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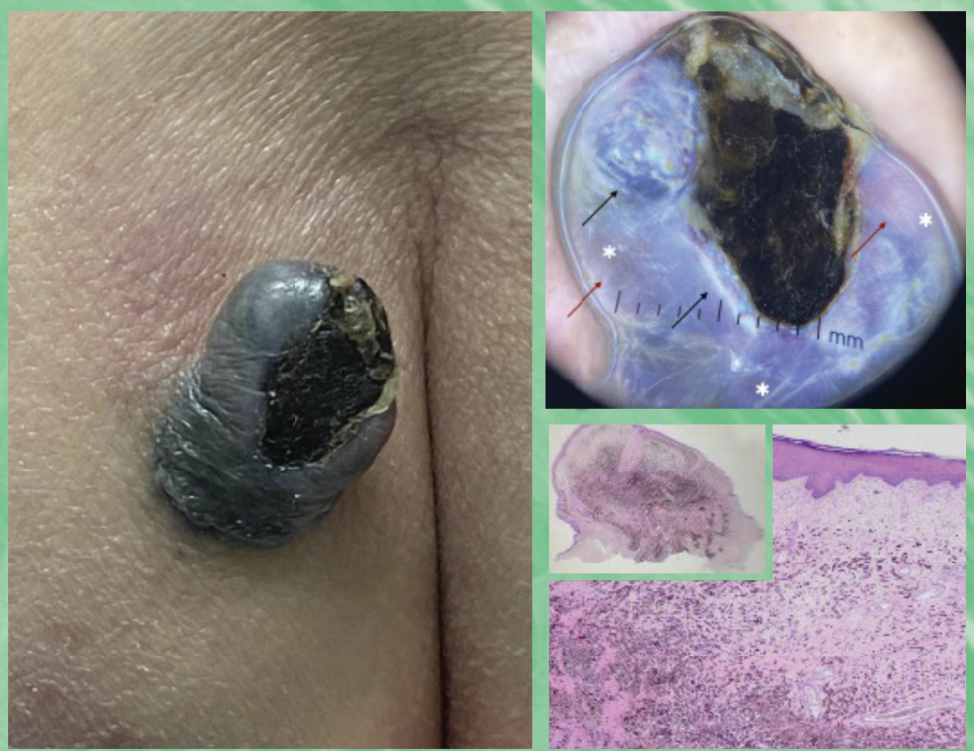

Dermoscopic rainbow pattern in malignant blue nevus

Gonçalves A.L. et al.

- Lipedema: pathophysiological insights and therapeutic strategies – An update for dermatologists
- Treatment response in chronic urticaria: analysis of clinical and laboratory predictors
- The role of phototherapy in pediatric dermatology
- Update on novel acne treatments: a narrative review focused on microbiome modulation and non-pharmacological approaches
- Rapid clinical response in refractory discoid lupus erythematosus treated with anifrolumab

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EDITORIAL

Anais Brasileiros de Dermatologia. Beginning a new five-year term, 2026-2030

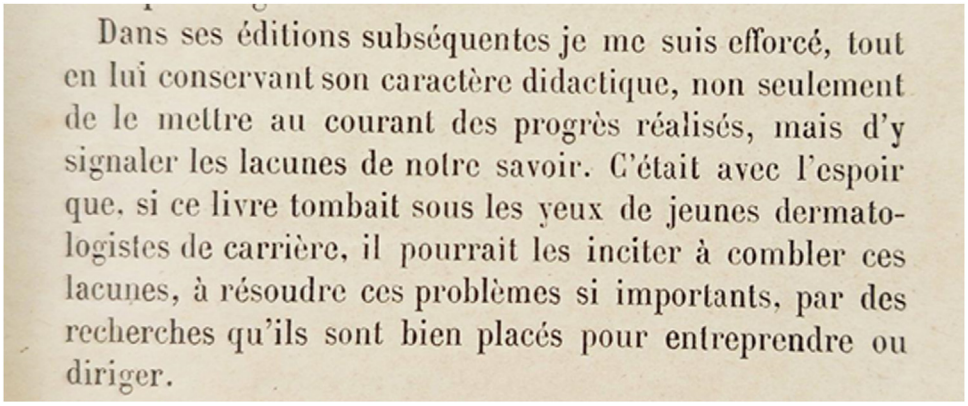
In 2026, a new five-year editorial period begins in the *Anais Brasileiros de Dermatologia*.

The group that starts now consists of myself as Scientific Editor with three Associate Editors: Jane Tomimori from Universidade Federal de São Paulo, Neusa Yuriko Sakai Valente from Universidade de São Paulo, and Renata Ferreira Magalhães from Universidade Estadual de Campinas.

Our mission will be to continue the work of the previous group,[1,2] valuing the quality of the selected articles, contributing solidly to the dissemination of scientific progress.

In the text excerpt depicted below (Fig. 1), ffrom the preface of the fourth edition of the *Précis de Dermatologie* of 1928, Darier expresses his concern, almost a century ago, to fill the knowledge gaps,[3] which we do to this day, in every research and in every publication.

Each piece of information that we make available to the global dermatological community helps to fill gaps and complete the complex understanding of skin diseases, which is experiencing so many diagnostic and therapeutic advances.



Dans ses éditions subséquentes je me suis efforcé, tout en lui conservant son caractère didactique, non seulement de le mettre au courant des progrès réalisés, mais d'y signaler les lacunes de notre savoir. C'était avec l'espoir que, si ce livre tombait sous les yeux de jeunes dermatologistes de carrière, il pourrait les inciter à combler ces lacunes, à résoudre ces problèmes si importants, par des recherches qu'ils sont bien placés pour entreprendre ou diriger.

Figure 1 Excerpt from the preface to the fourth edition of *Précis de Dermatologie of 1928*.
In subsequent editions, while maintaining its didactic characteristics, I have strived not only to make known the progress made, but also to point out the gaps in our knowledge. This is done in the hope that if this book falls before the eyes of young dermatologists, it may encourage them to fill these gaps, to solve these truly important problems, through research that they undertake.

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Authors' contributions

Hiram Larangeira de Almeida Junior: Approval of the final version of the manuscript; drafting and editing of the manuscript.

Conflicts of interest

None declared.

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CONTINUING MEDICAL EDUCATION

Lipedema: pathophysiological insights and therapeutic strategies – An update for dermatologists

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Abstract Lipedema is a chronic and progressive disorder characterized by disproportionate fat accumulation, mainly affecting the lower extremities of women, and commonly accompanied by sensations of heaviness, tenderness, and discomfort. While its pathogenesis remains largely unknown, genetic, hormonal, and microvascular factors have been implicated. The condition often coexists with psychological distress, which significantly detracts from the quality of life of affected individuals. Diagnosis is primarily clinical, as no specific biomarkers or imaging modalities have been proven sufficiently reliable for identification. Proposed managements are controversial, although current treatment focuses on symptom management and disease control through conservative methods such as compression and non-invasive device therapies, specialized diets, and physical rehabilitation or surgical treatments. Psychological support is vital in addressing the emotional challenges of the condition. Despite recent advancements in the understanding and management of lipedema, there remains a critical need for further research to establish standardized diagnostic criteria and targeted therapeutic strategies for this debilitating condition.

Introduction

Lipedema is a chronic, progressive disorder of adipose tissue characterized by a symmetrical and disproportional subcu-

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taneous fat accumulation, typically affecting one or more specific body regions, including the arms, lower abdomen, hips, buttocks, thighs, and lower legs. The condition was first described in 1940 as a clinical syndrome affecting women, marked by subcutaneous deposition of fat in the buttocks and lower extremities, and edema unresponsive to typical weight loss interventions.[1] Despite its early identification, lipedema remained largely underrecognized for decades and was frequently misdiagnosed as obesity, lymphedema, venous insufficiency, or even cellulite. This lack of awareness contributed to delayed diagnoses and inappropriate treatments for many patients.[2] Only recently, through the development of comprehensive clinical guidelines, such as the *German S2k Guidelines*, lipedema has been increasingly acknowledged as a distinct medical condition.[3] In the *S2k Guideline*, lipedema is defined as a ''painful, disproportionate symmetric distribution of adipose tissue of extremities occurring almost exclusively in women''.[3] The most affected areas include the lower abdomen, hips, buttocks, thighs, and lower legs.[4] Individuals with lipedema frequently report increased sensitivity to touch, pain, easy bruising, and a sensation of heaviness or fatigue in the affected limbs.[5] Its onset is often associated with periods of hormonal fluctuation, such as puberty, pregnancy, or menopause.[6–8]

The reported prevalence of lipedema varies significantly among European countries, ranging from 0.06% to 39%. In Brazil, it is estimated that approximately 8.8 million women (about 12.3% of the female population) present symptoms highly suggestive of lipedema, frequently associated with comorbidities like hypertension, anemia, anxiety, and depression.[9] Notably, body dissatisfaction and psychological distress have contributed to increased awareness and demand for diagnosis of this condition.[3,10]

Nevertheless, lipedema continues to be underdiagnosed or misdiagnosed, often confused with conditions such as lymphedema, lipohypertrophy, cellulite (also known as gynoid lipodystrophy), or obesity.[10,11] Currently, there is no reliable biomarker or widely accessible diagnostic tool for lipedema; diagnosis is based primarily on clinical history and physical examination. Treatment focuses on alleviating pain and managing symptoms, aiming to improve quality of life.[12]

This study aims to support the development of an evidence-based treatment protocol while emphasizing the urgent need for further research to enhance understanding and management of this complex condition.

Etiology and pathogenesis

The etiology of lipedema remains multifactorial and complex, reflecting the interplay of genetic, hormonal, and microvascular factors that are not yet fully elucidated. It has been reported that up to 60% of patients with lipedema have an affected first-degree relative with the same condition.[8] Based on the analyses of familial clusters, in which the most affected family members are grandmothers and mothers, an autosomal dominant inheritance pattern with incomplete penetrance (sex limitation) may be suggested. Mutations in genes like *AKR1C1* (linked to adipogenesis and progesterone levels) and *PIT1* (involved in growth and sex hormones) have been found in affected families.[13,14] *AKR1C1* mutation is believed to reduce aldo-keto reductase activity, increasing levels of allopregnanolone (a potent analgesic) while also decreasing prostaglandin F2-alpha levels and raising progesterone levels, which stimulate adipogenesis.[15]

The disproportionate accumulation of adipose tissue in the lower body, particularly coinciding with periods of hormonal fluctuation, suggests that dysregulation of estrogen signaling plays a key role in the pathophysiology of lipedema. This appears to be associated with an imbalance in estrogen receptor expression within subcutaneous adipose tissue in affected regions. Estrogen exerts its effects primarily through two types of intracellular receptors: Estrogen Receptor alpha (ERα) and Estrogen Receptor beta (ERβ). These receptors regulate distinct sets of genes, often with opposing metabolic effects. ERα is generally associated with promoting adipogenesis and reducing lipolysis, while ERβ tends to have anti-adipogenic and protective effects against excessive fat accumulation. In individuals with lipedema, studies suggest an increased ERα/ERβ ratio in the subcutaneous adipose tissue of the lower body. This shift leads to reduced inhibitory influence from ERβ and enhanced activation of ERα-dependent pathways. As a result, there is upregulation of genes involved in lipid and glucose uptake, inhibition of lipolysis, and mitochondrial dysfunction, which collectively contribute to fat accumulation and metabolic alterations in the affected areas.[15,16]

Furthermore, gene expression studies show increased aromatase *CYP19A1* – the enzyme that converts androgens to estrogen – in lipedema subcutaneous fat compared to healthy controls and even to the abdominal fat of the same patient. Additionally, estrogen has been found to induce *ZNF423*, a transcription factor also upregulated in lipedema. It is involved in preadipocyte differentiation via PPARG activation, suggesting a potential mechanism by which estrogen contributes to adipocyte hyperproliferation and fat accumulation in lipedema.[7] Also, adipocytes in lipedema may exhibit enhanced local production of steroidogenic enzymes, further increasing local estrogen activity through ERα activation and perpetuating adipose tissue expansion.[15]

Recent multi-omics studies have identified metabolic, lipid, and gene expression abnormalities in lipedema. Key findings include disrupted lipid metabolism and increased sphingolipids, which may drive cell proliferation. Additionally, Bub1 was identified as a key regulator of abnormal Adipose-Derived Stem Cell (ADSC) growth, and its inhibition reduced proliferation, highlighting it as a potential therapeutic target and a reason for optimism.[17]

Recent insights into lipedema pathophysiology reveal immune and vascular dysfunctions within affected adipose tissue. Histology shows increased infiltration of CD45+, CD68+, and CD163+ immune cells, with a predominance of M2 macrophages, indicating chronic low-grade inflammation and tissue remodeling. Concurrently, early microangiopathy and increased endothelial permeability have been identified, even in initial disease stages, marked by disrupted tight junctions and altered endothelial behavior. These vascular changes may lead to interstitial fluid buildup and tissue hypoxia, further driving fibrosis and inflammatory signaling.[18] Microvascular dysfunction – including increased capillary fragility and permeability – contributes to fluid leakage into the interstitial space, resulting in localized edema and a sustained inflammatory state. Inflammation

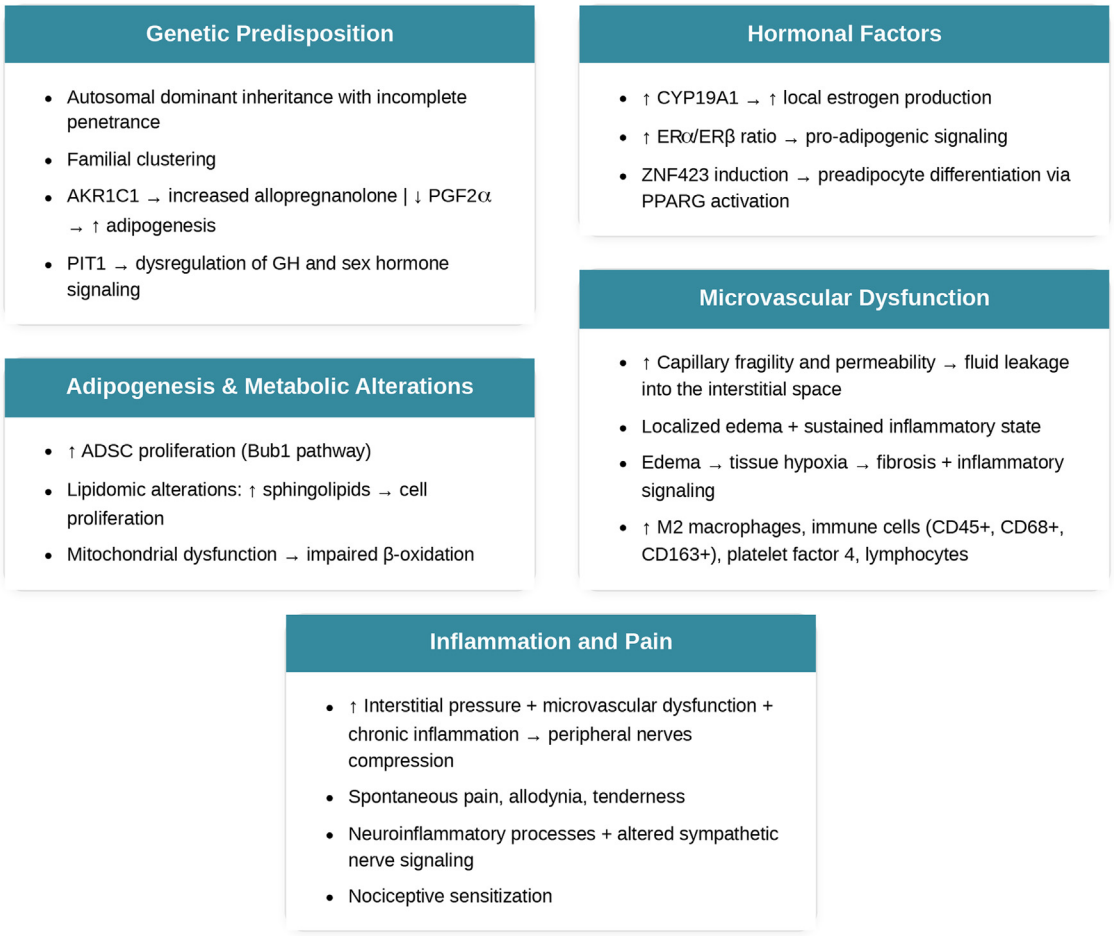

Figure 1 Pathogenic cascade of lipedema.

is thought to drive the microangiopathy in lipedema and is perpetuated by elevated M2 macrophages, platelet factor 4, and lymphocytes. These microvascular changes are believed to play a crucial role in both the onset and progression of lipedema.[15]

Additionally, pain in lipedema appears to be multifactorial. It is thought to arise from a combination of microvascular dysfunction, chronic inflammation, and increased interstitial pressure that may compress peripheral nerves. Patients often report spontaneous pain, allodynia, and tenderness, which are not fully explained by mechanical load or obesity alone. Neuroinflammatory processes and altered sympathetic nerve signaling have also been implicated in pain sensitization pathways. Collectively, these findings suggest that immune dysregulation, vascular fragility, and nociceptive sensitization interact to drive many of the hallmark symptoms of lipedema.[19] Fig. 1 summarizes the pathogenic cascade of lipedema.

