43 (1.21–4.88)	**0.012**	2.12 (0.95–4.73)	0.067
Male sex	1.28 (0.64–2.55)	0.481	–	–
BMI (per kg/m^2)	0.98 (0.92–1.05)	0.625	–	–
Current smoking	0.86 (0.43–1.72)	0.671	–	–
Disease Characteristics				
Disease duration (per year)	0.98 (0.94–1.03)	0.532	–	–
Baseline PASI (per unit)	0.91 (0.86–0.96)	**0.001**	0.94 (0.89–0.98)	**0.021**
Family history of psoriasis	0.89 (0.44–1.78)	0.743	–	–
Psoriatic arthritis	0.69 (0.33–1.44)	0.324	–	–
Special Area Involvement				
Scalp	0.88 (0.44–1.76)	0.721	–	–
Nail	0.34 (0.16–0.72)	**0.005**	0.18 (0.06–0.47)	**0.001**
Palmoplantar	0.82 (0.37–1.81)	0.623	–	–
Genital	0.91 (0.38–2.19)	0.834	–	–
Face	0.77 (0.33–1.79)	0.544	–	–
Treatment History				
Biologic-naive	2.78 (1.35–5.72)	**0.006**	3.24 (1.42–7.85)	**0.008**
Number of prior biologics				
0 (reference)	1.00	–	–	–
1	0.44 (0.20–0.97)	**0.041**	–	–
≥ 2	0.27 (0.11–0.65)	**0.003**	–	–
Comorbidities				
Any comorbidity	0.42 (0.16–1.11)	0.081	0.58 (0.19–1.76)	0.337
Hypertension	0.46 (0.21–0.98)	**0.045**	0.71 (0.29–1.74)	0.451
Diabetes mellitus	0.51 (0.20–1.31)	0.164	–	–
Dyslipidemia	0.74 (0.28–1.95)	0.541	–	–
Psychiatric disorders	0.58 (0.24–1.39)	0.223	–	–

OR, Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index.
Variables with p < 0.20 in univariate analysis were entered into the multivariate model. Final model was determined using backward stepwise selection with retention threshold p < 0.10.
OR < 1 indicates decreased odds of achieving PASI90 response; OR > 1 indicates increased odds of achieving PASI90 response.
Model performance: Area under the curve = 0.78 (95% CI 0.68–0.88); Hosmer-Lemeshow goodness-of-fit test p = 0.42.

(OR = 0.94; p = 0.021) and the presence of nail involvement (OR = 0.18; p = 0.001) were inversely associated with achieving the endpoint. The final predictive model yielded an Area Under the receiver operating Characteristic Curve (AUC) of 0.78.

Superior efficacy in biologic-naive patients with psoriasis carries substantial clinical implications. These findings underscore that the first biologic therapy represents the optimal opportunity for achieving robust and durable treatment response. This therapeutic window progressively narrows with each subsequent line of therapy – a phenomenon attributable to two key mechanisms: the selection of inherently treatment-resistant disease phenotypes and the emergence of neutralizing anti-drug antibodies.[7] Our data advocate for the strategic deployment of highly effective biologics early in the treatment algorithm to maximize long-term clinical outcomes. Physicians should prioritize positioning the most potent therapeutic agents as first-line treatment, rather than reserving these medications for treatment-refractory disease.

The inverse relationship between baseline PASI score and treatment success is also an important finding. For each one-unit increase in baseline PASI, the odds of achieving PASI-90 decreased by 6% (OR = 0.94, 95% CI 0.89–0.98). This result is consistent with reports for other highly effective biologics,[8] suggesting that a greater inflammatory burden may indicate a more persistent disease state that is difficult to resolve completely. This observation supports the current clinical strategy of early and effective intervention.

Nail involvement emerged as the strongest negative predictor of achieving near-complete skin clearance, highlighting a major therapeutic challenge. The nail unit presents significant treatment barriers due to its unique anatomical structure and specialized immune environment, which creates a drug-resistant site with limited drug penetration and persistent inflammatory cells.[9] This finding aligns with clinical observations showing nail psoriasis takes much longer to clear than skin lesions, even with highly effective biologics like bimekizumab.[10] The results show the need for realistic treatment expectations and potentially more intensive therapeutic approaches in patients with baseline nail involvement.

Findings from the initial 16-week treatment period underscore the importance of managing patient expec-

tations, particularly for individuals with nail psoriasis. Clinicians should counsel patients about the differential response rates: rapid skin clearance remains achievable, while nail disease resolution follows a more gradual trajectory requiring sustained treatment. Notably, traditional metabolic factors, including BMI and common comorbidities, did not emerge as significant predictors of response in this analysis. Bimekizumab appears to maintain robust efficacy across diverse patient subgroups. The consistent efficacy across different demographic and clinical profiles supports the broad applicability of our predictive model in routine practice.

In this real-world analysis of patients (n = 102) with moderate-to-severe psoriasis, three baseline factors were identified as independent predictors of an early high-level response to bimekizumab: prior exposure to biologics, severity of disease, and nail involvement. Patients without prior biologic exposure demonstrated superior treatment outcomes. Conversely, elevated baseline PASI scores and the presence of nail involvement were identified as negative predictors for achieving a PASI-90 response at the 16-week timepoint. The stratification of patients by expected treatment response, optimization of therapeutic choices, and establishment of realistic goals are made possible by these predictive factors. A practical framework is thus provided for the individualization of bimekizumab therapy and for guiding patient counseling regarding anticipated outcomes in routine practice.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Authors' contributions

Burhan Engin: Contributed to conceptualization, methodology, and supervision.

Yusuf Demir: Was responsible for data curation, investigation, and writing the original draft.

Gurbuz Yildirim: Performed data curation, formal analysis, and contributed to writing-review and editing.

Fatma Zehra Diken: Handled investigation, data curation, and visualization.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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LETTER – RESEARCH

Primary periocular basal cell carcinoma: recurrence, risk factors and follow-up☆

Dear Editor,

Primary basal cell carcinoma (BCC) is the most common periocular malignant tumor.[1] Periocular tumors present therapeutic challenges due to the need for radical surgical excision while preserving eyelid function and facial aesthetics.

Although established guidelines recommend long-term follow-up for patients diagnosed with BCC due to the high risk of developing new lesions,[1] Brazil lacks a national registry for skin or periocular cancers. Available data are derived from small hospital-based studies, and national guidelines do not include standardized long-term follow-up protocols, leaving monitoring decisions to individual clinicians.

To propose a tailored follow-up strategy for the Brazilian context, we retrospectively reviewed patients with primary periocular BCC who underwent surgical excision at our university hospital between March 2012 and December 2019 (Ethics approval: 39820420.1.0000.5411). All included patients who had complete excision of primary periocular BCC, confirmed histological subtype, documented margin status, and at least 12-months of follow-up. Non-periocular BCCs, recurrent tumors, prior radiotherapy or cryotherapy, immunosuppression, Gorlin-Goltz syndrome, and incomplete records were excluded.

We analyzed 135 histologically confirmed periocular BCC lesions from 116 patients, averaging 19.28 lesions treated annually. Periocular BCC predominantly affected elderly individuals, with a mean age of 69.47 ± 12.16 years old (range: 37–93) and a median age of 72. This trend likely reflects cumulative sun exposure, reduced DNA repair capacity, and age-related decline in immune response.[2]

Of the patients, 63 (54.31%) were female, with no significant gender difference in the occurrence of BCC. A higher incidence of periocular BCC in women has already been reported.[3] The vast majority of patients (111/95.69%) had phototypes I or II, reinforcing the established link between BCC and lighter pigmentation, especially in individuals chronically exposed to sunlight. In contrast, darker skin provides greater UV protection and is associated with lower BCC risk.[4]

The mean tumor size was 7.23 ± 4.96 mm (range: 2–40 mm; median: 8 mm). The lower eyelid was the most affected site (110/81.48%), followed by the medial canthus (11/8.15%), upper eyelid (7/5.19%), lateral canthus (6/4.44%), and eyebrow (1/0.74%), consistent with previous studies.[5,6] The lower eyelid and medial canthus are more exposed to UV radiation and inflammatory agents such as tear components. The upper eyelid, protected by the brow and orbital anatomy, showed a lower frequency. No significant laterality effect was noted, although some studies suggest a higher incidence on the side of the face more exposed during driving.[7]

Tumors were generally conventionally excised under local anesthesia with 2–5 mm safety margins, depending on lesion size, consistent with other reports.[8] Wider excision is recommended for aggressive subtypes of tumors (sclerodermiform, mixed), though it may compromise cosmetic and functional outcomes.[9]

In our clinic, frozen section or surgical excision with a safety margin is reserved for lesions with indistinct borders. This differs from other approaches that use frozen sections routinely or opt for wide local excision or Mohs surgery.[1]

The most common histological subtype was nodular (59/43.70%), followed by mixed (52/38.52%) (Table 1). Perineural invasion occurred in only one case (1/0.74%), consistent with other studies.[5,6,10]

We observed nine recurrences: 6 (66.67%) occurred in lesions with clear margins, underscoring that negative margins do not eliminate recurrence risk; 3 (33.33%) recurrences were from lesions with compromised margins. Of the 14 cases with involved margins, only 3 (21.43%) recurred. Reported recurrence rates for positive margins vary widely,[5,8,9] depending on histological subtype, surgical excision type, and follow-up duration.[1]

Recurrences in our cohort were significantly associated with histological subtype ($p = 0.037$), being more frequent in nodular (3/33.33%), mixed (2/22.22%), and sclerodermiform (2/22.22%) subtypes. While nodular BCC is generally well-defined and amenable to complete excision, its recur-

☆ Study conducted at the Faculty of Medicine, Universidade Estadual Paulista, Botucatu, SP, Brazil.

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Table 1 Histological classification and surgical margins of periocular BCC treated at Faculty of Medicine – UNESP, 2025.

Variable	Frequency	%
Histological classification		
Nodular	59	43.70
Mixed	52	38.52
Sclerodermiform	7	5.19
Multifocal	2	1.48
Other[a]	2	1.48
No information	13	9.63
Perineural involvement		
No	130	96.3
Yes	1	0.74
No information	4	2.96
Committed margins		
No	110	81.48
Yes	14	10.37
No information	3	2.22
Committed margins and location[b]		
Deep	11	42.31
Lateral	10	38.46
Nasal	2	7.69
Upper	2	7.69
Lower	1	3.85

[a] Others: Micronodular, multifocal, infiltrative, fibroepithelial, basosquamous, plexiform, keratotic and metatypy (WHO, 2006).
[b] More than one margin can be affected (Total = 26).

Table 2 Recurrence after exeresis according to histological subtype and years.

Histological subtype	Committed margins	Reccurrence (years)
Mixed	No	1,23
No information	No	1,68
Mixed	Yes	1,39
Sclerodermiform	No	1,09
Others	Yes	1,34
Nodular	Yes	1,34
Sclerodermiform	No	6,64
Nodular	No	6,25
Nodular	No	5,18

rence rate in our sample likely reflects its high prevalence rather than intrinsic aggressiveness. In mixed BCC, the lesion may be composed of either high-risk or low-risk subtypes, making it important for the histological report to specify which subtypes are present in the lesion. Conversely, aggressive subtypes such as sclerodermiform are known to pose greater risks of incomplete excision and recurrence. Most recurrences occurred in the lower eyelid (8/88.89%) or in the medial canthus (1/11.11%), which were also the most common tumor locations. No significant association was found between recurrence and tumor size or margin status. Tumor-free surgical margins were achieved in 110 (81.48%) lesions, while compromised margins were identified in 14 (10.37%) cases. Twelve (8.89%) cases had indefinite margins; a known possibility related to the quality of some specimens.

The most frequently affected margin was the deep plane (11/42.31%), like other reports.[1] Although BCC typically exhibits limited depth invasion, meticulous excision of the deep portion remains essential. In the medial canthus, erroneous efforts to preserve the lacrimal drainage system may inadvertently result in incomplete excision. Nevertheless, complete removal must remain the surgical goal to prevent orbital invasion and associated morbidity.

The mean follow-up duration was 3.41 ± 2.68 years (median: 2.84). Most patients' lesions (88/75.86%) remained in follow-up, 39 (28.89%) were lost to follow-up after two years, four (2.96%) died from unrelated causes, and four lesions (2.96%) were from patients without disposable data on the records. No BCC metastases were reported. Table 2 presents recurrence according to histological subtype, committed margins and time to observe lesion recurrence. Mean time to recurrence was 2.92 ± 2.37 years (range: 1.09–6.25; median: 1.39-years).

According to other studies, periocular BCC recurrence rates are influenced by tumor location, size, histological subtype (more aggressive subtypes include micronodular, infiltrative, sclerosing, and morphea), margin status, immune function, systemic diseases, prior recurrences, and adjuvant treatments.[6,10]

The approach to incomplete excision of BCC remains controversial. Since not all cases of low-risk tumors will recur,[9] we recommend that re-excision should be evaluated on a case-by-case basis, considering factors such as high-risk anatomical location, involvement of deep or lateral margins, and the patient's ability to adhere to follow-up.

Histologically compromised margins or incomplete lesion removal are not definitive predictors of recurrence. Recurrence may not occur even after several years, and clinical observation may be appropriate. Possible explanations for the absence of recurrence include devitalization of residual tumor cells by postoperative inflammation, containment within excision margins, differences in tumor biology, surgical technique, clinical management, or other biological mechanisms not yet fully understood. However, although re-excision is not necessary in all cases, it is strongly recommended for positive margins, particularly in high-risk histological subtypes, with meticulous excision of the affected margin.

Postoperative follow-up of excised periocular BCCs represents a significant workload for clinicians, and institutional protocols vary. For completely excised nodular BCC, recurrence risk is low, and follow-up for at least one year is recommended.

For aggressive subtypes, follow-up should extend to a minimum of five years, while recurrent tumors require indefinite surveillance. Approximately 30% of recurrences occur within the first year, and up to 82% within five years, reinforcing this period as the critical window for monitoring.

However, the purpose of follow-up is not only to detect local recurrence but also to identify new BCCs. Individuals who have already had one carry a 30%–40% risk of developing another,[9] and therefore the patient requires close surveillance.

Limitations and strengths

The limitations of this study include its retrospective design, which inherently involves incomplete information in medical records, the involvement of multiple surgeons, and histopathological evaluations performed by doctors in training – factors that may affect the external validity and reproducibility of the findings. Another study limitation is that surgical margin assessment was not specified in 100% of the margins; such a comprehensive evaluation could have provided additional data to strengthen the conclusions. Notable strengths include the relatively large number of lesions analyzed, which contributes to the statistical robustness of the data. Additionally, all surgical procedures and histopathological evaluations were conducted under the supervision of a senior ophthalmologist and a dermatopathologist, enhancing diagnostic accuracy and classification reliability.

Recommendations

- Early diagnosis, timely treatment, and consistent follow-up of periocular BCC are essential to reduce morbidity and mortality.
- Because patients with a history of BCC have an increased risk of developing additional tumors, follow-up should monitor both recurrence and the emergence of new lesions.
- Patient education on self-surveillance and sun protection is critical for early detection and prevention.
- Complete excision of low-risk lesions carries a low recurrence risk; such patients may be monitored for one year.
- Recurrences occurred on average three years post-surgery, with earlier recurrences (around one year) often associated with positive margins. Patients with compromised margins or confirmed recurrence should remain under annual follow-up, including routine dermatological assessments, for at least five years, regardless of subtype. After five years, patients may transition to primary care follow-up, provided that primary care teams are trained in lesion surveillance.

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Authors' contributions

Raquel Galvão Bezerra: Collection, analysis, and interpretation of data; drafting and editing of the manuscript; approval of the final version of the manuscript.

Daniela Cristina dos Santos Souza: Analysis of histological slides; Approval of the final version of the manuscript.

José Eduardo Correntes: Statistical analysis; Approval of the final version of the manuscript.

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Silvana Artioli Schellini: Design and planning of the study; critical review of important intellectual content; approval of the final version of the manuscript.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

Editor

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LETTER - RESEARCH

Prurigo nodularis: case series of 28 Brazilian patients treated with psychotropic medications☆

Dear Editor,

Prurigo nodularis (PN) is a chronic, intensely pruritic dermatosis of unknown cause. PN develops predominantly in adults,[1] affecting men and women equally; in a US study, 53.1% were women, while 46.9% were men.[2] The pathophysiology of PN remains unknown; mechanisms of neuronal sensitization and a cycle of itching and scratching contribute to the chronicity of the disease, with a clear influence of emotional factors.[1]

PN is defined as an intense, chronic pruritic condition with the presence of numerous localized or generalized papulo-nodular lesions. They are distributed symmetrically in areas of the skin accessible to scratching, being more common on the length of the limbs. A characteristic sign is the absence of lesions in areas inaccessible to scratching, such as the upper back, demonstrating that lesions are self-inflicted. Nodules present with a rough, sometimes excoriated surface and are generally dark in color. Most PN patients report a combination of sensations ranging from heat and cold to stinging, burning, and tingling.[3]

PN can occur in healthy individuals or in conjunction with systemic diseases: kidney disease, hepatitis C, obstructive pulmonary disease, congestive heart failure, and atopic diathesis (AD).[4] It is also associated with advanced HIV infection and mental health disorders.[2] Anxiety occurs in 37% of patients, followed by depression in 29%, and suicidal ideation in 19%.[5] It is believed that patients with PN have a threefold increased risk of depression compared to other inflammatory dermatoses. Furthermore, the severity of depression has been shown to have a direct impact on the intensity of pruritus, highlighting the importance of intervening in the mental state.[6]

Treatment of PN is challenging. Recommendations include topical corticosteroids, capsaicin, calcineurin inhibitors, phototherapy, and systemic gabapentinoids, μ-opioid receptor antagonists, antidepressants, immunosuppressants, or biologics such as dupilumab.[7] Our psychodermatosis group approaches the disease as being entirely secondary to scratching due to uncontrollable pruritus. We therefore present our findings on the treatment of PN with psychotropic medications that modify the sensation of pruritus.

Our objective is to describe the clinical characteristics and follow-up of 28 patients with PN seen at the Psychodermatology Clinic of the Department of Dermatology, Hospital das Clínicas, University of São Paulo, Brazil. We also present our findings on the treatment of PN with psychotropic medications that modify the sensation of pruritus.

We conducted a retrospective case series study of patients with PN from 2012 to 2024. Patients were included if they met the current diagnostic criteria: presence of firm, nodular lesions; pruritus lasting at least 6-weeks; and history or signs, or both, of repeated scratching, picking, or rubbing.[8] Characteristics are depicted in Table 1. Our results showed a higher prevalence of women (21/28, 75%), with a mean age of 52.93 years (28–81 years). Most patients had disseminated lesions (Figs. 1 and 2). Skin lesions were distributed across areas accessible to hand scratching: limbs, trunk, lower back, and face. The most frequent comorbidity was hypertension (n = 7), followed by diabetes mellitus type 2 (n = 4) and previously diagnosed depression (n = 2). Lichen simplex chronicus (LSC) was the most common skin comorbidity (n = 6), followed by AD (n = 2). Skin biopsies were performed in 13 patients and revealed hyperorthokeratosis, hypergranulosis, acanthosis, dermal fibrosis, and moderate lymphohistiocytic inflammatory infiltrate in all patients. Previous treatments, which mostly included oral antihistamines combined with topical corticosteroids and emollients, were completely ineffective. The treatments instituted by our group included doxepin (doses between 10–100 mg/day), amitriptyline (doses between 25–100 mg/day), fluoxetine and pregabalin. The follow-up period for these patients ranged from a single visit to 14 years (mean: 887 days). Four patients were lost to follow-up before any response could be assessed (4/28). Most patients who were followed up showed a satisfactory response, ranging from partial to complete. Only a small minority did not show a favorable outcome with doxepin.

☆ 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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Table 1 Characteristics of patients with PN and their treatments.

Case	Age	Gender	Medical records	Duration of disease (m)	Associated psychiatric disease	Treatment and dosage	Time of treatment (m)	Clinical response	Follow-up (m)
1	43	F	Allergic rhinitis and asthma	95	–	Amytriptyline 50 mg/d	73	Complete improvement	88
2	65	F	–	64	Paranoid schizophrenia	Amytriptyline 50 mg/d	45	Complete improvement	58
3	71	M	Metabolic syndrome	36	–	Amytriptyline 50 mg/d	9	Partial improvement	11
4	72	F	Hypertension and type II diabetes	45	–	Amytriptyline 50 mg/d	25	Complete improvement	30
5	66	F	Hypertension	81	Bipolar disorder/ depression	Doxepin 25 mg/d	56	Complete improvement	65
6	48	F	–	155	–	Doxepin 25 mg/d, Fluoxetine 20 mg/d, Gabapentin 900 mg/d	96	Partial improvement	149
7	28	F	–	67	–	Amytriptyline 25 mg/d	38	Partial improvement	59
8	55	F	–		–	Doxepin 10 mg/d	–	–	–
9	60	M	Epilepsy	103	–	Doxepin 40 mg/d	87	Complete improvement	98
10	75	F	–	20	–	Amytriptyline 50 mg/d	3	Partial improvement	8
11	30	F	–	49	–	Lost follow-up	0	–	0
12	66	M	Type II diabetes	14	–	Lost follow-up	0	–	0
13	40	F	Atopic dermatitis	12	–	Lost follow-up	0	–	0
14	64	M	Hypertension/ type II diabetes	75	–	Amytriptyline 75 mg/d	56	Complete improvement	63
15	53	F	Chronic venous insuficiência	8	–	Doxepin 20 mg/d	1	–	1
16	30	F	–	86	–	Doxepin 20 mg/d	72	Partial improvement	76
17	81	F	–	95	–	Doxepin 15 mg/d	78	Complete improvement	88
18	61	M	Rheumatoid arthritis	14	–	Doxepin 20 mg/d	8	Poor response	11
19	79	F	Hypertension/ dyslipidemia	84	–	Doxepin 20 mg/d	67	Poor response	75
20	44	M	–	63	–	Doxepin 35 mg/d	57	Complete improvement	52

Table 1 (*Continued*)

Case	Age	Gender	Medical records	Duration of disease (m)	Associated psychiatric disease	Treatment and dosage	Time of treatment (m)	Clinical response	Follow-up (m)
21	43	F	–	43		Amytriptyline 75 mg/d	34	Complete improvement	37
22	74	F	Hypertension	9	Depression	Lost follow-up	0		0
23	60	F	Fibromyalgia/Osteoporosis	38	–	Fluoxetine 20–60 mg/d, Gabapentin 1200 mg/d	25	Partial improvement	27
24	29	F	Sickle cell anemia	51	–	Amytriptyline 50 mg/d	38	Partial improvement	45
25	43	F	Rhinitis, asthma, Atopic dermatitis	9	–	Amytriptyline 50 mg/d	1	Complete improvement	2
26	59	F	Hypertension/ type II diabetes	11	–	Amytriptyline 50 mg/d	1	Partial improvement	2
27	54	F	–	86	–	Doxepin 30 mg/d	69	Partial improvement	73
28	56	M	HIV/Hypertension	20	–	Amitriptyline 50 mg/d, Doxepin 10 mg/d	13	Partial improvement	15

M, Male; F, Female, d, Day, m, Months.

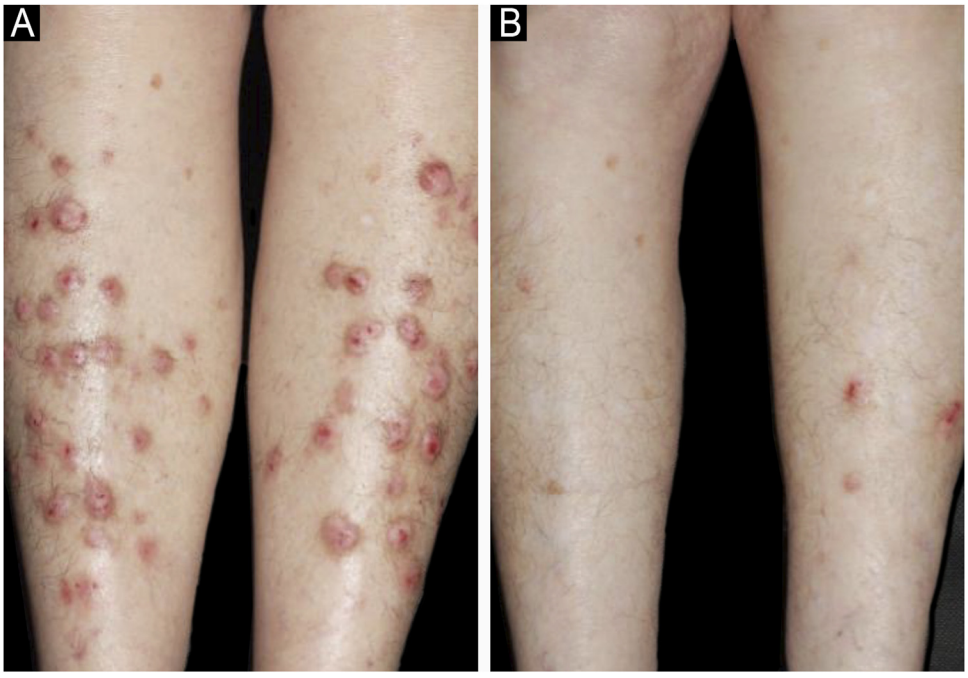

Figure 1 (A) Case 20 – the lesions were limited to the legs in this patient. (B) Same patient after 6-months taking doxepin 35 mg/day.

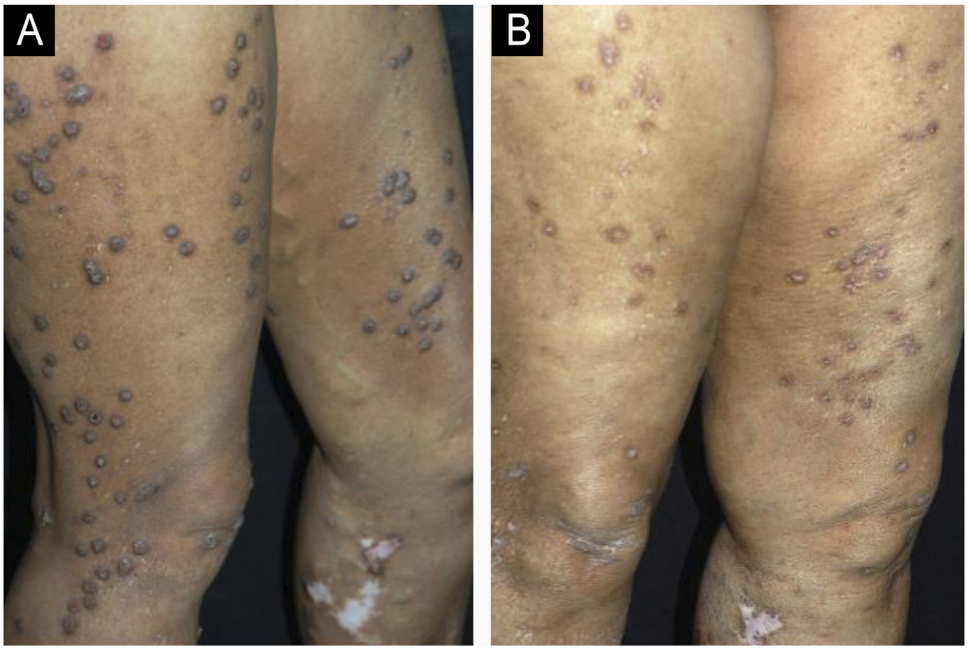

Figure 2 (A) Case 2 – numerous PN lesions. (B) Same patient after 8-months taking amitriptyline 50 mg/day.

To our knowledge, this is the first retrospective study to evaluate clinical characteristics, long follow-up, and treatment outcomes of patients with PN in Brazil.

PN patients often present with significant psychological changes and substantially impaired quality of life. Topical treatments and antihistamines are completely ineffective for the treatment of PN, as these drugs are poor antipruritics and histamine is not implicated in the genesis of this condition.

Gabapentinoids, immunosuppressants (methotrexate, cyclosporine, azathioprine), antidepressants (mirtazapine, selective serotonin reuptake inhibitors), thalidomide, dupilumab, and other immunobiological medications are reported as being more effective. We believe that medications that reduce itching may be more effective than immunosuppressants, since lesions are secondary to scratching, and not due to a primary inflammatory phenomenon.

Tricyclic antidepressants are effective antipruritic agents due to their action on the central nervous system, even if patients do not present with obvious depression on clinical examination. Even in the latter, we observe a clear influence of mental state on pruritus, and treatment with psychotropics should be attempted. In our Psychodermatology Clinic, we have obtained excellent results with their use in various pruritic conditions (neurotic excoriations, LSC, lichen amyloidosis). Doxepin is a tricyclic antidepressant not commercially available in our setting, being purchased through compounding pharmacies. It has strong antipruritic action, with an affinity for H1 receptors 56-times greater than that of hydroxyzine and 775-times greater than that of diphenhydramine. We begin with a dose of 10 mg/day (2.5–5 mg/day in the elderly), and we gradually increase every four weeks until the desired result is achieved. It is administered as a single nightly dose, and its main side effect is drowsiness, which can be controlled by adjusting the dose and timing of administration, so that sedation occurs in the early morning rather than during the day. Most of our cases were adequately controlled with doses less than 50 mg/day, with only a few requiring higher doses. Amitriptyline is a low-cost tricyclic antidepressant, a good alternative to doxepin, but the therapeutic range is more limited: it starts with 25 mg/day at night, and few patients tolerate doses higher than 75 mg/day due to the sedative effect.[9] Peculiarities regarding its prescription in patients with comorbidities should be individualized on a case-by-case basis.

Serotonin reuptake inhibitors (fluoxetine, paroxetine) have less antipruritic effect than tricyclics, but can be tried in cases where there is intolerance to the latter.[10] The mechanism of action of gabapentinoids is unclear; it is believed that they inhibit the $\alpha 2\delta$ subunit of voltage-gated calcium channels in the dorsal root ganglion and dorsal horn of the spinal cord, thus increasing the threshold for neuronal excitation by pruritic stimuli. The upper limit of the recommended dosage is 3,600 mg/day for gabapentin and 600 mg/day for pregabalin. The most common side effects are neurological symptoms such as drowsiness, dizziness, fatigue, and sedation.[11] We only use these drugs in exceptional cases.

Adjuvant therapy for PN includes intralesional corticosteroid injection in resistant lesions. These should be injected at a high concentration (10 mg/mL of triamcinolone hexacetonide), in a small volume, and within the nodules (and not underneath), thus causing their reduction through atrophy, without compromising the surrounding skin.

Studies have shown increased expression of STAT6 in PN lesional skin, which is a marker for Th2 cells that release IL-4,10,13. These cytokines are the focus of dupilumab, which targets the IL-4 receptor, and nemolizumab, which targets the IL-31 receptor.[12] Consistent with the central role of Th2 cytokines, blocking the IL-4/13 or IL-31 signaling pathways has demonstrated short and long-term efficacy in the treatment of PN.[5]

Limitations of our study included its retrospective design and results from a single academic center.

There are currently no therapeutic guidelines for the management of PN. As psychological factors definitively influence the course of PN (given the clear improvement in the condition with psychotropic drugs), we believe that, in the future, the association of psychotropics with modern interleukin inhibitors should be studied as a more comprehensive therapy, especially in cases where there is no response to simpler treatments.

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Authors' contributions

Paula Gerlero: Data analysis and interpretation, active participation in research supervision, intellectual participation in the therapeutic management of the case studies, final approval of the final version of the manuscript.

Shirley Stefania Ilvay-Mendoza: Study conception and design, data collection, article writing, data interpretation, critical review of the literature, and final approval of the final version of the manuscript.

Alexandre Jack Dwan: Data analysis and interpretation, active participation in research supervision, intellectual participation in the therapeutic management of the case studies, and final approval of the final version of the manuscript.

Marcello Menta Simonsen Nico: Study conception and design, data analysis and interpretation, critical review of important intellectual content, active participation in research supervision; intellectual participation in the therapeutic management of the case studies, final approval of the final version of the manuscript.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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The patients in this manuscript have given written informed consent to the publication of their case details.

Editor

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LETTER – RESEARCH

The efficacy and sustainability of a reduced risankizumab dose after achievement of low disease activity of psoriasis: a 24-week study☆

Dear Editor,

Biologic drugs have significantly transformed the management of psoriasis due to their high efficacy, enabling many patients to achieve complete or near-complete clearance.[1] While sustained treatment is recommended to maintain efficacy, continuous administration at the standard dosing regimen may lead to overtreatment for some patients.[2] Dose reductions may reduce the cumulative biologic drug exposure, potential adverse effects, and healthcare costs.[3–6] On the other hand, this approach requires individualized treatment with close monitoring for relapses.

Studies that report dose reductions primarily focus on TNF-alpha and IL-12/23 inhibitors.[3–7] Data on IL-23 inhibitors remain limited.[8,9] Risankizumab, an IL-23 inhibitor, is recommended for psoriasis at a dose of 150 mg subcutaneously at weeks- 0 and -4 and every 12-weeks thereafter. Our study aimed to evaluate the efficacy and sustainability of a reduced risankizumab dose (75 mg every 12 weeks) in patients achieving complete or near-complete clearance, and to explore factors associated with successful outcomes.

This retrospective study was conducted at a tertiary psoriasis clinic. We reviewed the patients treated with risankizumab between 2021 and 2024. The treatment was initiated according to the recommended standard dosing scheme. Eligibility for dose reduction required minimal disease activity after a minimum of 52-weeks of treatment, defined as absolute PASI (Psoriasis Area and Severity Index) $\leq$3 and inactive psoriatic arthritis for the preceding 24-weeks. With patient consent, the maintenance dose was reduced to 75 mg every 12-weeks.

Patients with flares (PASI score >3 and/or exacerbation of psoriatic arthritis) were escalated back to standard dosing or switched to another biologic. Demographic and clinical data included age, sex, Body Mass Index (BMI), involvement of special areas, presence of psoriatic arthritis, comorbidities, previous systemic treatments, and PASI scores at baseline, week-16, and week-52 of the recommended risankizumab dose, and at dose reduction, weeks-12 and -24 following reduced-dose maintenance treatment. PASI scores and psoriatic arthritis activity were recorded at week-12 in patients who were switched back to the standard risankizumab dose due to relapse of skin or joint symptoms.

Continuous variables are expressed as mean $\pm$ SD, categorical variables as n (%), and compared using appropriate tests. A two-tailed $p < 0.05$ was considered significant. The study received approval from the institutional review board (approval number: 72–2024).

A total of 21 patients (14 males, 7 females; mean age 47.5$\pm$16.7 years) were included; 7 (33.3%) had concomitant psoriatic arthritis. The characteristics of the patients are summarized in Table 1.

The mean PASI score at baseline was 14.3$\pm$6.2 (range 7.7–38.6). Dose reductions were made at a mean of 75.4-weeks from baseline (range 52–100 weeks), at which time the mean PASI score was 0.6 (range 0–2.4), with 47.6% of the patients having complete clearance. The PASI scores of the patients before and after dose reduction are summarized in Table 2.

Following dose reductions, loss of efficacy was observed in five patients. Two patients developed mild skin lesions that increased the absolute PASI score above 3 at weeks-12 and -24. Three patients had exacerbations of psoriatic arthritis at weeks-12 (n = 1) and 24 (n = 2), despite PASI scores of 0.

No significant differences were found between patients who sustained efficacy and those who did not in terms of age ($p = 0.842$), gender ($p = 0.280$), BMI ($p = 0.333$), disease duration ($p = 0.398$), or previous biologic experience ($p = 1.00$). The mean PASI scores at baseline were also similar ($p = 0.062$). None of the 10 patients who achieved a PASI score of 0 until dose reductions experienced relapses in skin lesions.

Of the five patients with loss of efficacy, standard maintenance dose treatment (150 mg every 12-weeks) was reinstituted in four. In one patient, who had experienced arthritis flares, the treatment was switched to certolizumab due to plans for pregnancy. Following dose elevations, remission was re-achieved in three patients. In one patient,

☆ Study conducted at the Department of Dermatology and Venereology, Haseki Training and Research Hospital, Istanbul, Turkey.

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Table 1 Demographic and clinical characteristics of patients and prior treatments.

	Total group (n = 21)
Age, mean ± SD	47.5 ± 16.7
Gender, n (%): male/female	14 (66.7) / 7 (33.3)
Body mass index, mean ± SD	27.1 ± 3.7
Psoriatic arthritis, n (%)	7 (33.3)
Comorbidities	n (%)
Dyslipidemia	4 (19.0)
Obesity	4 (19.0)
Coronary artery disease	3 (14.3)
Hypertension	3 (14.3)
Hepatosteatosis	2 (9.5)
Benign prostatic hyperplasia	2 (9.5)
Diabetes mellitus	1 (4.8)
Chronic hepatitis B infection	1 (4.8)
Pilocytic astrocytoma	1 (4.8)
Special area involvement	n (%)
Nails	14 (66.7)
Scalp	12 (57.1)
Intertriginous	9 (42.9)
Palmoplantar	2 (9.5)
Previous systemic treatments	n (%)
Methotrexate	18 (85.7)
Acitretin	8 (38.1)
Cyclosporine	5 (23.8)
Narrowband UVB	8 (38.1)
Etanercept	1 (4.8)
Adalimumab	1 (4.8)
Ustekinumab	2 (9.5)
Ixekizumab	1 (4.8)

SD, Standard Deviation.

although the PASI score could not be reduced below 3, the patient continued taking risankizumab because of maintenance of a PASI-75 response.

There has been growing interest in reducing biologic doses following remission of psoriatic manifestations without compromising efficacy and sustainability, with varying success rates. These variations may be partly due to differences in criteria for initiating dose reductions, dose reduction protocols, and study designs.[3,4,6–11] Eligibility criteria for dose reductions typically included a minimum duration of standard treatment (3- to 12-months) and achievement of stable minimal disease activity for 6 weeks to 12-months, as defined by one or more of the following criteria: an absolute PASI score of ≤3, ≤5, or ≤8; relative PASI improvements (PASI-75, PASI-90, or PASI-100); or a Physicians Global Assessment (PGA) score of 0 or 1.[3,4,6–11] Although most studies used relative PASI scores, we mainly utilized the absolute PASI score, as it more accurately reflects current disease severity. Absolute PASI is especially valuable in real-life settings, where baseline PASI scores are generally lower.[12]

Additionally, monitoring the maintenance of improvements following dose reductions is equally important. Most studies used the same criteria as those followed by dose reductions. This was also the case in our study. Some studies used higher absolute PASI scores (>5–8), losses in PASI 50–80–90–100 responses, an increased PGA score (≥3), and/or an increased disease activity unacceptable to the patient. Variations in these criteria may make it difficult to compare treatment outcomes.

Several studies evaluated factors affecting the maintenance of remission under reduced doses. Longer disease duration, higher baseline PASI, increased BMI, and concomitant psoriatic arthritis were factors associated with failure.[4,6] Achieving PASI-100 earlier and being treated with adalimumab instead of ustekinumab and etanercept were associated with a higher success rate.[3,11] In our study, gender, age, BMI, disease duration, PASI scores at baseline and at the time of dose reductions, and coexisting psoriatic arthritis did not predict dose reduction success.

In a randomized controlled trial, patients who achieved PASI-100 response at weeks 20–28 with guselkumab were assigned to receive either the standard every 8-week dosing or a prolonged dosing interval of every 16-weeks.[8] By week 68, the two groups were similar in terms of dis-

Table 2 PASI scores before and after dose reduction with comparison between groups of sustained efficacy and relapse.

	Total group (n = 21)	Relapse group (n = 5)	Maintaining group (n = 16)	p
Age, mean ± SD	47.5 ± 16.7	46.2±16.1	47.9 ± 17.4	0.842
Male/Female, n (%)	14 (66.7) / 7 (33.3)	2 (40) /3 (60)	12 (75) /4 (25)	0.280
Body mass index, mean ± SD	27.1 ± 3.7	27.6 ± 3.0	27.0 ± 4.0	0.333
Disease duration, years, mean ± SD	18.9 ± 17.1	12.6±9.9	20.8±18.7	0.398
Psoriatic arthritis, n (%)	7 (33.3)	3 (60)	4 (25)	0.280
PASI scores with standard dose of Risankizumab, mean ± SD (range)				
Baseline	14.3±6.2 (7.7–38.6)	11.3±1.4 (9.2–13.1)	15.3±6.9 (7.7–38.6)	0.062
Week 16	0.8±1.2 (0.0–3.6)	0.8±1.2 (0.0–2.8)	0.9±1.2 (0.0–3.6)	0.968
Week 52	0.4±0.8 (0.0–2.4)	0.5±1.1 (0.0–2.4)	0.4±0.7 (0.0–2.4)	1.000
Timing of dose reduction, weeks, mean ± SD (range)	75.4±16.7 (52–100)	80.8±16.1 (52–88)	73.8±17.1 (52–100)	0.445
PASI scores after reduced dose of Risankizumab, mean ± SD (range)				
Baseline	0.6±0.8 (0.0–2.4)	0.6±0.9 (0.0–2.0)	0.6±0.8 (0.0–2.4)	0.842
Week 12	0.7±1.1 (0.0–3.8)	1.3±1.8 (0.0–3.8)	0.5±0.8 (0.0–2.7)	0.495
Week 24	0.6±1.2 (0.0–4.4)	1.0±1.9 (0.0–4.4)	0.5±0.9 (0.0–3.0)	0.780

SD, Standard Deviation; PASI, Psoriasis Area and Severity Index.

ease control (PASI < 3) and levels of IL-17A, IL-17F, IL-22, and tissue-resident CD8-positive memory cells. These findings are of particular value as they demonstrate clinical and immunological disease control following prolongation of dosing intervals in patients with complete skin clearance with guselkumab. In our study, excellent skin response was maintained in all 10 patients after dose reductions of risankizumab following the achievement of a PASI-100 response.

The main limitations of our study include its retrospective design, the limited sample size, and the lack of a control group with similar patient characteristics. Nevertheless, our findings merit consideration as they demonstrate the feasibility of dose reductions following complete clearance of skin lesions in real-world risankizumab treatment. Prospective studies and randomized controlled trials are needed with larger patient populations.

In conclusion, following the achievement of low disease activity, reduced dose risankizumab maintained remission for at least 24-weeks in 76.2% of our patients. Of note, all patients who achieved complete skin clearance with standard risankizumab treatment maintained PASI-100 status following dose reduction, suggesting that the most suitable candidates for reliable and safe dose reduction are those achieving PASI-100 response. On the other hand, the higher incidence of adverse outcomes following dose reductions in patients with psoriatic arthritis warrants caution when considering dose reductions.

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Data availability statement

The entire dataset supporting the results of this study was published in this article.

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Authors' contributions

Gizem Pehlivan Ulutaş: 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.

Tuğba Özkök Akbulut: 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; manuscript critical review.

Algün Polat Ekinci: Approval of the final version of the manuscript; critical literature review; effective participation in research orientation; manuscript critical review; preparation and writing of the manuscript; study conception and planning.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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LETTER – RESEARCH

Zoonotic sporotrichosis in pediatric patients: analysis of 30 cases at a referral center in São Paulo, Brazil☆

Dear Editor,

Sporotrichosis is a subcutaneous and/or systemic mycosis caused by fungi of the genus *Sporothrix*, whose epidemiology has undergone significant changes in recent decades in Latin America, due to the increase in cases of zoonotic transmission by infected cats, mainly the species *S. brasiliensis*.[1–4] In this new scenario, a change in the profile of the most affected hosts has been observed, with a higher incidence in individuals at the extremes of age, such as the elderly and children, who maintain frequent contact with sick animals.[4,5] Despite the increase in cases in the pediatric population, which has its own clinical-epidemiological characteristics, studies focused on this group are still scarce.

Given this gap, a retrospective study was conducted analyzing the medical records of pediatric patients diagnosed with sporotrichosis at a referral center in the city of São Paulo, Brazil, between 2012 and 2024. The study was approved by the institution's Research Ethics Committee (CAAE: 86929625.0.0000.5479).

The inclusion criterion was a confirmed diagnosis of sporotrichosis in patients under 18 years of age during the aforementioned period. A total of 30 patients were included, aged between one and 16 years (mean 8.7 years). Table 1 shows their clinical and epidemiological characteristics. The most prevalent clinical forms of sporotrichosis in this study are shown in Fig. 1. The diagnosis was clinical-epidemiological in 20 cases (66.7%) and clinical-laboratory in 10 (33.3%). Laboratory confirmation was performed by isolating the fungus in culture in 24 patients (80%) and/or by histopathological examination with Grocott/PAS staining in 19 patients (63%). Table 2 summarizes the treatment instituted and the clinical evolution of the cases.

Table 1 Clinical, epidemiological, and laboratory characteristics of pediatric patients with sporotrichosis.

Variable	Category	n (%)
Sex	Female	16 (53.3%)
	Male	14 (46.7%)
Location	Face	14 (46.6%)
	Upper limbs	11 (36.6%)
	Trunk and cervical region	3 (10%)
	Lower limbs	2 (6.6%)
Clinical form	Cutaneous-lymphatic	17 (56.7%)
	Localized cutaneous	4 (13.3%)
	Multiple inoculations	4 (13.3%)
	Ocular mucosa	4 (13.3%)
	Immunoreactive	1 (3.3%)
Contact with feline	Yes	26 (86.6%)
Total number of cases	–	30 (100%)
	No	4 (13.3%)
Isolation of *Sporothrix spp.* in culture	Positive	18 (75%)
	Negative	6 (25%)
	Tests performed	24 (100%)
Evidence of yeast in Grocott-PAS	Positive	4 (21%)
	Negative	15 (79%)
	Tests performed	19 (100%)

The findings can be analyzed from two perspectives: in comparison to data from the adult population affected by the same mycosis, and in relation to pediatric data already described in the literature, both for the *S. schenckii* complex and the zoonotic clade *S. brasiliensis*.

The anatomical distribution of the lesions showed a predominance on the face, followed by the upper limbs. This pattern may be related to the characteristic behavior of children of petting animals close to their faces.[3,4] While an analysis of the general population in São Paulo (including all age groups) showed a higher frequency of lesions in the upper limbs (78.8%),[3] the importance of the face as an affected site in children during zoonotic outbreaks has already been reported, with reports of facial lesions in up to 50% of pediatric cases.[6]

The Lymphocutaneous (LC) form was the most frequent clinical presentation, in line with the Brazilian literature, which indicates a prevalence between 46% and 92%,[4] but contrasts with the findings of a study carried out in 704 chil-

☆ Study conducted at the Dermatology Clinic, Hospital da Santa Casa de Misericórdia de São Paulo, Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil.

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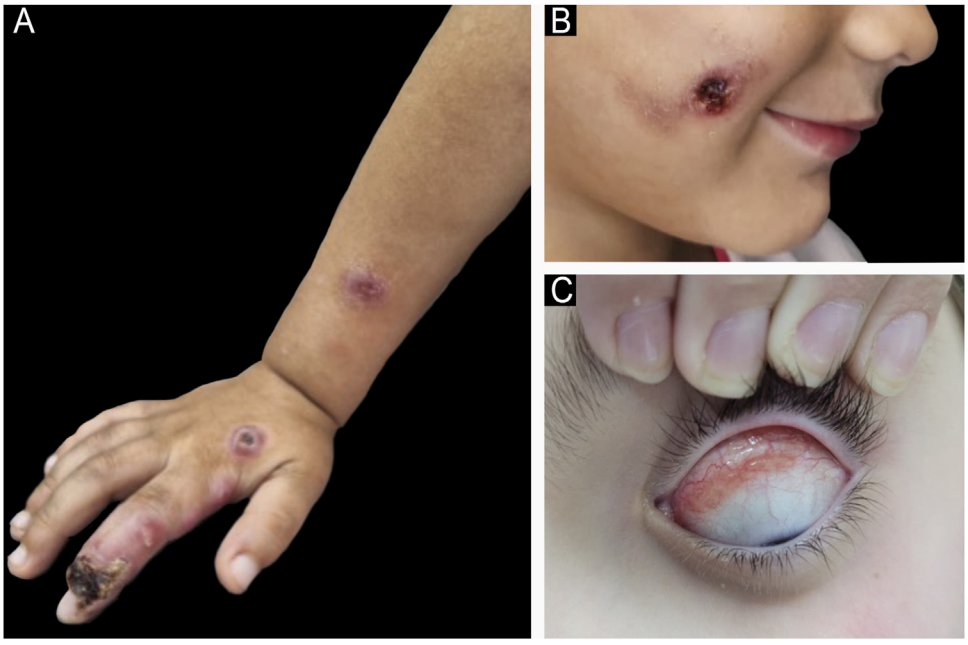

Fig. 1 Clinical presentation of sporotrichosis in children. (A) Cutaneous-lymphatic form. (B) Localized cutaneous form. (C) Mucosal (ocular) form.

Table 2 Treatment profile and clinical outcomes.

Medications used in the treatment	30 patients (100%)	Dose	Average treatment time until cure (months)	Cure (cure rate)	Loss to follow-up (number of cases)
Itraconazole	19 (63%)	100 mg day	3	13 (68.4%)	6
Potassium iodide	11 (37%)	max 50 mg/kg	5	9 (81.8%)	2

dren with sporotrichosis in China, where the main route of transmission was environmental and there was a predominance of the fixed cutaneous form.[2] With the advancement of the zoonotic epidemic caused by *S. brasiliensis*, presentations previously considered atypical have been on the rise, with immunoreactive forms such as erythema nodosum and Sweet's syndrome being reported more frequently in the context of the current epidemic.[1,3,4] Lesions in the ocular mucosa, for example, have become more frequent and are associated with exposure to aerosols from infected animals, autoinoculation after contact with fomites, or direct contact with the animals. Similarly, multiple inoculation in different cutaneous regions has been observed as a consequence of recurrent trauma (bites and scratches) common in childhood interactions with infected cats.[4]

The main vectors of zoonotic sporotrichosis transmission are infected felines, which have a high fungal load in their lesions.[3] In the present study, direct contact with sick cats was identified as the main route of exposure, and 42% of owners reported the loss or death of the animal. These data reinforce the impact of the abandonment of infected cats, also evidenced by Chaves et al.,[7] who observed an abandonment rate of 21% among 147 monitored cats, of which 54.4% died. Such evidence highlights the urgency of public policies that ensure the monitoring and proper veterinary management of these animals, a fundamental measure for controlling the epidemiological chain of sporotrichosis and for interrupting the infection in both humans and animals.

Sabouraud Dextrose Agar medium was used as the culture medium, considered the gold standard for the diagnosis of sporotrichosis.[4] It showed a positive result in 75% of the evaluated cases. Although it demonstrates high sensitivity, this performance does not reach the 95.2% sensitivity observed in cases of feline sporotrichosis, a difference attributed to the lower fungal load in human samples, clinical variability, or technical limitations in collection.[8] In this context, histopathological examination plays a complementary role in diagnostic investigation, with suggestive findings such as suppurative granulomas and granulomatous dermatitis.[2–4] In the present study, the examination revealed alterations compatible with sporotrichosis in 57.8% of cases. However, the visualization of yeasts using the special PAS and Grocott stains was possible in only 21% of cases with histopathological analysis (4/19). This limitation is expected and reflects the low sensitivity of this isolated examination, which varies between 18% and 35% in the literature, depending on the fungal load and the technique employed.[2] Nevertheless, the identification of fungal structures in two cases with negative cultures reinforces the relevance of histopathological examination as a complementary diagnostic tool, especially when culture fails, contributing to the clarification of challenging cases.

The predominant therapeutic strategy consisted of the administration of itraconazole, a first-line treatment for sporotrichosis, due to its efficacy and the high cure rates (90%–100%) reported in the literature.[4–10] In a prospective study that used Potassium Iodide (KI) in patients with sporotrichosis, including a cohort of children (<15 years), 100% cure rates were obtained,[11] demonstrating an efficacy close to that obtained in this study (81.8%). In addition, KI has the advantage of allowing formulation in syrup form, which facilitates administration in the pediatric population. The average treatment time observed, from three to five months, varied according to the medication used and was consistent with previous studies, which describe an average time for clinical resolution between two and four months.[2,4,11]

Based on the present findings, this study contributes to the recognition of sporotrichosis occurring in the pediatric age group as important in the current urban zoonotic epidemic caused by *S. brasiliensis*. The varied clinical manifestations, diagnostic challenges, and the impact of direct exposure to sick felines reinforce the need for specific protocols for the pediatric age group. In addition, the data highlight the urgency of public strategies focused on veterinary control and integrated surveillance, which are fundamental to containing the transmission chain and mitigating the impact of the disease on vulnerable groups.

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Authors' contributions

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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; acquisition, 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.

Guilherme Camargo Julio Valinoto: Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; approval of the final version of the manuscript.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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LETTER – CLINICAL

A progressive sclerotic depigmenting congenital melanocytic nevus in a Chinese patient☆

Dear Editor,

Congenital Melanocytic Nevi (CMN) present in approximately 1%–2% of newborns.[1] They are usually brown to black, hairy lesions with a consistency similar to that of the surrounding normal skin. CMN is classified according to the diameter of the lesion: <1.5 cm is classified as Small Congenital Melanocytic Nevi (SCMN), 1.5–20 cm as Medium Congenital Melanocytic Nevi (MCMN), 20–40 cm as Large Congenital Melanocytic Nevi (LCMN), and >40 cm as Giant Congenital Melanocytic Nevi (GCMN).

Spontaneous regression of medium-to-large congenital melanocytic nevi is rare, but regression presenting as depigmentation with sclerosis, alopecia, or pruritus is exceedingly so.

Herein, we present a 15-month-old Chinese child with progressive regression of pigmentation and hardness of a hairless pruritic medium-sized CMN. This male infant represents the first reported case in China of progressive sclerosing hypopigmented Congenital Melanocytic Nevus (CMN). The lesion has been present on his occipital scalp since birth. At 1-month of age, the lesion presented as a hard, slightly raised, black plaque measuring 10 × 8 cm, with a hypopigmented area in the upper left quadrant (Fig. 1A).

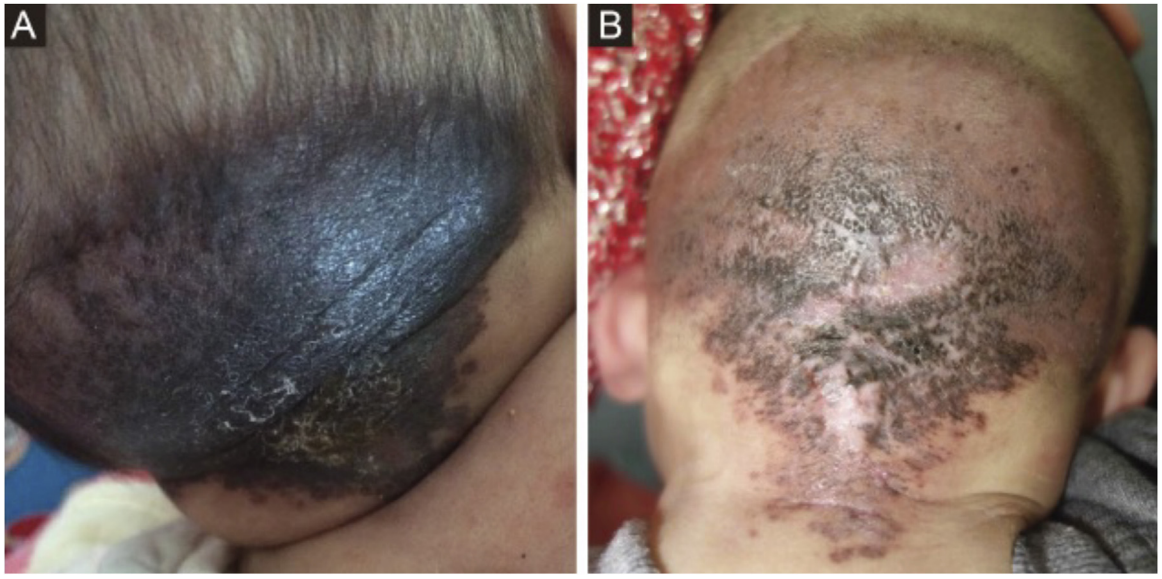

Fig. 1 (A) Lesion at 1-month of age: A 10 × 8 cm, hard, slightly raised black plaque with a hypopigmented area in the upper left quadrant. (B) Lesion at 15-months of age: A 14 × 11 cm, hardened, hairless surface with irregular dark-brown pigmentation and a bordered area of mild erythema.

☆ Study conducted at the Department of Dermatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China.

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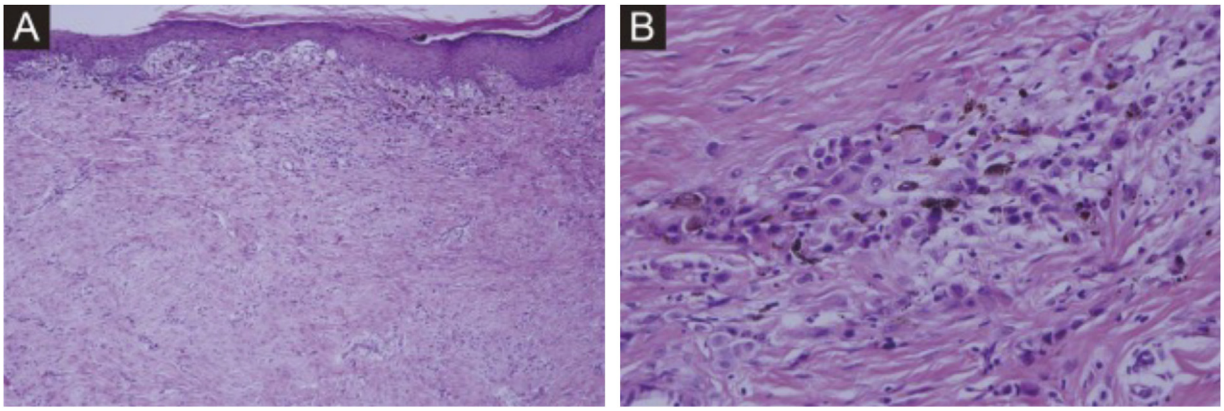

Fig. 2 (A) Nevus cell nests in the superficial dermis (Hematoxylin & eosin, ×100). (B) Collagen bundles and fibroblasts surrounding nevus cell nests (Hematoxylin & eosin, ×400).

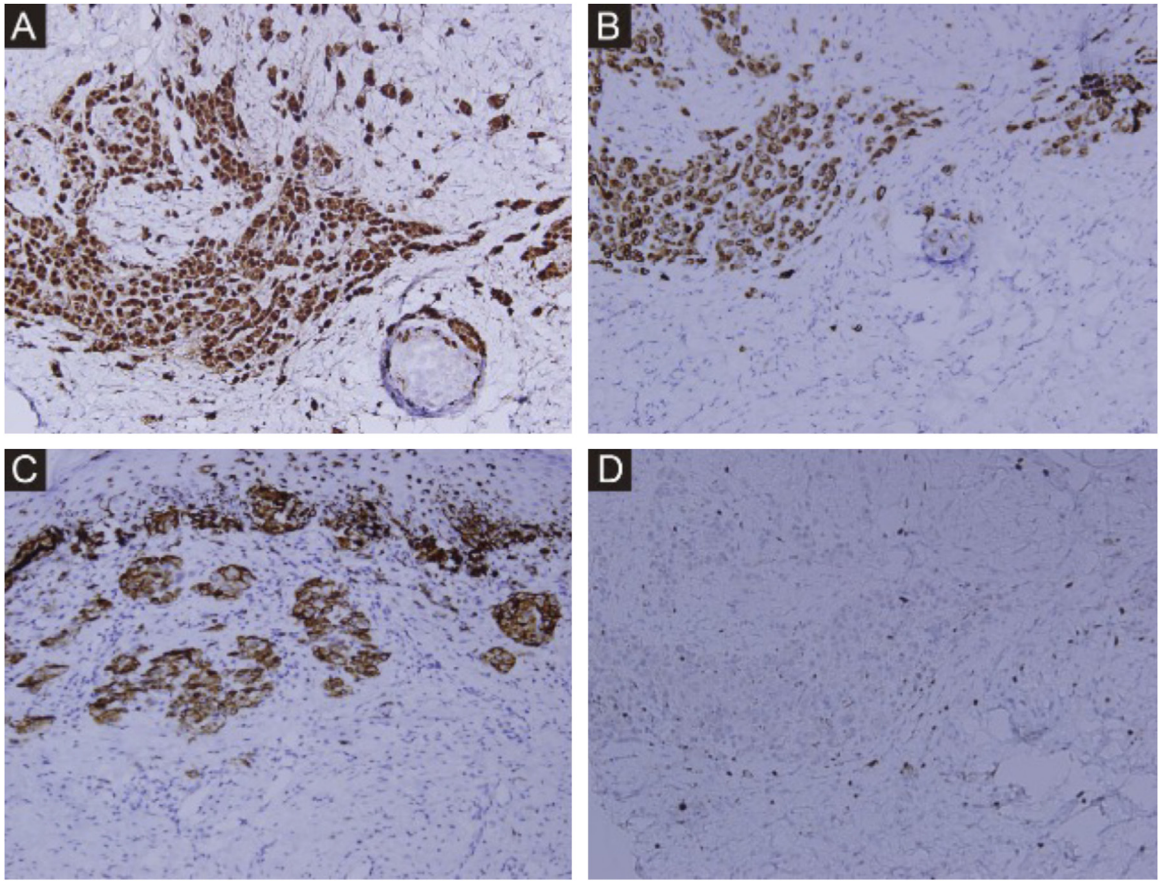

Fig. 3 Immunohistochemical staining (A) S100 Staining, ×200. (B) Melan-A Staining, ×200. (C) HMB45 Staining, ×200. (D) Ki-67 Staining, ×200.

As he grew older, the lesion exhibited progressive changes: hypopigmentation, sclerosis, hair loss, and pruritus. By 15-months, it had expanded to 14 × 11 cm, featuring a hardened, hairless surface with irregular dark-brown pigmentation and a bordered area of mild erythema. The periphery was accompanied by small-sized, scattered lesions and areas of hypopigmentation (Fig. 1B).

Histopathology demonstrated nests of melanocytes in the dermoepidermal junction and superficial dermis with markedly reduced skin appendages (Fig. 2A); the reticular dermis exhibited abundant collagen bundles and fibroblasts surrounding the nevus cell nests (Fig. 2B).

Immunohistochemistry (Fig. 3A–D) confirmed nevus cell positivity for S100, Melan-A, and HMB45, negativity for p53, and a Ki-67 proliferation index <10%. Both biopsied lymph nodes showed reactive hyperplasia.

PubMed was searched, and 13 cases of spontaneous regression of CMN with sclerosis. This cohort comprised

eight females and five males. The onset age ranged from birth to three years, and the depigmentation process lasted less than eight years. The lesions were most commonly present on the trunk (10/13), then were found on the scalp (2/13), feet, and ankles (1/13). All the lesions were >1.5 cm in diameter. Sclerosis and pigmentation regression occurred in all 13 cases. Hair loss (9/13), pruritus (6/13), and ulcer (4/13) were also observed. The mechanism for these has been proposed as an autoimmune reaction. The autoimmune response targeting melanocytes may be responsible for the regression of pigmentation. Meanwhile, this autoimmune response would produce large amounts of inflammatory factors that induce collagen proliferation, resulting in sclerosis.[2] There was induration in a few cases,[3,4] but no nodular lesions. Usually, induration denotes local hardening, whereas sclerosis means diffuse hardening. Localized induration on a CMN raises the possibility of malignant transformation, in contrast to the diffuse hardening of sclerotic CMNs, which is considered benign.[4,5] In our case, we performed immunohistochemistry staining and observed a low proliferation index with Ki-67. In addition, none of the CMNs described so far have progressed to melanoma; the longest recorded follow-up is 17-years.[5]

In conclusion, we reported the first case of progressive sclerotic hypopigmented CMN in a Chinese patient. Continuous monitoring is required for this rare disease, but there is no need for excessive panic and extensive excision due to the low possibility of malignant transformation.

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Authors' contributions

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Yuqing Wang: Preparation and writing of the manuscript; data collection, analysis and interpretation.

Juanmei Cao: Data collection, analysis and interpretation; final approval of the final version of the manuscript.

Tianqi Zhao: Data collection, analysis and interpretation; final approval of the final version of the manuscript.

Jing Yang: Approval of the final version of the manuscript; effective participation in research orientation; final approval of the final version of the manuscript.

Changzheng Huang: Approval of the final version of the manuscript; effective participation in research orientation; final approval of the final version of the manuscript.

Research data availability

All data supporting the findings are included within the article.

Conflicts of interest

None declared.

Editor

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LETTER - CLINICAL

Congenital mastocytoma: clinical and histopathological aspects of a case with unusual presentation☆

Dear Editor,

Mastocytosis constitutes a heterogeneous group of hematopoietic disorders characterized by the abnormal proliferation of mast cells in different tissues. The clinical presentation may be restricted to the skin (cutaneous mastocytosis), generally with a benign course, or involve other organs, configuring systemic mastocytosis, which may present with severe clinical manifestations.[1] Solitary cutaneous mastocytoma represents about 10% to 15% of all pediatric cases of cutaneous mastocytosis, and among these, 60% are congenital. Typically, the age of onset occurs in childhood, especially in the first three months of life.[2,3]

The present report describes a newborn female, 39 weeks, with no known family or gestational history. On initial physical examination, an erythematous plaque with brownish borders, infiltrated and hardened, with an "orange peel" appearance, well-defined borders, approximately 6 cm in its largest diameter, was observed on the posterior-lateral aspect of the left thigh (Fig. 1). At 9 days of age, there was a progressive increase in the lesion associated with infiltration, accompanied by the appearance of blisters on the plaque and the presence of Darier's sign (Fig. 1).

Given this clinical picture, the diagnostic hypothesis of congenital cutaneous mastocytoma was raised, with subcutaneous adiponecrosis of the newborn and juvenile xanthogranuloma being considered in the differential diagnosis, which can present with similar symptoms in infants.