Clinical manifestations

Disproportionate fat distribution

Recent research consistently demonstrates that lipedema is characterized by a distinct and recognizable pattern of fat deposition. Patients typically present with bilateral and symmetrical enlargement of the legs, with a clear demarcation at the ankles – commonly referred to as the ''cuffing sign'' – while the feet and hands remain unaffected. This adipose tissue accumulation is notably resistant to conventional weight loss strategies and is frequently associated with joint hypermobility.[7,12]

Symptoms often worsen throughout the day, particularly with heat exposure or prolonged standing, and are commonly accompanied by sensations of heaviness, tenderness, and discomfort in the affected areas.[10,20] Notably, the *S2k Guidelines* emphasize that ''a disproportionate increase of adipose tissue on the extremities without corresponding symptoms shall not be diagnosed as lipedema''. Additionally, although morphological staging has historically been used, there is currently insufficient evidence to determine disease severity based solely on appearance, and no validated symptom-based staging system is available.[3]

Despite this, lipedema is commonly described based on two classification systems: distribution types and morphological stages. According to distribution patterns (Table 1), lipedema is categorized into five types (Fig. 2): Type I involves fat accumulation primarily around the buttocks, hips, and pelvic area (Fig. 3); Type II extends from the hips to the knees, often including the inner thighs (Fig. 4); Type III affects the entire lower limb from hips to ankles (Fig. 5);

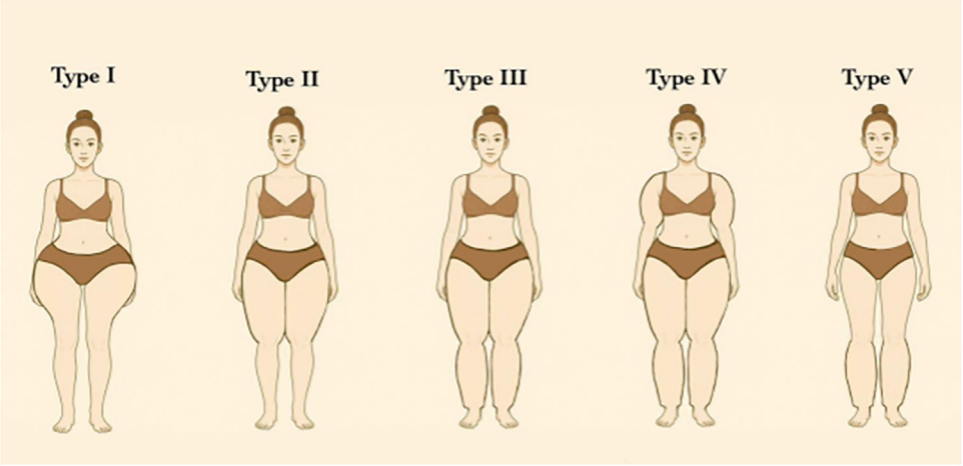

Figure 2 Graphical diagram representing the five subtypes of lipedema according to the distribution pattern.

Table 1 Classification of lipedema types based on anatomical fat distribution. Adapted from Amato et al (2021).

Type	Description
Type I	Fat accumulation primarily around the buttocks, hips and pelvic area
Type II	Fat distribution from hips to knees, often including the inner thighs and possibly the lower abdomen
Type III	Fat extends from hips to ankles, involving the entire lower limbs
Type IV	Involvement of the arms in addition to the lower body
Type V	Fat predominates in the calf region only (rare presentation)

Type IV includes additional involvement of the arms (Fig. 6); and Type V, although less common, is characterized by fat distribution predominantly in the calves Notably, some literature also describes involvement of the lower abdomen, especially in Types I and II, although this is not consistently reflected across all classification systems.[8,15,21,22]

Regarding morphological appearance, lipedema progresses through four clinical stages (Table 2): Stage I is characterized by smooth skin with thickened but soft subcutaneous tissue containing small nodules; Stage II presents with uneven skin surface due to the presence of larger nodules and increased fibrotic changes, often described as the ''mattress phenomenon''; Stage III features significant fibrosis, hardening of the subcutaneous tissue, and the development of prominent, disfiguring fat lobules, particularly in the inner thighs and around the knees, with possible overhanging masses; and Stage IV corresponds to the development of secondary lipo-lymphedema, where lymphatic dysfunction becomes evident.[8,15,21]

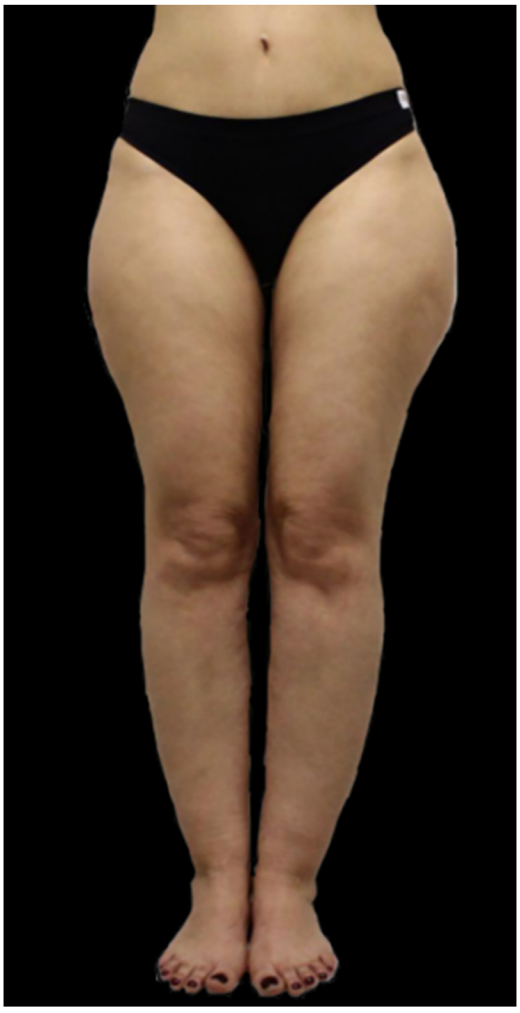

Figure 3 Lipedema, type I. Note the asymmetry between the limbs, with greater fat accumulation in the left lower limb.

Pain, tenderness and sensitivity

Pain is one of the most disabling features of lipedema. Patients frequently experience spontaneous pain and heightened tenderness in affected areas, even with minimal pressure.[19] This increased perception of pain – often described as a constant, throbbing sensation – is thought

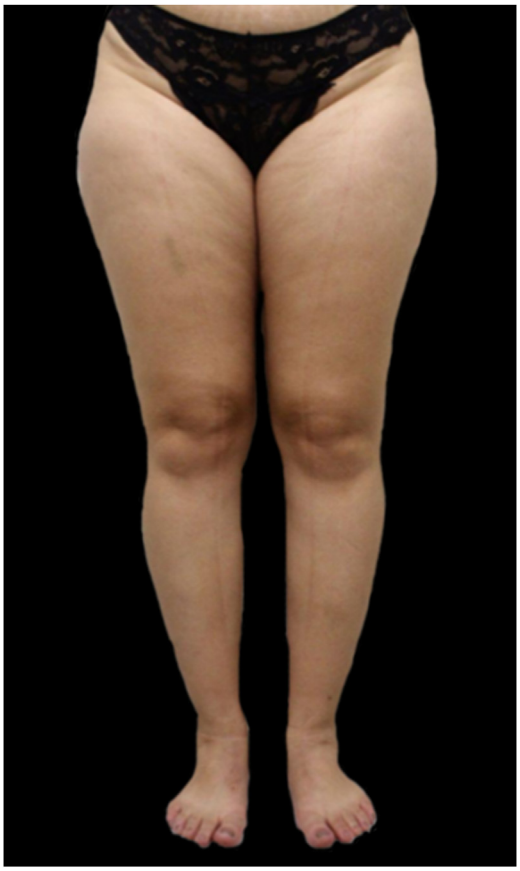

Figure 4 Lipedema, type II. Note the presence of spontaneous hematoma in the right lower limb.

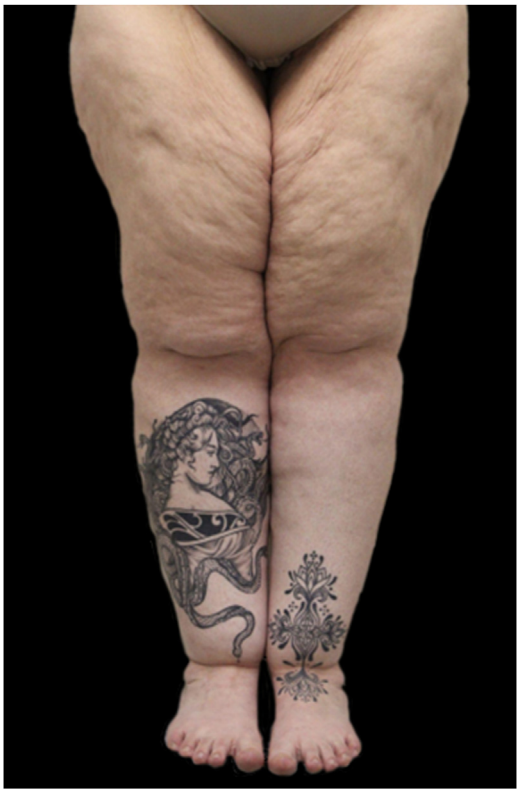

Figure 5 Lipedema, type III. The patient had tattoos made over the affected areas in an attempt to conceal the condition.

Table 2 Lipedema clinical stages based on morphological changes of the subcutaneous tissue over time. Adapted from Duhon et al (2022).

Stage	Description
Stage I	Smooth skin surface with thickened but soft subcutaneous tissue containing small nodules; tissue has a spongy consistency
Stage II	Uneven skin surface due to larger nodules and the presence of fibrotic tissue; often associated with the ''mattress phenomenon'' (dimpled appearance)
Stage III	Significant fibrosis and hardening of the subcutaneous tissue; presence of large, disfiguring fat lobules, particularly in the thighs and knees, with overhanging masses
Stage IV	Development of the secondary lipo-lymphedema, characterized by combined fat deposition and lymphatic dysfunction, leading to swelling and edema

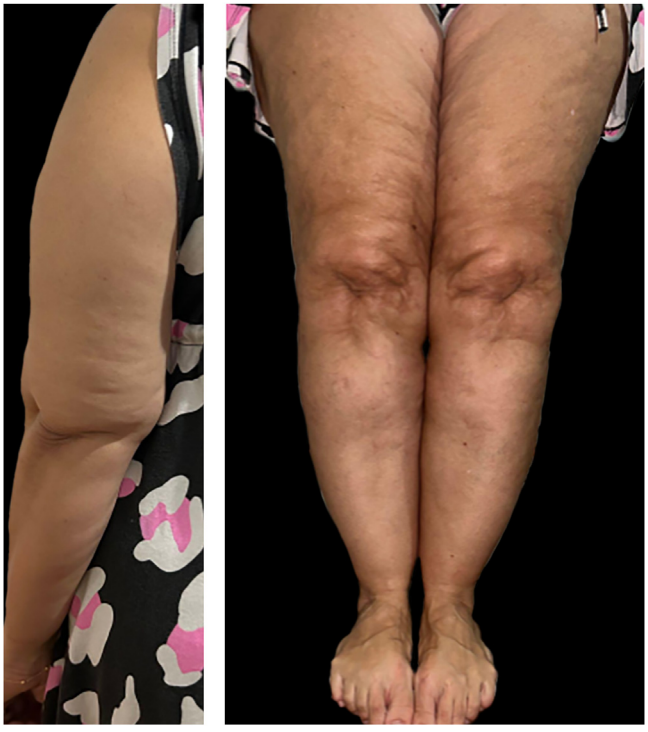

Figure 6 Lipedema, type IV.

to be linked to local inflammatory processes and possible micro-neuropathic changes within the subcutaneous tissue, leading to dysregulation of local-regional sensory nerve fibers.[12]

Edema and microvascular abnormalities

Non-pitting edema is another common manifestation, particularly as the disease progresses, which can be primarily due to an underlying chronic venous disease. Furthermore, capillary fragility and livedo reticularis are present in loose connective tissue, leading to easy bruising in the patients affected.[15,23]

However, it is important to note that the European Consensus Guidelines do not include edema in the diagnostic criteria for lipedema. It was posited that neither clinical examination nor diagnostic imaging showed a significant accumulation of fluid in the tissues of patients with lipedema, and therefore, the term ''lipedema'' was labeled as ''outdated'' and suggested that it could be renamed as ''lipalgia syndrome''.[24]

Metabolic and cardiovascular changes

Although lipedema is frequently associated with a high Body Mass Index (BMI), accumulating evidence suggests that its metabolic profile may differ from that typically seen in generalized obesity. In particular, women with lipedema appear to exhibit a relatively low prevalence of metabolic comorbidities such as diabetes and dyslipidemia, even in the presence of obesity-grade BMI values. For instance, studies have reported diabetes rates ranging from 2% to 6% among individuals with lipedema, whereas the prevalence in women with obesity in the general population is approximately 10%. This observation may be partially attributed to the predominance of gynoid fat distribution – localized to the hips, buttocks, and legs – which has been associated with reduced insulin resistance when compared to central or android fat accumulation.[15,25]

Similarly, blood pressure measurements in women with early-stage lipedema tend to remain within normal ranges, with hypertension primarily observed in more advanced stages. Lipid profiles also appear to be relatively preserved, with total cholesterol levels $\geq$240 mg/dL reported in only a minority of cases (11.7%), contrasting with higher rates observed among women living with obesity without lipedema (33.5%). Taken together, the authors suggest that the adipose tissue in lipedema may confer a degree of cardiometabolic protection.[25] However, more studies are needed to evaluate these findings.