Complementary tests were requested for diagnostic evaluation and exclusion of systemic mastocytosis, which, although rare, can lead to gastrointestinal and hematological disorders, with a potentially significant impact on the child's quality of life. Skin biopsy revealed dermal proliferation of monomorphic and fusiform round cells, diffusely arranged in the papillary and upper reticular dermis (Fig. 2), with granular cytoplasm evidenced by Giemsa staining (Fig. 3). Immunohistochemistry demonstrated diffuse

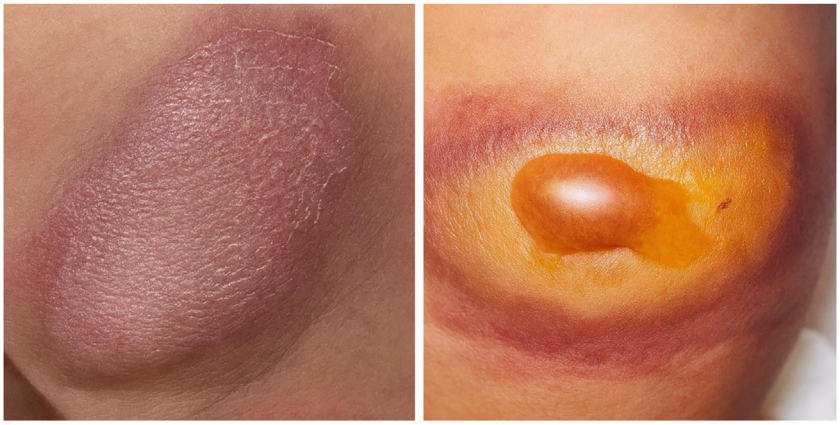

Fig. 1 The image on the left shows the mastocytoma at birth. The image on the right shows the mastocytoma on the 9th day of life, with the appearance of blisters.

☆ Study conducted at the Hospital Federal de Bonsucesso, Rio de Janeiro, RJ, Brazil.

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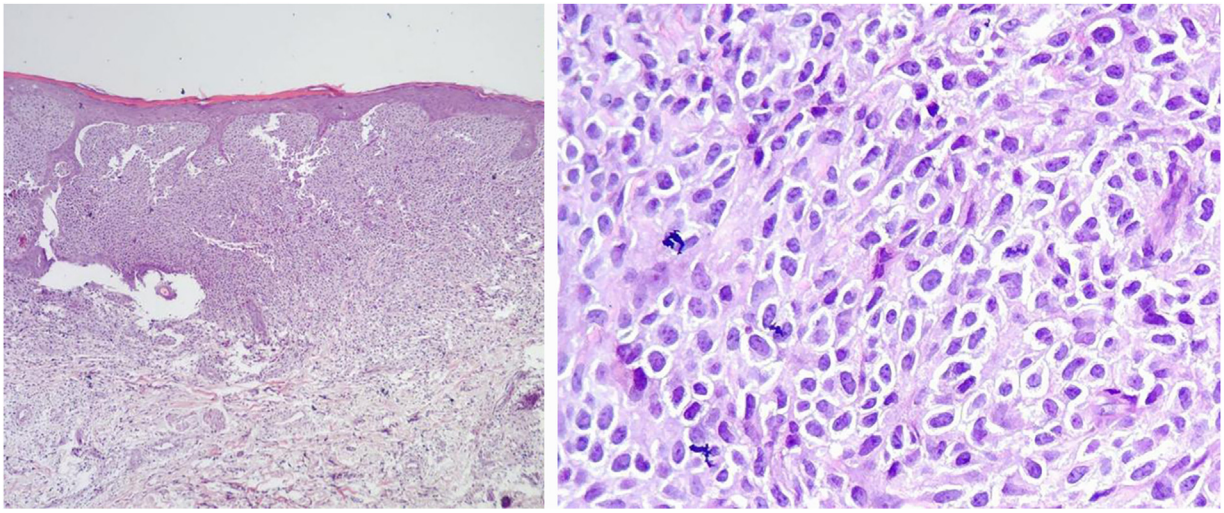

Fig. 2 The image on the left shows monomorphic and fusiform round cells, diffusely arranged in the papillary and upper reticular dermis. On the right, at higher magnification, numerous mast cells (Hematoxylin & eosin).

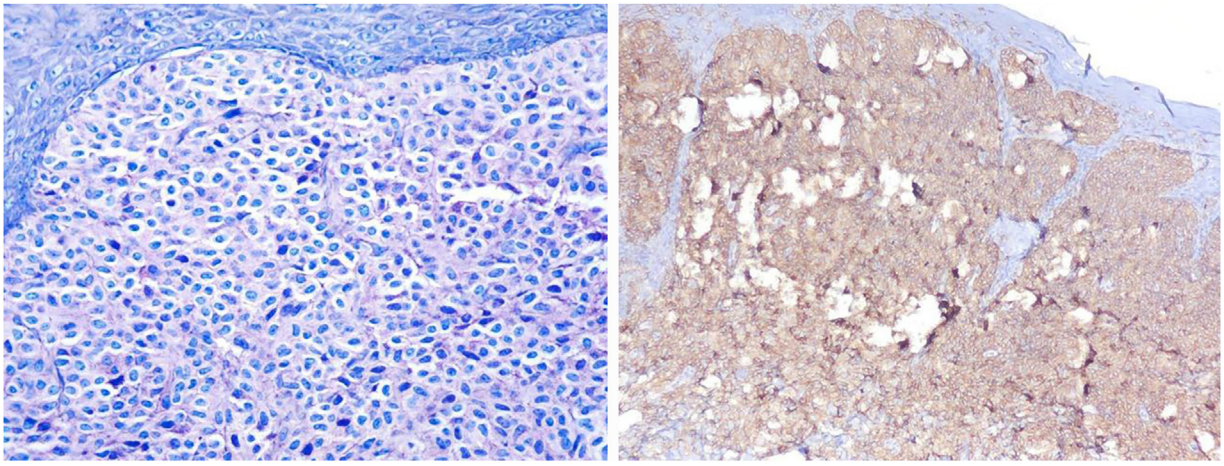

Fig. 3 The image on the left shows mast cell proliferation using Giemsa staining. On the right, the CD117 (c-KIT) immunohistochemical reaction is diffusely positive in mast cells.

positivity for CD117 (c-Kit), a sensitive marker for mast cells, corroborating the diagnosis (Fig. 3).

Serum tryptase levels were normal (5.31 μg/L), and abdominal ultrasound and laboratory tests (complete blood count, liver function, and renal function) showed normal results.

Due to the lesion size, excision was not performed, prioritizing clinical management. A medium-potency topical corticosteroid was prescribed as needed for symptomatic control.

Currently, the patient is two years old, with adequate neuropsychomotor development, without recurrence of blisters or systemic symptoms, in addition to gradual involution of the skin lesion (Fig. 4). She remains under regular clinical follow-up.

The correlation between clinical, histopathological, and immunohistochemical findings, associated with the exclusion of systemic forms and relevant differential diagnoses, was fundamental for confirming the diagnosis. The favorable evolution during the first two years of life, with gradual lesion involution and absence of systemic manifestations, reinforces the benign and self-limiting nature of the condition.

In the reported case, it is possible that the patient manifested the blister at the site of the lesion due to more intense manipulation of the region in the first days of hospital admission. This greater friction, added to the anatomical location close to the diaper area, a region subject to friction, moisture, and constant contact, may have contributed to the local triggering of the phenomenon. It is known that, in patients with cutaneous mastocytosis, several factors can act as triggers for mast cell degranulation and lesion exacerbation, including mechanical irritation (friction or massage), surgical trauma, physical exertion, stress, and extreme temperatures. In addition, external stimuli such as alcohol consumption, spicy foods, hot drinks, certain medications (aspirin, nonsteroidal anti-inflammatory drugs, antibiotics, and opioids), vaccines, and even iodinated radiocontrast agents are also described as potentially triggering.[3,4] Thus, the combination of local friction and repeated manipu-

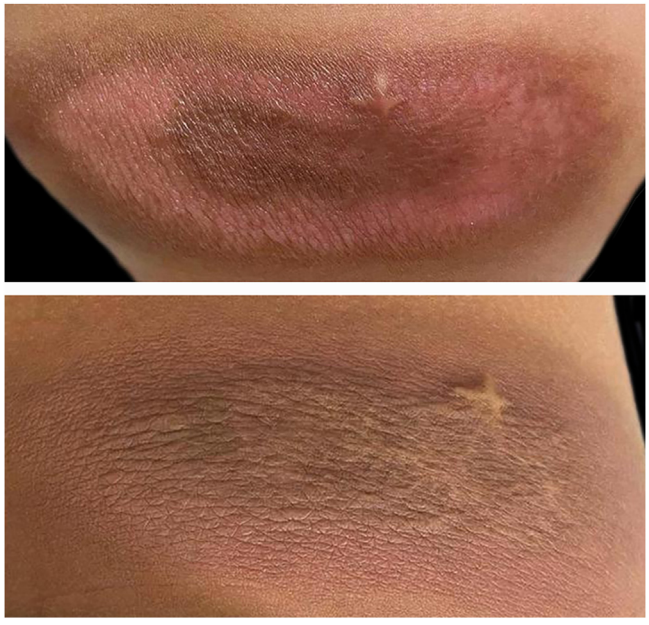

Fig. 4 The lesion involution can be observed by comparing it at the age at nine months (left) and two years (right).

lation may have acted as a precipitating factor in this case.

Solitary mastocytoma usually has an excellent prognosis, even with a positive Darier sign for years and the presence of blisters in the initial phase. In most cases, remission is achieved by adulthood, without transition to systemic mastocytosis.[5]

Early recognition of congenital mastocytoma is extremely important, not only to establish the correct diagnosis and avoid unnecessary procedures, but also to guide families regarding the natural progression of the disease, possible complications, and preventive measures related to mast cell degranulation. Furthermore, ruling out malignant conditions or systemic mastocytosis directly contributes to the safe management of the condition.[3]

Authors' contributions

Daniela da Guarda Ribeiro: Design and planning of the study; data collection; drafting and editing of the manuscript; 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.

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All authors approved the final version of the manuscript and are fully responsible for the published content.

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Conflicts of interest

None declared.

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LETTER - CLINICAL

Dupilumab-resistant Netherton syndrome associated with a novel SPINK5 variant: c.575A>G (p.Asn192Ser)☆

Dear Editor,

Netherton Syndrome (NS; OMIM #256500) is a rare autosomal recessive disorder caused by pathogenic variants in SPINK5, encoding Lymphoepithelial Kazal-type-related Inhibitor (LEKTI), a protein essential for epidermal barrier integrity.[1] Loss of LEKTI function results in dysregulated protease activity and the hallmark triad of congenital ichthyosiform erythroderma, trichorrhexis invaginata, and severe atopic diathesis. Although dupilumab has shown therapeutic potential in NS, we report a case of severe, dupilumab-resistant NS associated with a novel SPINK5 variant, c.575A>G (p.Asn192Ser).[2]

An 11-year-old Chinese boy presented with a lifelong history of generalized erythroderma and scaling. He had been repeatedly misdiagnosed with infected eczema or pustular psoriasis, showing minimal response to conventional therapies. Physical examination revealed short stature (height 130 cm, -2.2 SDS) with normal cognitive development. Dermatological assessment demonstrated diffuse erythema with fine-to-lamellar scaling over the head, face, trunk, and limbs, with sparse scalp hair (Fig. 1A–B). Dermoscopy revealed dotted vascular dilatation, scattered scales, and trichorrhexis invaginata (Fig. 2A–B). Histopathological examination revealed hyperkeratosis, acanthosis, and superficial perivascular lymphocytic infiltration (Fig. 2C). Immunological evaluation showed markedly elevated serum IgE (> 2500 IU/mL), with allergen-specific IgE positivity to multiple food allergens. Notably, only IL-4 was markedly elevated in the lesional skin (71.33 pg/mg), while other key cytokines – including IL-2, IL-6, IL-10, IL-17, TNF-α, and IFN-γ – remained within normal limits both in the lesion and in serum (Fig. 3).

Whole-exome sequencing identified two SPINK5 variants: a previously reported pathogenic nonsense mutation, c.652C>T (p.Arg218*),[3] and a novel missense variant, c.575A>G (p.Asn192Ser). Sanger sequencing and familial segregation analysis confirmed that the variants were in trans, consistent with a compound heterozygous genotype (Fig. 4A–B). The novel variant was absent from population databases (gnomAD, LOVD) and was predicted deleterious by multiple in silico tools (SIFT: deleterious; PolyPhen-2: probably damaging; CADD score: 33, top 0.1% of predicted deleterious variants). According to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines, it was classified as ''likely pathogenic'' (PM2, PM3, PP3). To our knowledge, this is the first report of this variant in NS.

To further explore the functional impact of these variants, we performed structural modeling of both wild-type and mutant LEKTI using AlphaFold3.[4] The results revealed that the p.Arg218* nonsense mutation introduces premature termination that truncates the C-terminal domain, likely leading to complete loss of protein function (Fig. 5A–B). In contrast, the p.Asn192Ser missense mutation does not markedly alter the overall conformation but locally disrupts key hydrogen bonds within a loop region, thereby potentially compromising structural stability (Fig. 5C). Multiple sequence alignment further showed that both residues are highly conserved across species (Fig. 5D), underscoring their critical roles in maintaining LEKTI integrity and function.

As an IL-4 receptor α antagonist, dupilumab has been repeatedly reported to ameliorate Netherton Syndrome (NS) by suppressing Th2-mediated inflammation and improving skin microbiome homeostasis.[5,6] Despite the patient's pronounced atopic phenotype and markedly elevated serum IgE, five doses of dupilumab (300 mg each) produced minimal improvement in erythema or pruritus, with facial inflammation even worsened. This lack of clinical efficacy, despite the tissue-specific IL-4 elevation, underscores the immunologic heterogeneity of NS. Although NS is traditionally considered a Th2-polarized disorder, emerging evidence indicates that the erythrodermic subtype exhibits enhanced type I interferon activity, with IL-17, IL-23, and IL-36 pathways also implicated in its pathogenesis.[7,8] While a direct causal link between the SPINK5 variants and dupilumab resistance

☆ Study conducted at the Department of Dermatology, Wuhan Hospital of Traditional Chinese and Western Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. The laboratory investigations were conducted at the Hubei Province Key Laboratory of Skin Infection and Immunity, Wuhan, China.

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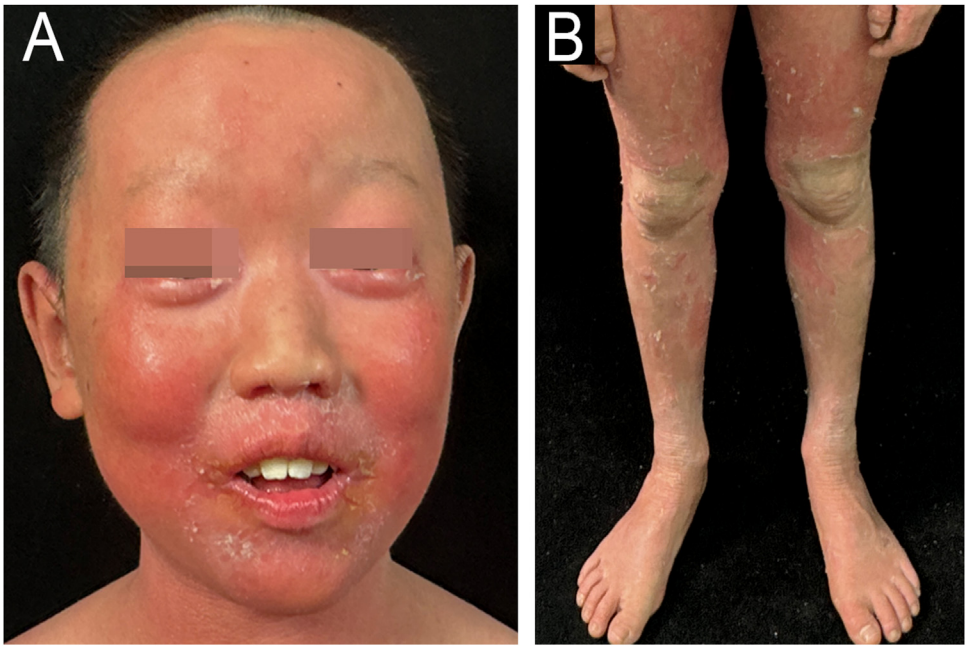

Figure 1 Clinical presentation. (A) Diffuse erythema and fine-to-lamellar scaling over the head and face, accompanied by sparse scalp hair. (B) Diffuse erythema on the limbs.

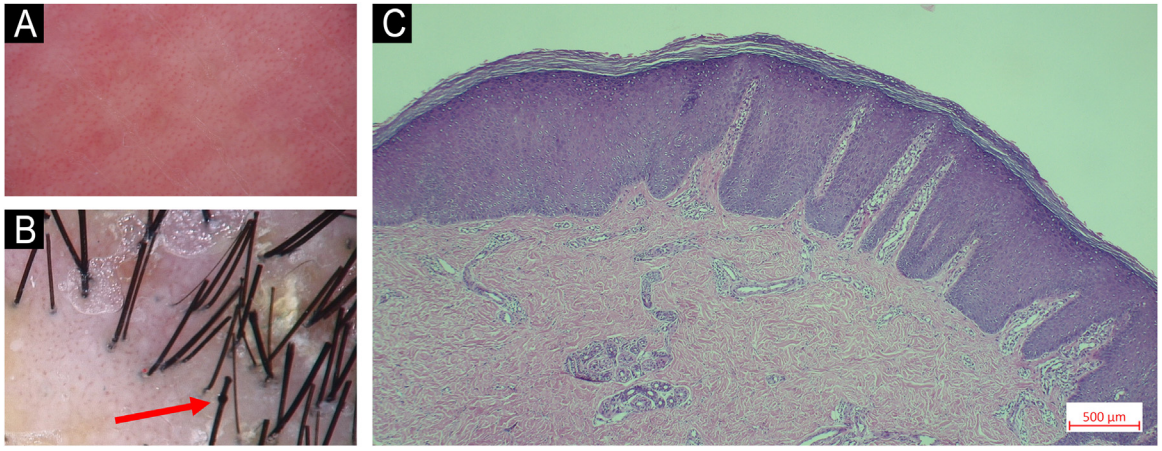

Figure 2 Dermoscopic and histopathological findings. (A) Dermoscopy showing dotted vascular dilatation and scattered scales. (B) Trichoscopy with trichorrhexis invaginata ('bamboo hair') on the scalp. (C) Histopathological examination revealing hyperkeratosis, acanthosis, and superficial perivascular lymphocytic infiltration (Hematoxylin & eosin, 200×).

cannot be definitively established, genotype-phenotype correlations are well recognized, with 5′-end mutations often associated with more severe clinical manifestations.[9,10] In this patient, both variants localize to the 5′ region, likely resulting in profound LEKTI deficiency and epidermal barrier disruption. We propose that this upstream defect sustains inflammation via persistent antigen exposure and innate immune activation, thereby undermining the efficacy of Th2-targeted therapy and explaining the observed refractory erythroderma.

In summary, we identified and characterized a novel SPINK5 variant, c.575A>G (p.Asn192Ser), upgrading its classification from uncertain significance to ''likely pathogenic'' based on ACMG/AMP criteria. Beyond expanding the mutational spectrum of NS, this case of dupilumab-resistant NS underscores the importance of integrating genetic analysis, clinical subtype assessment, and cytokine profiling to guide personalized therapy. Importantly, classical atopic features (e.g., elevated IgE) do not necessarily predict response to Th2-targeted therapy. For patients with severe erythrodermic NS and 5′-region SPINK5 mutations, targeting the IL-4/IL-13 pathway alone may yield limited benefit, even with a marked atopic background.

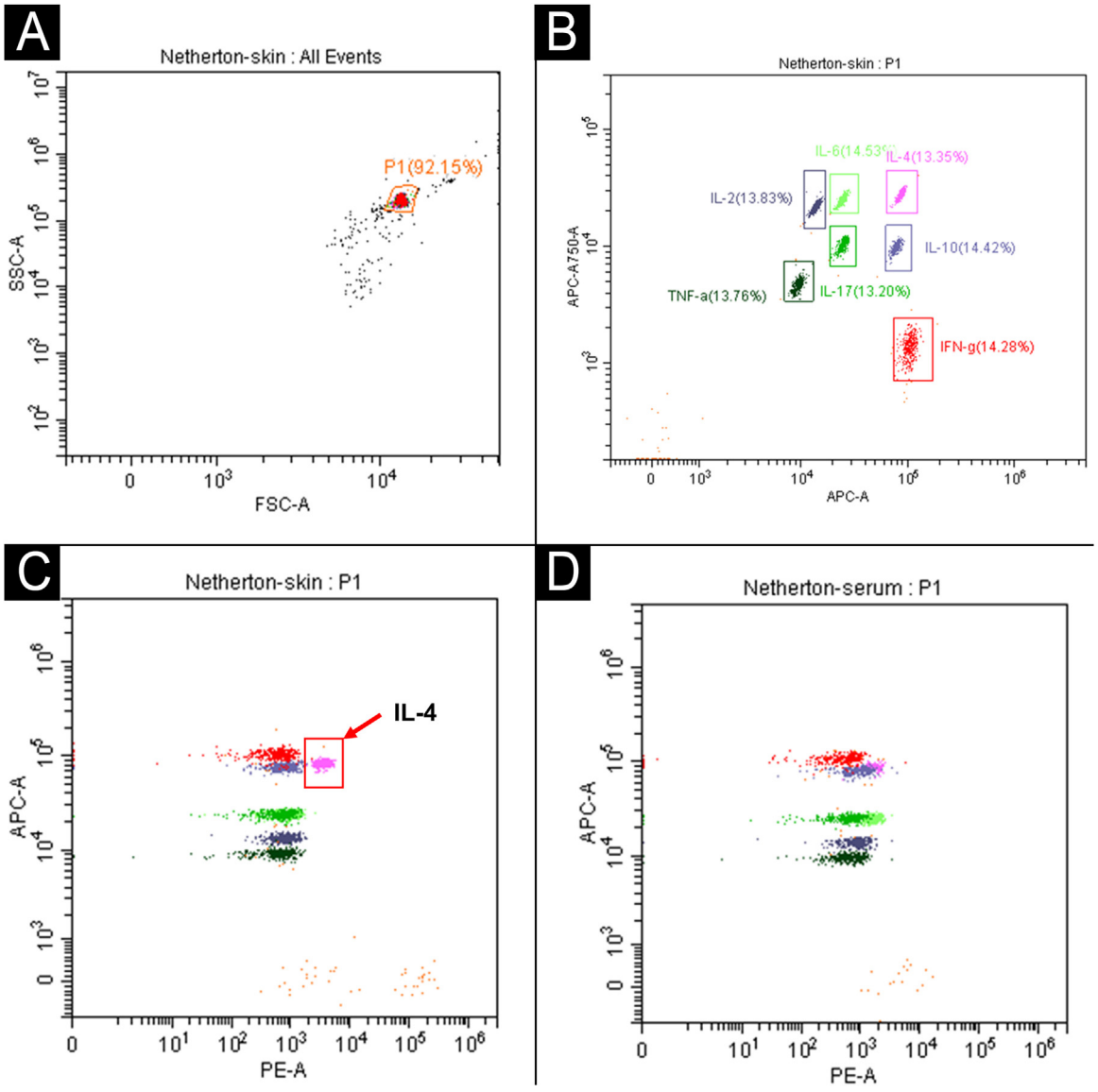

Figure 3 Cytokine profiling reveals tissue-specific elevation of IL-4 in skin lesions of the patient. (A–B) Schematic of the gating strategy for cytokine bead array analysis. (A) The target bead Population (P1) was gated based on Forward and Side Scatter (FSC-A/SSC-A). (B) Within the P1 population, seven distinct bead subsets were distinguished by APC-A and APC-A750-A signals, each corresponding to a specific cytokine for detection (IL-2, IL-4, IL-6, IL-10, IL-17, TNF-α, and IFN-γ); quantification of each cytokine was ultimately performed via the PE fluorescence channel. (C) Selective elevation of IL-4 in lesional skin (71.33 pg/mg, indicated by a red arrow) against normal reference levels, while other key cytokines – including IL-2, IL-6, IL-10, IL-17, TNF-α, and IFN-γ – were within normal limits. (D) All cytokine concentrations in peripheral blood were within the normal range. Cytokine levels were quantified by flow cytometry using a commercial bead array (Microtech Biotech Co., Ltd.) and analyzed with BD FCAP Array software.

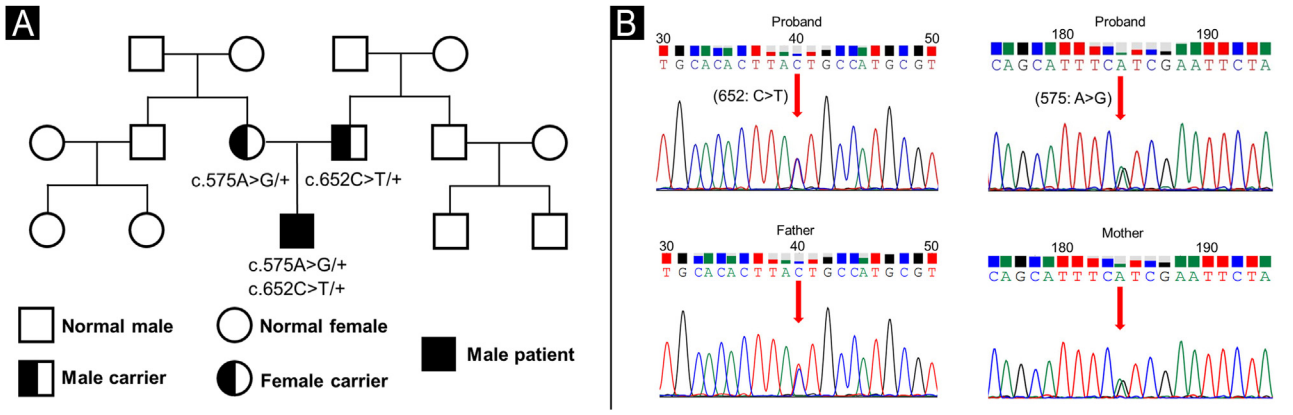

Figure 4 Genetic findings. (A) Family pedigree illustrating the co-segregation of SPINK5 variants. (B) Sanger sequencing of the proband showing compound heterozygosity for c.652C>T (p.Arg218*) and c.575A>G (p.Asn192Ser); each parent heterozygous for one variant.

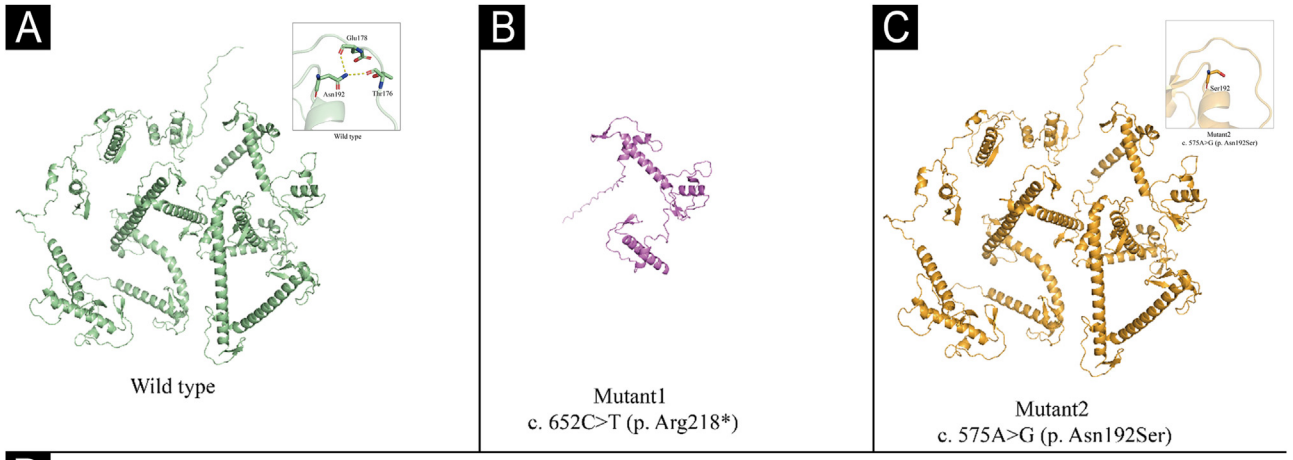

Figure 5 Structural modeling and evolutionary conservation of SPINK5 variants. (A) Wild-type LEKTI protein structure with intact loop conformation (inset). (B) The p.Arg218* truncation mutation results in loss of the C-terminal domain, suggesting complete or severe loss of protein function. (C) The p.Asn192Ser missense mutation disrupts local hydrogen bonds in a loop region (red dashed lines in inset), potentially compromising structural stability. (D) Cross-species sequence alignment shows high conservation of Arg218 and Asn192, indicating their critical roles in maintaining LEKTI structure and function.

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Research data availability

Does not apply.

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Author's contribution

Qingyuan Zhou: Performed the experiments and data analysis, and wrote the manuscript.

Changchun Wang: Performed the experiments and data analysis, and wrote the manuscript.

Qian Jiang: Critical review of important intellectual content.

Ruili Jiang: Critical review of important intellectual content.

Zilu Qu: Conceptualized the study and designed experiments; Critically reviewed the manuscript.

Liuqing Chen: Conceptualized the study and designed experiments; Critically reviewed the manuscript.

Conflicts of interest

None declared.

Editor

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All procedures performed in this study involving human participants were in accordance with relevant laws and institutional guidelines. The study was approved by Reviewed and approved by the Institutional Ethics Committee of Wuhan No.1 Hospital (Approval nº [2023]53-1). Written informed consent was obtained from the patient's legal guardians. The privacy rights of the patient have been respected.

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LETTER - CLINICAL

Eosinophilic annular erythema in a patient with hepatitis B-related cirrhosis☆

Dear Editor,

Eosinophilic Annular Erythema (EAE) is a rare, benign dermatosis characterized by annular or polycyclic erythematous plaques and a dermal eosinophil-rich infiltrate on histopathology. Although initially described in children, it has also been reported in adults, occasionally in association with chronic systemic disorders or malignancy.[1,2]

An 89-year-old man with decompensated cirrhosis secondary to chronic hepatitis B infection developed multiple annular plaques on the neck, upper limbs, and proximal thighs during hospital admission. The lesions were erythematous-violaceous, well-demarcated, with central clearing and mild pruritus (Fig. 1A–B). The patient recalled a similar self-limiting eruption approximately one year earlier.

A 4-mm punch biopsy from the thigh revealed a dense perivascular and interstitial dermal infiltrate composed predominantly of eosinophils, with associated dermal edema and erythrocyte extravasation (Fig. 1C–D). No vasculitis or flame figures were observed. Peripheral blood eosinophil count was within normal limits. The clinico-pathological correlation supported the diagnosis of eosinophilic annular erythema. The lesions gradually resolved over four weeks with only topical corticosteroids.

The differential diagnosis of annular plaques includes tinea corporis, annular urticaria, subacute cutaneous lupus erythematosus, erythema annulare centrifugum, and Wells syndrome.[3] In EAE, diagnosis relies on clinical morphology together with the characteristic eosinophil-rich dermal infiltrate.

Although often idiopathic, adult-onset EAE has been linked to various systemic conditions, including hepatitis C infection, autoimmune thyroiditis, chronic renal failure, autoimmune pancreatitis, and malignancy.[4,5] Recent evidence suggests that EAE represents part of a broader spectrum of eosinophilic dermatoses driven by type 2 inflammation, in which IL-5-mediated eosinophil activation and dermal recruitment play a central pathogenic role. This paradigm is supported by reports of therapeutic response to IL-5 blockade in refractory cases.[6]

The association between EAE and liver disease is increasingly recognized. Hepatic dysfunction (whether viral, autoimmune or cholestatic) creates a systemic inflammatory environment characterized by altered cytokine metabolism, impaired antigen clearance, and enhanced Th2-skewed immunity, all of which may facilitate eosinophil activation and dermal migration. Cases linking EAE to autoimmune hepatitis, including situations in which cutaneous lesions preceded the diagnosis of hepatic autoimmunity, reinforce the possibility of EAE acting as a cutaneous marker of evolving liver disease.[7] Similarly, EAE has also been described in association with primary biliary cholangitis.[8] In our patient, the onset of EAE during hepatic decompensation suggests that fluctuations in systemic inflammation related to chronic liver disease may act as a triggering factor.

Management of EAE remains challenging due to its relapsing course. Topical corticosteroids are frequently used, but systemic therapy is often required. Antimalarials such as chloroquine and hydroxychloroquine have demonstrated efficacy, although prolonged treatment may be necessary to achieve sustained remission.[9,10] Other therapeutic options include dapsone, doxycycline, systemic corticosteroids, ciclosporin and methotrexate, with variable responses. In refractory disease, emerging therapies such as JAK inhibitors and biologics targeting Th2 cytokine pathways have shown benefit in isolated cases.[6,8] This case expands the clinical spectrum of EAE and strengthens the hypothesis that advanced chronic liver disease may contribute to disease expression.

☆ Study conducted at the Department of Dermatovenereology, Santo António dos Capuchos Hospital, Unidade Local de Saúde de São José, Lisbon, Portugal.

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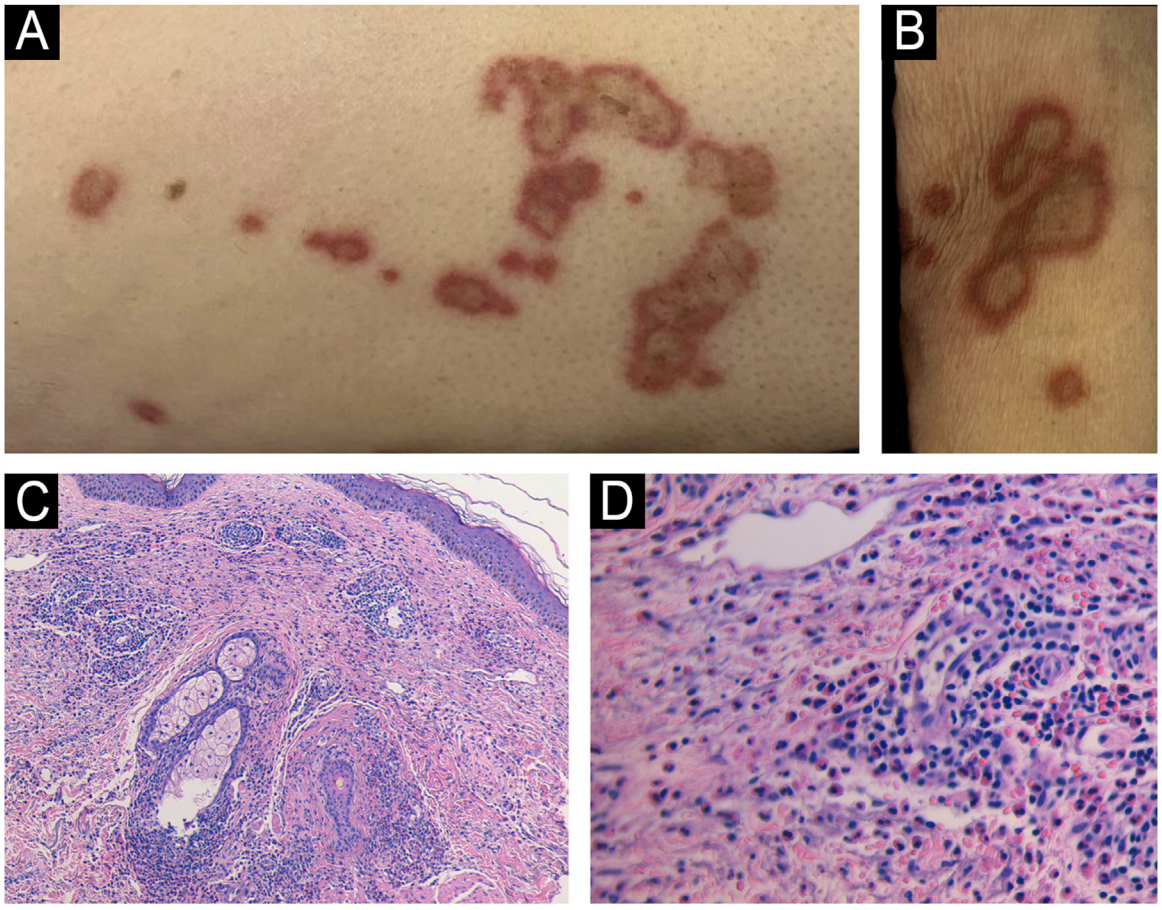

Fig. 1 (A) Annular erythematous-violaceous plaques with central clearing on the thigh. (B) Well-demarcated annular plaques on the upper limb. (C) Dense perivascular and interstitial eosinophil-rich dermal infiltrate with edema and erythrocyte extravasation (Hematoxylin & eosin, ×100). (D) Eosinophil-rich infiltrate without vasculitis or flame figures (Hematoxylin & eosin, ×400).

Authors' contributions

Beatriz F. Vilela: Design and planning of the study; drafting and editing of the manuscript; data survey, collection, analysis and interpretation of data; critical review of the literature; approval of the final version of the manuscript.

Maria Cristina Fialho: Analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied case; critical review of the literature; approval of the final version of the manuscript.

Ana Ferreirinha: Analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied case; critical review of the literature; approval of the final version of the manuscript.

Cândida Fernandes: Analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied case; critical review of the literature; approval of the final version of the manuscript.

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LETTER – CLINICAL

Indeterminate cell histiocytosis with ETV3::NCOA2 fusion detected by optical genome mapping☆

Dear Editor,

Following observation of a generalized eruption in a young patient with a unique histopathology, the term Indeterminate Cell Histiocytosis (ICH) was described and coined by Wood GS et al. in 1985.[1] It is a rare cutaneous proliferative disorder characterized by a proliferation of CD1a + and CD207/langerin- mononuclear phagocytic cells, lacking Birbeck granules on electron microscopy. It is currently included in Group L of the 2016 revised classification of histiocytosis, catalogued as ''indeterminate dendritic cell histiocytosis'' and as ''indeterminate dendritic cell tumor'' in the 2022 WHO classification of dendritic cell neoplasms.[2] This classification has been reaffirmed in the 5th edition (2024) of the WHO Classification of Haematolymphoid Tumours.[3] Recent advances have shown that a subset of patients carries the ETV3::NCOA2 fusion gene, generally detected by Fluorescence In Situ Hybridization (FISH) or Next-Generation Sequencing (NGS).[4–6] In this paper, we report a case of a patient with florid ICH in which the ETV3::NCOA2 fusion was identified for the first time using Optical Genome Mapping (OGM), achieving a favorable outcome after treatment with cladribine.

A 17-year-old male presented with rapidly progressing cutaneous lesions over the last 6-months. Physical examination revealed numerous flesh-colored papules with a generalized, cobblestone-like distribution, respecting the acrofacial regions (Fig. 1A–C). There were no lymphadenopathies, mucosal involvement, or systemic symptoms. Laboratory tests, including blood count, autoimmunity (ANA, myositis, and sclerosis blots), blood smear, and serologies, were normal. Histopathology (Fig. 1D) showed a dermal infiltrate that dissected the collagen fibers, consisting mainly of dense histiocytoid cells, with few lymphocytes and no eosinophils. Immunohistochemistry, the tumor cells were positive for CD1a (Fig. 2A) and S100, but negative for CD207/langerin (Fig. 2B). His clinical presentation and histopathological findings supported the diagnosis of ICH.

As part of the extension study, a positron emission tomography-computed tomography scan and bone marrow biopsy were performed, both of which were normal. A NGS study using the Ampliseq™ Comprehensive Cancer Panel was performed on DNA from the surgical specimen, covering more than 400 genes, including *BRAF, KRAS, NRAS, MAP2K1, NTRK1-3*, and was negative except for the presence of the variants c.1288C > T p.(Pro430Ser) in the MLLT10 gene, with a Variant Allele Frequency (VAF) of 49.7% and the variant c.49997 G > A p.(Gly1666Asp) in the *RNF213* gene, with a VAF of 43.4%, both of them of unknown clinical relevance.

Subsequently, an OGM analysis was performed on a papular specimen, which had been previously snap-frozen in liquid nitrogen at −196 °C for 3-minutes and subsequently stored at −80 °C. Data analysis was conducted using Bionano Access® Software (Bionano Genomics), applying the ''Rare Variant Analysis'' pipeline with the GRCh38 genome as reference. This analysis (Fig. 2C–D) identified an interchromosomal translocation t(1;8)(q23.1;q13.3) with a VAF of 35%, leading to the formation of the ETV3::NCOA2 fusion gene.

The patient was started on prednisone 30 mg/d and methotrexate 15 mg/week. However, due to progression of the lesions after two months, treatment with cladribine 5 mg/m^2/day (days 0–5) was started for 4-months.

☆ Study conducted at the Hospital Universitario y Politécnico La Fe, Valencia, Spain.

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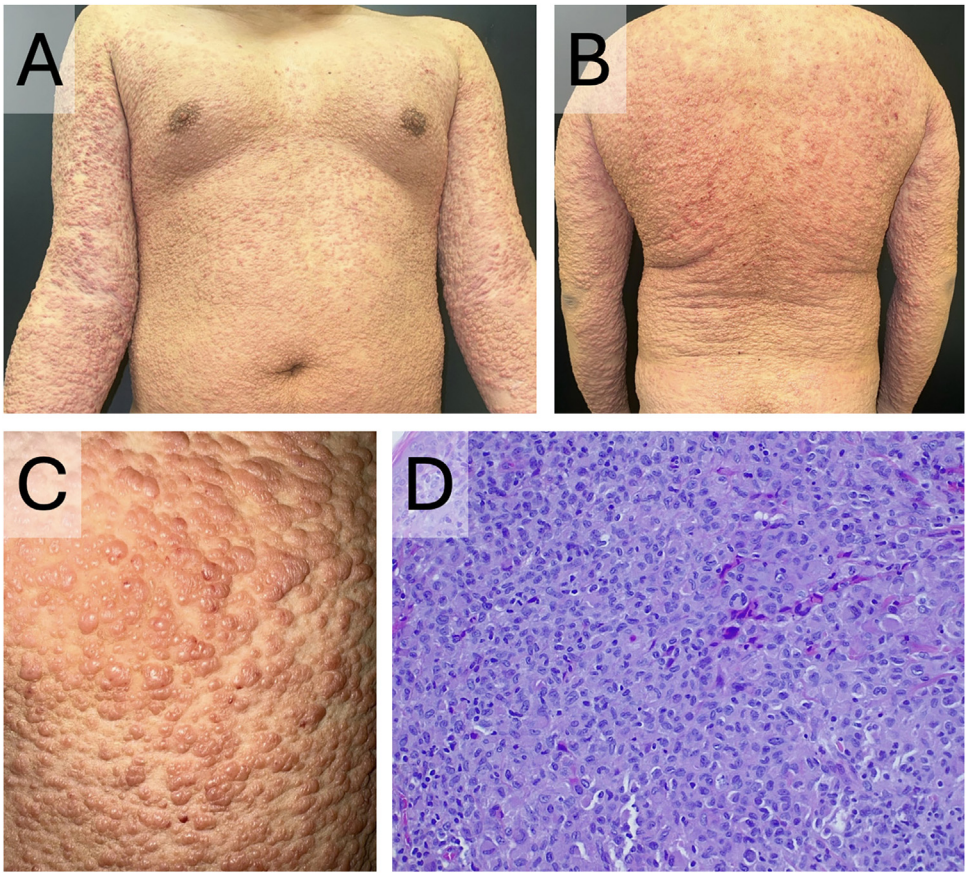

Fig. 1 Clinical presentation of the lesions and histopathological examination of one of the lesions. (A–B) Generalized flesh-colored papules with a 'cobblestone' appearance of the skin. (C) Close-up view of the lesions. (D) Dermal infiltrate, predominantly histiocytic, with few lymphocytes, plasma cells and no eosinophils (Hematoxylin & eosin, ×200).

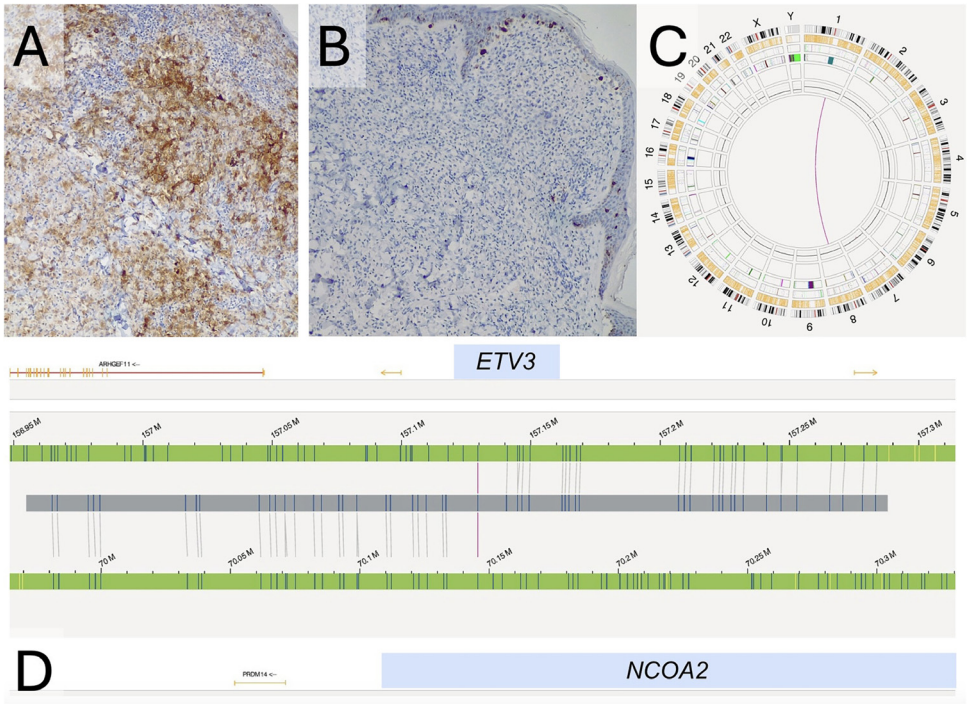

Fig. 2 Immunohistochemistry of one of the lesions and optical genomic mapping of the tumor sample. (A) Diffuse positivity for CD1a (CD1a, 10×). (B) Negativity for CD207/langerin (CD207/langerin, 10×). (C and D) Graphical representation of the Optical Genomic Mapping with the interchromosomal translocation t(1;8) (q23.1;q13.3).

He experienced a complete response of the lesions with no adverse effects or relapse at 8-month follow-up.

In recent years, advances in genetics and molecular biology techniques have led to the identification of two subtypes of ICH. The first is characterized by a predominance of mutations in the *BRAF, KRAS*, and *MAP2K1* pathways and is often associated with multisystemic disease and other hematological disorders (especially chronic myelomonocytic leukemia). The second, defined by the presence of the ETV3::NCOA2 fusion gene (detected by FISH, NGS or, in our case, by OGM), generally has a more indolent course and a favorable prognosis.[2,5,6]

This case highlights the utility of OGM for detecting cryptic structural variants that may go unnoticed by conventional techniques, providing valuable diagnostic and prognostic information.[7]

Numerous treatments have been reported, with surgical excision generally being the first choice for localized cutaneous forms, and methotrexate, phototherapy or chemotherapeutic agents in monotherapy (cyclophosphamide, busulfan, cladribine, vinblastine) for extensive cutaneous forms. Polychemotherapy regimens and/or hematopoietic cell transplantation are typically preferred for progressive cutaneous or multisystem involvement.[4,5]

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Authors' contributions

Miguel Mansilla-Polo: Directed the diagnosis and management of the patients and the initial writing of the manuscript.

Rafael Andreu-La Piedra: Directed the diagnosis and management of the patients and the initial writing of the manuscript.

Montserrat Évole-Buselli: Directed the diagnosis and management of the patients and the initial writing of the manuscript.

Esperanza Such-Taboada: Performed the genetics study, the final writing of the manuscript and supervised the work.

Irene Luna-del Valle: Performed the genetics study, the final writing of the manuscript and supervised the work.

Research data availability

Does not apply.

Conflicts of interest

None declared.

Editor

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LETTER – CLINICAL

Indeterminate cell histiocytosis with ETV3::NCOA2 fusion detected by optical genome mapping☆

Dear Editor,

Following observation of a generalized eruption in a young patient with a unique histopathology, the term Indeterminate Cell Histiocytosis (ICH) was described and coined by Wood GS et al. in 1985.[1] It is a rare cutaneous proliferative disorder characterized by a proliferation of CD1a + and CD207/langerin- mononuclear phagocytic cells, lacking Birbeck granules on electron microscopy. It is currently included in Group L of the 2016 revised classification of histiocytosis, catalogued as ''indeterminate dendritic cell histiocytosis'' and as ''indeterminate dendritic cell tumor'' in the 2022 WHO classification of dendritic cell neoplasms.[2] This classification has been reaffirmed in the 5th edition (2024) of the WHO Classification of Haematolymphoid Tumours.[3] Recent advances have shown that a subset of patients carries the ETV3::NCOA2 fusion gene, generally detected by Fluorescence In Situ Hybridization (FISH) or Next-Generation Sequencing (NGS).[4–6] In this paper, we report a case of a patient with florid ICH in which the ETV3::NCOA2 fusion was identified for the first time using Optical Genome Mapping (OGM), achieving a favorable outcome after treatment with cladribine.

A 17-year-old male presented with rapidly progressing cutaneous lesions over the last 6-months. Physical examination revealed numerous flesh-colored papules with a generalized, cobblestone-like distribution, respecting the acrofacial regions (Fig. 1A–C). There were no lymphadenopathies, mucosal involvement, or systemic symptoms. Laboratory tests, including blood count, autoimmunity (ANA, myositis, and sclerosis blots), blood smear, and serologies, were normal. Histopathology (Fig. 1D) showed a dermal infiltrate that dissected the collagen fibers, consisting mainly of dense histiocytoid cells, with few lymphocytes and no eosinophils. Immunohistochemistry, the tumor cells were positive for CD1a (Fig. 2A) and S100, but negative for CD207/langerin (Fig. 2B). His clinical presentation and histopathological findings supported the diagnosis of ICH.

As part of the extension study, a positron emission tomography-computed tomography scan and bone marrow biopsy were performed, both of which were normal. A NGS study using the Ampliseq™ Comprehensive Cancer Panel was performed on DNA from the surgical specimen, covering more than 400 genes, including *BRAF, KRAS, NRAS, MAP2K1, NTRK1-3*, and was negative except for the presence of the variants c.1288C > T p.(Pro430Ser) in the MLLT10 gene, with a Variant Allele Frequency (VAF) of 49.7% and the variant c.49997 G > A p.(Gly1666Asp) in the *RNF213* gene, with a VAF of 43.4%, both of them of unknown clinical relevance.

Subsequently, an OGM analysis was performed on a papular specimen, which had been previously snap-frozen in liquid nitrogen at −196 °C for 3-minutes and subsequently stored at −80 °C. Data analysis was conducted using Bionano Access® Software (Bionano Genomics), applying the ''Rare Variant Analysis'' pipeline with the GRCh38 genome as reference. This analysis (Fig. 2C–D) identified an interchromosomal translocation t(1;8)(q23.1;q13.3) with a VAF of 35%, leading to the formation of the ETV3::NCOA2 fusion gene.

The patient was started on prednisone 30 mg/d and methotrexate 15 mg/week. However, due to progression of the lesions after two months, treatment with cladribine 5 mg/m^2/day (days 0–5) was started for 4-months.

☆ Study conducted at the Hospital Universitario y Politécnico La Fe, Valencia, Spain.

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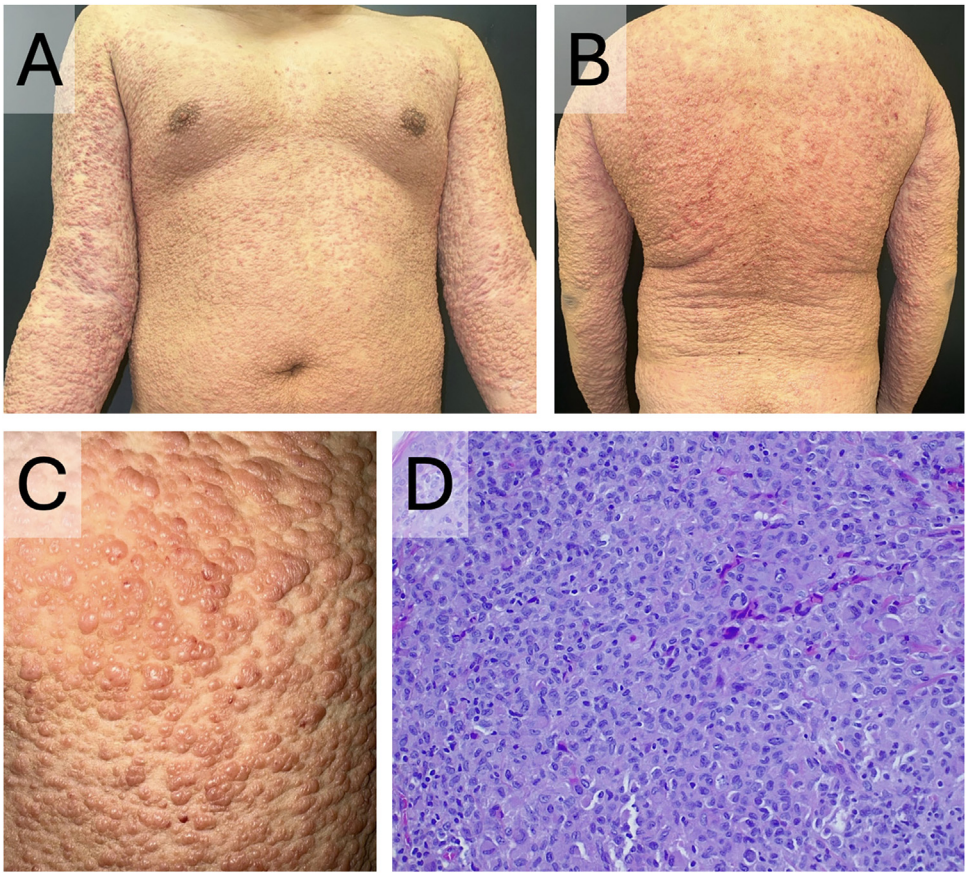

Fig. 1 Clinical presentation of the lesions and histopathological examination of one of the lesions. (A–B) Generalized flesh-colored papules with a 'cobblestone' appearance of the skin. (C) Close-up view of the lesions. (D) Dermal infiltrate, predominantly histiocytic, with few lymphocytes, plasma cells and no eosinophils (Hematoxylin & eosin, ×200).

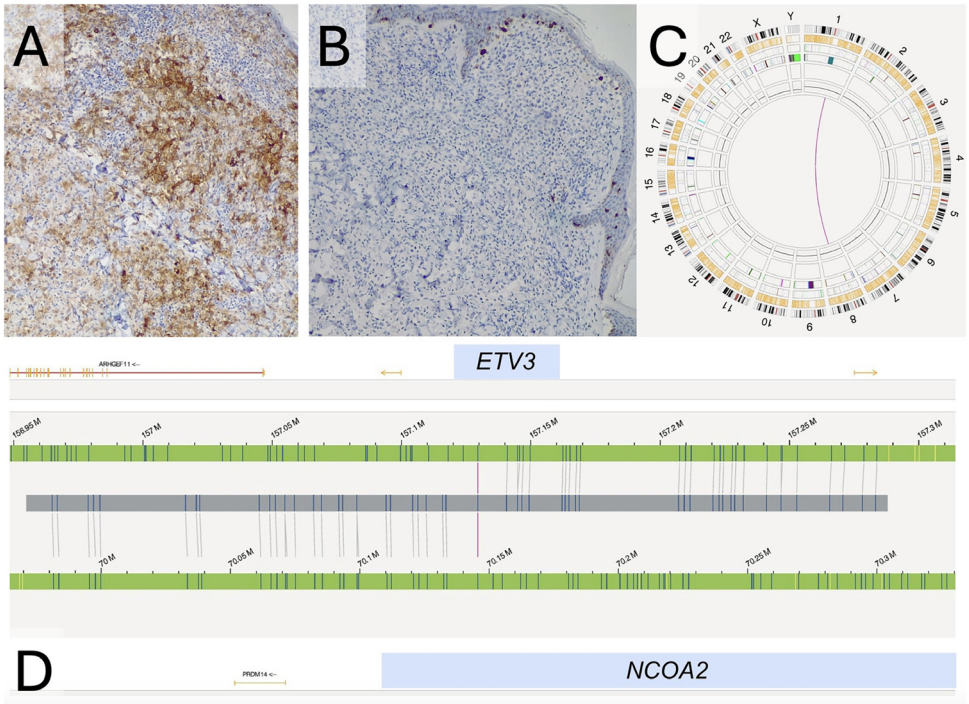

Fig. 2 Immunohistochemistry of one of the lesions and optical genomic mapping of the tumor sample. (A) Diffuse positivity for CD1a (CD1a, 10×). (B) Negativity for CD207/langerin (CD207/langerin, 10×). (C and D) Graphical representation of the Optical Genomic Mapping with the interchromosomal translocation t(1;8) (q23.1;q13.3).

He experienced a complete response of the lesions with no adverse effects or relapse at 8-month follow-up.

In recent years, advances in genetics and molecular biology techniques have led to the identification of two subtypes of ICH. The first is characterized by a predominance of mutations in the *BRAF, KRAS*, and *MAP2K1* pathways and is often associated with multisystemic disease and other hematological disorders (especially chronic myelomonocytic leukemia). The second, defined by the presence of the ETV3::NCOA2 fusion gene (detected by FISH, NGS or, in our case, by OGM), generally has a more indolent course and a favorable prognosis.[2,5,6]

This case highlights the utility of OGM for detecting cryptic structural variants that may go unnoticed by conventional techniques, providing valuable diagnostic and prognostic information.[7]

Numerous treatments have been reported, with surgical excision generally being the first choice for localized cutaneous forms, and methotrexate, phototherapy or chemotherapeutic agents in monotherapy (cyclophosphamide, busulfan, cladribine, vinblastine) for extensive cutaneous forms. Polychemotherapy regimens and/or hematopoietic cell transplantation are typically preferred for progressive cutaneous or multisystem involvement.[4,5]

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Research data availability

Does not apply.

Conflicts of interest

None declared.

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LETTER – CLINICAL

Poliosis as a clinical sign of melanoma arising on a congenital nevus☆

Dear Editor,

Poliosis, a localized patch of white hair, may rarely signal underlying melanoma, particularly when appearing over a melanocytic lesion.[1] We report a case of poliosis over the scalp associated with melanoma arising on a congenital nevus and provide a brief literature review.

A 30-year-old man with no relevant medical history presented with a painful, palpable nodule on the right parotid region, evolving over five months. Histological evaluation of the lesion confirmed intraparotid lymph node metastasis of melanoma. Clinical examination revealed a congenital melanocytic nevus measuring 8 × 6 cm in the right temporal scalp, with recent enlargement and a central area of white hair (Fig. 1). Partial biopsy confirmed melanoma arising in a congenital nevus.

The patient underwent complete excision of the lesion, total parotidectomy with facial nerve preservation, and

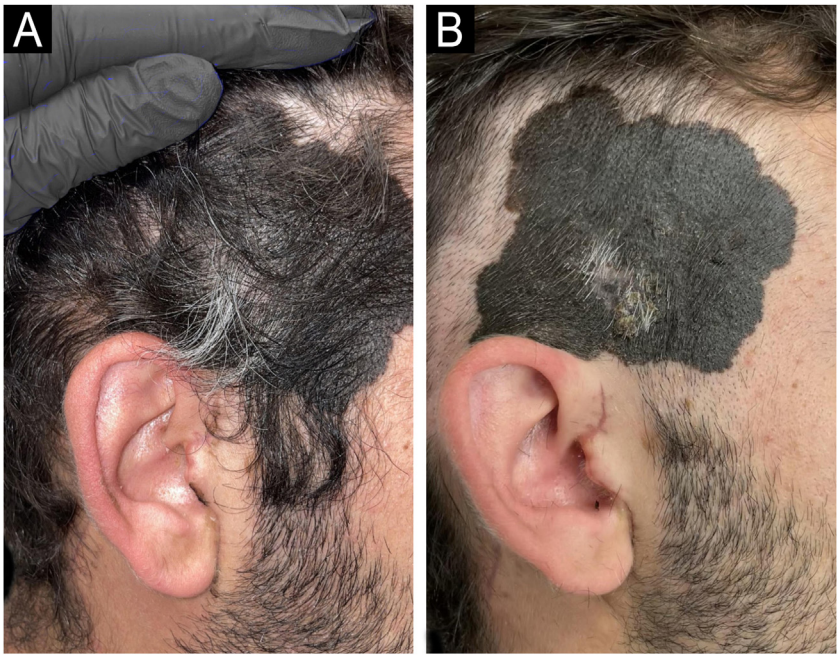

Fig. 1 (A) Initial presentation showing localized white hair (poliosis) within a congenital nevus on the right temporal scalp. (B) Same lesion after partial shaving reveals central ulceration and color heterogeneity; histopathology confirmed invasive melanoma arising within the nevus.

☆ Study conducted at the Department of Dermatology, Hospital Regional Universitario de Málaga, Málaga, Spain.

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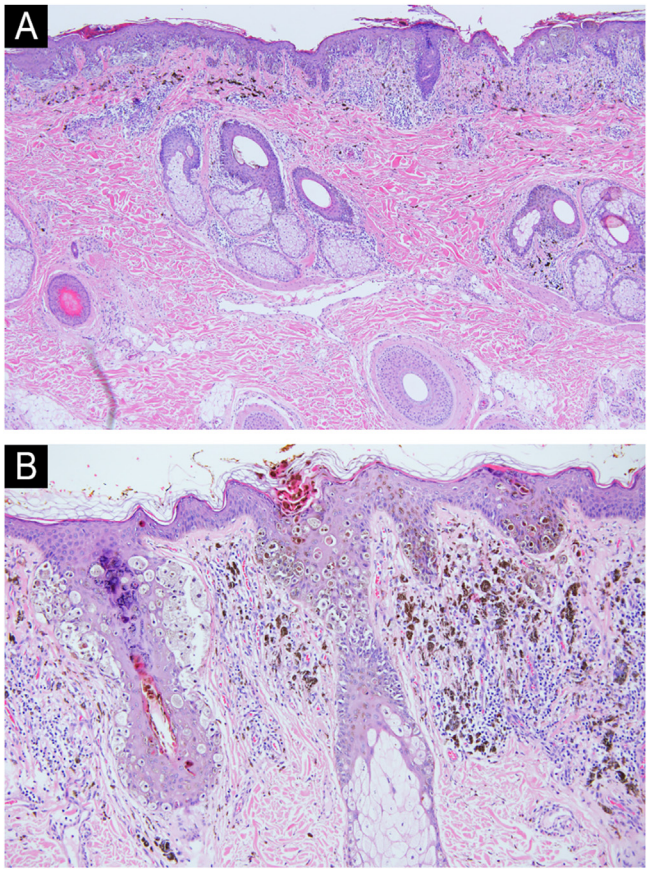

Fig. 2 (A) Hematoxylin & eosin stain, original magnification ×10. Continuous lentiginous growth of atypical melanocytes with formation of large nests. Melanocytic infiltration of the deep dermis and adnexal structures is also observed, a characteristic feature of congenital nevi. (B) Hematoxylin & eosin stain, original magnification ×40. Large, atypical melanocytes showing pagetoid spread and infiltration of the hair follicle.

right posterior cervical lymphadenectomy. A staging body CT scan excluded distant metastasis (M0). Histopathology showed invasive melanoma on a congenital nevus (Breslow 1.8 mm, Clark level III, ulceration, regression, 2 mitoses/mm^2, BRAF V600E positive) (Fig. 2), with 4 of 37 lymph nodes involved, one with extracapsular extension, corresponding to stage IIIC (AJCC 8). Adjuvant immunotherapy with pembrolizumab was administered for one year, and after 15-months of follow-up, the patient remains free of metastasis.

Poliosis has been associated with a broad spectrum of conditions, including autoimmune diseases (e.g., vitiligo, Vogt-Koyanagi-Harada, alopecia areata), inflammatory dermatoses, drug reactions (e.g., prostaglandin analogues, checkpoint inhibitors), and both benign and malignant tumors.[2,3] In melanoma, poliosis may reflect the destruction of follicular melanocytes through immune-mediated mechanisms. Molecular mimicry or shared antigens between melanoma cells and follicular melanocytes may explain this phenomenon.

We identified 8 previously reported cases in the literature directly linking circumscribed poliosis to melanoma (Table 1, Supplementary Table S1 and Fig. S1). Among these cases, most occurred in men and involved the scalp. Two cases described poliosis of the eyelashes associated with ocular melanomas – one conjunctival and one orbital – highlighting the relevance of poliosis in this site as a potential clue to intraocular disease. Additionally, in two cases, poliosis appeared at locations distant from the primary tumor, including the scalp and eyelashes, while the melanoma was located on the lower limb. This suggests that poliosis may occasionally act as a clinical marker of metastatic spread from a distant primary melanoma.

Histological features frequently included areas of regression and fibrosis in association with poliosis. Though regression in melanoma remains a debated prognostic factor, recent meta-analyses suggest it may be associated with improved survival.[4] Nevertheless, in this small series, 5 of 9 patients showed nodal or systemic involvement, underscoring the importance of prompt recognition and staging. With these findings, poliosis may represent a late-stage sign, potentially associated with a poorer prognosis in melanoma.

Scalp melanomas comprise 3%–5% of cutaneous melanomas but are associated with delayed diagnosis and worse outcomes. Their frequent amelanotic presentation contributes to diagnostic difficulty.[5] In this context, the emergence of localized poliosis over a nevus, particularly in adults, should prompt immediate dermoscopic evaluation and consideration of biopsy.

In conclusion, we present a rare case of melanoma arising in a congenital scalp nevus associated with circumscribed poliosis. Clinicians should consider recent onset of poliosis over melanocytic lesions as a potential clinical sign of melanoma requiring early investigation. Special attention should be paid to poliosis of the eyelashes, which may reflect not only ocular melanoma but also metastatic disease from a distant primary tumor.

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Silvestre Martínez García: Conceptualization; methodology; writing-original draft preparation.

Alejandro Arroyo Córdoba: Writing-final draft preparation; editing and validation.

Irene López Riquelme: Supervision; critical review and editing.

Table 1 Clinical and histopathological characteristics of reported melanoma cases associated with poliosis.