Despite potential cardiometabolic advantages, the condition imposes significant clinical and functional burdens. Lipedema fat is resistant to conventional weight loss methods, often leading to further fat accumulation, mobility limitations, joint overload, and fatigue. Additionally, recent findings suggest that individuals with lipedema may present with altered vascular parameters, such as increased aortic stiffness, potentially associated with connective tissue changes secondary to hypermobility. While some cardiovascular risk markers may appear favorable in early stages, these findings underscore the need for further investigation into long-term cardiovascular outcomes and the full systemic impact of lipedema.[13,15,25]

Psychological and quality-of-life impacts

The physical symptoms of lipedema, including chronic pain, functional limitations, and visible changes in body contour, have a profound impact on individuals suffering from this condition.[26] Patients with lipedema frequently experience reduced quality of life, along with increased rates of anxiety, depression, and body image disturbances. The psychosocial impact is further compounded by the frequent misdiagnosis or underdiagnosis of the condition, which can delay appropriate care.[27] Several studies have demonstrated that the quality of life in patients with lipedema is markedly reduced compared to age-matched controls.[15,17,28] Some of the tools used included assessments of symptom severity, quality of life, satisfaction with life, psychological flexibility, and social connectedness. Multiple hierarchical regression analyses showed that a higher quality of life was associated with greater psychological flexibility and social connectedness. Thus, Functional Analytic Psychotherapy (Acceptance and Commitment Therapy), targeting psychological flexibility and social connectedness as key mechanisms of change, may be useful in treating women with lipedema.[28] Furthermore, on a standardized measure of health-related quality of life, anxiety or depression was found in 42% of individuals with lipedema, and a history of eating disorders – particularly anorexia and binge eating – is also common, being identified in 74% of 100 participants in another study.[15] The impact of psychological distress in this condition can be vastly underestimated, and early diagnosis and treatment may help reduce the impact of lipedema on mental health.[24]

Imaging findings

Imaging modalities have become essential adjuncts in the evaluation of suspected lipedema, particularly when the clinical picture overlaps with other conditions. Among these, high-frequency ultrasound stands out as a widely accessible and informative tool, capable of detecting characteristic changes in the subcutaneous tissue, including increased hypodermal thickness, a reticular pattern of hyperechogenic fibrous septa, and echogenic nodules likely representing microfibrotic alterations. These features are typically bilateral and symmetrical, with preservation of dermal thickness and echogenicity. Notably, the absence of dermal edema or fluid collections helps distinguish lipedema from lymphedema. Recent studies have proposed clinically applicable and reproducible ultrasound cutoff values to support the diagnosis of lipedema. The authors identified the pretibial region as the most accurate anatomical site for measurement, followed by the thigh and lateral leg. Based on the findings by Amato et al. (2021), the suggested ultrasound thresholds for diagnosing lipedema were 11.7 mm for the pretibial region, 11.9 mm for the thigh, and 8.4 mm for the lateral leg, with corresponding sensitivities of 0.77–0.79 and specificities up to 0.96. These values were derived from ROC curve analysis in a single-center study of 89 women and have not yet been externally validated or standardized across centers. These measurements aim to enhance diag-

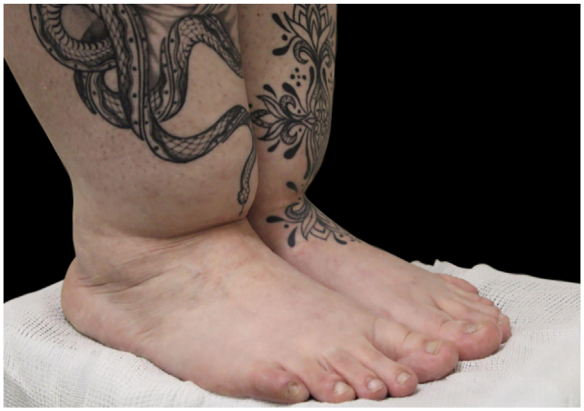

Figure 7 The cuffing sign.

nostic precision and support the differentiation of lipedema from other conditions in clinical practice.[22]

Furthermore, Dual-Energy X-Ray Absorptiometry (DEXA), also known as bone densitometry, traditionally employed to assess bone density and body composition, has recently emerged as a potential auxiliary tool in the diagnostic process of lipedema. In a single-center case-control study, Buso et al. analyzed body composition in 222 women (74 with lipedema and 148 controls) using DEXA and proposed a diagnostic index based on the ratio of leg fat mass to total fat mass. An optimal cutoff value of 0.384 was identified as a potential indicator of lipedema, while values below 0.383 were considered useful for excluding this condition with reasonable confidence. In patients with a suggestive clinical presentation, but not fully compatible with established diagnostic criteria, DEXA may help distinguish lipedema from obesity by objectively quantifying regional fat distribution. When incorporated into a broader diagnostic algorithm, it may enhance diagnostic accuracy, particularly in borderline or ambiguous cases.[29]

Differential diagnosis

Lipedema is frequently misdiagnosed due to its overlapping clinical presentation with several other disorders, including lymphedema, obesity, cellulite, lipohypertrophy, chronic venous insufficiency, and rare adipose tissue disorders such as Dercum's disease and Madelung's disease. A thorough differential diagnosis is therefore essential to ensure appropriate management (Table 3). One of the primary distinctions lies in the distribution and nature of the adipose tissue. Lipedema typically affects females and manifests as bilateral, symmetrical enlargement of the extremities – particularly the legs – while sparing the feet, resulting in a characteristic demarcation above the ankles. The so-called ''cuffing sign'' is a clinical hallmark of lipedema (Fig. 7). In contrast, lymphedema often begins in the distal extremities, involves the feet, and is commonly unilateral or asymmetrically bilateral. The presence of Stemmer's sign (inability to pinch the skin on the dorsum of the toes) strongly suggests lymphedema but is absent in pure lipedema. Additionally, skin changes such as fibrosis, papillomatosis, and recurrent infections (e.g., erysipelas) further support a diagnosis of lymphedema.[8,19]

Distinguishing lipedema from obesity is equally important. Unlike obesity, which affects both sexes and typically presents with central fat accumulation, lipedema fat is more resistant to weight loss, diet, and bariatric surgery. Moreover, lipedema is often associated with pain, tenderness, and easy bruising, symptoms that are generally absent in obesity. Lipohypertrophy, a condition resembling lipedema in its fat distribution, differs in the lack of associated pain, edema, or hematoma tendency.[8] Chronic venous insufficiency may present with limb swelling, varicosities, and hyperpigmentation, but these features typically improve with rest and elevation, unlike in lipedema.[30]

Advanced imaging techniques – such as duplex ultrasound, lymphoscintigraphy, Magnetic Resonance Imaging (MRI), and Computed Tomography (CT) – can assist in the diagnostic process by revealing distinct patterns of tissue involvement and venous or lymphatic function. Ultimately, an accurate diagnosis requires a comprehensive clinical evaluation in conjunction with imaging and exclusion of other possible conditions.[8,19]

Lipedema vs. cellulite

Although often underappreciated in the differential workup, cellulite, also known as gynecoid dystrophy, may also contribute to diagnostic confusion, particularly in early or mild cases of lipedema. Historically, lipedema has often been misclassified as a severe or atypical variant of cellulite, particularly within aesthetic and dermatologic literature prior to the early 2000s. For instance, a 2002 review discussing the classification of cellulite based on skin consistency referred to an ''edematous type'', characterized by sensations of leg heaviness and soreness – features that overlap with those of lipedema and likely contributed to diagnostic ambiguity.[31] In some contexts, lipedema was even referred to as an ''extreme form of cellulite''.[32]

This misclassification was likely influenced by shared epidemiological and clinical features, including female predominance, involvement of the lower body, and changes in subcutaneous adipose tissue. Nevertheless, it is now well established that lipedema and cellulite represent distinct clinical entities. Cellulite is defined by the presence of skin dimpling, producing the characteristic ''orange peel'' or ''mattress-like'' appearance. It primarily affects the thighs, buttocks, hips, and, occasionally, the abdominal region. Unlike lipedema, cellulite is typically painless.[33–35] While lipedema is a progressive and painful condition involving subcutaneous fat accumulation, cellulite is considered a morphological alteration of the dermis and subcutaneous tissue, typically painless and largely aesthetic in nature. In an effort to improve clinical evaluation, Hexsel et al. developed and validated the Cellulite Severity Scale (CSS), a standardized tool that quantifies severity based on five morphological parameters: number and depth of skin depressions, surface appearance (such as the characteristic ''orange peel'' or ''mattress'' pattern), degree of flaccidity or sagging, and the traditional Nurnberger-Muller classification. Each criterion is scored from 0 to 3, yielding a total score between 1 and 15, which stratifies cellulite as mild, moderate, or severe. Accordingly, in this most adopted classification of cellulite severity in research settings, the

Table 3 Differential diagnosis of lipedema. Modified from Kruppa et al. (2020) and Kumar et al. (2022).

Feature	Lipedema	Lymphedema	Obesity	Lipohypertrophy	Cellulite	Chronic venous insufficiency
Sex	Female	Both sexes	Both sexes	Mostly female	Almost exclusively female	Both sexes
Family history	Often positive	May be positive (primary), negative in secondary	Common	Possible	Common	Possible
Symmetry	Symmetric	Often asymmetric	Symmetric	Symmetric	Symmetric	Often asymmetric
Feet involvement	Spared	Involved	Possible	Spared	Spared	Involved
Edema	Variable (non-pitting)	Pitting, persistent	Pitting, improves with rest	Absent	If present, it is not related	Pitting, increases with standing, improves with leg elevation
Tenderness/ Pain	Present	Absent or mild	Absent	Absent	Generally painless	May have heaviness, aching, or cramps
Bruising	Frequent	Rare	Rare	Rare	Uncommon	Possible, but due to venous fragility or trauma
Fat distribution	Lower limbs, thighs, arms	Starts distally (feet), may be focal	Central / Generalized	Thighs and buttocks	Localized buttocks and thighs	No disproportionate fat deposition
Response to weight loss	No significant change	Not applicable	Responds to diet, exercise, surgery	No change	Partial improvement	Weight loss may lessen edema but not eliminate venous reflux
Skin changes	Skin typically smooth	Thickened, discolored, or warty	Normal	Normal	Dimpling, ''orange peel'' and ''mattress'' pattern	Hyperpigmentation, lipodermatosclerosis, venous ulcers in advanced stages

presence of symptoms is not considered a criterion. This further reinforces the notion that cellulite and lipedema are clinically distinct entities.[36]

Histologically, cellulite-prone areas like the gluteal region show subcutaneous tissue organized into layers separated by fibrous septa, which are key to its pathogenesis. These collagen-rich septa connect the dermis to deeper fascia and vary in size and orientation. In women, they run perpendicularly to the skin, forming vertical partitions that create a honeycomb structure of fat lobules. When the inward pull of septa is outweighed by the outward pressure of enlarged fat lobules, the skin surface becomes uneven, leading to dimpling. In individuals with low BMI, this imbalance causes subtle depressions, but as BMI increases, fat lobules expand, and septal tension is further disrupted, worsening the dimpling. In some cases, fat may even herniate through weakened septa, although this is seen as a secondary effect rather than a primary cause of cellulite.[33]

Sexual dimorphism in the structure of fibrous septa helps explain why cellulite mainly affects women. In men, septa form a crisscross pattern at oblique angles, offering greater support and reducing fat protrusion. They are also typically stronger, more numerous, and associated with smaller, evenly distributed fat lobules – factors that minimize skin irregularities even with higher adiposity. In contrast, women have fewer, vertically oriented septa and larger, elongated fat lobules, making their dermal-subcutaneous interface more susceptible to cellulite.[33]

Treatment and clinical management

Lipedema is currently considered a chronic disorder with progressive characteristics rather than a classical disease entity. Therapeutic approaches aim primarily at symptom reduction and prevention of disease progression. To date, no specific etiological treatment has been described.[8,13] Therefore, the main pillars of lipedema management are conservative treatments and surgical or other non-conservative interventions.

Conservative treatment approaches

Physical activity and rehabilitation: Regular physical activity reduces proinflammatory adipokines and macrophages and improves blood flow, thereby counteracting hypoxia in adipose tissues.[24] Exercise routines should be tailored to individual needs and ideally supervised by qualified

health professionals.[12] Beneficial exercises – which should start slowly and progress as tolerated – include swimming, aquatic therapy, elliptical machines, yoga, stationary biking, whole-body vibration, and walking.[15] The goals of physical activity are weight control, improved muscle strength and mobility, and enhanced self-esteem.[20]

Special diets: Since lipedema is considered a polygenic disorder associated with chronic low-grade inflammation, some authors recommend anti-inflammatory diets such as the Mediterranean or ketogenic diet to reduce symptoms.[37] Dietary management should prioritize reducing hyperinsulinemia and insulin resistance. Professional guidance from a nutritionist or a nutrologist physician is essential to ensure adherence and prevent relapse.[20]

Compression therapy: Combined decongestive therapy (CDT) integrates manual lymphatic drainage, compression, exercise, and skincare. CDT comprises two phases: phase 1 includes education, skin care, manual lymphatic drainage, and multilayer non-elastic compression bandaging; phase 2 involves continuation of phase 1 plus self-massage and compression garments. CDT primarily aims to reduce pain but does not prevent fat accumulation or disease progression. Flat-knit compression stockings are preferred due to their higher bending stiffness, allowing better support of deep tissue folds without constriction, and are more comfortable.[3,24] Compression therapy should be tailored to disease stage and individual tolerance. In the initial or more edematous phases, non-elastic multilayer compression bandages are often indicated to achieve effective volume reduction and tissue stabilization before transitioning to maintenance garments. These short-stretch bandages provide high working pressure and low resting pressure, promoting lymphatic return and reducing orthostatic edema. Once limb volume has stabilized, flat-knit compression stockings are recommended for long-term management, as their firm, inelastic structure provides consistent containment of the subcutaneous tissue while minimizing constriction and rolling. The compression class should be selected according to the degree of edema and fibrosis: class II (23–32 mmHg) is generally appropriate for stage I–II lipedema, while class III (34–46 mmHg) may be required for stage III disease with tissue induration or concomitant lymphedema. Proper fit and donning technique are essential to ensure efficacy and comfort, and periodic reassessment is recommended to adapt compression strength as clinical features evolve.[20]

Pharmacological therapy: Although no pharmacological therapies have been officially approved specifically for lipedema, recent advances in the understanding of its pathophysiology and its overlap with metabolic mechanisms have prompted the off-label use of anti-obesity medications, aiming to reduce inflammation and the volume of functionally impaired adipose tissue. Glucagon-Like Peptide-1 (GLP-1) and GLP-1 / Glucose-dependent Insulinotropic Polypeptide (GIP) receptor agonists (semaglutide, liraglutide, tirzepatide) suppress appetite, improve glycemic control, induce significant weight loss, and may modulate tissue inflammation. Emerging evidence suggests that weight reduction achieved with GLP-1 receptor agonists may relieve pain, joint pressure, and edema associated with lipedema. Case reports and observational data indicate improvements in quality of life, edema, and pain – particularly with tirzepatide, which has been associated with weight losses exceeding 20% in some patients.[38] While traditional weight loss strategies tend to have limited effects on lipedematous fat, GLP-1 agonists have demonstrated benefits in a retrospective cohort, including pain relief, reduced limb volume, and improved physical function, even when lipedematous fat is not entirely resolved.[39] The use of anti-obesity pharmacotherapy in lipedema should be considered, particularly in cases of lipolymphedema or coexisting obesity, refractory pain and functional limitation, failure to respond to intensive lifestyle modification, and as preoperative preparation for surgical intervention. Although randomized controlled trials are still needed, clinical experience points to a promising therapeutic horizon for women with lipedema, through a transdisciplinary approach that integrates pharmacological treatment, physiotherapy and exercise, nutritional therapy, psychological support, and aesthetic or surgical procedures.[37,39]

Long-term use of diuretics is discouraged because they do not address the underlying inflammatory processes. Metformin may be considered for patients with metabolic complications due to its potential to inhibit hypoxia-induced fibrosis in adipose tissue.[40] Oral analgesics may be used for pain management, although systematic data on pharmacological therapies are lacking.[8]

Despite its association with sex hormones, there is no scientific basis for the use of estrogens, progestins, testosterone, or hormonal implants in the treatment of lipedema. These therapies may worsen the condition by stimulating adipose tissue growth or causing uncontrolled changes in body composition. The use of hormonal implants containing compounds such as gestrinone or testosterone has been inappropriately employed in aesthetic practice without any evidence of benefit for lipedema and with potential cardiovascular, metabolic, and endocrine risks.[39]