Author/Year	Type of Study	Sex	Age	Evolution	Medical history	Melanoma	Location Melanoma	Histological examination	Poliosis	Location Poliosis	Sentinel lymph node	Dx
Dunn CL 1995	Case report	Man	42	2 years	No medical history	Superficial spreading melanoma	Scalp	Breslow 1.3 mm, regression	In melanoma	Scalp	Unrealized	Localized disease
de Alba Campomanes AG 2008	Case report	Woman	71	2 months	Melanoma 4 years before	Conjunctival	Conjunctival	Not appear	In melanoma	Eyelashes	Unrealized	Localized disease
Alsuhaibani AH 2011	Case report	Man	60	3 months	No medical history	Orbital	Orbital	Not appear	In melanoma	Eyelashes	Unrealized	Localized disease
Yeo L 2015	Concise report	Man	28	1 year	No medical history	Superficial spreading melanoma	Scalp	Breslow 0.8 mm, regression, no ulcerate, 4 mitoses per mm^2	In melanoma	Scalp	Negative	Localized disease
Fernández-Díaz MR 2019	Medicine in images	Man	74	1 month	Melanoma 3 years before	Superficial spreading melanoma	Right leg	Not appear	Not adjacent	Eyelashes, eyebrows and scalp	Lymph node positive	Disseminated disease
Schollenberger MD 2019	Case report	Woman	31	1 year	No medical history	Superficial spreading melanoma	Scalp	Pigmented melanophages and early dermal fibrosis; no melanocytic proliferation	In melanoma	Scalp	Lymph node positive	Lymph node disease
Burzi L. 2021	Letters to the Editor	Woman	65	2 meses	No medical history	Amelanotic	Plantar	Not appear	Not adjacent	Eyelashes	Lymph node positive	Disseminated disease
Karch JL 2023	Case report	Man	44	Since birth	No medical history	Ex blue nevus	Scalp	Breslow 16 mm	In melanoma	Scalp	Lymph node positive	Lymph node disease
Our case 2025		Man	30	6 months	No medical history	Congenital naevus	Scalp	Breslow 1.8 mm, ulceration, regression, 2 mitoses per mm^2, BRAF-positive	In melanoma	Scalp	Lymph node positive	Lymph node disease

Research data availability

Does not apply.

Conflicts of interest

None declared.

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.2026.501340.

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LETTER - CLINICAL

Remission of refractory lichen amyloidosis with baricitinib☆

Dear Editor,

Lichen amyloidosis is the most frequent form of primary localized cutaneous amyloidosis, characterized by hyperkeratotic, pruritic, and lichenoid papules, resulting from the dermal deposition of amyloid material derived from keratin, without systemic involvement.[1] Its etiopathogenesis involves the apoptosis of basal keratinocytes and the subsequent dermal deposition of cytokeratin fragments, frequently associated with the activation of the IL-31 pathway, responsible for intense pruritus.[1] Treatment is quite challenging, with limited responses to topical corticosteroids, retinoids, immunosuppressants, and phototherapy.[1]

The present report describes a 22-year-old woman with pruritic lesions of five years' duration, distributed in the anterior region of her legs (Fig. 1). Histopathological examination revealed acanthosis, hypergranulosis, and compact hyperorthokeratosis. PAS and crystal violet staining revealed globular structures in the papillary dermis, and Congo red stain showed discreet marking, supporting the diagnosis of lichen amyloidosis. The patient had undergone multiple conventional therapies, including high-potency topical corticosteroid (clobetasol 0.05%), cyclosporine 300 mg for six months, acitretin 50 mg for one month, amitriptyline 50 mg (still in use), and antihistamines, without significant clinical improvement. The lesions persisted with intense pruritus, significantly impacting her quality of life.

Considering the refractory nature and emerging evidence on the role of JAK/STAT and IL-31 pathways in the pathophysiology of lichen amyloidosis,[1,2] baricitinib 4 mg/day was chosen, off-label, for the case. The drug was chosen for its safety profile in chronic inflammatory skin conditions and for previous reports of efficacy in cases of lichen amyloidosis associated with atopic dermatitis.[3]

The clinical response was rapid and significant. Pruritus ceased completely on the second day of treatment, and the lesions began to regress progressively with flattening, leaving residual hyperpigmentation. After 30 days, notable improvement in the texture and color of the lesions was observed (Fig. 2), progressing to almost complete resolution at 90 days (Fig. 3), when compared to the initial appearance. No adverse events were recorded during the three-month follow-up.

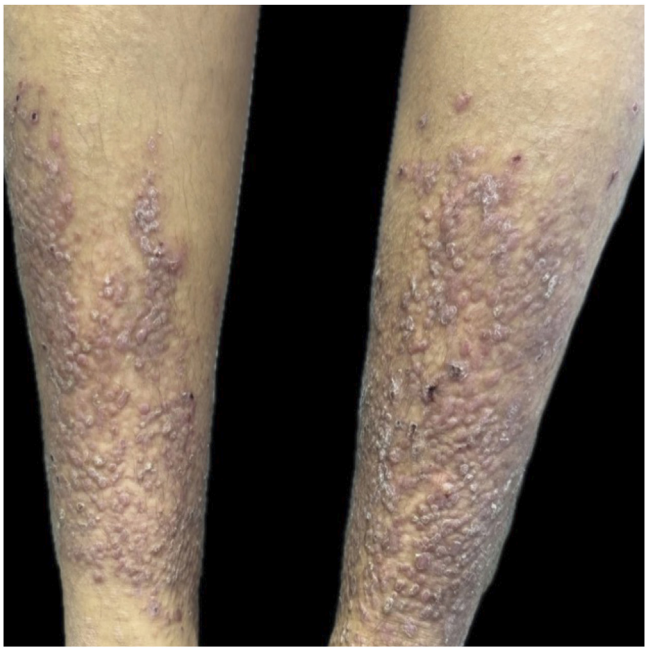

Fig. 1 Erythematous and hyperkeratotic papules on the legs, before treatment.

Recent studies reinforce that lichen amyloidosis is frequently associated with alterations in signaling of the JAK-STAT pathways, especially JAK1 and JAK2, implicated in IL-31 activation and the pruritus-lesion-amyloid deposition cycle.[2,3] This pathophysiological basis explains the effectiveness of JAK inhibitors in controlling both pruritus and persistent dermal inflammation. Several reports support this rationale: the use of dupilumab has shown benefit in refractory cases of lichen amyloidosis, including when there is co-occurrence with atopic dermatitis;[4–6] nemolizumab, an IL-31RA blocker, promoted complete remission after two years of use[2]; abrocitinib, a selective JAK1 inhibitor, resulted in marked clinical improvement

☆ Study conducted at the Clínica Médica Desenvolver, Florianópolis, SC, Brazil.

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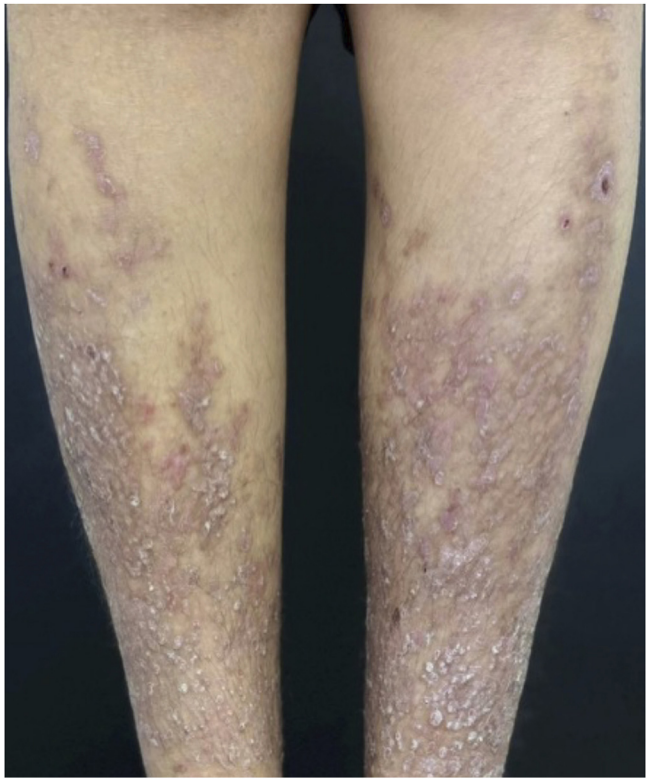

Fig. 2 After 30 days of baricitinib 4 mg/day: Papules begin to resolve.

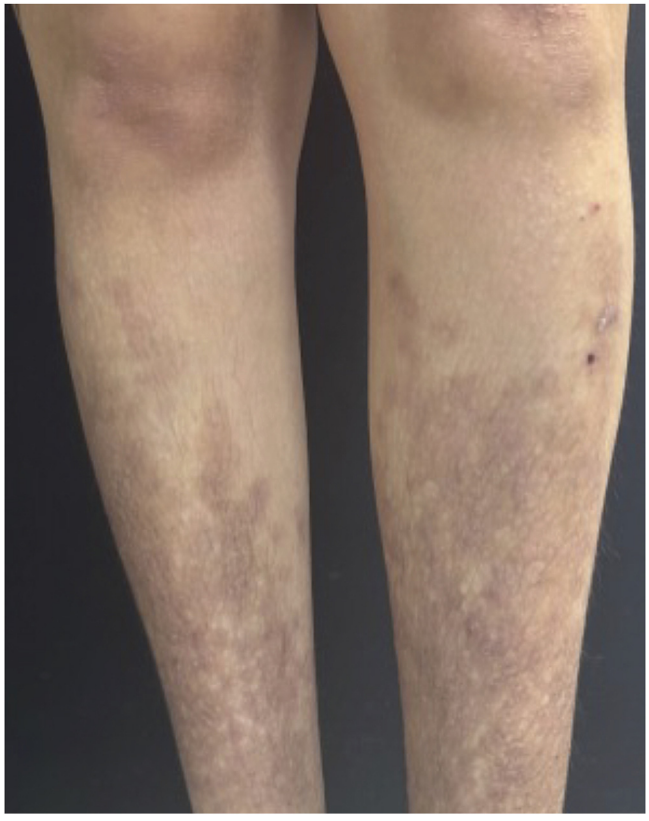

Fig. 3 After 90 days of baricitinib 4 mg/day: almost complete resolution of the lesions, with residual hyperpigmentation.

and reduction of the EASI score in patients with lichen amyloidosis associated with atopic dermatitis[7]; and upadacitinib, another JAK1 inhibitor, demonstrated rapid and sustained responses in isolated cases of resistant lichen amyloidosis.[6,8]

The present case corroborates these observations, demonstrating the effectiveness of baricitinib, a selective JAK1/JAK2 inhibitor, in the complete control of pruritus and clinical regression of lesions. Early improvement and the absence of adverse effects reinforce the potential of this class as a promising therapeutic alternative for refractory forms of lichen amyloidosis, especially when classic immunosuppressants and retinoids fail.

In conclusion, baricitinib proved to be an effective and safe option in the management of refractory lichen amyloidosis, with rapid resolution of pruritus and significant improvement of lesions in the short term. This report contributes to expanding the evidence on the use of JAK inhibitors in primary cutaneous amyloidosis, highlighting the need for controlled studies that consolidate their therapeutic role.

Authors' contributions

Thiago Lenoir da Silva: Design and planning of the study; drafting and editing of the manuscript; critical review of intellectual content; approval of the final version of the manuscript.

Gleison Vieira Duarte: Design and planning of the study; drafting and editing of the manuscript; critical review of intellectual content; approval of the final version of the manuscript.

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Conflicts of interest

Thiago Lenoir da Silva declares potential conflicts of interest related to scientific, educational, or consulting activities with the following pharmaceutical companies: AbbVie, Sun Pharma, and Sanofi.

Gleison Duarte Vieira declares potential conflicts of interest related to scientific, educational, consulting, or research activities with the following pharmaceutical companies: AbbVie, Eli Lilly, Celldex, Amgen, Johnson & Johnson (J&J), Novartis, Galderma, LEO Pharma, UCB, Pfizer, Sun Pharma, and Sanofi.

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LETTER - CLINICAL

Use of dupilumab in the management of refractory prurigo nodularis in an immunosuppressed double transplanted patient☆

Dear Editor,

Prurigo nodularis is a chronic inflammatory dermatosis characterized by intensely pruritic nodules. Its pathophysiology involves a complex neuro-immunological interaction, with a Th2-type inflammatory response and neurogenic mediators such as substance P.[1,2] Its management is complex, and conventional treatments are often insufficient to control pruritus and lesions.[3]

There is evidence that immunosuppression, whether due to underlying diseases or specific treatments, may be associated with the onset of prurigo nodularis, although the relationship is neither exclusive nor pathognomonic.[1] However, while there are new therapies for nodular prurigo, including the use of dupilumab, immunosuppressed patients have been systematically excluded from clinical trials evaluating them.

We present the case of a double transplant recipient and immunosuppressed patient with refractory prurigo nodularis who was successfully treated with dupilumab.

A 71-year-old male patient with a history of type 1 diabetes mellitus and chronic kidney disease due to diabetic nephropathy. He underwent a double kidney and pancreas transplant and has been on immunosuppressive treatment since 2005, currently with tacrolimus 3 mg every 12-hs and prednisone 10 mg every 24-hs.

His last hospitalization was due to septic shock of gastrointestinal origin, where he developed a purpuric vesicular-bullous rash predominantly on the trunk and extremities, consistent with septic vasculitis due to *Streptococcus pyogenes* with skin involvement. An antibiotic regimen with ceftriaxone was completed, and multiple surgical cleanings and escharectomies were performed for necrotic lesions. After resolution of the condition, the patient was discharged with dermatology follow-up.

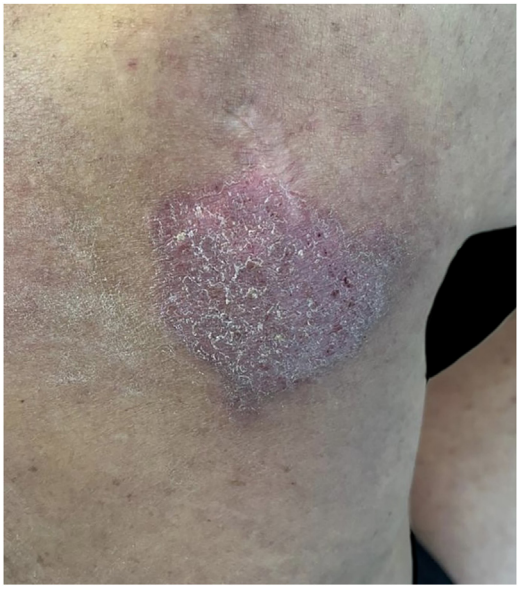

Figure 1 Rounded, erythematous, eczematous plaques consistent with nummular eczema.

One month after discharge, well-defined, pruritic, rounded erythematous skin lesions were observed on the right shoulder and back, consistent with nummular eczema (Fig. 1). General measures and treatment with topical corticosteroids and antibiotics were indicated. One month later, the lesions became more hypertrophic and widespread, involving the abdomen and chest, associated with intense pruritus that interrupted sleep. Given the progression of the condition, systemic therapy with prednisone was initiated, and a skin biopsy was requested, which revealed drug-induced spongiotic dermatitis.

He subsequently continued with partial improvement of symptoms, with the addition of indurated erythematous-violaceous nodules on the anterior aspect of both arms (Fig. 2). A diagnosis of nodular prurigo associated with severe, extensive nummular eczema was established, and therapy was adjusted. Despite multiple topical and systemic therapeutic strategies and phototherapy, he persisted without clinical improvement.

☆ Study conducted at the Universidad de los Andes, Santiago, Chile.

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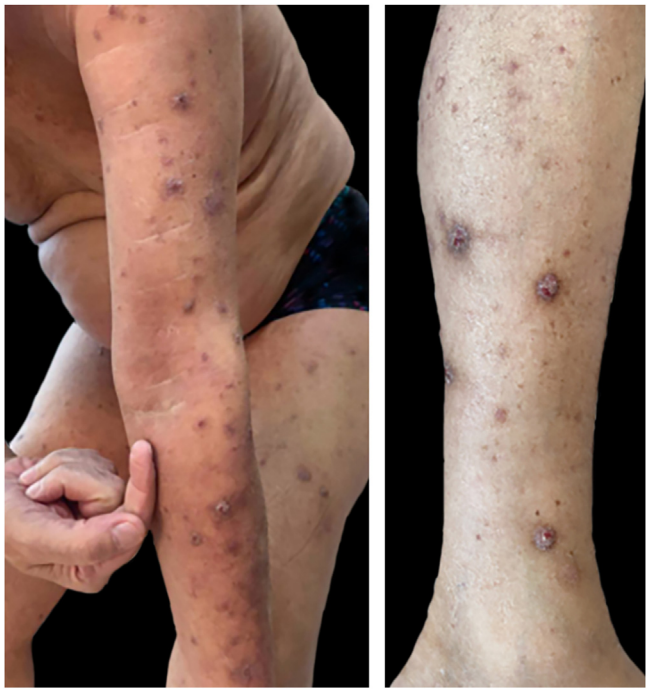

Figure 2 Prurigo nodularis. Indurated, erythematous-violaceous nodules on the anterior aspect of both arms and legs.

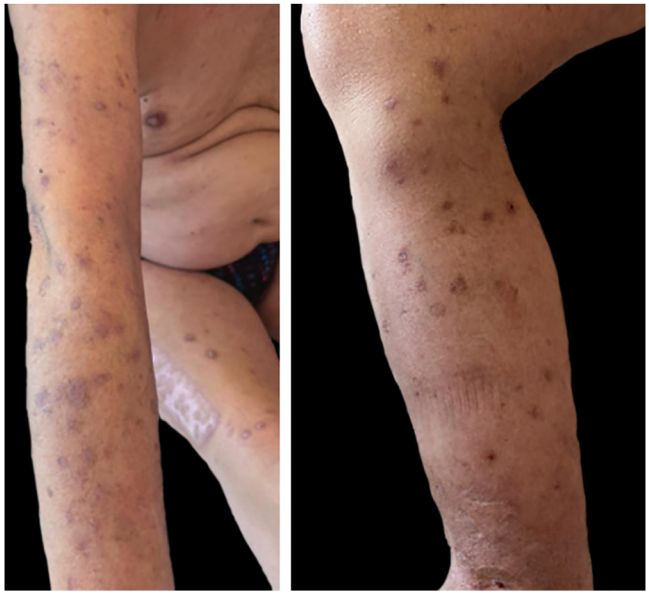

Figure 3 Skin lesions after 4-months of treatment with dupilumab.

Given the difficulty in managing the condition due to the patient's history of double transplantation and immunosuppression, treatment with dupilumab was initiated. At the time of the last check-up, after 8 injections (4-months of treatment), a good response was reported, with a decrease in the number of active lesions (Fig. 3) from 30 to 7, relief of pruritus to 2/10, and improvement in nighttime sleep. Thus, biological treatment proved to be effective in controlling the disease, significantly improving the patient's quality of life.

The case presented illustrates the complexity of managing prurigo nodularis in a patient with multiple comorbidities and coexisting dermatological conditions, which hinder treatment and remission. This complexity is accentuated in the context of organ transplantation, where nodular prurigo may be related to both immunosuppression and additional risk factors, such as chronic infections or host-specific immunological alterations.[4]

Kidney transplant patients, especially those with end-stage kidney disease or transplantation, are particularly susceptible, with the severity of renal disease being an independent and significant risk factor for the development of prurigo nodularis.[5]

In this scenario, dupilumab has emerged as an effective therapeutic alternative, blocking the IL-4/IL-13 pathway, reducing both pruritus and the number and severity of nodular lesions, positioning itself as the treatment of choice in cases refractory to conventional therapies.[6] Clinical trials have demonstrated its efficacy and safety, with no relevant increase in serious infections or major adverse events.[7] However, these studies systematically excluded patients with significant immunosuppression, including solid organ transplant recipients, so evidence in this group is limited to case reports and small series.[4,7]

The reviewed literature suggests that dupilumab could be a valid therapeutic option in patients with prurigo nodularis and immunosuppression, due to its targeted mechanism of action and safety profile that does not cause global immunosuppression, unlike other classic immunomodulators.[4,7] Moreover, drug interactions are almost absent, making it suitable for elderly patients with comorbidities and polypharmacy.[8]

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Conflicts of interest

None declared.

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LETTER – DERMATOPATHOLOGY

Atypical fibroxanthoma in sun-protected sites: two cases in the inguinal region and thigh☆

Dear Editor,

Atypical fibroxanthoma (AFX) is an uncommon cutaneous soft-tissue neoplasm with low metastatic potential but occasional local recurrence.[1,2] It typically arises on sun-exposed head and neck skin in older patients, while cases on sun-protected regions are uncommon.[3–5] We report two cases of AFX arising in the inguinal region and thigh of middle-aged immunocompetent men.

Case 1

A 54-year-old man presented with a 7–8 mm smooth, grayish-brown papule on the inguinal region that had persisted for 7–8 months (Fig. 1). The patient had no history of trauma, radiotherapy, or immunosuppression. Histology showed a well-demarcated dermal tumor without subcutaneous invasion, with pleomorphic spindle and epithelioid cells, foamy histiocyte-like cells, and atypical mitoses (Fig. 2 A–B). Immunohistochemistry (IHC) revealed CD68 positivity, partial CD31 positivity, and negativity for CD34, HMB45, and pan-cytokeratin, with Ki-67 ∼10% (Fig. 2C–D). The lesion was completely excised, and no metastasis was detected.

Case 2

A 53-year-old man presented with a 6 mm smooth, dark-brown papule on the right thigh that had persisted for 5-years (Fig. 3). He was a hepatitis B virus carrier but otherwise immunocompetent. Histology revealed a dermal tumor of densely packed spindle cells with pleomorphic nuclei and foamy cells (Fig. 4A–B). IHC revealed CD68, CD10, and SMA positivity, CD34 negativity, and Ki-67 ∼10% (Fig. 4 C–D). The patient was diagnosed with spindle-cell-type AFX. Re-

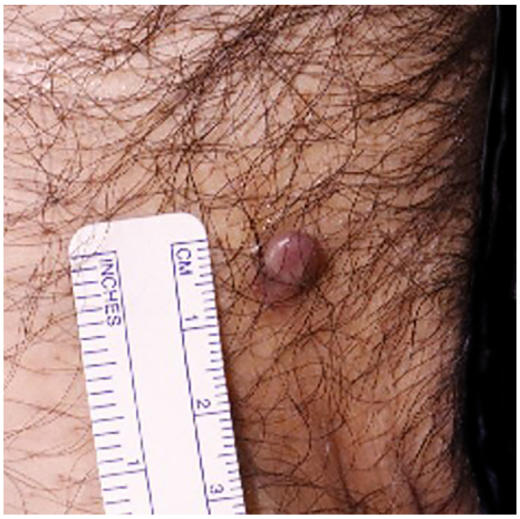

Fig. 1 Case 1: Atypical fibroxanthoma on the inguinal region.

excision was recommended, but the patient declined; a two-month follow-up revealed no recurrence.

AFX typically presents as a solitary dome-shaped papule or nodule on sun-exposed skin in older males. Ultraviolet (UV) radiation is regarded as the main etiological factor, inducing p53 mutations and UV-specific DNA damage.[2] Other contributing factors include previous radiation exposure, trauma, or immunosuppression.[1]

AFX on sun-protected sites is exceptionally uncommon, with few cases reported on the trunk, proximal limbs, or genital regions.[3–5] Koch et al.[1] noted that only ∼15% of AFX cases involved the trunk or extremities, with even fewer arising in the thigh or inguinal region. Our patients were relatively young, immunocompetent, and lacked known risk factors, suggesting that other mechanisms may be involved in the condition's etiology. Recent genomic studies have identified that recurrent alterations in FAT1, NOTCH1/2, CDKN2A, TP53, and the promoter of the *TERT* gene may be linked to AFX.[6] Some AFX-associated mutations are clearly UV-related (e.g., C>T transitions), whereas others (e.g., locus loss or copy number variations) can arise either from UV-induced genomic instability or through UV-independent mechanisms, highlighting alternative pathogenetic pathways.[6]

☆ Study conducted at the College of Medicine, Sanggye Paik Hospital, Inje University, Seoul, South Korea.

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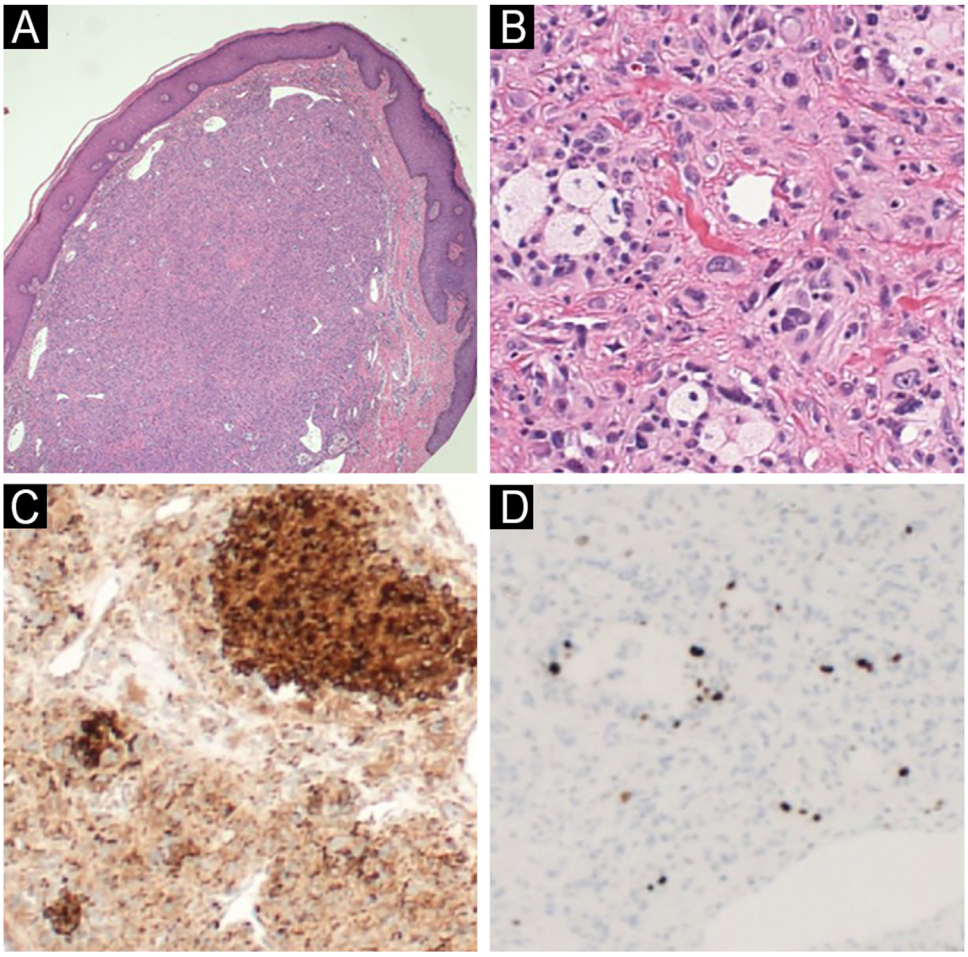

Fig. 2 Case 1: (A) Hematoxylin and eosin staining showing a well-demarcated, non-encapsulated dermal tumor (40× magnification). (B) Hematoxylin & eosin staining showing pleomorphic spindle and epithelioid cells, as well as foamy histiocyte-like cells with atypical mitoses (400× magnification). (C) CD68 Immunohistochemistry (IHC) showing strong positivity in the tumor cells (100× magnification). (D) Ki-67 IHC showing a labeling index of around 10% in tumor cells (100× magnification).

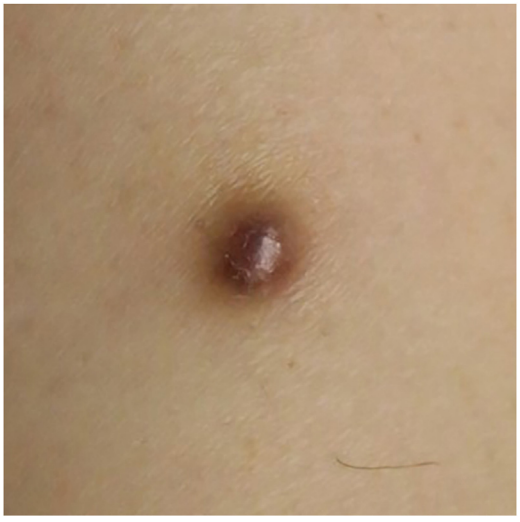

Fig. 3 Case 2: Atypical fibroxanthoma of the right thigh.

Histologically, AFX is a well-circumscribed, dermal-based tumor that spares subcutaneous and adnexal structures. Pleomorphic spindle and epithelioid cells, foamy histiocyte-like cells, and atypical mitoses are characteristic.[1,2] Differential diagnoses include Pleomorphic Dermal Sarcoma (PDS), Undifferentiated Pleomorphic Sarcoma (UPS), melanoma, leiomyosarcoma, poorly-differentiated squamous cell carcinoma, Atypical Dermal Fibroma (ADF), Malignant Dermal Fibroma (MDF), and Dermatofibrosarcoma Protuberans (DFSP). PDS typically shows deeper invasion and perineural or lymphovascular involvement, whereas UPS is more aggressive and frequently metastasizes.[7] ADF and MDF can be differentiated from AFX, as ADF shows a well-defined grenz zone, epidermal hyperplasia, and fewer atypical mitoses (<1%), while MDF exhibits deep invasion and necrosis, with repeated local recurrences.[8,9] IHC is essential, as AFX typically expresses CD68 and vimentin, but is negative for cytokeratins, Factor XIIIa, and CD34. SMA or CD10 positivity may also be present in spindle-cell variants.[1] By contrast, SCC is cytokeratin-positive, melanoma expresses SOX-10 or Melan-A, leiomyosarcoma expresses SMA/desmin,

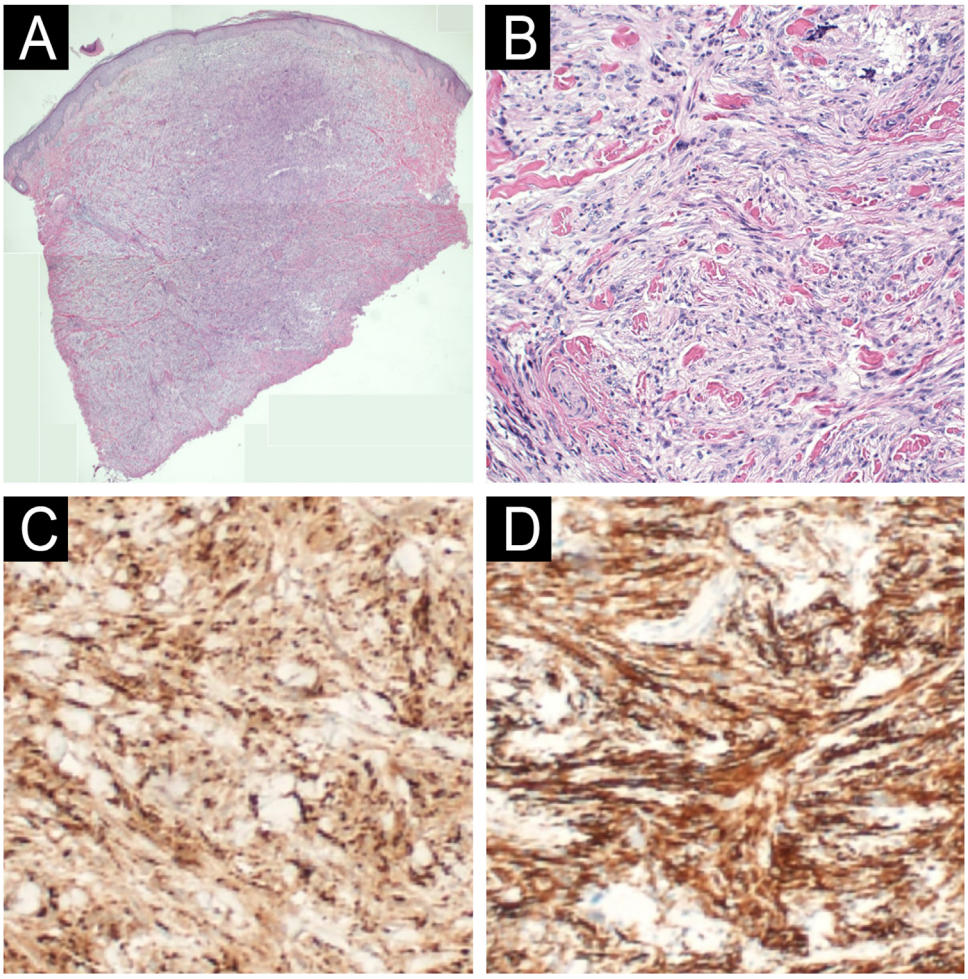

Fig. 4 Case 2: (A) Hematoxylin & eosin staining showing a dermal-based spindle cell tumor (40× magnification). (B) Hematoxylin & eosin showing spindle cells with pleomorphic nuclei and foamy cells (200× magnification). (C) CD68 IHC showing strong positivity in the tumor cells (100× magnification). (D) SMA IHC showing strong positivity in the tumor cells (100× magnification).