Non-invasive interventions

Although liposuction seems to be the surgical method of choice for the reduction of the affected subcutaneous tissue of lipedema, it is also accompanied by a significant risk of complications. Adverse effects may include postprocedural pain, infection, prolonged recovery, scarring, bruising, ecchymosis, or edema, along with substantial financial costs. Nowadays, non-invasive devices have been confirmed as safer, more affordable methods for the reduction of localized fat deposits. There are five leading non-invasive techniques currently being used to treat subcutaneous adipose tissue deposits: Low-level laser therapy (LLLT), cryolipolysis, radiofrequency (RF), high-intensity focused ultrasound (HIFU), and shock wave therapy (SWT).[41]

LLLT: This therapeutic approach uses LLLT in the 635–680 nm wavelength range to promote adipocyte membrane permeability, allowing for the release of intracellular lipids without cell destruction. In the study by Savoia et al., LLLT was applied to areas including the hips, thighs, abdomen, and knees in patients with localized adiposity and cellulite. The results demonstrated a significant reduction in circumference in treated areas – up to 2.15 cm in the abdomen and 1.87 cm in the thighs – after a cycle of treatment sessions. Additionally, improvements in skin firmness

and texture were observed, with high levels of patient satisfaction and no reported adverse effects. These findings support LLLT as a safe and effective noninvasive technique for body contouring and cellulite treatment, but there are no studies with lipedema.[42]

Cryolipolysis: This device therapy is a non-invasive technique that uses controlled cooling to selectively target and induce apoptosis of subcutaneous adipocytes by crystallizing intracellular lipids. These crystallized lipids are subsequently recognized as ''foreign bodies'' by the immune system, triggering localized panniculitis and apoptosis of the affected cells without damaging surrounding tissues. Several case reports have suggested that cryolipolysis may be an effective non-invasive option for lipedema treatment, reporting symptom improvement in small patient cohorts.[43] According to a systematic review by Ingargiola et al. (2015), cryolipolysis has demonstrated efficacy in noninvasively reducing subcutaneous fat, with studies reporting an average fat reduction of 14.67% to 28.5% across treated areas such as the abdomen and flanks. The procedure is generally well tolerated, with high patient satisfaction and a low incidence of mild, transient adverse side effects like erythema, edema, and sensory changes.[44] Despite its success in treating localized adiposity, the application of cryolipolysis for lipedema remains under-investigated. The pathophysiology of lipedema differs from simple localized fat accumulation, involving inflammatory components and microvascular abnormalities, which might influence treatment outcomes. Therefore, although cryolipolysis represents a promising adjunct therapy for symptom management and fat reduction in lipedema patients, more specific clinical trials are needed to establish its efficacy and safety in this population.[45]

RF: This technology employs high-frequency electromagnetic waves to induce thermal effects in subcutaneous tissues, leading to adipocyte disruption and gradual fat reduction. The mechanism involves deep tissue heating, which may promote lipolysis through sympathetic stimulation and increased metabolic activity. Clinical studies have shown reductions in abdominal circumference and fat thickness following RF treatment, with minimal side effects such as mild erythema and transient discomfort. However, while initial results are promising, limitations include small sample sizes and short follow-up durations, emphasizing the need for more robust and long-term clinical trials to validate efficacy and safety.[46,47] There are no studies evaluating RF for lipedema treatment.

HIFU: This noninvasive lipolysis technique uses focused ultrasonic energy to target adipose tissue, inducing thermal coagulation and mechanical disruption of adipocytes while preserving surrounding structures. It has gained popularity for body contouring applications, particularly in the abdominal, waist, and flank regions.[48,49] Several commercially available devices utilize HIFU technology, i.e. micro- and macro-focused ultrasound to deliver thermal energy to specific dermal and subcutaneous layers. Clinical studies report its efficacy in skin tightening, collagen remodeling, and fat reduction, with significant improvement in skin elasticity and lifting effects.[50,51] Clinical studies report favorable outcomes in terms of fat reduction and skin tightening; however, discrepancies between subjective patient assessments and objective clinical findings have been noted. Adverse events are generally mild and transient, including erythema, mild burning sensations, and occasional blistering, all of which typically resolve spontaneously without lasting sequelae.[48,49] There are no studies evaluating HIFU for lipedema treatment.

SWT: This is a non-invasive localized treatment method that utilizes either radial or focused acoustic waves to promote dermal remodeling. The initial mechanical stimulus by the pressure peaks induces cellular changes through mechanotransduction, mobilizing the extracellular matrix. This process promotes neocollagenesis and collagen remodeling, enhances microcirculation, and supports lymphatic drainage.[35] In addition to improving skin elasticity and the appearance of cellulite, acoustic waves may also help reduce localized adiposities through mechanical disruption and improved tissue structure.[34] A meta-analysis conducted by Knobloch and Kraemer (2015) evaluated 11 clinical studies – including 5 randomized controlled trials involving a total of 297 female patients with cellulite – and demonstrated that both radial and focused extracorporeal SWT significantly reduced cellulite severity. Treatment protocols typically included 6 to 8 sessions, delivered once or twice weekly, with outcomes assessed via standardized photography, circumference measurements, and ultrasonographic analysis. The authors reported improvements in skin texture, reduction in tissue edema, and increased dermal elasticity. Although the methodological quality of the included studies was variable (scores ranging from 22 to 82), the overall findings support the clinical efficacy of extracorporeal SWT in aesthetic indications.[52] While the data pertain specifically to cellulite, the underlying mechanisms – improved lymphatic flow, microvascular function, and connective tissue remodeling – are also pathophysiologically relevant to lipedema. In this context, a recent pilot study evaluated 15 patients with stage II lipedema with the combined use of defocused and radial shock wave therapy, mesotherapy, and *Kinesio Taping* (elastic therapeutic taping applied to the skin to reduce pain). The mesotherapy solution consisted of Lymdiaral® (Pascoe), a homeopathic compound containing Conium D3 (2.5 mg), Hydratis D3 (2.5 mg), Viscum album D2 (2.5 mg), Phytolacca D4 (2.0 mg), Scilla D1 (2.0 mg), and sodium chloride. This study reported reductions in limb circumference, pain, and tissue stiffness, along with improved quality of life. However, the study's lack of a control group, small sample size, short follow-up, and the use of multiple simultaneous therapies limit the ability to attribute the observed benefits specifically to shock wave therapy.[53] Thus, the SWT appears to be a promising therapeutic approach for lipedema, warranting further investigation through controlled trials.

Surgical interventions

Lipedema reduction surgery is currently the sole technique for eliminating abnormal lipedema tissue, including adipocytes, nodules, fibrotic extracellular matrix, and other non-adipocyte components. Besides, it is the only treatment known to slow the progression of lipedema and is ideally performed before complications and functional impairments arise.[15]

Tumescent liposuction

For patients who do not respond sufficiently to conservative treatments, tumescent liposuction has emerged as a reliable surgical option. The German S2k Guideline recommends that it should be performed with a tissue and lymph-vessel conserving method, in 1 to 4 sessions on both legs, 1 or 2 sessions on both arms, and a maximum aspiration volume of 10% of the body weight. Moreover, immediately after the surgical procedure, CDT should be performed.[3]

According to the *European Lipedema Forum*, liposuction is effective only when patients are appropriately selected. Key criteria include: 1) Persistent symptoms despite 12-months of comprehensive conservative treatment; 2) Significant functional limitations, such as reduced mobility; 3) Stable body weight for at least 12-months to reduce the risk of postoperative weight regain; 4) Preoperative psychological evaluation to rule out eating disorders or mental health conditions that may affect outcomes; and 5) A BMI of 35 kg/m^2 or lower.[24] Liposuction is not recommended for individuals with a BMI exceeding 35 kg/m^2 who also present with central obesity (waist-to-height ratio [WHtR] > 0.5). However, in rare cases where central obesity is not present, liposuction may still be considered for individuals with a higher BMI.[3,37,40] Although many studies reported improving the disease's symptoms, such as reduction of spontaneous pain, bruising, and mobility impairment, there is still not enough evidence to support liposuction as the gold standard in treating lipedema.[37,54] It is also important to highlight that liposuction carries risks and potential complications, including post-procedural pain, infection, prolonged recovery, scarring, bruising, ecchymosis, edema, and substantial financial costs, which must be carefully considered in clinical decision-making.[54]

Bariatric surgery

Bariatric surgery may be considered for individuals with lipedema and a BMI $\geq$ 40 kg/m^2, and potentially for those with a BMI between 35–40 kg/m^2. Recent studies report significant benefits in patients with lipedema and severe obesity following surgery. In cases with BMI 35–40 kg/m^2, assessing the WHtR can offer additional guidance. A WHtR below 0.5 suggests low metabolic risk, indicating that bariatric surgery may not be necessary for these patients.[24]

Psychosocial and emotional support

Addressing the psychological aspects of lipedema involves a multifaceted approach. Cognitive behavioral therapy focuses on modifying negative thought patterns and behaviors, thereby reducing symptoms of anxiety and depression; it can help patients develop effective coping strategies to manage the emotional challenges posed by lipedema. On the other hand, acceptance and commitment Therapy encourages patients to accept their experiences without judgment and commit to actions aligned with their values, fostering improved mental health outcomes. This approach has shown promise in enhancing psychological flexibility and emotional regulation in women with lipedema.[26,28]

A holistic approach to lipedema treatment acknowledges the interplay between physical and psychological health. Incorporating psychological therapies alongside medical and physical interventions can lead to more comprehensive and effective management of the condition. Healthcare providers are encouraged to assess lipedema patients' mental health needs routinely and facilitate appropriate referrals to mental health professionals when necessary.[17]

Role of the dermatologist

Dermatologists play a central role in the diagnosis and management of lipedema, as the condition often presents initially with cutaneous and subcutaneous manifestations that mimic other dermatologic or vascular disorders. Their expertise in recognizing patterns of adipose tissue distribution, assessing skin changes, and distinguishing lipedema from other disorders is critical for early and accurate diagnosis. Moreover, dermatologists are essential in coordinating multidisciplinary care, which includes vascular specialists, endocrinologists, nutritionists, physiotherapists, and mental health professionals. In clinical practice, dermatologists guide conservative treatment strategies – such as compression therapy, skincare, and non-invasive device-based approaches – and are frequently involved in the pre- and postoperative care of patients undergoing liposuction or aesthetic interventions. By integrating diagnostic precision with therapeutic and psychosocial management, dermatologists contribute significantly to improving outcomes and quality of life in patients with lipedema.

Conclusion

Lipedema is a complex and often misunderstood condition, recently recognized as a distinct clinical entity. It affects many women and causes a significant physical and psychological impact. Despite growing awareness and advances in understanding, diagnosis remains difficult due to the absence of specific biomarkers and standardized criteria. While some treatments offer symptom relief, they do not stop disease progression, making surgical options like tumescent liposuction viable for many. Effective management requires a multidisciplinary approach combining medical care, rehabilitation, and psychological support. Future research should focus on clarifying its mechanisms, improving diagnosis, and developing targeted, innovative therapies to enhance outcomes and quality of life.

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Research data availability

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Authors' contributions

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Conflicts of interest

None declared.

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ORIGINAL ARTICLE

The Brazilian Portuguese version of the psoriasis epidemiology screening tool (PEST-bp) is reliable and accurate: a cross-sectional study from southern Brazil☆,☆☆

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Abstract
Background: Psoriatic arthritis (PsA) remains diagnostically challenging in clinical practice. The Psoriasis Epidemiology Screening Tool - Brazilian Portuguese version (PEST-BP) offers a potential solution for simplified case identification.
Objective: To evaluate the diagnostic accuracy of PEST-BP in detecting PsA among patients with psoriasis in a novel Southern Brazilian population.
Methods: In this cross-sectional study, psoriasis patients from a dermatology clinic underwent dual assessment: PEST-BP screening and gold-standard rheumatologic evaluation using CASPAR criteria for PsA diagnosis. Statistical analyses included sensitivity, specificity, and ROC curve determination.

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☆☆ Study conducted at the Dermatology Clinic, Hospital Universitário de Santa Maria, Universidade Federal de Santa Maria, Santa Maria, RS, Brazil.

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Results: Among 100 patients, 21 (21%) met the CASPAR criteria for PsA. A PEST-BP score $\geq$ 3 showed the best diagnostic performance with 81% sensitivity, 79.7% specificity, and 80% overall accuracy (AUC = 0.845, p < 0.001). Patients with PsA had a significantly higher prevalence of dactylitis (38.1% vs. 11.4%; p = 0.004), nail psoriasis (66.7% vs. 35.4%; p = 0.01), and Psoriasis Area and Severity Index (PASI) $\geq$ 10 (42.9% vs. 19%; p = 0.023). In multivariate analysis, a PEST-BP score $\geq$ 3 (OR = 32.43; p < 0.001) and PASI $\geq$ 10 (OR = 9.26; p = 0.007) were independently associated with PsA.
Study limitations: Single-center design in a tertiary care hospital and small sample size may overrepresent patients with severe disease.
Conclusion: The PEST-BP is a reliable and accurate tool for PsA screening in Brazilian dermatology settings. Its simplicity and strong diagnostic performance support its integration into routine clinical practice for early PsA detection.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease that develops in some patients with psoriasis. Usually, there is a period of preclinical disease before the characteristic manifestations, which include arthritis, enthesitis, dactylitis, axial disease, or nail involvement.[1,2]

Cutaneous lesions precede the development of musculoskeletal symptoms in the majority of patients. As a consequence, dermatologists and primary care physicians are in a favorable position to diagnose PsA.[3] In fact, periodic screening is recommended by the most important medical societies in patients receiving topical treatment for psoriasis, those on systemic treatment, those with extensive affected areas, and those with nail or intergluteal involvement.

Because PsA can be difficult to diagnose, the CASPAR criteria were developed to help physicians identify people who have PsA. In the original study, these criteria presented both high sensitivity and specificity (0.987 and 0.914, respectively).[4] However, there are several challenges and limitations when applying the criteria, particularly in cases of early or axial PsA.[5]

One simple way to increase the diagnosis of PsA is to use screening questionnaires, which are recommended by guidelines.[6–9] Several questionnaires for screening PsA have been developed over the last years. Some of these screening tests are complex and time-consuming, while others have different initial purposes rather than PsA screening.[1] The PEST (Psoriasis Epidemiology Screening Tool) questionnaire was developed to screen for PsA in outpatients with psoriasis.[10] This tool was originally published in English, and it was characterized by its quick applicability and easy understandability by patients. Recently, Mazzotti et al. translated the PEST into Portuguese (PEST-bp), validating it for the Brazilian population. They showed that the questionnaire is reliable in patients with psoriasis. According to their results, a cutoff score $\geq$ 3 has good sensitivity (84.6%) and specificity (63.3%) for the detection of PsA.[11]

Since there are no additional studies using the PEST-bp, the aim was to determine the accuracy of this tool in a distinct Brazilian population.

Materials and methods

This was an observational cross-sectional study, consisting of 100 adult patients ($\geq$18 years-old) with psoriasis. Patients were followed at the dermatology outpatient clinic at the Hospital Universitário de Santa Maria, Brazil. This is a university hospital in Santa Maria, Brazil, that is a reference for psoriasis care for a population of approximately 500,000 inhabitants. From March to September 2023, the authors evaluated all patients with psoriasis under follow-up at the dermatology outpatient clinic. The diagnosis of cutaneous psoriasis was made by two dermatologists certified by the Brazilian Society of Dermatology (LPV and RMLC), based on a clinical or histopathological examination of all patients. The exclusion criteria included individuals with a previous diagnosis of PsA or cognitive impairment that did not allow the questionnaire or the consent form to be completed. All patients were evaluated by a rheumatologist (MRRS) for the diagnosis of PsA using the CASPAR classification criteria, through detailed medical history and specialized physical examination, complemented, if necessary, by laboratory tests and imaging studies. The present study was approved by the local Research Ethics Committee.

To determine the required sample, the authors referred to the methodology employed by Mazzotti et al. In their cross-cultural validation and psychometric analysis, a sample size of 116 patients was estimated as necessary to achieve adequate statistical power. This calculation was based on an expected sensitivity of 97% and specificity of 79% for the PEST-bp questionnaire in detecting psoriatic arthritis (PsA), with a PsA prevalence of 20% among psoriasis patients. Cronbach's alpha coefficient of 0.80 was considered for internal consistency, and a confidence interval of 95% was set. Utilizing these parameters, and accounting for a significance level (α) of 0.05 and a desired statistical power (1 - β) of 80%, the authors aim to recruit a minimum of 116 participants.

Statistical analysis

The analyses were performed with the Statistical Package for Social Sciences (SPSS), version 21.0. The distribution

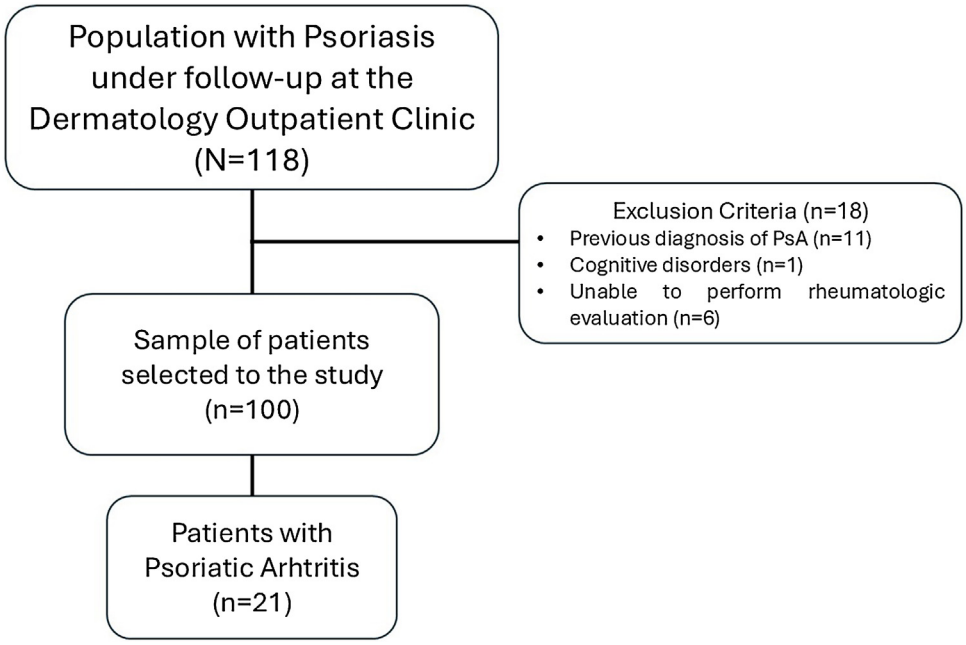


Fig. 1 The flowchart of selection and initial results.

of quantitative data was verified using the Kolmogorov-Smirnov test. The continuous variables were described as mean and standard deviation, or median and interquartile range, according to the distribution of data. Categorical variables were presented as absolute and relative values. For each PEST score, analysis of accuracy, sensitivity, and specificity was performed, and a Receiver Operating Characteristic (ROC) curve was constructed. The optimal cutoff point for the PEST score to identify patients at high risk for PsA was chosen using the Youden J index. A ROC curve > 0.7 was considered to indicate sufficient predictive accuracy. A multivariate logistic regression analysis was performed to determine the independent predictors associated with PsA.

Flowchart of the study population (Fig. 1). Psoriasis patients were followed at the outpatient clinic (n = 118), with exclusions and the PsA identification process.

Results

From the 118 patients with psoriasis under regular follow-up at the Dermatology Outpatient Clinics, eighteen were excluded from the present study for the following reasons: eleven had a priori diagnosis of PsA; one had cognitive disorders; and six patients were unable to undergo the complete rheumatological evaluation. The flow chart of selection and initial results is depicted in Fig. 1.

A total of 100 patients were eligible for the study. The mean age was 52.1 ± 14.8 years, 50 (50%) were female, and 18 (18%) were active smokers. The median Body Mass Index (BMI) was 29.8 kg/m^2 (Interquartile Range (IR): 26.3–32.4 kg/m^2). Seventy-five patients (75%) presented comorbidities, such as obesity in 39 (39%), and systemic arterial hypertension (SAH) in 37 (37%). A family history of psoriasis was present in 33 (33%). Eighty-five (85%) patients were users of Rheumatic Disease-Modifying Antirheumatic Drugs (DMARDs) at the inclusion in the study. Plaque psoriasis was the most common type with 73 (73%) patients, followed by palmoplantar in 17 (17%). The mean duration of the disease was 13.23 ± 9.41 years. Regarding psoriasis severity, 76 (76%) patients had mild disease with the median PASI score of 3.75 (IR: 1.13–9.3). A history of dactylitis was reported by 17 (17%) of the patients, and nail psoriasis was diagnosed in 42 (42%) cases. The median PEST score was 2 (IR: 1–3). Concomitant rheumatological diseases were present in 38 patients, with osteoarthritis occurring in 24 patients, followed by fibromyalgia in 5, gout in 3, and osteoporosis in 3. The baseline characteristics are shown in Table 1.

According to the CASPAR criteria, 21 (21%) of patients received the diagnosis of PsA. Their mean age was 55.7 ± 10.3 years, 12 (57.1%) were female, and the median BMI was 30 kg/m^2 (IR: 26.6–32.6 kg/m^2). The PASI score was ≥ 10 in 9 (42.9%) patients, corresponding to moderate to severe psoriasis. Dactylitis was present in 8 (38.1%), while nail psoriasis occurred in 14 (66.7%). Regarding joint involvement of PsA, the oligoarticular type was the most common, occurring in 10 (47.6%), followed by polyarticular in 7 (33.3%), and axial in 2 (9.5%). Among the 21 patients with PsA, the PEST-BP score was ≥ 3-points in 17 (81%). The main characteristics of patients with PsA are described in Table 2.

In patients with PsA, there was a higher prevalence of dactylitis (38.1 vs. 11.4%; p = 0.004), and nail psoriasis (66.7% vs. 35.4%; p = 0.01). Also, there was a higher prevalence of PASI score ≥ 10 (42.9% vs. 19%; p = 0.023).

The ROC curve statistics showed the PEST-BP ≥ 3 presented the best cutoff for diagnosis of PsA, with the area under the curve of 0.845 (p < 0.001), accuracy of 80%, sensitivity of 81% and specificity of 79.7% (Fig. 2). The multivariate logistic regression revealed that a PEST-BP score ≥ 3 (OR = 32.43; p < 0.001) and a PASI score ≥ 10 (OR = 9.26; p = 0.007) were significantly associated with the diagnosis of PsA, as shown in Table 3.

Table 1 Clinical and demographic characteristics of patients with psoriasis at the Dermatology Outpatient Clinic.

Characteristics	n (%)
Age (years)[a]	52.1 (14.8)
Female Sex	50 (50)
Obesity	39 (39)
SAH	37 (37)
Type 2 DM	18 (18)
Dyslipidemia	13 (13)
Depression	12 (12)
Cerebrovascular disease	2 (2)
Coronary artery disease	2 (2)
Body Mass Index (Kg/m^2)[b]	28.3 (26.3 – 32.4)
Active smoking	18 (18)
Former smoker	18 (18)
Family history of psoriasis	33 (33)
Using DMARDs	85 (85)
Psoriasis diagnosis (years)[a]	13.23 (9.41)
Psoriasis type	
Plaque	73 (73)
Palmoplantar	17 (17)
Guttate	6 (6)
Inverse	3 (3)
Pustulosis	1 (1)
Dactylitis	17 (17)
Nail psoriasis	42 (42)
PASI Score[b]	3.75 (1.13 – 9.3)
PASI Score < 10	76 (76)
PASI Score ≥ 10	24 (24)
PEST-bp Score[b]	2 (1 – 3)
Other rheumatologic diseases	n = 38 (38)
Osteoarthritis	24 (63.2)
Fibromyalgia	5 (13.2)
Gout	3 (7.9)
Osteoporosis	3 (7.9)

SAH, systemic arterial hypertension; DM, diabetes mellitus; DMARDs, Disease-Modifying Rheumatologic Drugs.
[a] Values described as mean and Standard Deviation.
[b] Values described as median and interquartile range.

Table 2 Demographic, articular, and skin characteristics of patients diagnosed with psoriatic arthritis at the Dermatology Outpatient Clinic.

	n = 21 (%)
Age (years)[a]	55.7 (10.3)
Female sex	12 (57.1)
BMI (Kg/m^2)[b]	30 (26.6 – 32.6)
Comorbidities	
Obesity	10 (47.6)
HTN	7 (33.3)
DM Type 2	2 (9.5)
Dyslipidemia	5 (23.8)
Depression	3 (14.3)
Smoking	
Former smoker	1 (4.8)
Active smoker	5 (23.8)
Family history of psoriasis	7 (33.3)
Nail psoriasis	14 (66.7)
Dactylitis	8 (38.1)
DMARDs	18 (85.7)
PASI[b]	7.2 (0.8 – 9.3)
Severity of psoriasis	
Up (PASI < 10)	12 (57.1)
Moderate/Severe (PASI ≥ 10)	9 (42.9)
PEST-BP	
< 3	4 (19)
≥ 3	17 (81)
Joint pattern	
Oligoarticular	10 (47.6)
Polyarticular	7 (33.3)
Oligoarticular/Axial	2 (9.5)
Axial	2 (9.5)

BMI, Body Mass Index; HTN, Hypertension; DM, Diabetes mellitus; DMARDs, Disease-Modifying Drugs; PASI, Psoriasis Area and Severity Index; PEST-BP, Psoriasis Epidemiology Screening Tool, Portuguese (Brazilian) version.
[a] Values described as mean and standard deviation.
[b] Values described as median and interquartile range.

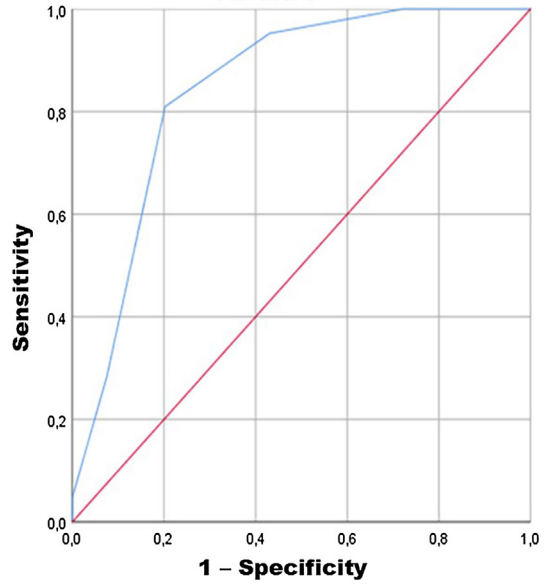
Discussion

The PEST is a simple tool designed for screening PsA, enabling those at greatest risk to be referred to rheumatologic evaluation. In its original publication by Ibrahim et al., the cutoff determined by the ROC curve was ≥ 3, and the PEST presented a sensitivity of 92% and specificity of 78% for screening PsA.[10] Recently, Mazzotti et al. translated and validated the PEST questionnaire into Portuguese, adapting it to the Brazilian population (PEST-bp). They observed an 81% accuracy with a cutoff ≥ 3 as suggestive of PsA, with a sensitivity of 84.6% and specificity of 63.3%.[11] The present study, performed in a different Brazilian population, confirms the usefulness of the PEST-bp ≥3 for diagnosing PsA, with an accuracy of 80%, sensitivity of 81% and specificity of 79.7%.

There are other screening questionnaires developed for screening PsA, like the Toronto Psoriatic Arthritis Screen (ToPAS), the Psoriatic Arthritis Screening Evaluation (PASE), and EARP.[12–14] The studied group chose to use the PEST tool due to its slightly superior performance, fast application, understandability by patients, and ease of application by physicians across different countries.[1,15–17]

Regarding the severity of psoriasis, the authors observed that moderate to severe psoriasis (corresponding to a PASI score ≥ 10) is associated with a 9.26 times higher chance of PsA compared to mild disease. Similar results were observed by other authors, like Eder et al., who observed that severe psoriasis (PASI > 20) was a predictor of risk for PsA.[18] A retrospective study by Wilson et al. showed that the risk of PsA was 2.24 times higher if skin was affected in more than 3 sites.[19] Similarly, in a North American study with 27,220 patients who answered a questionnaire, Gelfand et al. observed that the prevalence of PsA was higher in patients who had more skin involvement.[20] The association between psoriasis severity and PsA observed in several studies can be explained by a higher degree of systemic inflammation, which can be a trigger for musculoskeletal involvement.[8]

A



B

	PEST-BP				
CASPAR	**≥ 1**	**≥ 2**	**≥ 3**	**≥ 4**	**≥ 5**
Sensitivity	100%	95.2%	81%	28.6%	4.8%
Specificity	27.8%	57%	79.7%	92.4%	100%

C

PEST-BP ≥ 3	
Acuracy	80%
Sensitivity	81%
Specificity	79.7%
PPV	51.5%
NPV	94%

Fig. 2 (A) The ROC curve shows sensitivity versus specificity of the scores used to discriminate patients with Psoriatic Arthritis (PsA). (B) Cumulative sensitivity and specificity for different cutoff points of the PEST-BP score according to CASPAR criteria. (C) Accuracy, sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for the cutoff PEST-BP ≥3.

Table 3 Multivariate logistic regression model for analysis of the association of variables with the diagnosis of psoriatic arthritis.

	Univariate Analysis		Multivariate Analysis	
	OR (95% IC)	p	OR (95% IC)	p
Age	1.06 (0.99–1.13)	0.094		
Female sex	0.36 (0.06–2.04)	0.247		
Comorbidities	0.54 (0.08–3.63)	0.528		
Obesity	0.63 (0.14–2.85)	0.550		
PASI ≥ 10	26.38 (2.85–244.17)	0.004	9.26 (1.81–47.35)	0.007
Ungual psoriasis	2.38 (0.42–13.54)	0.327		
Dactylis	4.73 (0.91–24.72)	0.065		
PEST ≥ 3	36.33 (4.43–297.73)	0.001	32.43 (6.58–159.92)	<0.001
DMRDs	1.05 (0.13–8.36)	0.963		
Smoking	0.68 (0.13–3.54)	0.649		
Family history of psoriasis	1.05 (0.20–5.44)	0.958		

OR, Odds Ratio; 95% IC, 95% Confidence Interval; PASI, Psoriasis Area and Severity Score; PEST-BP, Psoriasis Epidemiology Screening Tool – Brazilian Portuguese; DMRDs, Disease-Modifying Rheumatic Drugs.

In the present study, the authors observed that there was a significantly higher prevalence of nail psoriasis in patients with PsA than in patients with cutaneous disease. These findings were also observed by other authors. For example, Wilson et al. observed that nail dystrophy was a predictor of risk for PsA.[19] The association of nail psoriasis with PsA is thought to be due to the nail's proximity to the distal interphalangeal enthesis. When inflammation occurs, there is also a reflection in the nail apparatus.[21]

Dactylitis is also a pivotal manifestation of PsA, being part of the CASPAR criteria. It's considered a marker of severe joint disease. In the present study, the authors observed a higher prevalence of dactylitis in patients with PsA and PEST-bp ≥ 3. Brockbanck et al. observed that radiological progression of psoriasis was more prominent in the group with dactylitis. Scriffignano et al. observed that patients with early-onset psoriasis were more likely to have dactylitis. Dactylitis is an early sign in 10% of patients with PsA, and half of patients with dactylitis have their first episode before the diagnosis of psoriatic joint disease.[22–24]

The authors acknowledge that the present study has limitations. First, this is a single-center study conducted in a tertiary hospital. As a consequence, the population had potentially more severe disease. Second, the sample size is considered small. Given the constraints of patient recruitment within the outpatient clinic, all eligible patients were initially considered for participation. However, following the application of inclusion and exclusion criteria, a total

of 100 patients were successfully recruited for this study. While this sample size is smaller than the original study by Mazzotti et al. it represents the entirety of the accessible patient population within the study timeframe.[11] Third, most patients were under systemic treatment with DMARDs at the time of the evaluation, which may have influenced the evaluation of the severity and extent of psoriasis and joint symptoms.