ADF and MDF express Factor XIIIa, and DFSP shows strong CD34 positivity.[1,8,9]

AFX has a favorable prognosis with low metastatic potential but ∼5% recurrence.[1,2] Complete surgical excision with negative margins remains the standard treatment, and Mohs micrographic surgery offers the lowest recurrence (∼2% vs. ∼9% for wide local excision).[10] In Case 2, although the tumor involved all resection margins, no recurrence was observed during the two-month follow-up. Given the relatively short duration of follow-up, the possibility of local recurrence cannot be completely excluded, representing a limitation.

These two cases illustrate that AFX can arise in atypical, sun-protected sites, such as the inguinal region and thigh, even in middle-aged immunocompetent patients. Dermatologists and pathologists should remain aware of this possibility, as careful histopathological evaluation combined with IHC is crucial for accurate diagnosis and appropriate surgical management.

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Research data availability

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LETTER - DERMATOPATHOLOGY

Spitz nevus in a patient with oculocutaneous albinism: dermoscopic and histopathologic correlation☆

Dear Editor,

In oculocutaneous albinism (OCA), an autosomal recessive disorder characterized by total or partial absence of melanin production, melanocytic lesions pose a diagnostic challenge due to their atypical dermoscopic presentation.[1] The present report describes a patient with OCA followed by digital mapping, in whom a Spitz nevus (SN) was identified and confirmed by histopathologic examination.

A 25-year-old female patient with OCA, with no family history of albinism or other skin diseases, underwent digital dermoscopic follow-up at a tertiary dermatology center due to multiple atypical nevi. During the dermoscopic follow-up, a 0.4 cm light brown papule was identified on the left upper limb. Dermoscopy revealed globular structures with a yellowish appearance and uniform distribution throughout the lesion (Fig. 1) and fine punctate vessels, distributed globally and symmetrically (Fig. 2). Given the atypical appearance of the lesion, excision was chosen. The lesion area had been examined approximately one year prior without any lesion being detected.

The evaluation of the histological sections revealed a well-defined, compound melanocytic proliferation, formed by large and varied nests of epithelioid and fusiform melanocytes. The dermal component was restricted to the superficial reticular dermis. Some cells showed ample cytoplasm, sometimes granular, with discrete cytological atypia. Junctional nests showed separation gaps in relation to the

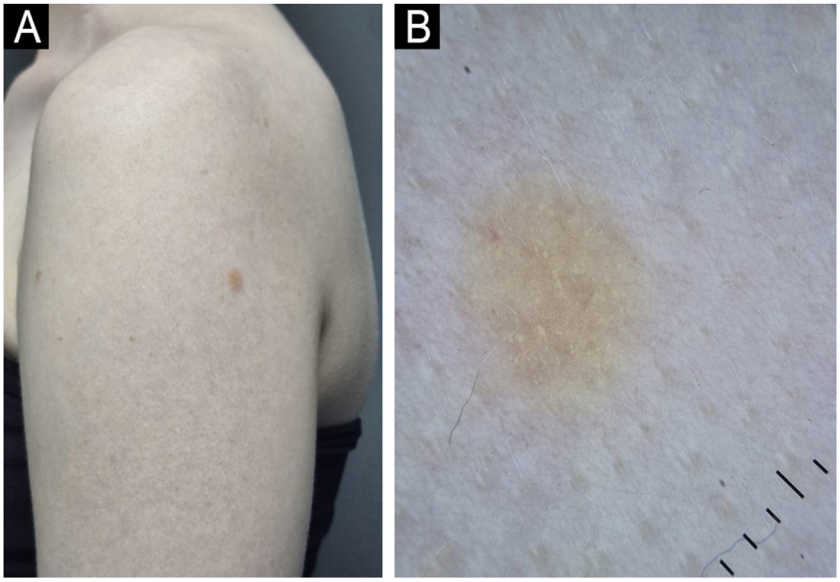

Figure 1 (A) Patient with oculocutaneous albinism presenting with a 0.4 cm non-pigmented nevus on the left upper limb. (B) Dermoscopy with polarized light reveals yellowish structures in the central region.

☆ Study conducted at the Dermatology Clinic, Hospital da Santa Casa de São Paulo, Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil.

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adjacent epidermis, in addition to eosinophilic globular structures compatible with Kamino bodies. Subtle acanthosis was observed, without mitotic activity or pagetoid dissemination of melanocytes. There was no melanocytic pigmentation (Fig. 3). Immunohistochemistry showed preserved p16 expression, negative BRAF test, and positivity for Melan-A (Fig. 4). The test was reviewed by two experienced dermatopathologists, who confirmed the diagnosis of Spitz nevus.

Spitz nevus is a melanocytic neoplasm consisting of epithelioid and/or spindle cells. Clinically, it presents as a solitary, well-defined papule or nodule, usually <1 cm, with rapid initial growth and predominance on the limbs of young adults. The classic dermoscopic presentation involves a punctate vascular pattern in about 50% of cases, with regularly distributed monomorphic vessels on a homogeneous pink background. Other, less common patterns include reticular or homogeneous depigmentation.[2]

Histologically, it is characterized by symmetry, well-defined delimitation, presence of epithelioid/fusiform melanocytes, progressive dermal maturation, mild cytological atypia, Kamino bodies, occasional mitoses, and discrete lymphocytic inflammatory infiltrate.[3,4] The preserved p16 expression observed in the patient reinforces the lesion's benignity, since its loss is associated with malignant Spitzoid neoplasms. Melan-A, in turn, confirmed the melanocytic nature.[5]

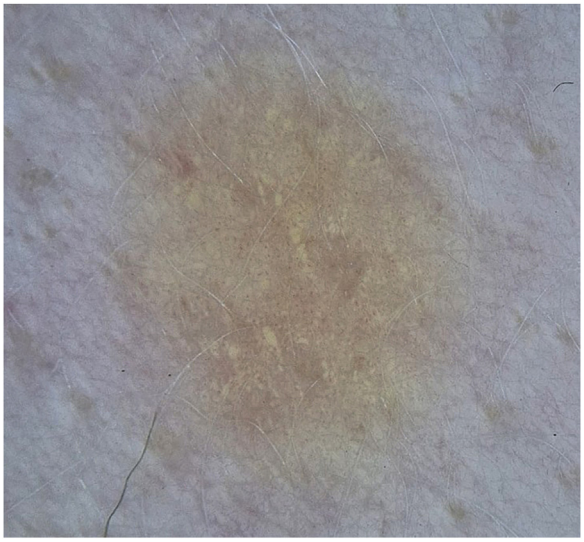

Figure 2 Higher dermoscopic magnification with polarized light showing millimeter-sized punctate vessels, distributed globally and symmetrically throughout the lesion.

From a dermoscopic point of view, the yellowish globules observed may correspond to the melanocytic nests identified histologically, whose absence of pigment in the context of

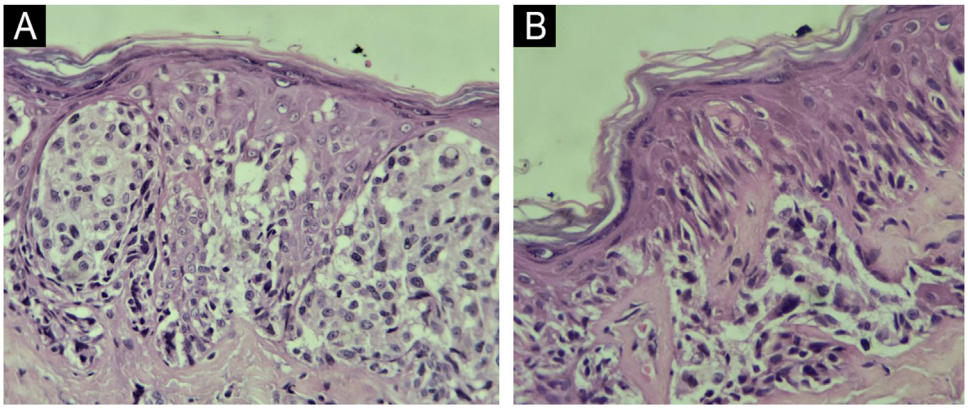

Figure 3 Patient's histopathologic examination. (A) Large nests of epithelioid and spindle cells with ample cytoplasm. Slight acanthosis can be observed. (Hematoxylin & eosin, ×100). (B) Irregular nests of epithelioid and spindle cells, presence of Kamino bodies (Hematoxylin & eosin, ×100).

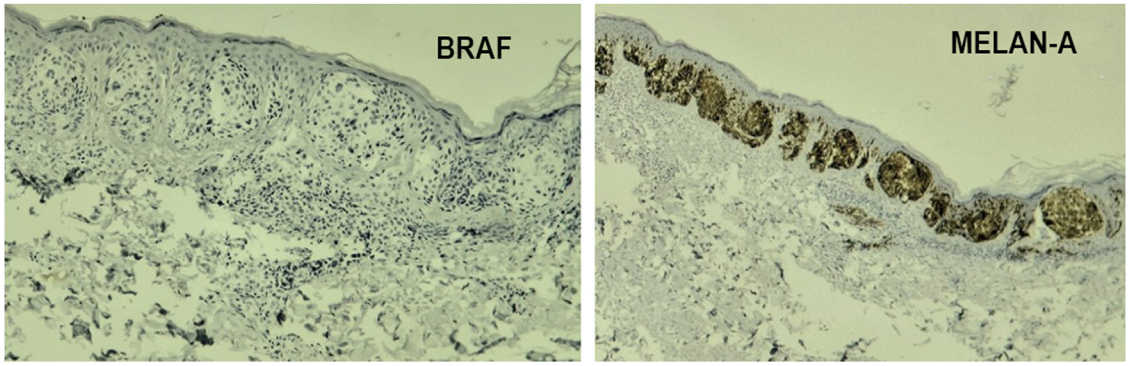

Figure 4 Immunohistochemistry examination of the patient: left showing negative BRAF staining in cells of interest (BRAF ×10); right showing positive Melan A staining in cells of interest (Melan A ×10).

OCA results in a yellowish hue instead of the homogeneous pink background coloration usually observed.

Regarding molecular biology, activating mutations in BRAF and NRAS are known to be rare in Spitz nevi, although age may influence their occurrence. Fusions involving BRAF are described in about 5% of epithelioid lesions, and a small percentage may evolve into melanoma.[6,7] The negative result for BRAF in this case is consistent with the expected profile for Spitz nevi, which usually show gene fusions that are not detectable by this method.[8]

Despite the extensive description of Spitz nevi in the literature, there is still a scarcity of data on their dermoscopic presentation in patients with oculocutaneous albinism, which reinforces the relevance of this report. In particular, the observation of yellowish structures under polarized light is highlighted, which, in hypopigmented lesions, may correspond to clusters of melanocytic cells, a finding of potential diagnostic value. During the literature review, the authors did not find a dermoscopic description of Spitz nevus in patients with oculocutaneous albinism.

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Conflicts of interest

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LETTER – TROPICAL/INFECTIOUS AND PARASITIC DERMATOLOGY

Cutaneous leishmaniasis caused by Leishmania infantum arising within a psoriatic plaque: a case report☆

Dear Editor,

Cutaneous leishmaniasis (CL) is a neglected tropical disease with incidence estimates of 700.000 to 1.2 million cases per year; approximately 95% of those cases occur in the Americas, the Mediterranean basin, the Middle East, and Central Asia.[1] Typical clinical presentation varies from single granulomatous lesions or ulcerations on the site of inoculation, but can also resemble other dermatological diseases, such as pyoderma gangrenosum and psoriasis.[2,3] However, CL developing in pre-existing skin lesions has rarely been reported. This report describes the first case of an immunocompetent host with the appearance of CL in a longstanding psoriasis plaque.

A 64-year-old Caucasian man presented to the dermatology department with a painless non-healing wound on his right elbow. He had had psoriasis on this site for 7 years, waxing and waning, and he had noticed some oozing six months before our first consultation, while he was staying in his coastal house south of Valencia, Spain, where he spends several months every winter. He didn't recall any trauma. He had travelled to Cambodia and Vietnam five years before, but had no recent visits to tropical regions. He was otherwise in good general health. Prior to referral to our tertiary centre, a dermatologist treated him empirically with three courses of antibiotics – amoxicillin-clavulanic acid (dose unspecified) and two other regimens of unknown composition – without improvement. Cultures from the wound and purulent material obtained before the first antibiotic course yielded only normal skin flora. The lesion fluctuated in size, occasionally almost closing but never fully healing. At presentation, his sole therapy was topical disinfection with povidone-iodine solution. Aside from long-standing psoriasis, his medical history was unremarkable. His chronic medications consisted of rosuvastatin 20 mg once daily and pantoprazole 20 mg once daily.

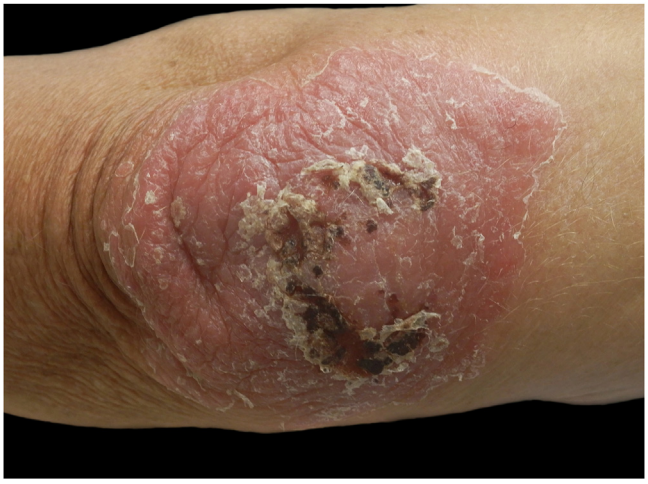

Fig. 1 Hematic crusts, ulceration and discrete oozing arising within a psoriatic plaque on the right elbow as the first manifestation of CL caused by L. infantum.

On dermatological examination, the right elbow displayed an erythematous, infiltrated lesion with scaling, crusting, slight oozing, and an irregular border, centred within an 8 cm psoriatic plaque (Fig. 1). Classic erythrosquamous psoriatic plaques were present on the extensor aspects of both knees and the other elbow, and also the oil-drop pigmentation of the fingernails was consistent with psoriasis. No hepatomegaly, splenomegaly, or palpable lymphadenopathy was detected on physical examination.

The differential diagnosis included atypical pyoderma gangrenosum, deep cutaneous mycosis, cutaneous leishmaniasis (despite weak epidemiological risk), squamous cell carcinoma, and allergic contact dermatitis.

Ultrasound of the upper arm and right axilla demonstrated reactive lymphadenopathy without hepatosplenomegaly. Routine laboratory tests, including complete blood count and inflammatory markers, were within normal limits.

A punch biopsy from the lesion centre revealed a dense dermal infiltrate of plasma cells and histiocytes forming granulomas; no amastigotes were found. The first PCR deter-

☆ Study conducted at the Department of Dermatology, Universitair Ziekenhuis Antwerpen, Edegem, Antwerpen, Belgium.

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mined on a skin sample was positive for Leishmania spp. but lacked species identification. A second biopsy confirmed Leishmania infantum by PCR (Hsp-70 sequencing).[4]

Following confirmation of the diagnosis and identification of the Leishmania infantum subtype, therapeutic options were carefully evaluated. Because the lesion was located within a psoriatic plaque, local therapy – typically considered first-line in Old World CL standard cases – was not deemed appropriate. The patient was therefore admitted for intravenous amphotericin B at a dosage of 5 mg/kg/day for five consecutive days. This regimen has demonstrated efficacy against L. infantum and is more readily accessible in Belgium compared to pentavalent antimonials, which continue to represent the first-line systemic treatment for cutaneous leishmaniasis in many countries.[5] The crusting and oozing subsided completely within six weeks. However, the original psoriasis lesion persisted; to treat the remaining psoriatic plaques on the right elbow and other body sites, a topical spray of calcipotriol + betamethasone dipropionate was applied once daily for two weeks, then tapered to a maintenance schedule. All psoriasis lesions improved within two months.

CL arising within psoriatic plaques is exceedingly rare. To date, only one comparable case has been reported: a 42-year-old Italian man on long-term methotrexate and adalimumab who developed multiple ulcerations within his psoriatic lesions.[6] Tumour necrosis factor-α inhibitors are well-recognized risk factors for granulomatous infections, including leishmaniasis.[7] Our patient was immunocompetent.

CL often mimics a range of dermatoses, but its emergence within pre-existing skin lesions is exceptionally rare, underscoring the uniqueness of this case. Equally noteworthy is the culprit species – Leishmania infantum – traditionally linked to visceral disease yet increasingly implicated in cutaneous infections in Spain, amongst other countries in the Mediterranean region.[8,9] This trend highlights the importance of including CL in the differential diagnosis of chronic skin lesions in patients with a history of travel to Spain, even in the absence of journeys to classic endemic hotspots.

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Author' contributions

Pieter Bourgeois: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; critical review of the literature; critical review of the manuscript.

Research data availability

Does not apply.

Conflicts of interest

None declared.

Editor

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LETTER - THERAPY

Efficacy of tofacitinib in the treatment of refractory palmoplantar psoriasis (non-pustular): case report and literature review☆

Dear Editor,

Palmoplantar psoriasis is a chronic condition of the palms and/or soles, with a prevalence of 2%–40% among patients with psoriasis; however, specific epidemiological data are scarce. Although it can manifest in a localized form, it has a greater impact on quality of life compared to other areas. Its morphology varies from pustular lesions to erythematous-desquamative and hyperkeratotic plaques, or with overlapping lesions, being classified based on these phenotypes.[1]

Non-pustular palmoplantar psoriasis (NPPP), or hyperkeratotic psoriasis, represents one of the most challenging psoriasis phenotypes in clinical practice.[1] It is a recalcitrant type, even with available therapeutic advances. Furthermore, the lack of parallelism in the clinical response of psoriasis vulgaris (PV) in relation to NPPP suggests a distinct pathogenesis, with reports of success with JAK inhibitors (JAKi) in the treatment of refractory NPPP.

In this text, the authors report a case of NPPP refractory to conventional and biological therapies with a complete response to oral tofacitinib. The authors also review analogous published cases and discuss relevant pathophysiological aspects.

A 48-year-old woman was diagnosed with NPPP (hands and feet), in addition to discrete plaques on the scalp, for 14 years. She reported previous treatments with topical corticosteroids, methotrexate (eight months), acitretin (eight months), adalimumab (five years), and secukinumab (three years), without a satisfactory response. On examination, she showed hyperkeratotic plaques and fissures on both soles (Fig. 1A). She reported being unable to perform physical activities or light walks.

Histopathological examination of the palmar and plantar regions revealed chronic psoriasiform dermatitis, characterized by acanthosis with hypogranulosis and neutrophils in the epidermis, elongation of the interpapillary ridges with focal fusion, slight spongiosis, compact hyperparakeratosis with neutrophils, elongated capillaries, and lymphocytic infiltration in the papillary dermis (Fig. 2). The search for fungi by periodic acid-Schiff staining was negative.

Considering the refractoriness and quality of life impairment, tofacitinib 5 mg orally, twice a day, was prescribed after clinical screening and complementary examinations. Clobetasol 0.05% ointment was maintained in the first month of treatment.

After 30 days, improvement in erythema, desquamation, and pain in the feet was observed, with complete remission of the hand lesions. The plantar fissures healed in 45 days, allowing a full return to physical activities.

After 60 days of treatment, she developed an upper respiratory tract infection, prompting temporary drug suspension for seven days. Upon reintroduction, she reported a mild headache, which subsided with a dose reduction to 7.5 mg/day, taken once daily.

After 120 days of treatment, she showed significant improvement in plantar lesions, full functionality, with resolution of difficulty and pain when walking, running, climbing stairs, and standing barefoot, as well as a reduction in severity scores (Fig. 1B). The patient has been followed for 12 months, with a current dose reduction to 5 mg/day. No changes were observed in laboratory tests during follow-up.

Topical medications and phototherapy constitute the first-line treatment in NPPP. However, most patients require systemic treatment, such as acitretin, methotrexate, and biologics. Biologics act on cytokines specific to the pathophysiology of psoriasis, including anti-TNFα, anti-IL-12/23, anti-IL-23, and anti-IL-17.[2] The efficacy of these agents in NPPP, however, tends to be lower than in other forms of psoriasis.

Psoriasis is an immunologically based disease, with distinct inflammatory circuits among its phenotypes. Th1/IFN-γ inflammation predominates in NPPP compared to PV and palmoplantar pustular psoriasis (PPP), which shows inflammatory activity more associated with neutrophils.[3]

Tofacitinib is a JAKi, especially of JAK 1 and 3, and to a lesser extent JAK 2, which suppresses Th1, Th17 pathways, and innate immune cell signaling, reducing the expression

☆ Study conducted at the Hospital das Clínicas, Faculty of Medicine, Universidade Estadual de São Paulo, Botucatu, SP, Brazil.

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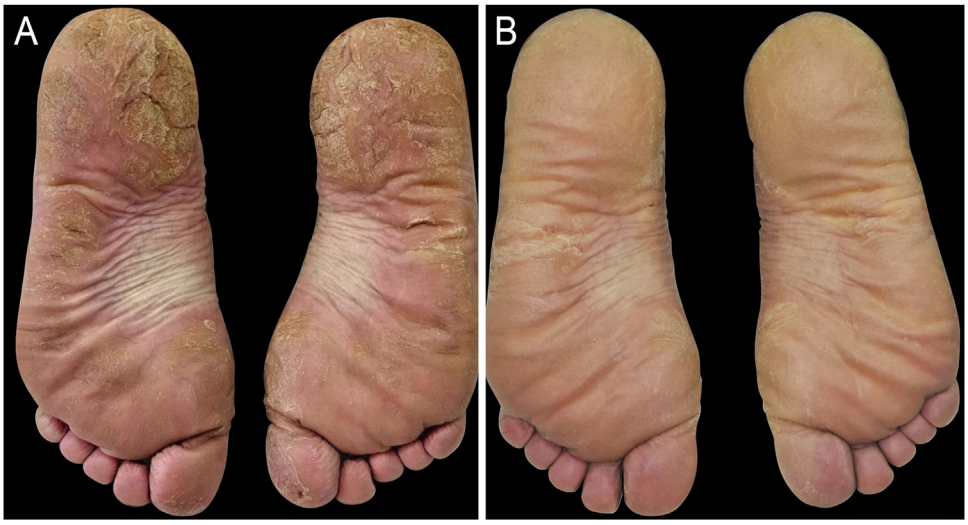

Figure 1 Non-pustular palmoplantar psoriasis treated with oral tofacitinib. (A) Pre-treatment: Physician's Global Assessment of Hands and/or Feet (hf-PGA) 4; modified Palmoplantar Psoriasis Area and Severity Index (m-PPPASI) 30; Palmoplantar Quality-of-Life Instrument (PPQLI) 38; and Dermatology Life Quality Index (DLQI) 7. (B) After 120 days of treatment: hf-PGA 2; m-PPPASI 3; PPQLI 23; and DLQI 0.

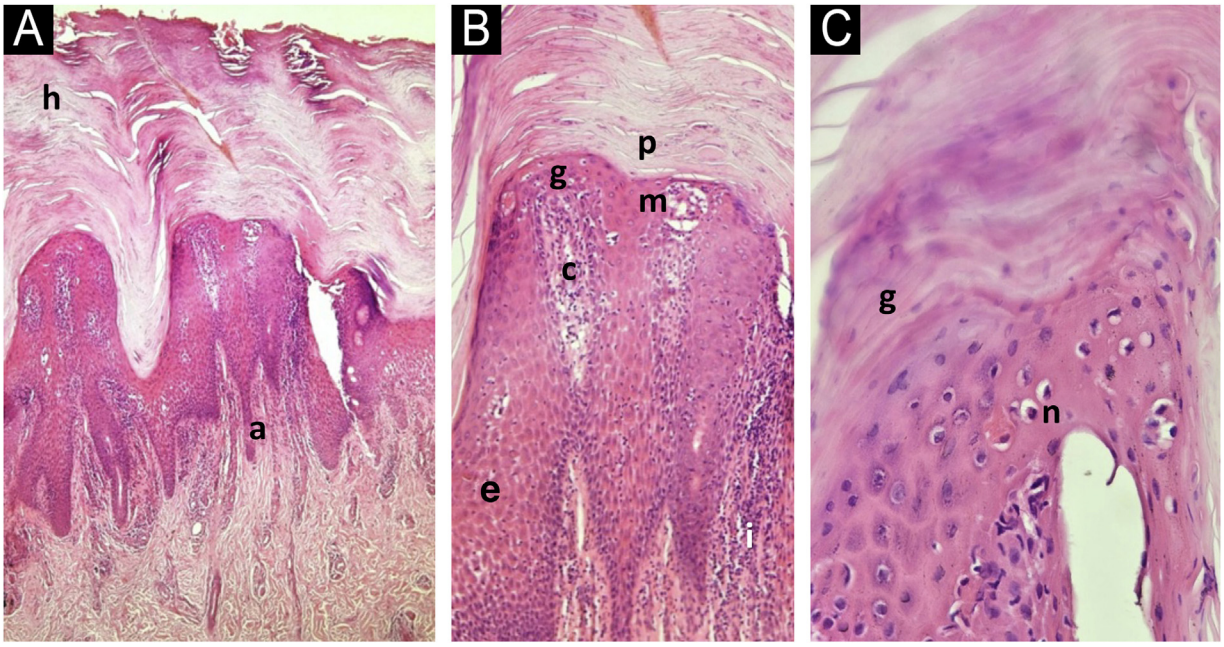

Figure 2 Histopathological examination of the plantar region. Panel A: Acanthosis, hyperkeratosis (h), elongation (a) of the epithelial ridges (Hematoxylin & eosin, ×100). Panel B: Proliferation of papillary capillaries (c), inflammatory infiltrate (i), parakeratosis (p), hypogranulosis (g), intraepidermal microabscess (m), discrete spongiosis (e) (Hematoxylin & eosin, ×200). Panel C: Hypogranulosis, with the presence of intraepidermal and subcorneal neutrophils (n) (Hematoxylin & eosin, ×400).

of cytokines such as IFN-γ, IL-17A/F, IL-22, IL-23, and IL-36.[4] This broad action may justify its effectiveness in refractory cases of NPPP.

Table 1 Reviews several reports of JAKi for the treatment of NPPP.[5–9] There are also descriptions of therapeutic success in PPP, considered part of the psoriasis spectrum.[7,10]

Despite the clinical-histopathological correlation of the presented case, compatible with NPPP, it is important to recognize that some forms of psoriasis show an exuberant inflammatory phenotype and eczematous areas, which may simulate or even coexist with chronic palmoplantar eczema. The distinction between these entities is challenging, especially when there is clinical overlap of fissures, erythema, pruritus, and hyperkeratosis. In these contexts, the diagnostic spectrum should include both NPPP and hyperkeratotic eczema of the palms and soles, whose differentiation may require an exercise in clinical, histopathological, and therapeutic response correlation.[11] Furthermore, there are

Table 1 Cases of palmoplantar psoriasis treated with oral Janus kinase inhibitors.

Report	Diagnosis	Study design	Sex/age	Previous treatment failure	Treatment	Response	Adverse events	Follow-up time
Valor-Méndez et al., 2021[5]	NPPP (palmoplantar), PV and PsA	Case report	Male, 55 years	Methotrexate, infliximab, secukinumab, and ustekinumab	Tofacitinib 5 mg 2× day	Improvement in 5 days; resolution in 6 months.	NR	6 months
Muzumdar et al., 2021[6]	NPPP (palmar) and PV	Case series (1/7)	Female, 65 years	Topical drugs, adalimumab, ixekizumab, and ustekinumab.	Tofacitinib XR 11 mg 1×/day	Resolution in 4 months	None	4 months
	NPPP (palmoplantar) and PsA	Case series (2/7)	Female, 63 years	Topical drugs, methotrexate, adalimumab, ixekizumab, secukinumab, and ustekinumab.	Tofacitinib XR 11 mg 1×/day	Improvement within 1 month; palmar resolution within 8 months and slight desquamation on the dorsum of the feet.	None	8 months
	NPPP (palmoplantar)	Case series (3/7)	Female, 57 years	Topical drugs, cyclosporine, methotrexate, adalimumab, certolizumab, guselkumab, ixekizumab, risankizumab, and secukinumab.	Tofacitinib XR 11 mg 1×/day	Almost complete resolution within 1 month.	None	1 month
	Mixed PP (palmoplantar) and PV	Case series (4/7)	Female, 45 years	Topical drugs, methotrexate, adalimumab, certolizumab, etanercept, guselkumab, ixekizumab, secukinumab, and ustekinumab.	Tofacitinib XR 11 mg 1×/day	Improvement within 1 month; resolution within 3 months.	None	3 months
	NPPP (plantar)	Case series (5/7)	Female, 69 years	Topical drugs, apremilast and methotrexate	Tofacitinib 5 mg 2×/day	Improvement within 3 months; palmar resolution and mild plantar hyperkeratosis within 6 months.	None	6 months
	NPPP (plantar) PsA	Case series (6/7)	Female, 61 years	Topical drugs, apremilast, methotrexate, guselkumab, and ixekizumab	Tofacitinib 5 mg 2×/day	Improvement within 2 months with slight residual plantar desquamation.	None	2 months
	NPPP (palmar) and PsA	Case series (7/7)	Female, 66 years	Topical drugs, methotrexate, ixekizumab, and secukinumab	Tofacitinib XR 11 mg 1×/day	Almost complete resolution within 1 month.	None	1 month
De Luca et al., 2024[7]	PPP (palmar) and PV	Case series (1/5)	Male, 33 years	Apremilast and secukinumab	Deucravacitinib 6 mg 1×/day and etanercept 50 mg/week	Exacerbation in weeks 4 and 16	NR	4 months

Table 1 (*Continued*)

Report	Diagnosis	Study design	Sex/age	Previous treatment failure	Treatment	Response	Adverse events	Follow-up time
	PPP (plantar) and PV	Case series (2/5)	Female, 49 years	Phototherapy, fumaric acid, apremilast and cyclosporine	Deucravacitinib 6 mg 1×/day	Improvement at week 16; loss to follow-up at week 28.	NR	7 months
	PPP (palmoplantar) and PV	Case series (3/5)	Male, 51 years	Alitretinoin and adalimumab	Deucravacitinib 6 mg 1×/day and methotrexate 15 mg/week	Exacerbation in weeks 4 and 16; exacerbation of ankylosing spondylitis.	NR	4 months
	PPP (palmo-plantar), PV and PsA	Case series (4/5)	Female, 41 years	Adalimumab and secukinumab	Deucravacitinib 6 mg 1×/day and methotrexate 15 mg/week	Exacerbation in week 4; improvement in week 16.	NR	12 months
	PPP (palmo-plantar), PV and PsA	Case series (5/5)	Female, 31 years	Phototherapy, methotrexate, cyclosporine, bimekizumab, certolizumab, and guselkumab.	Deucravacitinib 6 mg/day and PUVA cream in week 12	Improvement in week 16; failure in week 48.	Palpitations, herpes simplex, cystitis, and folliculitis in three of five cases.	12 months
Choi et al., 2025[8]	NPPP (palmoplantar) and PV	Case series (1/2)	Female, 61 years	Topical drugs, phototherapy, acitretin, and secukinumab.	Upadacitinib 15 mg 1×/day	Resolution within 3 months	Elevated triglycerides (2.24 mmoL/L)	3 months
	NPPP (palmoplantar)	Case series (2/2)	Female, 52 years	Topical drugs, alitretinoin, apremilast, cyclosporine, ixekizumab, risankizumab, secukinumab, and ustekinumab.	Upadacitinib 15 mg 1×/day	Pruritus improvement within 2 weeks; resolution within 3 months.	Elevated ALT (124 U/L)	3 months
Hardy et al., 2025[9]	NPPP (palmoplantar) and AA associated with CVID	Case report	Female, 33 years	Topical drugs	Upadacitinib 15 mg 1x/day	Improvement within 2 weeks; resolution within 12 weeks.	None	20 months
Present case	NPPP	Case report	Female, 48 years	Topical drugs, acitretin, methotrexate, adalimumab, and secukinumab.	Tofacitinib 5 mg 2×/day	Pruritus improvement within 2 weeks; resolution within 4 months.	Headache	12 months

PP, Palmoplantar Psoriasis; NPPP, Non-pustular palmoplantar psoriasis; PPP, Pustular Palmoplantar Psoriasis; PV, Psoriasis Vulgaris; PsA, Psoriatic Arthritis; AA, Alopecia Areata; CVID, Common Variable Immunodeficiency; XR, Extended Release; ALT, Alanine Aminotransferase; NR, Not Reported.

reports of modification of the psoriasis vulgaris phenotype to eczematous conditions after therapies with biologics.[12] Therefore, JAKi, by modulating multiple inflammatory pathways (such as IL-4, IL-13, IL-22, and IFN-γ), constitutes a therapeutic alternative considering the immunopathological complexity of these presentations.[13]

Regarding safety, tofacitinib requires vigilance regarding infections, updated vaccination status, and drug interactions. Caution should be exercised in patients with renal or hepatic failure, thrombophilia, cardiovascular risk, and neoplasms. Monitoring tests include complete blood count, lipid profile, liver and kidney function tests, and screening for viral and bacterial infections.[14]

Although oral tofacitinib has a satisfactory safety and efficacy profile, it has not been approved for psoriasis by the Food and Drug Administration due to side effects and the availability of other therapies. However, it was approved in 2012 for rheumatoid arthritis and subsequently for psoriatic arthritis, ulcerative colitis, juvenile idiopathic arthritis, and ankylosing spondylitis. Deucravacitinib is the only JAKi approved for moderate to severe plaque psoriasis; however, there are no comparative studies evaluating other JAKi (e.g., tofacitinib, upadacitinib, abrocitinib, baricitinib) in the treatment of NPPP.