Conclusion

Despite the limitations observed, the present work was able to confirm the high accuracy of the PEST-bp in tracking PsA. Considering the high rate of joint damage in the first years of the disease, the use of simple screening questionnaires becomes a tool for early detection of PsA, providing dermatologists with a unique opportunity to screen for this disease.

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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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ORIGINAL ARTICLE

Comparison of meglumine antimoniate versus miltefosine in the treatment of new world cutaneous leishmaniasis: a systematic review and meta-analysis☆

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Abstract

Background: Cutaneous leishmaniasis (CL) affects up to 1.2 million people annually, mainly in resource-limited regions. Meglumine antimoniate, the standard treatment, is limited by systemic toxicity, injectable administration, and increasing resistance. Miltefosine, an oral alternative, offers practical advantages, although comparative efficacy and safety data remain inconsistent.

Objective: To compare the efficacy and safety of miltefosine versus meglumine antimoniate for New World CL.

Methods: The authors systematically searched PubMed, Embase, Scopus, and the Cochrane Library for randomized controlled trials directly comparing miltefosine and meglumine antimoniate. Risk Ratios (RRs) with 95% Confidence Intervals (95% CIs) were calculated using random-effects models. Heterogeneity was assessed with the I^2 statistic. Risk of bias was evaluated using the Cochrane RoB-2 tool. Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.

Results: Eight trials involving 898 patients (502 treated with miltefosine, 396 with meglumine antimoniate) were included. Miltefosine showed significantly higher cure rates at two months (RR = 0.83; 95% CI: 0.71–0.98; I^2 = 0%). Differences at six months were not statistically significant. Gastrointestinal side effects were more frequent with miltefosine, whereas hepatic enzyme elevations, arthralgia (RR = 10.08; 95% CI: 2.36–43.12), and fever (RR = 2.98; 95% CI: 1.53–5.80) were more common with meglumine antimoniate.

Study Limitations: High heterogeneity, short follow-up, small sample sizes, and interstudy variability may limit precision.

☆ Study conducted at the Universidade Santo Amaro, São Paulo, SP, Brazil.

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Conclusion: Miltefosine shows superior early response and a safer systemic profile. However, the certainty of evidence, as assessed by GRADE, ranged from very low to high across outcomes, and long-term data remain limited, highlighting the need for further high-quality studies with extended follow-up.

Introduction

Cutaneous leishmaniasis (CL) is a neglected tropical disease (NTD) that primarily affects impoverished populations in tropical and subtropical regions worldwide. It is broadly categorized into two main forms: Old World CL, occurring in parts of Africa, Europe, and Asia, and New World CL. These forms differ significantly in geographic distribution, *Leishmania* species, clinical manifestations, and treatment response.[1]

New World CL, also referred to as American CL (ACL) or american tegumentary leishmaniasis (ATL), is especially prevalent in tropical and subtropical areas of the Americas. The infection is transmitted by the bite of *Lutzomyia* sandflies and typically leads to persistent skin ulcers that may result in significant scarring. In more severe cases, the disease can extend to the mucous membranes of the nose, mouth, and throat.[2,3]

Multiple *Leishmania* species are responsible for ACL, with *Leishmania (Viannia) braziliensis*, *Leishmania (Leishmania) amazonensis*, and *Leishmania (Viannia) guyanensis* being the most commonly identified in Brazil.[2] These parasites, classified within the *Leishmania* and *Viannia* subgenera, show notable differences in their capacity to cause severe disease and in their responsiveness to treatment options.[3]

This biological and clinical diversity contributes to the difficulty of controlling ACL, especially in endemic countries such as Brazil, Colombia, and Peru.[4,5] This complexity is reflected in the substantial and persistent burden of disease. Although it is estimated that between 600,000 and 1 million new CL cases occur globally each year, only about 200,000 are officially reported to the World Health Organization (WHO).[6]

In 2023 alone, 272,098 new CL cases were reported, with 94% originating from the Eastern Mediterranean Region and the Americas. Brazil, alongside Afghanistan, Algeria, Colombia, Iran, Iraq, Pakistan, Peru, Sri Lanka, Syria, and Yemen, accounted for over 90% of all globally reported cases. Notably, case numbers in the Americas have rebounded following declines during the COVID-19 pandemic, reflecting both renewed transmission and improvements in case detection. Despite this, underreporting remains a persistent issue due to limited surveillance infrastructure, barriers to healthcare access, and variations in national reporting systems.[7]

Given the substantial disease burden and the considerable variability in clinical presentation and *Leishmania* species across endemic regions, the treatment of CL remains particularly challenging.[8] Pentavalent antimonials (SbV) have been the primary treatment for leishmaniasis since 1945, with meglumine antimoniate being the most commonly used. Although the mechanism of action of SbV is not fully understood, it is believed that its antileishmanial activity is due to the stimulation of the host's macrophages. However, the use of SbV is associated with serious adverse effects, including hepatotoxicity, cardiotoxicity, and nephrotoxicity.[9,10] Since the 1980s, resistance to meglumine antimoniate has increased, largely due to inappropriate use.[11] Furthermore, its parenteral administration presents additional challenges, particularly in remote and resource-limited areas where adherence to treatment regimens can be difficult.[10]

Miltefosine, an oral medication, is an alternative in cases of antimonial resistance. Its mechanism of action involves interfering with the lipids in the membrane of the *Leishmania* parasite and its mitochondrial function. Studies suggest miltefosine may be better tolerated compared to other treatments. Although there are also reports of side effects such as vomiting, diarrhea, and, to a lesser extent, hepatotoxicity and nephrotoxicity.[11] A major limitation of miltefosine is its teratogenic potential, compounded by its prolonged persistence in the body for up to four months after treatment.[12]

Notwithstanding the availability of these therapies, relapse remains common. Parasitic resistance and incomplete eradication of *Leishmania*, particularly its persistence in scar tissue, may contribute to disease recurrence. Almeida-Santos et al., in a systematic review, reported relapse rates of 52% after a single drug, with 45% of patients treated with Glucantime (meglumine antimoniate), alone or in combination, experiencing treatment failure, most often defined between 6–12 months after treatment. These findings highlight the ongoing difficulty in achieving sustained parasitological cure in CL.[13]

Although the efficacy of miltefosine has been demonstrated in various studies, the comparison between miltefosine and meglumine antimoniate remains limited and inconsistent, as different studies report varying results regarding the efficacy of the two drugs.[14] Given the toxicity of antimonial drugs and the difficulty of their use in remote areas, miltefosine presents an important alternative for the treatment of CL, especially in low-income populations, due to its ease of administration.[10]

While this comparison is clinically relevant, no comprehensive synthesis has yet resolved the conflicting evidence regarding the relative efficacy and safety of meglumine antimoniate and miltefosine across diverse settings. Several prior meta-analyses, published between 2013 and 2021, have examined aspects of this question. However, most combined studies from both Old World and New World cutaneous leishmaniasis, despite the significant differences in species distribution, clinical presentation, and treatment response between the two regions.[14–17] Consequently, their findings

lacked geographic specificity and provided limited guidance for treatment decisions in the Americas.

The present analysis will specifically address this gap by focusing solely on New World CL, evaluating cure rates from early time points through long-term follow-up and systematically assessing treatment failure rates, an outcome often underreported in previous studies. Therefore, this systematic review and meta-analysis aims to compare the efficacy and toxicity of meglumine antimoniate and miltefosine for the treatment of New World cutaneous leishmaniasis.

Methods

This systematic review was conducted in accordance with the protocols established by the Cochrane Collaboration and adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[18,19] The study protocol was preregistered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identification number CRD420251044262.

Eligibility criteria and study selection

The eligibility criteria were structured according to the PICOS framework: Population: patients with New World CL; Intervention: miltefosine; Comparison: meglumine antimoniate; Outcomes: cure rates at various follow-up points, treatment failure, and adverse events; Study type: Randomized Controlled Trials (RCTs).

Two reviewers (A.C.P.V. and F.C.L.) independently screened the articles for inclusion, resolving any discrepancies through consensus. Inclusion in this systematic review was restricted to studies that met all the following eligibility criteria: (1) RCTs; (2) In vivo studies; (3) Human studies; and (4) Direct comparisons of miltefosine and meglumine antimoniate for the treatment of New World CL. Exclusion criteria included: (1) Review articles, case reports, case series, observational studies and non-randomized clinical trials; (2) Studies that did not explicitly specify meglumine antimoniate as the pentavalent antimonial used; (3) Unpublished or incomplete clinical trials; (4) In vitro studies; (5) Studies that did not directly compare miltefosine to meglumine antimoniate; (6) Studies on old world cutaneous leishmaniasis; and (7) Duplicate publications.

Search strategy and data extraction

The authors systematically searched PubMed, Embase, Scopus and Cochrane Library databases, from inception to November 1, 2024. The search strategy used was (''Meglumine Antimoniate'' OR ''Glucantime'' OR ''N-Methylglucamine Antimonate'') AND (''Miltefosine'' OR ''hexadecylphosphocholine'' OR ''Impavido'' OR ''Miltex'') AND (''Cutaneous Leishmaniasis'' OR ''American cutaneous leishmaniasis'' OR ''tegumentary leishmaniasis'' OR CL OR ACL OR ''skin'' OR ''dermal leishmaniasis'').

Following the removal of duplicates, the titles and abstracts of the remaining studies were screened in Rayyan. The studies' titles and abstracts were reviewed based on eligibility criteria. Subsequently, selected papers underwent a thorough examination by full-text reading. These screening processes were carried out independently by two reviewers (A.C.P.V. and F.C.L.) to minimize bias. Disagreements were addressed through discussion and consensus by the two reviewers.

Two authors (A.C.P.V. and F.C.L.) independently extracted data to obtain the following information from each study: (1) Study characteristics: name of authors, year of publication, country of origin, parasite species, inclusion criteria, number of patients, age of patients, follow-up, interventions; (2) Outcomes: cure rates at 1-, 2-, 3-, 4-, 6-, and 12-months, cure failure at 6-months, cure rates at 2-, 3- and 6-months in *L.braziliensis* infections, vomiting, nausea, abdominal pain, and diarrhea, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), arthralgia, fever, and headache. Other adverse effects, such as cardiac and renal changes, were not evaluated due to insufficient data across the included studies to allow for statistical analysis. Discrepancies in data extraction were resolved by consensus.

Quality assessment

Two authors (A.C.P.V. and F.C.L.) assessed the quality of the included studies. As suggested by Cochrane, risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB-2).[20] Studies included in this meta-analysis were classified as having a low risk of bias and some concerns for risk of bias. In addition, the overall quality of evidence was assessed following the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines.[21] Studies were categorized as having very low, low, moderate, or high-quality evidence on the basis of considerations including risk of bias, inconsistency of results, imprecision, publication bias, and magnitude of treatment effects.

Statistical analysis

The statistical analysis was performed using *R* statistical software version 4.5.0 (R Foundation for Statistical Computing). The following packages were used: ''metaprop'', ''metafor, ''dmetar'', ''ggplot2'', and ''meta''. The outcomes were evaluated using proportions with 95% Confidence Intervals (95% CI). According to Cochrane's recommendations, a random-effects model was used for all outcomes, accounting for variability between studies. The Cochrane *Q* test and I2 statistics were performed to quantify heterogeneity. Endpoints were considered to have low heterogeneity if I^2 < 25%. To minimize heterogeneity and detect outliers, sensitivity analysis using ''leave-one-out'' was conducted. Additionally, Baujat plots were generated for outcomes presenting moderate to high heterogeneity (I^2 > 25%) to identify studies contributing most to heterogeneity and influence.

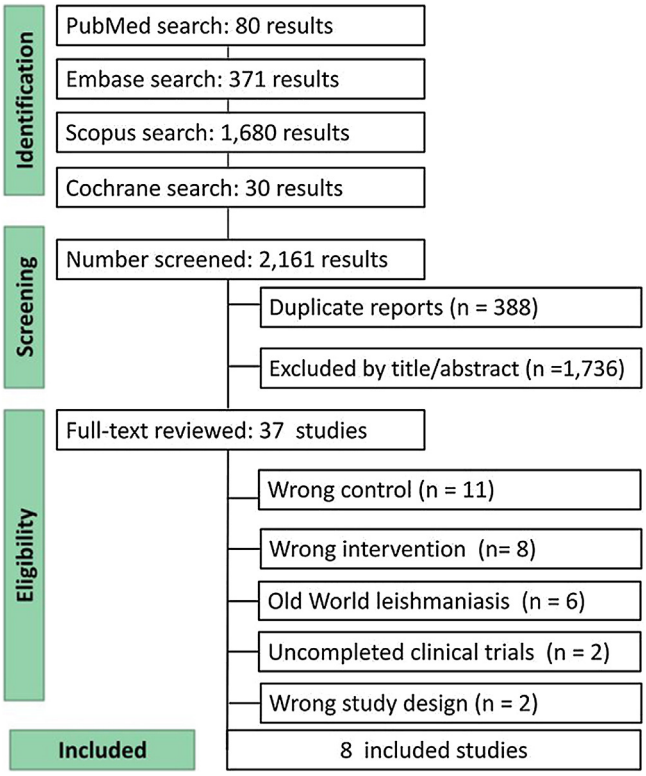


Fig. 1 PRISMA search flow diagram.

Results

Selection of studies

As depicted in Fig. 1, this search identified 2.161 results: 80 from PubMed, 371 from Embase, 1,680 from Scopus, and 30 from Cochrane Library. Of these, 388 were identified as duplicates, and 1,736 were excluded based on their title and/or abstract for not meeting the inclusion criteria. Subsequently, 37 studies underwent full-text review, of which 8 RCTs met the eligibility criteria and were included in this systematic review. A total of 898 patients were included, with 396 receiving meglumine antimoniate and 502 receiving miltefosine.[22–29]

Pooled analysis of all studies

The present analysis included eight RCTs evaluating the efficacy of meglumine antimoniate and miltefosine for the treatment of CL. Participants were aged 0 to 65 years, and all had confirmed diagnoses of CL. The most frequently identified parasite species was *L. braziliensis*. Follow-up periods ranged from 1 to 12 months, with most studies reporting outcomes at 3 and 6 months post-treatment.[22–29] Study characteristics are detailed in Table 1.[22–29]

Efficacy outcomes over time

Regarding efficacy outcomes, no significant difference was observed between the groups in cure rates at 1-month (RR = 1.20; 95% CI: 0.86, 1.69; p = 0.283; I^2 = 77.3%; Supplemental Fig. S1). This meta-analysis included two studies with a total of 144 patients (73 treated with miltefosine and 44 treated with meglumine antimoniate).[22,28] While one study demonstrated a significant benefit with miltefosine (RR = 1.41; 95% CI: 1.17, 1.71),[28] the overall effect was not statistically significant due to considerable heterogeneity (Chi^2 = 4.40; p = 0.0359). Baujat plot analysis is available in the Supplemental Material (Supplemental Fig. S2). The certainty of evidence for this outcome was very low due to inconsistency and serious imprecision (Fig. 2).

This trend shifted notably at 2-months, when miltefosine demonstrated a statistically significant higher cure rate compared to meglumine antimoniate (RR = 0.83; 95% CI: 0.71, 0.98; p = 0.024; I^2 = 0%; Fig. 3A). Based on two studies encompassing 161 patients (105 treated with miltefosine and 56 with meglumine antimoniate),[23,27] this effect was consistent across trials, with no indication of heterogeneity (Chi^2 = 1.60; p = 0.6596), reinforcing the robustness of the finding. Consistent results across studies and narrow confidence intervals supported a high certainty rating for this outcome (Fig. 2).

By 3-months, miltefosine continued to show a numerical advantage, although the difference did not reach statistical significance (RR = 0.89; 95% CI: 0.67, 1.19; p = 0.443; I^2 = 79.9%; Fig. 3B). This analysis included four studies with a total of 345 patients, of whom 155 received miltefosine and 134 received meglumine antimoniate.[24,25,27,29] Leave-one-out sensitivity analyses demonstrated minimal changes in the pooled effect size. Heterogeneity decreased the most when Machado et al. 2021 was excluded (I^2 = 57%).[26] Baujat plot analysis indicated that Velez et al. 2010 contributed most to both heterogeneity and influence on the overall effect estimate, followed by Machado et al. 2021 (Supplemental Figs. S3–S4).[24,29] The certainty of evidence was rated moderate due to imprecision and inconsistency (Fig. 2).

At 4-months, cure rates remained comparable between groups (RR = 0.95; 95% CI: 0.79, 1.13; p = 0.553; I^2 = 12.5%; Supplemental Fig. S5). This analysis included two studies with a total of 155 patients, 101 treated with miltefosine and 54 with meglumine antimoniate. Both studies reported consistent results, and heterogeneity was low (Chi^2 = 1.14; p = 0.2851).[22,27] Despite low heterogeneity, the confidence interval crossed the line of no effect, leading to a moderate certainty rating with one downgrade for imprecision (Fig. 2).

At 6-months, no significant difference was found in long-term cure rates, although it slightly favored miltefosine (RR = 0.89; 95% CI: 0.74, 1.06; p = 0.179; I^2 = 73%; Fig. 3C). This analysis included eight studies comprising 898 patients, with 502 treated with miltefosine and 396 with meglumine antimoniate.[22–29] Leave-one-out analyses revealed moderate variability in effect estimates (RR range: 0.81 to 1.03). The exclusion of Velez et al. 2010 reduced heterogeneity, although the overall interpretation remained unchanged. Baujat plot analysis again identified Velez et al. 2010 as having the highest contribution to both heterogeneity and influence on the overall pooled effect, followed by Machado et al. 2021 (Supplemental Figs. S6–S7).[24,29] Despite these influences, the overall result was stable. The certainty of evidence was low (Fig. 2).

At 12-months, no statistically significant difference in cure rates was observed between treatments (RR = 0.95; 95% CI: 0.71, 1.29; p = 0.755; I^2 = 59.9%; Supplemental Fig.

Table 1 Baseline characteristics of the included studies.

Study, year	Study Design	Parasite Species	Inclusion Criteria	Nº of Patients MF/MA	Age Range (years)	Follow - Up	Interventions
Chrusciak Talhari et al. 2011[22]	RCT	*L. guyanensis* *L. braziliensis* *L. lainsoni*	1–5 lesions, 1 ulcerated, < 3-months, Leishmania amastigotes in biopsy, no prior treatment	56 / 28	2 – 65	6 and 12 mo	MA: IV 20 mg (13–65 yrs) or 15 mg (2–12 yrs) for 20 days (max 3 ampoules/day). MF: Oral 2.5 mg/kg daily for 28 days
Machado et al. 2010[23]	RCT	*L. braziliensis*	Typical ulcer, positive Montenegro test, in endemic area; age 2–65; up to 5 ulcers, 2 regions; 10–50 mm; < 90 days since first ulcer.	60 / 30	4 – 65	2 w, 1, 2, 4 and 6 mo	MA: IV 20 mg SbV/kg/day for 20 days (max 3 ampoules or 1,215 mg SbV/day). MF: Oral 2.5 mg/kg BW (max150 mg) daily for 28 days
Machado et al. 2021[24]	RCT	*L. braziliensis*	Age 18–65, 1–3 ulcers (10–50 mm), < 90 days since onset.	47 / 45	4 – 65	2 and 6 mo	MA: IV 20 mg SbV/kg/day for 20 days. MF: Oral 2.5 mg/kg BW (max150 mg) daily for 28 days + Placebo
Mendes et al. 2020[25]	RCT	*L. guyanensis* *L. braziliensis* *L. naifi*	Age 18–65 years, 1–5 ulcers (10–50 mm), illness duration 30–90 days, no prior treatment.	50 / 50	27 – 50	2, 3 and 6 mo	MA: IV 20 mg SbV/kg/day for 20 days. MF: Oral 2.5 mg/kg BW (max150 mg) daily for 28 days + Placebo
Rubiano et al. 2012[26]	RCT	*L. panamensis/ guyanensis*	Parasitologically confirmed CL	58 / 58	2 – 12	6 mo	MA: (81 mg Sb/mL) 20 mg Sb/kg/ day IM for 20 days. MF: 10 mg/capsule, 1.5–2.5 mg/kg/ day orally for 28 days, divided into 2–3 doses
Soto et al. 2007[27]	RCT	*L. braziliensis*	NA	45 / 26	NA	2,4 and 6 mo	MA: IM for 28 days MF: Oral for 28 days
Soto et al. 2008[28]	RCT	*L. braziliensis*	*Leishmania*-positive ulcer (Giemsa), 12+, no ML, no treatment in 6-months, no significant comorbidities	41 / 16	≥12	1, 3, 6 and 12 mo	MA: IM 20 mg/kg/d for 20 days. MF: Oral 2.5 mg/kg/d for 28 days
Vélez et al. 2010[29]	RCT	*L. (V.) panamensis* / *braziliensis*	Confirmed leishmaniasis; no treatment in 6-weeks; normal renal, hepatic, and hematological functions.	145 / 143	19 – 38	6 mo	MA: IM 20 mg/kg/day for 20 days MF: 50 mg capsule was taken 3 times a day for 28 days

RCT, Randomized Controlled Trial; NA; Not Available; CL, Cutaneous Leishmaniasis; ML, Mucosal Leishmaniasis; MA, Meglumine Antimoniate; MF, Miltefosine; ± mean or median; IV, Intravenous; IM, Intramuscular.

Author(s):
Question: Meglumine Antimoniate compared to Miltefosine for New World Cutaneous Leishmaniasis
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meglumine Antimoniate	Miltefosine	Relative (95% CI)	Absolute (95% CI)		
Cure Rate (follow-up: 1 months)												
2	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	37/44 (84.1%)	73/100 (73.0%)	**RR 1.20** (0.86 to 1.69)	**146 more per 1,000** (from 102 fewer to 504 more)	⨁◯◯◯ Very low[a,b]	IMPORTANT
Cure Rate (follow-up: 2 months)												
4	randomised trials	not serious	not serious	not serious	not serious	none	80/134 (59.7%)	155/211 (73.5%)	**RR 0.83** (0.71 to 0.98)	**125 fewer per 1,000** (from 213 fewer to 15 fewer)	⨁⨁⨁⨁ High	IMPORTANT
Cure Rate (follow-up: 3 months)												
4	randomised trials	not serious	not serious	not serious	serious[c]	none	174/254 (68.5%)	207/285 (72.6%)	**RR 0.89** (0.67 to 1.19)	**80 fewer per 1,000** (from 240 fewer to 138 more)	⨁⨁⨁◯ Moderate[c]	IMPORTANT
Cure Rate (follow-up: 4 months)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	39/54 (72.2%)	80/101 (79.2%)	**RR 0.79** (0.66 to 0.95)	**166 fewer per 1,000** (from 269 fewer to 40 fewer)	⨁⨁⨁◯ Moderate[d]	IMPORTANT
Cure Rate (follow-up: 6 months)												
8	randomised trials	not serious	serious[e]	not serious	serious[b]	none	257/396 (64.9%)	360/502 (71.7%)	**RR 0.89** (0.74 to 1.06)	**79 fewer per 1,000** (from 186 fewer to 43 more)	⨁⨁◯◯ Low[b,e]	CRITICAL
Cure Rate (follow-up: 12 months)												
2	randomised trials	not serious	serious[b]	not serious	serious[a]	none	32/45 (71.1%)	77/97 (79.4%)	**RR 0.95** (0.71 to 1.29)	**40 fewer per 1,000** (from 230 fewer to 230 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
Cure Rate L. braziliensis (follow-up: 6 months)												
5	randomised trials	not serious	serious[e]	not serious	serious[b]	none	108/169 (63.9%)	179/244 (73.4%)	**RR 0.93** (0.71 to 1.23)	**51 fewer per 1,000** (from 213 fewer to 169 more)	⨁⨁◯◯ Low[b,e]	CRITICAL
Cure Failure (follow-up: 6 months)												
5	randomised trials	not serious	serious[e]	not serious	very serious[b]	none	64/275 (23.3%)	85/360 (23.6%)	**RR 1.23** (0.63 to 2.40)	**54 more per 1,000** (from 87 fewer to 331 more)	⨁◯◯◯ Very low[b,e]	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. High heterogeneity across the included studies
b. This decision was based on the wide confidence intervals observed, which included both potential benefit and harm.
c. Downgraded one level for imprecision due to a confidence interval that includes the null effect and fails to confirm a definitive clinical benefit
d. Downgraded one level for imprecision due to a confidence interval that includes both potential benefit and harm, with no statistically significant difference between groups
e. Moderate heterogeneity was observed across the included studies

Fig. 2 GRADE assessment – efficacy outcomes.

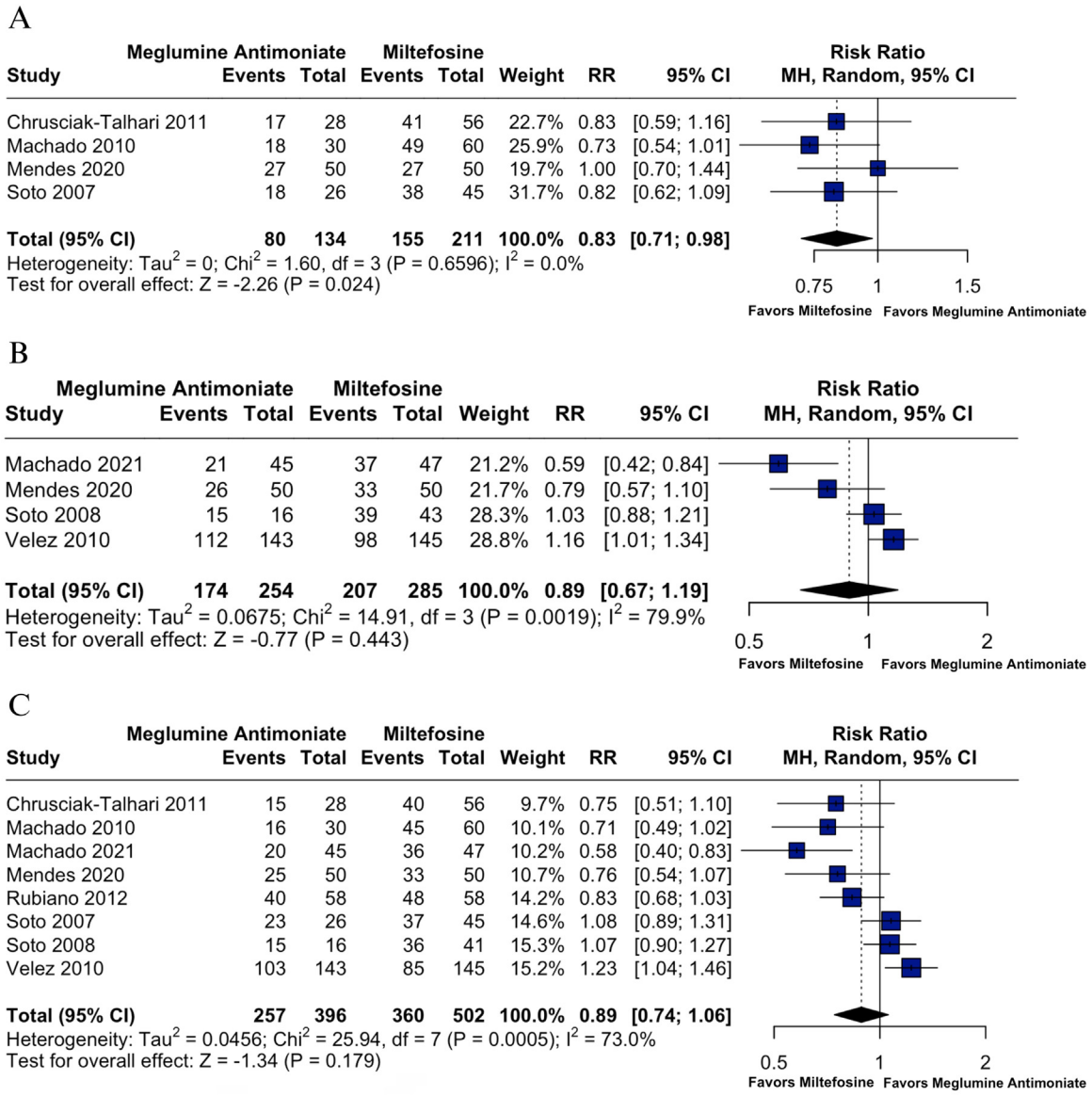


Fig. 3 (A) Cure rates at 2-months post-treatment. (B) Cure rates at 3-months post-treatment. (C) Cure rates at 6-months post-treatment.

S8). This analysis was based on two studies, including 142 patients, with 97 treated with miltefosine and 45 with meglumine antimoniate.[22,28] Baujat plot analysis is available in the supplemental material (Supplemental Fig. S9). The certainty of evidence was low, due to the wide confidence intervals observed and the heterogeneity observed across the included studies (Fig. 2).

Leishmania braziliensis

To further investigate potential subgroup differences, efficacy at 2-, 3-, and 6-months was also assessed specifically in patients infected with *L. braziliensis*.