This case documents a significant clinical response in refractory NPPP, corroborating the therapeutic potential of JAKi and reinforcing the need for controlled studies for this specific phenotype.

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Authors' contributions

Paula Hitomi Sakiyama: Design and planning of the study; collection, analysis, and interpretation of data; drafting and editing of the manuscript; critical review of important intellectual content; critical review of the literature; approval of the final version of the manuscript.

Luciane Donida Bartoli Miot: Design and planning of the study; collection, analysis and interpretation of data; drafting and editing of the manuscript; 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.

Hélio Amante Miot: Design and planning of the study; collection, analysis, and interpretation of data; drafting and editing of the manuscript; 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.

Conflicts of interest

None declared.

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LETTER – THERAPY

Eruptive sebaceous hyperplasia induced by oral tacrolimus with good therapeutic response to systemic isotretinoin: a case report☆

Dear Editor,

Sebaceous hyperplasia (SH) is a benign and common condition characterized by an increase in the size of the sebaceous glands that occurs as a result of aging, exposure to ultraviolet radiation, genetic/familial predisposition, or as part of syndromes such as Muir-Torre.[1,2] Clinically, it presents as small, yellowish or normochromic papules with a central umbilication, usually restricted to the face.[3]

Eruptive sebaceous hyperplasia (ESH) was originally reported in patients receiving solid organ and hematopoietic stem cell transplants using cyclosporine.[3] The multiplicity of lesions and their occurrence in exposed areas can negatively impact self-esteem, reflecting on interpersonal relationships and the quality of life of these patients. In addition, treatment is challenging due to the number of lesions and the possibility of permanent dyschromias resulting from ablative interventions. Systemic isotretinoin has proven effective in the treatment and control of ESH.[1,4,5] This report describes a patient with exuberant tacrolimus-induced ESH, with good response to oral isotretinoin monotherapy and control with continuous use of low doses.

A 53-year-old male patient, a kidney transplant recipient, complained of a "skin rash for three to four months." On examination, multiple normochromic asymptomatic papules with central umbilication were present on the face, neck, and anterosuperior thorax (Fig. 1), with abrupt onset months before and progressive worsening. He underwent kidney transplantation four years ago and is currently maintained on tacrolimus monotherapy. He was also an insulin-dependent diabetic. ESH was suspected, and molluscum contagiosum was considered as a differential diagnosis due to immunosuppression, along with eruptive syringoma. An incisional biopsy was performed at two points (face and neck), with histopathological examination showing sebaceous hyperplasia (Fig. 2). Combining the clinical findings, histopathology, and the patient's medication history, a diagnosis of tacrolimus-induced ESH was concluded. This was discussed with the transplant team, and treatment with isotretinoin 20 mg/day was initiated for two months, with significant improvement in the lesions (Fig. 3). Currently, the patient maintains isotretinoin 10 mg, three times a week, without complications or complaints and with maintenance of the therapeutic response.

Currently, ESH seems to be an occurrence practically restricted to adult men, consistent with the present findings, and is strongly associated with immunosuppression induced by medications (cyclosporine, prednisone, mycophenolate mofetil, and tacrolimus) in multiple clinical contexts (kidney disease, allogeneic transplantation, and other systemic inflammatory disorders that require immunosuppression).[6] Cyclosporine-induced ESH in patients receiving solid organ transplants, such as kidney and heart; and hematopoietic cells is well documented in the literature, showing its association with the development not only of ESH, but also of multiple seborrheic lesions.[7] As for tacrolimus as a causative agent of ESH, there are few reports, especially when considering its isolated use.[3]

Both cyclosporine and tacrolimus are calcineurin inhibitors, with lipophilic properties that favor their accumulation in the skin.[1,3,6] This characteristic may contribute to the aberrant proliferation of immature sebocytes, leading to the emergence of ESH.[3] This effect is believed to result from chronic inhibition of the local immune response and indirect stimulation of sebaceous gland activity.[6]

The aesthetic impact of facial lesions, especially when numerous as in ESH, can negatively affect patients' self-esteem and quality of life.[1] Furthermore, treatment is challenging due to the multiplicity of lesions, risk of scarring and recurrence.[5] Ablative procedures, such as electrodissection, cryotherapy, CO_2 laser and photodynamic therapy, although effective, present a risk of dyschromia and scarring sequelae.[4]

Systemic isotretinoin, on the other hand, acts diffusely and globally, with well-established sebostatic and antiproliferative effects.[2] In the present case, monotherapy with isotretinoin resulted in significant and rapid clinical improvement, with good tolerance and sustained control with a low dose (10 mg, three times/week).

☆ Study conducted at the Hospital Municipal Universitário de Taubaté, Universidade de Taubaté, Taubaté, SP, Brazil.

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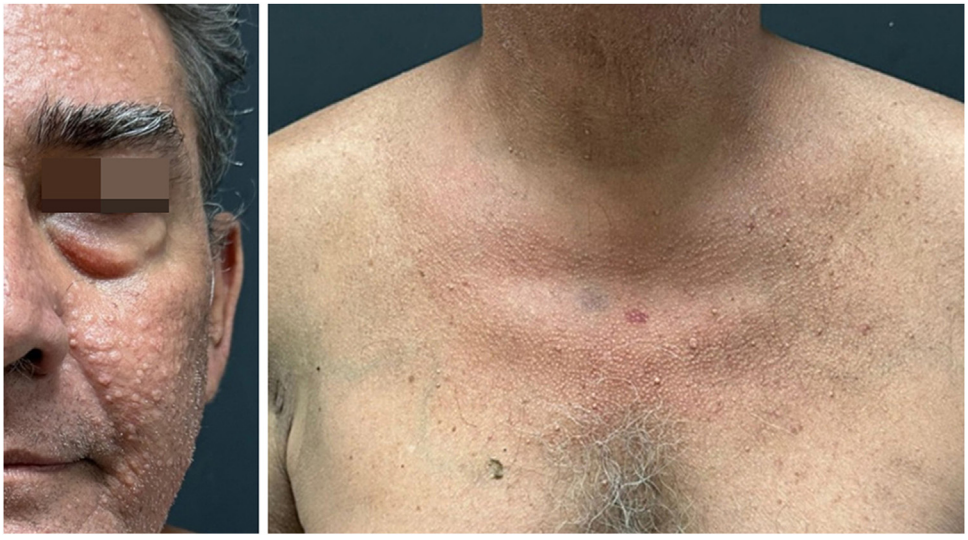

Fig. 1 Multiple normochromic papules with central umbilication on the face, neck, and anterosuperior thorax.

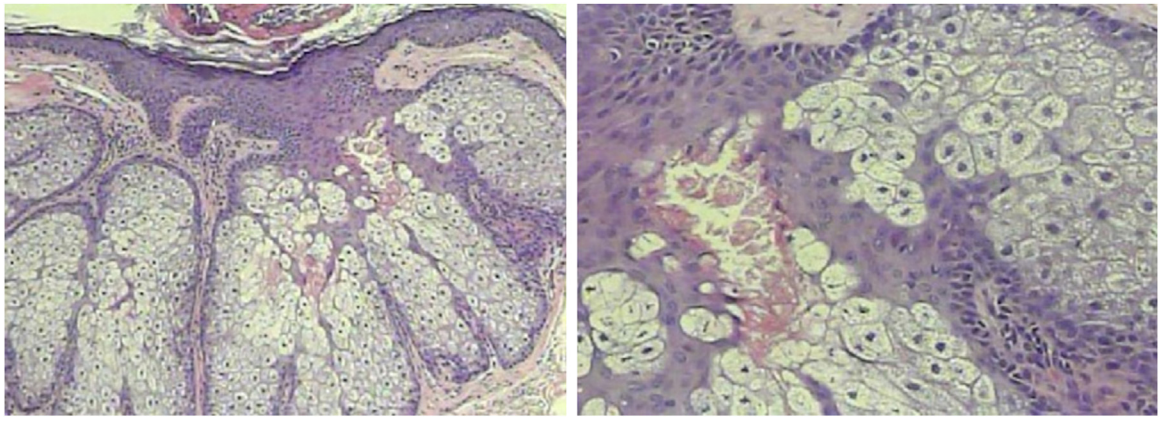

Fig. 2 Histopathology showing sebaceous hyperplasia (Hematoxylin & eosin, ×100/400).

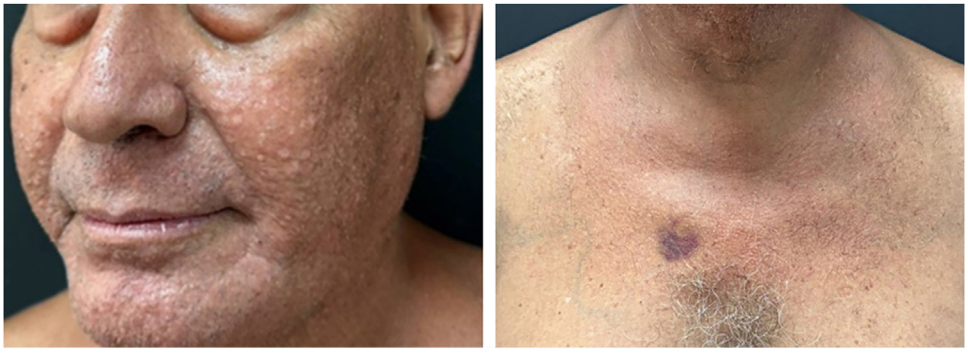

Fig. 3 After 2 months of oral isotretinoin (20 mg/day): complete regression of lesions on the trunk and cervical region, with significant improvement in facial lesions.

In conclusion, this report reinforces tacrolimus as a causative agent of ESH, corroborating the scarce reports in the literature, and highlights the efficacy and safety of oral isotretinoin as a therapeutic option, whether in monotherapy or not.

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Authors' contributions

Guilherme Paiva da Silva: Design and planning of the study; drafting and editing of the manuscript; critical review of the literature; photographic documentation and approval of the final version of the manuscript.

Flávia Regina Ferreira: Design and planning of the study; critical review of the manuscript; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases and approval of the final version of the manuscript.

Fernanda G. Moya: Histopathology (analysis and photographic documentation) and approval of the final version of the manuscript.

Research data availability

Does not apply.

Conflicts of interest

None declared.

Editor

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LETTER - THERAPY

Psoriasiform adult blaschkitis triggered by adalimumab: a rare paradoxical reaction☆

Dear Editor,

Blaschkitis is an acquired, self-limited inflammatory dermatosis that follows Blaschko's lines, typically affecting adults and involving the trunk. Although its pathogenesis remains unclear, it has been associated with biologic therapies. These paradoxical cutaneous reactions have been reported with Tumor Necrosis Factor Alpha (TNFα) inhibitors such as infliximab, etanercept, certolizumab and adalimumab.[1,2]

A 74-year-old woman with seronegative spondyloarthritis, on adalimumab for three months, developed a gradually progressive, pruritic, erythematous desquamative eruption following Blaschko's lines on the right trunk (Fig. 1A), with sharp midline demarcation (Fig. 1B). It appeared three months after initiating adalimumab and resolved completely, and without sequelae, following drug discontinuation and substitution to secukinumab. No infectious or other pharmacologic triggers were identified.

Histopathology revealed epidermis with psoriasiform hyperplasia with focal thinning of the suprapapillary epidermis, light spongiosis, and mild vacuolar alteration at the interface, as well as acanthosis and focal parakeratosis. There were also aggregates of neutrophils within the stratum corneum. The dermis showed an inflammatory infiltrate composed of lymphocytes, histiocytes, and a few plasma cells around the superficial dermal vasculature, consistent with psoriasiform dermatitis (Fig. 2). Immunohistochemistry was positive in the superficial dermal infiltrate for CD3, CD4 and CD7, whereas CD20 showed negativity (Fig. 3).

TNFα is a cytokine that plays a pivotal role in the inflammatory response. Its inhibitors have demonstrated significant efficacy in the management of inflammatory diseases such as rheumatoid arthritis, psoriasis, psoriatic arthritis, spondyloarthritis and inflammatory bowel disease. Paradoxically, however, these agents may induce or exacerbate psoriasis.[3] This phenomenon has been observed across multiple underlying diseases and does not appear to be

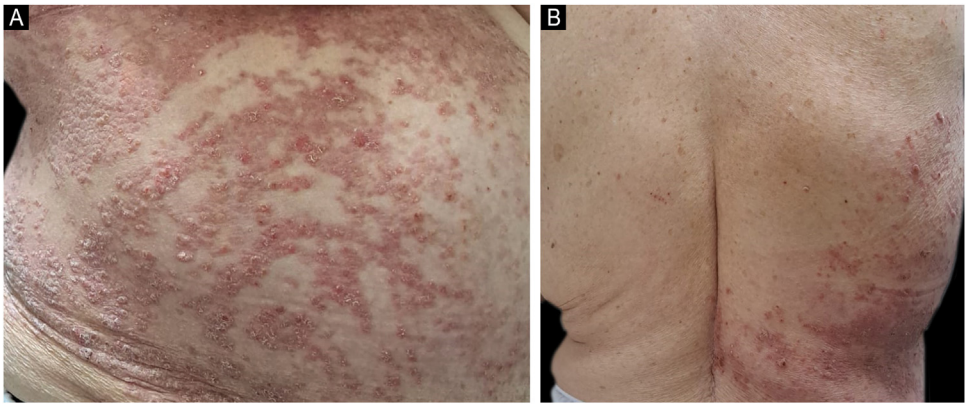

Fig. 1 Clinical features. (a) Psoriasiform eruption following Blashko's lines on the trunk. (b) Midline demarcation on the back.

☆ Study conducted at the Universidade Católica de Pelotas, Brazil and Santa Casa de Misericórdia of Porto Alegre, Brazil.

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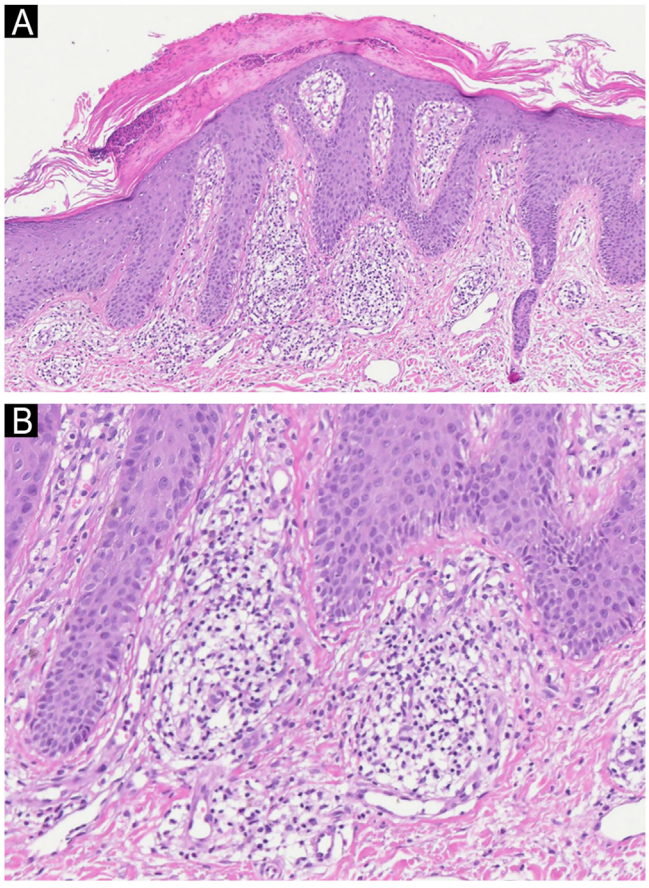

Fig. 2 Light microscopy. (A) Psoriasiform hyperplasia with acanthosis and focal parakeratosis, with aggregates of neutrophils within the stratum corneum (Hematoxylin & eosin, ×100). (B) Detail of the dermal infiltrate with lymphocytes and histiocytes (Hematoxylin & eosin, ×200).

disease-specific. Moreover, it has been associated with all agents within the anti-TNF class.

A retrospective cohort study compared the risk of psoriasis development among patients with Spondyloarthritis treated with anti-TNF agents versus those receiving conventional therapy. The investigation utilized data from the Korea National Health Insurance Claims Database between January 2007 and December 2016. Psoriatic diseases were identified in 1.8% of patients following initiation of anti-TNF therapy, whereas only 1.1% of patients treated with conventional therapies developed psoriasis.[4]

These findings are further supported by data from a recent meta-analysis.[5] A statistically higher risk for psoriasis or psoriasiform lesions during anti-TNF therapy was observed in female patients, younger age, smokers, Crohn's disease, and those who are using adalimumab or certolizumab.

When managing anti-TNF-induced psoriasis or psoriasiform eruptions, clinicians must weigh whether to continue, discontinue, or switch anti-TNF therapy to another drug class. This decision should be individualized, taking into account factors such as the underlying disease, the therapeutic efficacy of the anti-TNF agent, the severity of the cutaneous eruption, and the feasibility of alternative treatment options.

According to the treatment algorithm proposed by Li and Perez-Chada,[3] the severity of paradoxical psoriasis should first be classified as mild or moderate-to-severe.

For mild cases, if the underlying disease is well controlled, continuation of anti-TNF therapy is recommended, combined with conventional psoriasis treatments (e.g., topical corticosteroids, phototherapy, methotrexate). Furthermore, discontinuation of anti-TNF therapy may have detrimental effects on the control of the underlying inflammatory disease.

When the underlying disease remains uncontrolled despite anti-TNF therapy, switching to another anti-TNF agent combined with conventional psoriasis management may be considered.

In patients presenting with moderate-to-severe eruptions and stable underlying disease, substitution of the anti-TNF agent with a drug from another therapeutic class, in combination or not with conventional psoriasis therapy, is recommended.

If anti-TNF therapy fails to control the underlying condition and paradoxical psoriasis is moderate to severe, switching to an alternative biologic class, along with standard psoriasis treatment, should be considered.

Additionally, similar cases of immunobiologicals-induced psoriasis have been described in patients receiving anti-PD-1 immunotherapy, very likely related to T-lymphocytic infiltration of the skin, as evidenced by our immunohistochemical findings, with positivity to CD3, CD4 and CD7, all T-cell markers.[6]

Some authors have used the denomination Blaschkolinear psoriasis to describe these cases,[7] the term Blaschkolinear Acquired Inflammatory Skin Eruption (BLAISE) ha salso been used.[8]

The pathogenesis of these paradoxical lesions is not fully understood, very likely, uncontrolled IFN production is released after TNF inhibition, a process driven by the innate immune system, leading to keratinocyte inflammation and proliferation,[9] our immunohistochemical findings support this, since T-cells are predominant in the dermal infiltrate.

This case highlights psoriasiform blaschkitis as a rare paradoxical dermatologic reaction to TNF-α inhibitors. To date, only one case linked to adalimumab has been reported, making this the second in the literature. Recognizing this self-limited condition,[1] is essential for appropriate management and to avoid unnecessary discontinuation of effective biologic therapies.

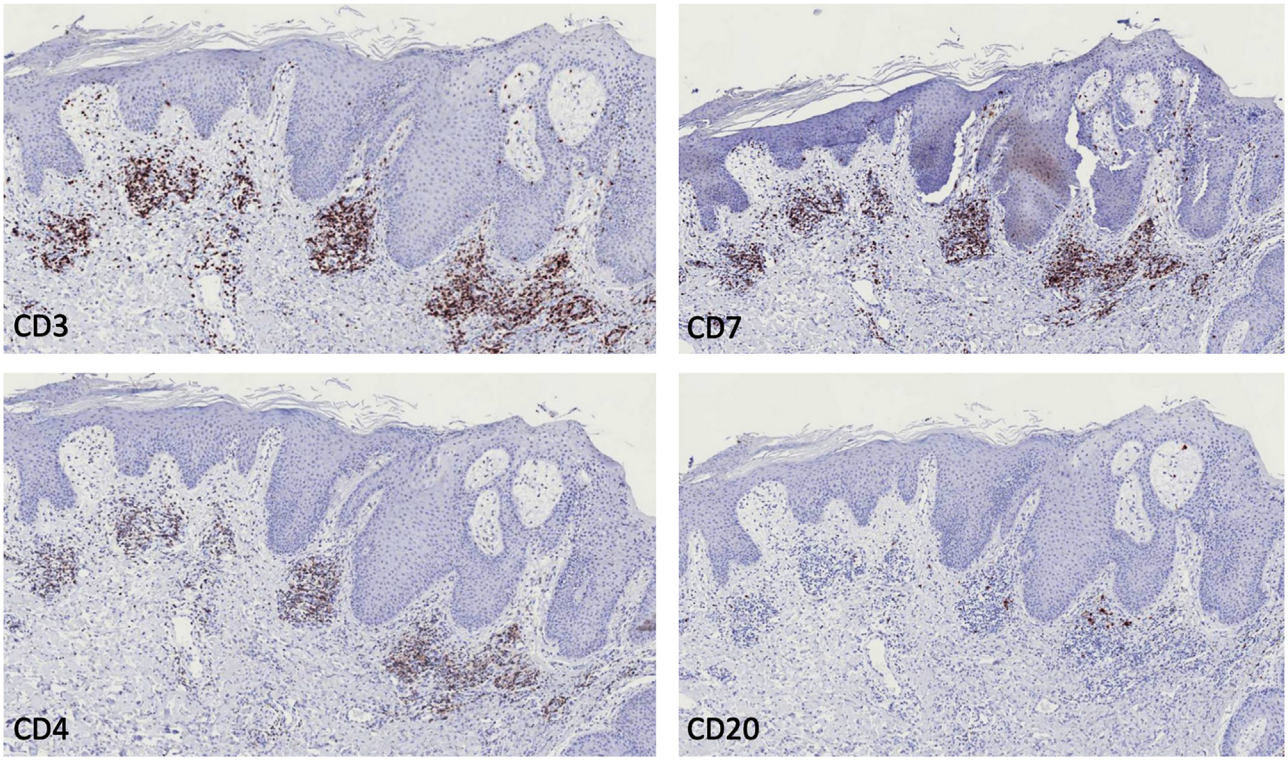

Fig. 3 Immunohistochemistry. Positivity in the superficial dermal infiltrate for CD3, CD4 and CD7, and negative for CD20 (×100).

Authors' contributions

Hiram Larangeira de Almeida Jr: Study concept and design; Data collection, or analysis and interpretation of data; Writing of the manuscript or critical review of important intellectual content; Critical review of the literature, final approval of the final version of the manuscript.

Martina Souilljee Birck: Study concept and design; Data collection, or analysis and interpretation of data; Writing of the manuscript or critical review of important intellectual content; Critical review of the literature, final approval of the final version of the manuscript.

Laura Marcon Bischoff Bialecki: Study concept and design; Data collection, or analysis and interpretation of data; Writing of the manuscript or critical review of important intellectual content; Critical review of the literature, final approval of the final version of the manuscript.

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LETTER - THERAPY

Successful treatment of refractory primary follicular mucinosis with Tofacitinib

Dear Editor,

Follicular Mucinosis (FM), a rare cutaneous mucinosis, is characterized by erythematous infiltrated plaques with follicular prominence. There is no consensus on the treatment of FM. Current therapeutic options include mild-to-moderate potency topical corticosteroids, topical and oral antibiotics, retinoids, dapsone, sulfacetamide, imiquimod, pentoxifylline, pimecrolimus, Psoralen Plus Ultraviolet A (PUVA), and nitrogen mustard.[1] Emerging evidence suggests that tofacitinib may be effective for cutaneous mucinoses, with reported efficacy in both pretibial myxedema and refractory papulonodular mucinosis.[2,3] Here, we report a patient with refractory FM who was successfully treated with tofacitinib.

A 55-year-old female patient presented to the dermatology clinic with a 4-month history of a left facial plaque. She denied any topical application, drug intake, or photosensitivity. Her systemic and family history was unremarkable. Physical examination demonstrated a poorly demarcated, edematous, erythematous plaque on the left cheek. (Fig. 1A) No other cutaneous involvement was observed. According to clinical and histopathological features, the patient was diagnosed with Primary Follicular Mucinosis (PFM). Initial treatment with hydroxychloroquine (200 mg twice daily) and high-potency topical corticosteroids (clobetasol propionate 0.05% ointment) resulted in no clinical improvement after 8-weeks of therapy. Monotherapy with tofacitinib 5 mg twice daily was started. After 3-months of treatment, significant clinical improvement was observed, manifested by complete resolution of skin lesions (Fig. 1B). No recurrence was observed during the three-month follow-up period following treatment discontinuation. Histopathological examination revealed the accumulation of mucin in pilosebaceous follicles and sebaceous glands, with perifollicular infiltrates of lymphocytes and eosinophils observed (Fig. 2A). Alcian blue staining confirmed mucin deposition within the follicular epithelium (Fig. 2B). Immunohistochemical analysis demonstrated that lymphocytes were positive for Leukocyte Common Antigen (LCA), Ki-67 (20% positivity rate), CD8, CD20, CD7, CD79a, CD4, and CD3, with a balanced $CD4^+/CD8^+$ ratio. (Figs. 2C–D) The result of the T-cell Receptor (TCR) gene rearrangement was negative.

Follicular mucinosis is characterized by the extensive deposition of mucin at the external root sheath and sebaceous glands. FM can be categorized as Primary Follicular Mucinosis (PFM) and Secondary Follicular Mucinosis (SFM). The most common clinical symptom of PFM is a solitary lesion in the head or neck region in young patients. As for the histopathological findings, the presence of extensive mucin deposition in cystic spaces, minimal perivascular and periadnexal polyclonal infiltration of non-atypical lymphocytes, the absence of epidermotropism, and an equivalent $CD4^+/CD8^+$ cell rate pointed towards a diagnosis of PFM. Secondary Follicular Mucinosis (SFM) may be associated with certain medications, benign conditions, and malignancies (most commonly lymphomas). Lymphoma-associated FM typically presents with multiple extracranial lesions in elderly patients. Histopathological examination reveals a dense band-like infiltrate with atypical lymphocytes, epidermotropism, a prominent $CD4^+$ immunophenotype, and monoclonal gene rearrangement of the infiltrate.[1]

The pathogenesis of Follicular Mucinosis (FM) remains incompletely understood. Current evidence suggests that follicular keratinocytes may be the source of mucin deposition, a process activated by T-cell-mediated immune mechanisms and cytokines. T-lymphocytes secrete IL-4, IL-2, and IL-26, inducing phosphorylation of Signal Transducer and Activator of Transcription (STAT), thereby affecting keratinocyte function.[4] Tofacitinib, as a pan-JAK1/JAK3 inhibitor, can interrupt pathological signaling by blocking STAT phosphorylation.[5] Studies have also demonstrated a significant correlation between the quantity of mucin within hair follicles and the severity of perifollicular inflammatory infiltration. Mediators released by T-lymphocytes, including IFN-γ, IL-5, TGF-β, and IL-4, trigger and amplify inflammatory cascades.[4] The JAK-STAT pathway plays a vital role in immune regulation, cell differentiation, apoptosis, and proliferation.[5] By inhibiting JAK1/JAK3, tofacitinib effectively reduces the production of proinflammatory cytokines in T-lymphocytes. Tofacitinib, in our case, was selected primarily due to its comparatively lower cost relative to other highly selective JAK inhibitors. Furthermore, published lit-

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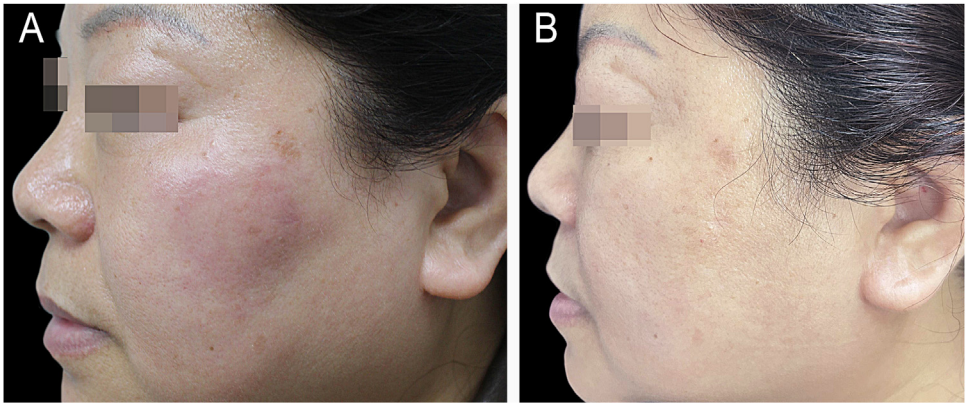

Figure 1 (A) A poorly demarcated edematous erythematous plaque was observed on the right cheek. (B) Complete clinical resolution was achieved after 3-months of tofacitinib monotherapy.

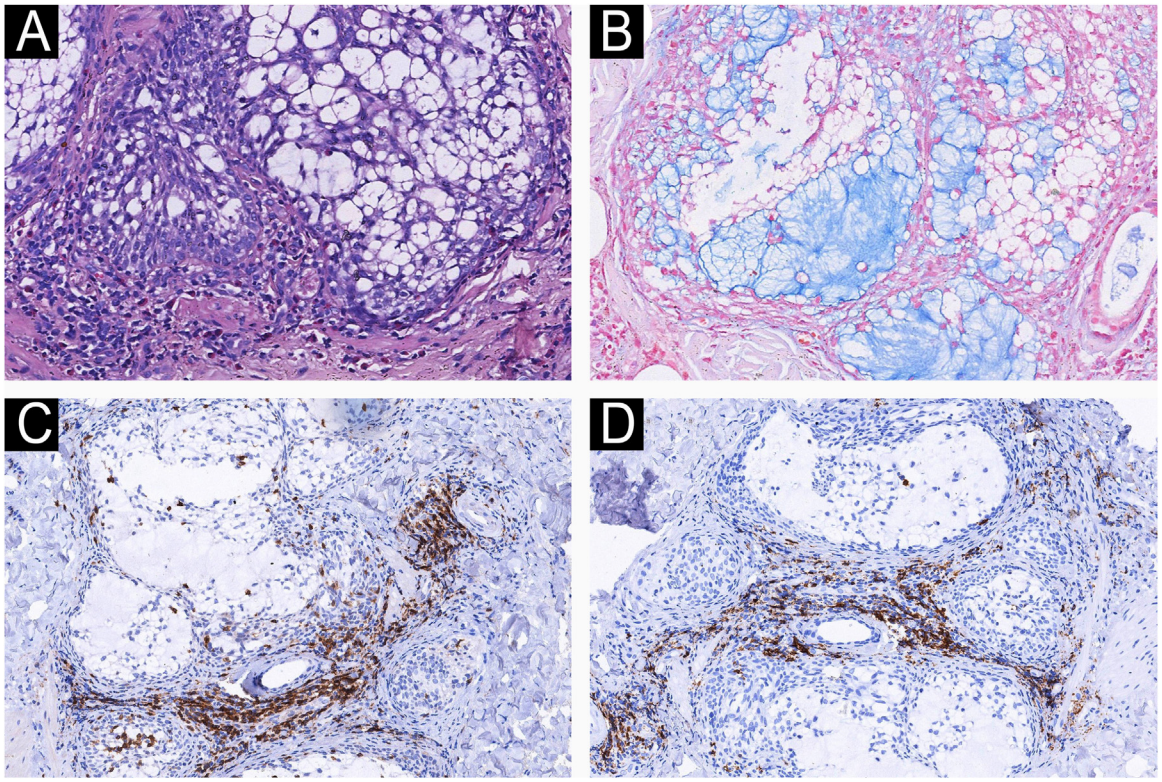

Figure 2 (A) Massive mucin deposition in the follicular epithelium (Hematoxylin & eosin, ×40). (B) Deposition of mucin confirmed by Alcian blue staining (×200). Immunohistochemical analysis demonstrated that lymphocytes were positive for CD4 (C) and CD8 (D) with a balanced $CD4^+/CD8^+$ ratio (×100).

erature has indicated its promising efficacy in the treatment of mucinous dermatosis.[2,3]

There are currently no established treatment guidelines for follicular mucinosis, and management remains individualized. Available therapeutic options have demonstrated limited efficacy in clinical practice. This pioneering case demonstrates the first successful therapeutic application of JAK inhibitors in follicular mucinosis. While these findings are promising, the inherent limitations of this single-case study underscore the need for validation through large-scale randomized controlled trials. Additionally, further mechanistic investigations are essential to elucidate the precise therapeutic pathways of tofacitinib in FM.

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Research data availability

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Authors' contributions

Yu-Lian Li: Data curation; Methodology; Formal analysis; Visualization; Validation; Writing-original draft.

Sheng Fang: Conceptualization; Methodology; Resources; Supervision; Writing-review & editing.

Conflicts of interest

None declared.

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LETTER - THERAPY

Therapeutic synergy in long-standing plasma cell gingivitis: integrating photobiomodulation and immunomodulatory management☆

Dear Editor,

Plasma Cell Gingivitis (PCG) is a rare chronic inflammatory gingival disorder characterized by a dense subepithelial infiltrate of mature plasma cells and marked erythema, unrelated to biofilm accumulation. Its multifactorial etiology includes hypersensitivity reactions, systemic conditions, and immune dysregulation.[1] Recent evidence suggests that it may mimic or overlap with Autoimmune Mucocutaneous Disorders (AMDs) (including oral lichen planus and mucous membrane pemphigoid), which can manifest as desquamative gingivitis with plasma-cell-rich infiltrates, highlighting the need for histopathologic analysis before confirming PCG.[2]

A 39-year-old woman with a five-year history of persistent gingival inflammation (Fig. 1) unresponsive to conventional periodontal therapy, was referred to the Oral Pathology service for further assessment. Her medical history included untreated hypercholesterolemia and hypothyroidism, dysautonomia, keloid formation, and a family history of rheumatoid arthritis. At initial examination, the gingival tissues were free of plaque and calculus, excluding plaque-induced periodontal disease. The working diagnosis initially considered AMDs; however, the bright scarlet erythema with a velvety surface, in the absence of Wickham striae or vesiculobullous lesions, strongly suggested PCG. Extensive blood testing excluded autoimmune diseases. The patient's untreated conditions were recognized as potential contributors to immune dysregulation. To address this, management with rosuvastatin (10 mg/day) and levothyroxine (25 μg/day) was initiated, aiming to restore metabolic balance and reduce systemic inflammation.

An incisional punch biopsy was performed. Histopathologic examination revealed stratified squamous epithelium with focal erosion and spongiosis, accompanied by a dense subepithelial infiltrate of mature plasma cells within the lamina propria. Immunohistochemical staining demonstrated a polyclonal pattern, with positive reactivity for both kappa and lambda light chains, thereby excluding plasma cell neoplasia and autoimmune diseases, and confirming the diagnosis of PCG (Fig. 2).[3]

Further dermatological evaluation ruled out mucocutaneous or gastrointestinal involvement. Patch testing revealed hypersensitivity to cinnamon, honey, wheat flour, nickel, methylisothiazolinone, and thimerosal. Allergen elimination was implemented as the primary therapeutic measure,[1] and topical tacrolimus 0.1% mouthwash was prescribed twice daily for one month as an initial immunomodulatory approach, given its efficacy in plasma cell-mediated mucosal inflammation.[4] Additionally, nutritional support with vitamin C, vitamin E, and omega-3 fatty acids was prescribed to promote mucosal healing.[5]

However, prolonged tacrolimus use was limited by its high cost, risk of gingival atrophy, and herpes labialis reactivation in the third week (Fig. 1B).[6] To reduce drug exposure while maintaining inflammation control, Photobiomodulation Therapy (PBMT) was added three times weekly for 8-weeks using a portable dual-wavelength diode laser (LASER DUO, MM Optics Ltda., São Carlos, Brazil) (LASER DUO, MM Optics, São Carlos, Brazil; 660 nm InGaAlP, continuous mode). Each site received 4 J at 100 mW for 40 s (133 J/cm^2). All irradiation parameters are detailed in Supplementary Tables S1–3.[7]

PBMT exerts its effects through multiple biological mechanisms. Photon absorption by cytochrome c oxidase enhances mitochondrial ATP synthesis, restoring cellular energy metabolism and promoting tissue repair. It transiently increases Reactive Oxygen Species (ROS), triggering adaptive antioxidant responses and redox-sensitive signaling. PBMT downregulates proinflammatory mediators such as IL-1β, IL-6, TNF-α, and PGE, while upregulating IL-10 and TGF-β. It also suppresses NF-κB activation, down-regulating the transcription of pro-inflammatory genes. Additional effects include vasodilation, angiogenesis, improved lymphatic drainage, and analgesia through modulation of nerve conduction and endorphin release. The proliferative effects on fibroblasts and keratinocytes accelerate

☆ Study conducted at the Clínica Universidad de los Andes, Las Condes, Santiago, Chile.

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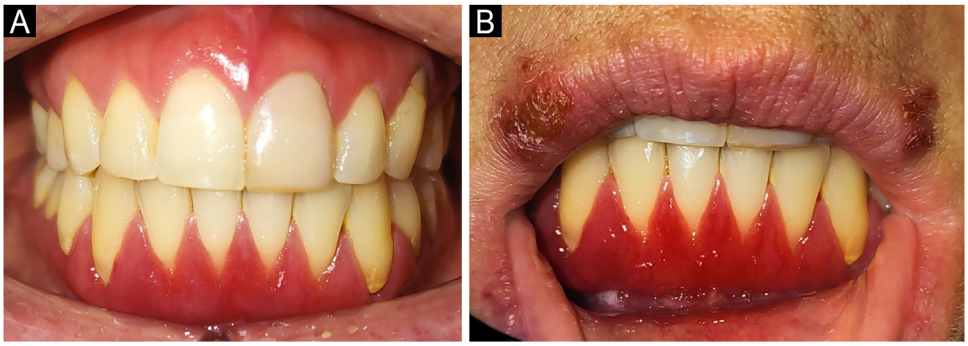

Fig. 1 Clinical presentation and early treatment phase of PGC.
(A) Baseline presentation showing chronic inflammation of marginal and attached gingiva with pronounced erythema, edema, loss of knife-edge contour, and superficial erosion. (B) Bilateral herpes labialis in crusting stage, three weeks after initiation of topical tacrolimus 0.1% mouthwash. Gingival erythema remains unchanged at this stage; PBMT was subsequently introduced as adjunctive therapy.

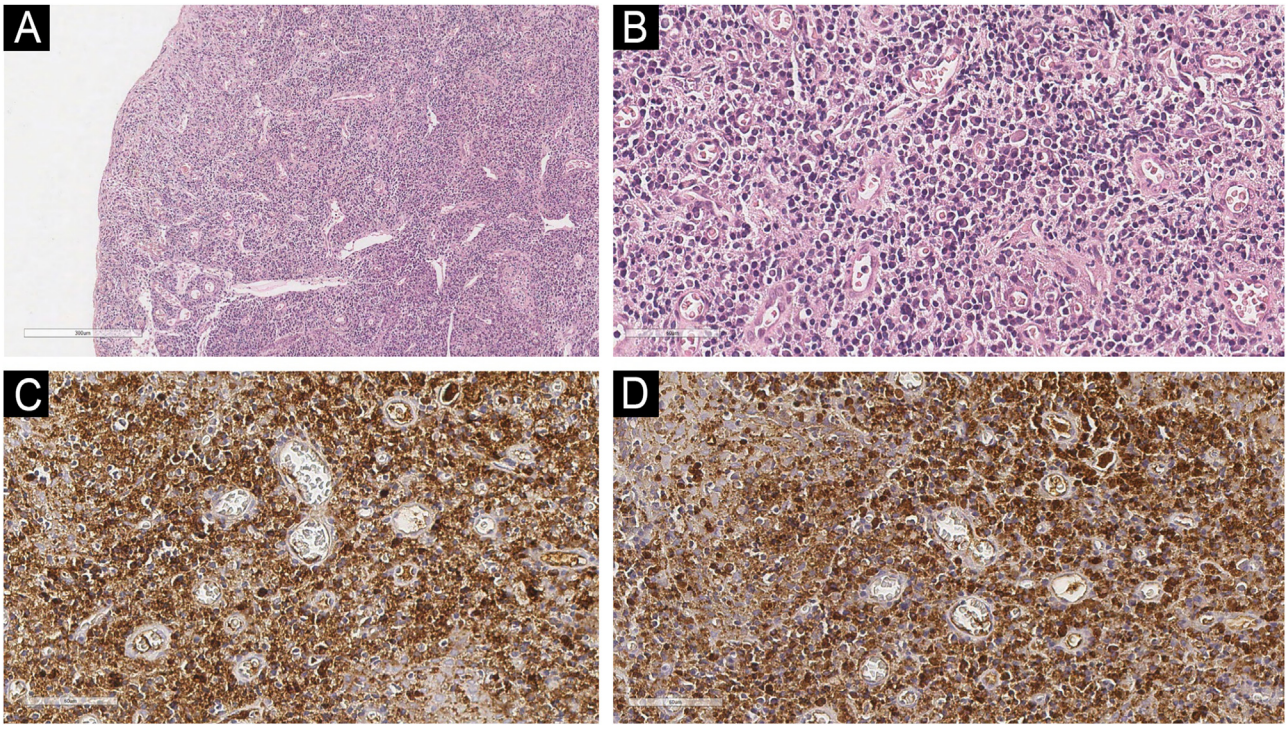

Fig. 2 Histopathological and immunohistochemical findings.
(A) Stratified squamous epithelium with surface erosion and spongiosis (Hematoxilyn & eosin, 100×). (B) Dense subepithelial plasma-cell infiltrate with eccentric nuclei and basophilic cytoplasm (Hematoxilyn & eosin, 400×). (C) Positive cytoplasmic staining for kappa light chains in plasma cells (immunostaining, digital magnification equivalent to 400×). (D) Positive cytoplasmic staining for lambda light chains confirming polyclonality (immunostaining, digital magnification equivalent to 400×).

epithelial healing, which is particularly beneficial in erosive lesions.[5,8,9]

PBMT produced a marked reduction in erythema, bleeding, and pain after the third session, with progressive normalization of gingival contour (Fig. 3). Its combination with short-term topical immunosuppression created a favorable environment for tissue repair, while allergen elimination addressed the underlying trigger. Correction of systemic comorbidities likely improved immune homeostasis. Notably, hypothyroidism reduces LDL receptor expression and promotes lipid oxidation, sustaining the proinflammatory state underlying PCG chronicity.[10] Finally, a strict oral hygiene protocol was maintained, emphasizing professional plaque control and patient education, both essential for long-term stability. During the three-month follow-up, the patient exhibited complete clinical remission (Fig. 3). Regular follow-up by dermatology, endocrinology, and immunology services was maintained to prevent recurrence and to monitor systemic conditions.

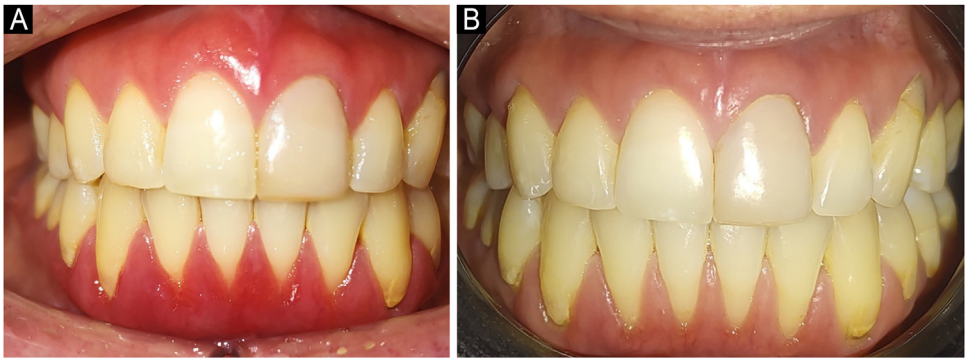

Fig. 3 Clinical evolution: baseline and three-month post-treatment comparison.
(A) Baseline clinical presentation (as shown in Fig. 1A). (B) Three-month follow-up showing resolution of erythema and edema, re-establishment of knife-edge contour, and residual recession due to previous gingival attachment loss.

This case illustrates that effective PCG management requires a multimodal approach. The integration of PMBT as an adjuvant therapy offers a non-invasive and well-tolerated option for managing the chronic inflammatory environment in PCG, minimizing prolonged tacrolimus or corticosteroid exposure and associated risks.[3]

Authors' contributions

Josefina Hurtado: Literature search; draft writing and review.

Víctor Meza: Review and editing, and visualization.

Fernando Valenzuela: Project conception; draft writing, review and editing, and visualization.

Isidora Mujica: Project conception; draft writing, review and editing, and visualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used CLAUDE (Sonnet 4.5) in order to improve readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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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.2026.501354.

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LETTER – THERAPY

Topical tapinarof (benvitimod) for papulopustular rosacea: two cases☆

Dear Editor,

Rosacea is a chronic inflammatory disorder that primarily affects the central face or eyes, characterized by flushing, persistent erythema, telangiectasia, papules, pustules, edema, and phymatous changes, with ocular involvement manifesting as blepharitis, conjunctival hyperemia, and dry eye symptoms. Current first-line topicals (metronidazole, azelaic acid, and ivermectin) offer variable efficacy and tolerability, while systemic agents may cause dysbiosis, dizziness, photosensitivity, and teratogenicity in selected populations.[1,2] Tapinarof (also known as benvitimod) is a nonsteroidal small-molecule agonist of the Aryl hydrocarbon Receptor (AhR) with anti-inflammatory, barrier-restoring, and sebo-suppressive effects.[3] It is approved for plaque psoriasis and has shown benefit in atopic dermatitis.[4] To our knowledge, tapinarof has not been reported for the treatment of rosacea. We presented two patients with Papulopustular Rosacea (PPR) treated with topical 1% tapinarof cream. Disease severity was assessed by Investigator Global Assessment (IGA; 0–4) by the treating dermatologist and patient-reported Dermatology Life Quality Index (DLQI; 0–30).

Case 1

A 66-year-old man presented with a 2-month history of persistent nasal erythema accompanied by several inflammatory papules and mild discomfort. Previous therapy with 0.75% metronidazole gel had yielded minimal improvement. Physical examination revealed centrofacial erythema with discrete erythematous papules and seborrhoea. Topical 1% tapinarof cream was applied once nightly. By week 4, erythema and papules were almost cleared (IGA 2 to 1), the DLQI improved from 5 to 0, and seborrhoea was reduced (Fig. 1A–B). Then the tapinarof was discontinued. No local or systemic adverse events occurred. Without maintenance therapy, the therapeutic response was maintained at the 6-month mark.

Case 2

A 48-year-old woman reported a 5-year history of centrofacial persistent erythema, papules, and papulopustules accompanied by excessive facial sebum. She declined systemic therapy. Serological screening for autoimmune connective-tissue disease (antinuclear, anti-extractable nuclear antigen, anti-dsDNA, and anti-mitochondrial antibodies) was negative. Baseline IGA was 3, and DLQI was 14. Treatment with 1% tapinarof cream, applied nightly for 4-weeks and then every other night for a further 4-weeks, was initiated. The lesion count and erythema were substantially reduced (IGA 3 to 1), and sebum production diminished; DLQI improved to 3 (Fig. 2A–B). The patient received no maintenance therapy. No adverse effects were observed. The therapeutic response persisted throughout 4-months of follow-up. The patient reported a mild relapse at 4-months post-discontinuation, characterized by faint central facial erythema and fewer than five scattered papulopustular lesions; these lesions improved following self-initiated tapinarof.

Rosacea has different manifestations. PPR is characterized by a centrofacial eruption of multiple papules and/or papulopustules with persistent centrofacial erythema.[1,2] These two cases demonstrated that 1% tapinarof cream, applied once nightly, rapidly attenuated papulopustular lesions and reduced seborrhoea, with sustained remission over 3-months. The improvement in DLQI underscored meaningful patient-reported benefit. No cutaneous irritation, contact sensitization, or systemic toxicity was observed, supporting favorable tolerability.

The observed efficacy aligns with mechanistic insights. Demodex infestation rates are significantly higher in the rosacea group than in healthy controls.[1,2] Demodex mites may activate Toll-Like Receptor-2 (TLR2). TLR2-dominated innate immunity contributes to the development of rosacea. When TLR2 is activated, keratinocytes produce proinflammatory cytokines and chemokines. Skin samples from patients with rosacea exhibit increased expression of proinflammatory cytokines such as IL-8, IL-1β, and TNF-α. IL-8

☆ Study conducted at the Renji Hospital, Shanghai Jiao Tong University, Shanghai, PR, China.

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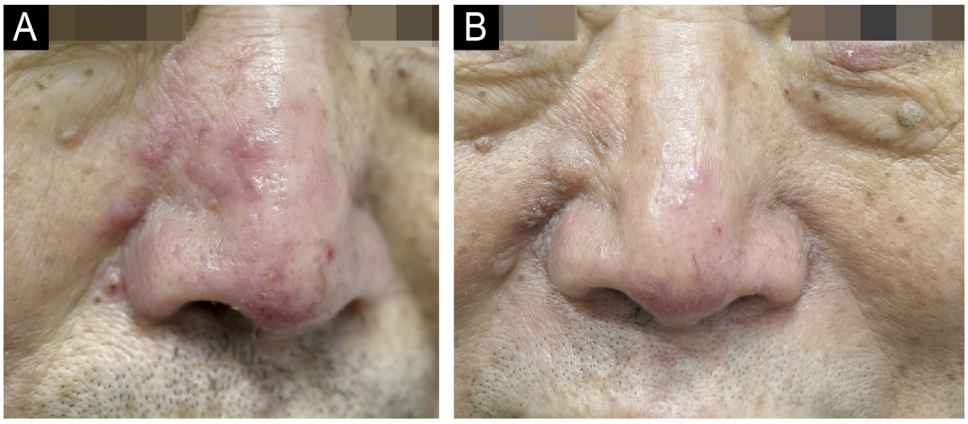

Fig. 1 Clinical images of Patient 1 with papulopustular rosacea. (A) Nasal erythematous papules at baseline. (B) After 4-weeks of once-daily 1% tapinarof cream.

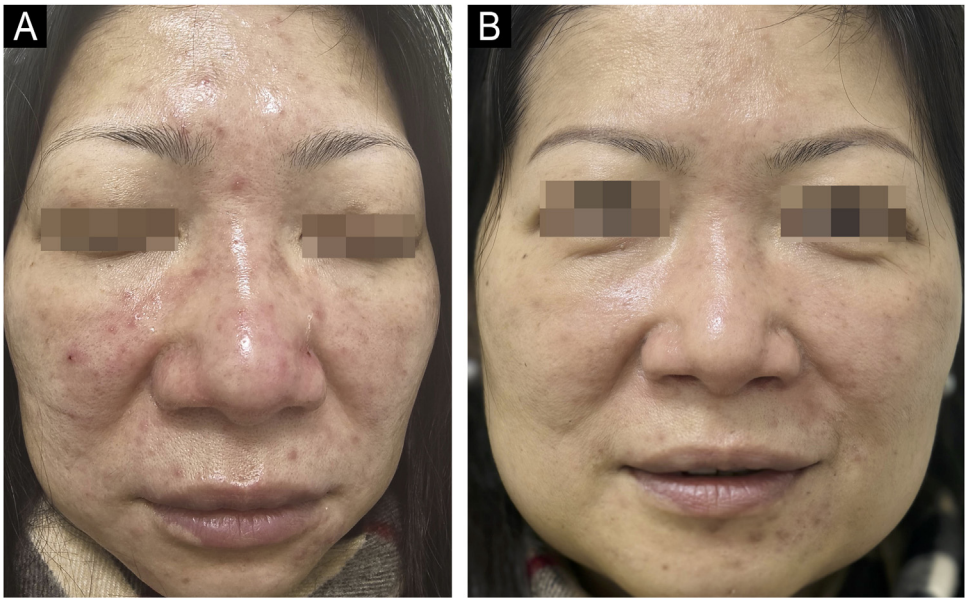

Fig. 2 Clinical images of Patient 2 with papulopustular rosacea. (A) Centrofacial persistent erythema with papules and pustules at baseline. (B) After 8-weeks of treatment.

leads to the chemotaxis of neutrophils in the skin. IL-1β and TNF-α promote further inflammatory reactions. TLR2 helps to increase the expression of KLK5, which is essential for activation of LL37.[5] Adaptive immune system activation, shown by the presence of T-Helper 1 (TH1) and T-Helper 17 (TH17) cells with their corresponding immune mediators in skin lesions of rosacea, results in increased inflammation and further immune activation. An upregulation of IFN-γ and IL-17A in rosacea-affected skin was also identified. IL-17 has been shown to induce angiogenesis through VEGF and affect the expression of LL-37 in human keratinocytes.[1,2] AhR activation by tapinarof suppresses TLR2-mediated innate responses, curtails Th17 cytokine production, and down-regulates sebaceous lipogenesis, thereby mitigating both inflammatory lesions and the lipid-rich milieu that favors Demodex proliferation.[3,5–7] However, the precise mechanisms underlying tapinarof's effect in rosacea require further investigation.

Our study suggests that topical tapinarof might be a potentially effective alternative for PPR. The small sample size and short follow-up period are limitations of this study. Controlled studies are warranted to confirm these preliminary findings and to establish optimal dosing frequency.

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Sitong Li*: Preparation and writing of the manuscript; data collection, analysis and interpretation; approval of the final version of the manuscript.

Jiacheng Lin: Preparation and writing of the manuscript; manuscript critical review; approval of the final version of the manuscript.

Qiong Wu: Preparation and writing of the manuscript; manuscript critical review; approval of the final version of the manuscript.

Qiang Ju: Effective participation in research orientation; study conception and planning; data analysis and interpretation; manuscript critical review; approval of the final version of the manuscript.

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Research data availability

Does not apply.

Conflicts of interest

None declared.

Editor

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LETTER - THERAPY

Voriconazole-induced lentiginosis in a child: a phototoxicity warning sign

Dear Editor,

Voriconazole, a triazole antifungal, is widely used in children with invasive fungal infections, especially in the context of hematologic malignancies and transplantation. Despite its efficacy, long-term therapy has been increasingly associated with phototoxic reactions, lentiginosis, and accelerated Non-melanoma Skin Cancer (NMSC) and melanoma.[1–3] Because the skin is one of the main target organs for the adverse effects of this drug, we present a case that illustrates one of these manifestations and illustrates the importance of early recognition.

A 7-year-old boy with acute lymphoblastic leukemia, atopic dermatitis, and autism spectrum disorder was started on oral voriconazole in August 2023 for an angioinvasive fungal infection. After several months of therapy, he developed multiple, asymptomatic, well-demarcated hyperpigmented macules (2–5 mm) symmetrically distributed on the cheeks, nasal dorsum, and frontal region (Figs. 1A–B). No mucosal, palmar, or plantar involvement was present. There was no family history of lentiginosis or syndromic associations. A diagnosis of chronic voriconazole-induced phototoxicity was made. Because antifungal substitution was not feasible, strict photoprotection (SPF 50+, hat, protective clothing) was recommended. At the 6-month follow-up, the lesions persisted without progression or development of new lesions.

Voriconazole-induced phototoxicity occurs in 17%–36% of children, particularly with cumulative exposure or long-term use.[1,2] Manifestations range from erythema and lentiginosis to premalignant lesions and aggressive Squamous Cell Carcinoma (SCC).[3] The persistence of lentiginous macules, as in this case, is a marker of chronic UV-induced damage and may represent a potential precursor to malignant transformation. It's also important to make an adequate differential diagnosis of lentigines localized on the head, neck, and acral to exclude conditions such as Peutz-Jeghers syndrome, Laugier-Hunziker syndrome, Cowden syndrome, centrofacial lentigines, and inherited patterned lentigines (Table 1).[4,5]

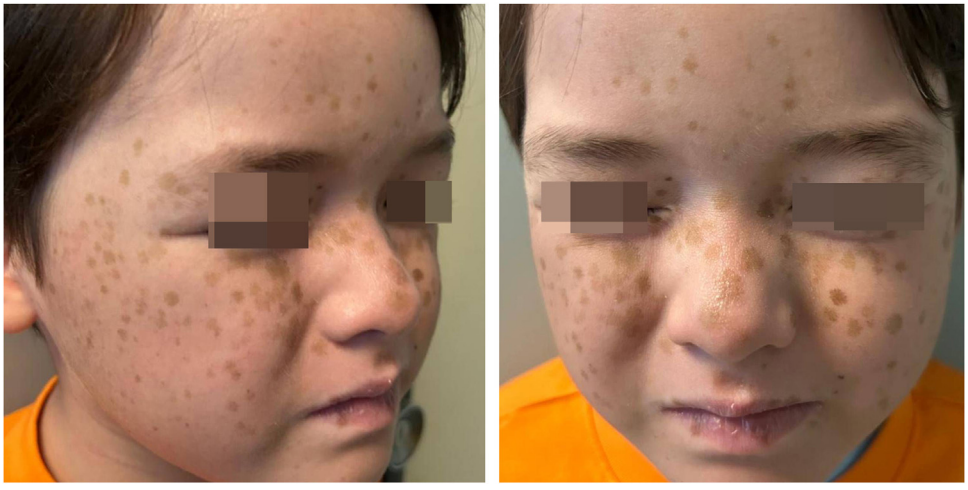

Figure 1 (A and B) 7-year-old boy with multiple well-demarcated hyperpigmented macules symmetrically distributed on the cheeks, nasal dorsum, and frontal region.

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Table 1 Differential diagnosis of localized multiple lentiginosis.

Head and neck involvement	Other localizations
Peutz-Jeghers syndrome	Genital involvement: Bannayan-Riley-Ruvalcaba syndrome
Laugier-Hunziker syndrome	
Cowden disease	Photodistribution: Xeroderma pigmentosum
Centrofacial lentiginosis	Segmental: Partial unilateral lentiginosis
Inherited patterned lentiginosis	

Pathogenesis remains incompletely understood. Proposed mechanisms include the UVA-absorbing properties of voriconazole's N-oxide metabolite, generating reactive oxygen species that induce oxidative DNA injury.[6] Additionally, a retinoid-like effect mediated by disrupted retinoic acid metabolism has been hypothesized to contribute to both phototoxicity and keratinocyte changes.[6]

Children represent a particularly vulnerable population due to their prolonged life expectancy, frequent exposure to immunosuppressive regimens, and the need for extended antifungal prophylaxis. Several reports have documented the rapid development of SCC in pediatric transplant recipients under chronic voriconazole therapy.[3,7] Recent pharmacovigilance analyses by regulatory agencies reaffirmed the importance of phototoxicity surveillance in children treated with voriconazole.[8]

Management includes early dermatologic evaluation, patient and caregiver counseling on rigorous photoprotection, and long-term cutaneous follow-up. Substitution with alternative antifungals such as posaconazole or isavuconazole may be considered in cases of recurrent or severe toxicity, although clinical circumstances may limit this option.

Voriconazole can induce chronic phototoxicity and lentiginosis in children receiving prolonged therapy. It is important for the dermatologist to be familiar with the adverse effect profile of this drug in order to make an adequate differential diagnosis and establish appropriate management, which should include photoprotection and follow-up to identify potential skin neoplasms early.

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Authors' contributions

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Camila Downey: Manuscript writing and editing; supervision of the project; approved the final version of the manuscript.

Conflicts of interest

None declared.

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CORRESPONDENCE

Comment on ''The Brazilian Portuguese version of the psoriasis epidemiology screening tool (PEST-bp) is reliable and accurate: a cross-sectional study from southern Brazil''☆

Dear Editor,

We read with great interest the study by Thomé et al., which evaluates the diagnostic performance of the Psoriasis Epidemiology Screening Tool Brazilian Portuguese version (PEST-BP) for psoriatic arthritis detection in a Southern Brazilian population.[1] The integration of rheumatologic evaluation using the Classification Criteria for Psoriatic Arthritis (CASPAR) as the diagnostic gold standard, combined with multivariate logistic regression, constitutes a robust analytic framework. The study's ability to validate a PEST-BP score threshold of $\geq$3 with high sensitivity and specificity has practical implications for dermatologic triage.

However, the reliance on a static cutoff score without stratified performance evaluation across different patient subgroups may limit interpretability in heterogeneous clinical settings.[2] For example, patients with isolated nail disease or early-onset plaque psoriasis may not present with the systemic features that drive higher PEST-BP scores, potentially delaying referral.[3] Incorporating differential positive predictive values for subsets such as nail psoriasis or dactylitis-dominant cases could enhance the tool's discriminatory capacity in routine care.

Another important concern is the absence of calibration assessment between PEST-BP responses and actual joint involvement patterns. Although the authors report dactylitis and nail psoriasis as significantly more prevalent in patients with psoriatic arthritis, it is unclear whether these variables were independently associated with elevated PEST-BP scores or acted as confounders in the logistic model. Without such calibration analysis, the strength of PEST-BP as a proxy for early joint inflammation remains partially inferential.

Finally, while the authors rightly emphasize the association between higher Psoriasis Area and Severity Index (PASI) scores and psoriatic arthritis, the inclusion of PASI $\geq$10 as an independent predictor raises a potential conflation between skin severity and joint risk.[4] Future investigations may benefit from dissecting whether PASI exerts an additive or synergistic effect alongside PEST-BP in composite screening models, especially in populations with low baseline disease activity.

We commend the authors for advancing localized validation of a time-efficient screening tool and for integrating dermatologic and rheumatologic expertise within the same clinical setting. Expanding this work through multicenter cohorts and longitudinal validation could meaningfully inform early intervention strategies and reduce diagnostic delays in psoriatic arthritis.

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Conflicts of interest

None declared.

☆ Study conducted at the Dr. D. Y. Patil Medical College Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth (Deemed-to-be-University), Pimpri, Pune, Maharashtra, India.

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Hiram Larangeira de Almeida Jr.

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CORRESPONDENCE

Comment on ''The Brazilian Portuguese version of the psoriasis epidemiology screening tool (PEST-bp) is reliable and accurate: a cross-sectional study from southern Brazil'' – Reply☆

Dear Editor,

We read with great interest the comments on our article[1] and appreciate the opportunity to further discuss and clarify our findings, which we believe helps to advance knowledge in this field.

First, regarding the use of a single static cutoff without stratified performance across specific patient subgroups, our primary objective was to assess the diagnostic accuracy of the PEST-BP in a new Southern Brazilian cohort using the same cutoff ($\geq$3) proposed in the original English version and in the first Brazilian validation. Ibrahim et al. identified $\geq$3 as the optimal cutoff with high sensitivity and specificity, and Mazzotti et al. confirmed the same threshold in Brazilian patients.[2,3] In our sample, a score $\geq$3 yielded an AUC of 0.845 ($p < 0.001$), with 81% sensitivity, 79.7% specificity, and 80% overall accuracy, thus supporting the robustness of this cutoff in a distinct setting. As acknowledged in our discussion, the single-center design and relatively small sample size limit the power for reliable subgroup analyses (e.g., isolated nail psoriasis or early-onset disease), and we agree that future larger, multicenter studies should address stratified performance. Nonetheless, the PEST-BP already incorporates relevant PsA features, such as dactylitis and nail disease, and is intended as a simple, pragmatic screening tool for dermatology practice, in keeping with current recommendations favoring feasible questionnaires for PsA detection in routine care.[4,5]

Second, concerning calibration between PEST-BP responses and actual joint involvement patterns, and whether dactylitis and nail psoriasis may have acted as confounders: in our study, patients with PsA had higher frequencies of dactylitis (38.1% vs. 11.4%; $p = 0.004$), nail psoriasis (66.7% vs. 35.4%; $p = 0.01$), and PASI $\geq$ 10 (42.9% vs. 19%; $p = 0.023$). However, in the multivariate logistic regression, only PEST-BP $\geq$ 3 and PASI $\geq$ 10 remained independently associated with PsA (OR = 32.43; $p < 0.001$ and OR = 9.26; $p = 0.007$, respectively), whereas nail psoriasis and dactylitis did not retain independent statistical significance. This supports that the predictive value of PEST-BP is not merely a reflection of these isolated manifestations, but of a broader composite of PsA-related symptoms and signs. PsA diagnosis was established using the CASPAR criteria, and PEST-BP performance was evaluated via ROC analysis against this established standard, which is an accepted approach for validating screening tools.[3,6] We agree that more granular calibration analyses linking specific PEST-BP response patterns to particular joint phenotypes would be valuable and should be pursued in larger, dedicated cohorts.

Third, regarding the inclusion of PASI $\geq$ 10 as an independent predictor and the possibility of conflating skin severity with joint risk, our results are consistent with evidence showing that higher psoriasis severity is associated with increased PsA risk. Eder et al. reported that severe psoriasis was a predictor of incident PsA in a prospective cohort, and Gelfand et al. observed higher PsA prevalence in patients with more extensive skin involvement.[7,8] In our multivariate model, PEST-BP $\geq$ 3 and PASI $\geq$ 10 were both independently associated with PsA, suggesting that they capture distinct but complementary dimensions of risk – symptom-based screening versus cutaneous inflammatory burden – rather than representing a simple overlap. We therefore view PASI $\geq$ 10 not as conflating the construct of the PEST-BP, but as an additive clinical parameter that may help prioritize rheumatologic referral, particularly among patients with moderate-to-severe disease. Future research may formally evaluate whether combined or stepwise strategies (e.g., PEST-BP plus PASI thresholds) can further optimize screening performance.

In conclusion, our study confirms that the PEST-BP with a cutoff $\geq$3 is a reliable and accurate screening tool for PsA in Brazilian dermatology settings, reinforcing its role in prompting timely rheumatologic evaluation rather than replacing specialist assessment. We are grateful for the con-

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structive comments, which underline important directions for future research on subgroup performance and composite screening models.

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Authors' contributions

Vanessa Thomé: Conceptualization; data curation; formal analysis; investigation; project administration; resources.

Marcia Regina Rosa Scalcon: Conceptualization; investigation; validation; project administration; writing-original draft.

Denise Teresinha Antonelli da Veiga: Conceptualization; validation; visualization; project administration; writing-original draft.

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Diego Chemello: Conceptualization; funding acquisition; methodology; supervision; writing-original draft.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

Editor

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