At 2-months, miltefosine demonstrated significantly higher cure rates compared to meglumine antimoniate (RR = 0.78; 95% CI: 0.63, 0.96; p = 0.022; I^2 = 0%; Fig. 4A), with consistent findings across studies and no heterogeneity. This analysis was based on two studies encompassing 161 patients (105 treated with miltefosine and 56 with meglumine antimoniate).[23,27]

At 3-months, no statistically significant difference was found (RR = 0.80; 95% CI: 0.46, 1.38; p = 0.421; I^2 = 87.8%; Fig. 4B). This analysis included two studies with a total of 151 patients, 90 treated with miltefosine and 61 with meglumine antimoniate.[24,28] Baujat analysis indicated inconsistency mainly due to Machado et al. 2021 (Supplemental Fig. S10).[24]

At 6-months, no statistically significant difference in cure rates was observed between miltefosine and meglumine antimoniate (RR = 0.93; 95% CI: 0.71, 1.23; p = 0.608; I^2 = 74.7%; Fig. 4C). This analysis included five studies comprising 413 patients, with 244 treated with miltefosine and 169 with meglumine antimoniate.[23,24,27–29] Leave-one-out sensitivity analysis showed that heterogeneity decreased most when Machado et al. 2021 was excluded (I^2 = 52.7%), suggest-

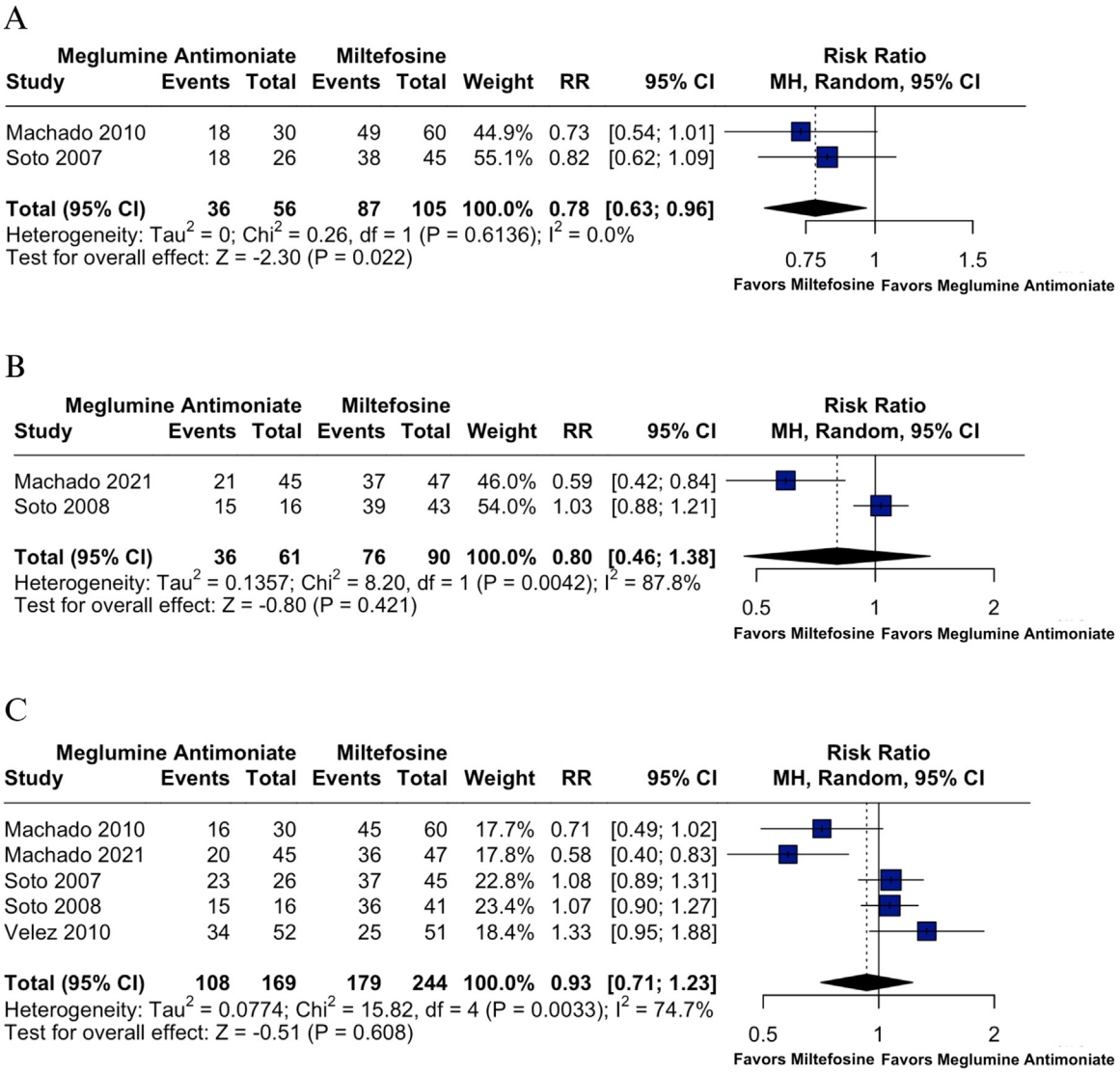


Fig. 4 (A) Cure rates at 2-months post-treatment in *L. braziliensis* infections. (B) Cure rates at 3-months post-treatment in *L. braziliensis* infections. (C) Cure rates at 6-months post-treatment in *L. braziliensis* infections.

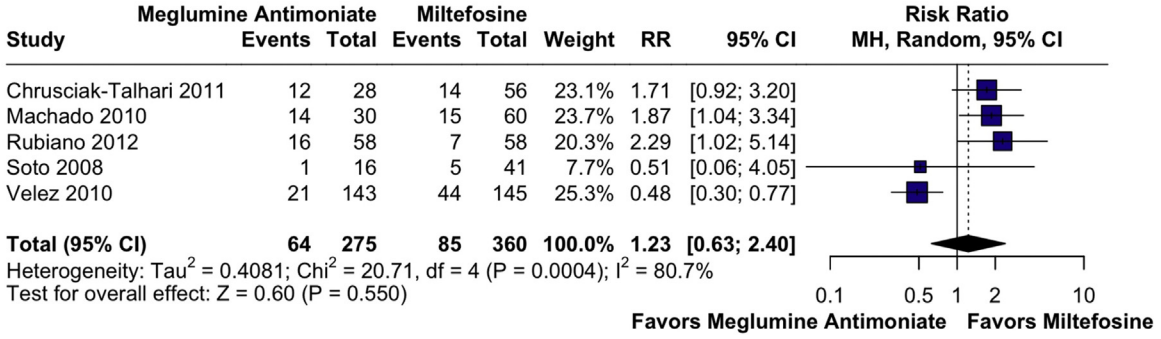


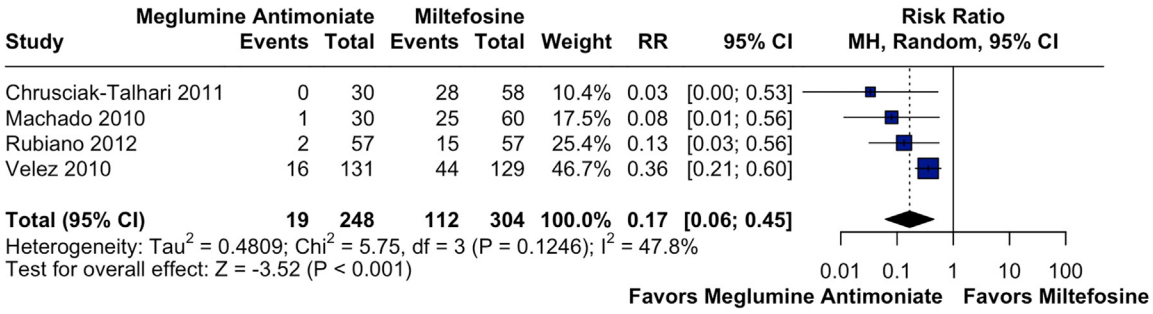
Fig. 5 Cure failure at 6-months.

ing it contributed notably to heterogeneity. Consistently, the Baujat plot indicated that Machado et al. 2021 and Velez et al. 2010 were the main contributors to both heterogeneity and influence on the pooled result (Supplemental Figs. S11–S12).[24,29]

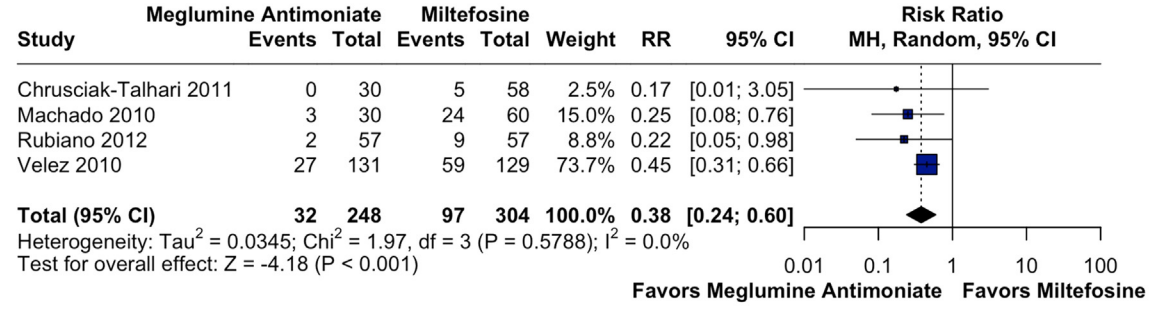
Cure failure at 6-months

Cure failure at 6-months was also evaluated as a complementary efficacy outcome. In the pooled analysis, no statistically significant difference was found between milte-

A



B



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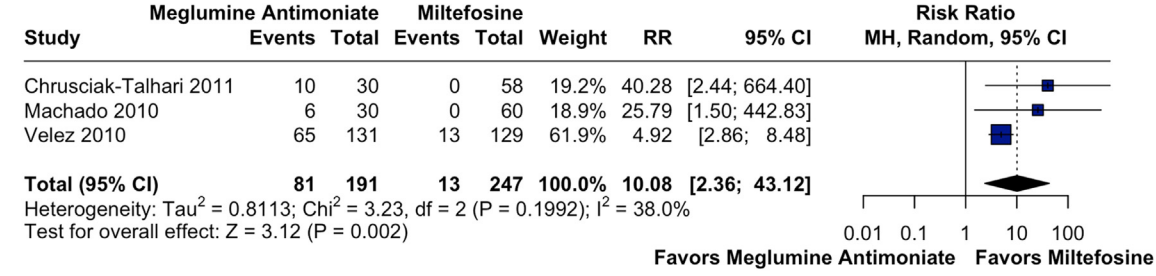

Fig. 6 (A) Vomiting. (B) Nausea. (C) Arthralgia.

fosine and meglumine antimoniate (RR = 1.23; 95% CI: 0.63, 2.40; p = 0.550; I^2 = 80.7%; Fig. 5). This analysis included five studies encompassing 635 patients, with 360 treated with miltefosine and 275 with meglumine antimoniate.[22,23,26,28,29] Leave-one-out analysis confirmed the instability of the pooled estimate, with only the removal of Velez et al. 2010 markedly reducing heterogeneity (I^2 = 0%) and shifting the result in favor of meglumine antimoniate (RR = 1.81; 95% CI: 1.25, 2.63), suggesting this study substantially influenced the overall effect. Baujat plot analysis again identified Velez et al. 2010 as having the highest contribution to both heterogeneity and influence on the overall pooled effect (Supplemental Figs. S13–S14).[29] The certainty of evidence was very low (Fig. 2).

Safety outcomes

Gastrointestinal adverse events were consistently more frequent in the miltefosine group. Vomiting and nausea were assessed in four studies involving 552 patients, showing significantly lower risks with meglumine antimoniate: vomiting (RR = 0.17; 95% CI: 0.06–0.45; p < 0.001; I^2 = 47.8%; Fig. 6A) and nausea (RR = 0.38; 95% CI: 0.24–0.60; p < 0.001; I^2 = 0%; Fig. 6B).[22,23,26,29] Abdominal pain was evaluated in three studies including 464 patients, and also occurred significantly less often with meglumine antimoniate (RR = 0.33; 95% CI: 0.13–0.86; p = 0.023; I^2 = 23.8%; Supplemental Fig. S15).[23,26,29] Diarrhea was assessed in four studies with 552 patients, and although more frequent with miltefosine, the difference was not statistically significant (RR = 0.43; 95% CI: 0.18–1.07; p = 0.070; I^2 = 0%; Supplemental Fig. S16).[22,23,26,29] The certainty of evidence for vomiting was rated moderate due to inconsistency (Supplemental Fig. S17).

In contrast, hepatic adverse events were more common with meglumine antimoniate, with significantly higher rates of ALT (RR = 2.31; 95% CI: 1.24–4.29; p = 0.008; I^2 = 0%; Supplemental Fig. S18) and AST elevation (RR = 2.77; 95% CI:

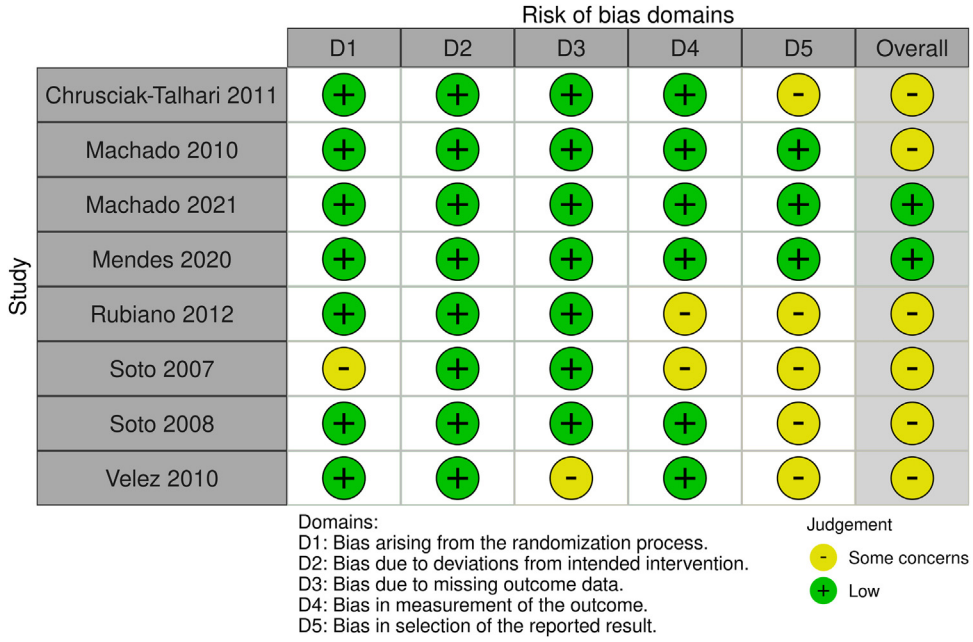

Fig. 7 Risk of bias assessment of the included randomized controlled.

1.39–5.52; p = 0.004; I^2 = 0%; Supplemental Fig. S19), favoring miltefosine. These findings were based on two studies including 374 patients, with 186 treated with miltefosine and 188 with meglumine antimoniate.[26,29]

Similarly, musculoskeletal and systemic symptoms were also more frequent with meglumine antimoniate. Arthralgia was assessed in three studies involving 438 patients and occurred significantly less often in the miltefosine group (RR = 10.08; 95% CI: 2.36–43.12; p = 0.002; I^2 = 38.0%; Fig. 6C).[22,23,29] Fever was evaluated in three studies, including 464 patients and also showed a significantly lower risk with miltefosine (RR = 2.98; 95% CI: 1.53–5.80; p = 0.001; I^2 = 37.3%; Supplemental Fig. S20).[23,26,29] Headache was assessed in two studies with a total of 204 patients and showed a non-significant trend in the same direction (RR = 1.57; 95% CI: 0.94–2.63; p = 0.086; I^2 = 0%; Supplemental Fig. S21).[23,26] Arthralgia and fever were both rated as high certainty of evidence (Supplemental Fig. S17).

Leave-one-out and Baujat sensitivity analyses for vomiting, arthralgia, and fever are presented in the Supplemental material (Supplemental Figs. S22–S27).

Quality and evidence assessment

The individual appraisals of RCTs using the RoB-2 tool are illustrated in Fig. 7. Overall, most studies were rated as having ''some concerns'', primarily due to bias in the selection of the reported result, as the majority of studies did not provide a trial protocol or statistical analysis plan.

Discussion

This meta-analysis compared the efficacy and toxicity of meglumine antimoniate and miltefosine for CL, including 903 patients. The main findings were: (1) Miltefosine demonstrated superior cure rates at 2-months, with consistent effects across studies and high certainty of evidence; (2) No statistically significant difference was found at 1-, 3-, 4-, 6- or 12-months, although miltefosine showed a slight numerical advantage at 3- and 6-months; (3) In patients infected with *L. braziliensis*, miltefosine showed significantly higher cure rates at 2-months. However, no significant differences were observed at 3- or 6-months; (4) Miltefosine was associated with more gastrointestinal adverse events (e.g., nausea, vomiting), whereas meglumine antimoniate had higher rates of hepatic enzyme elevations, arthralgia, and fever. These findings suggest that while miltefosine offers some efficacy advantages and fewer systemic side effects, its gastrointestinal toxicity and potential for relapse should be carefully considered.

To contextualize these findings, it is important to review the therapeutic context. Miltefosine is recommended in endemic areas where injectable alternatives, such as pentavalent antimonials, liposomal amphotericin B, and paromomycin, present limitations. Despite its demonstrated efficacy, miltefosine has notable contraindications, including strict avoidance during pregnancy due to teratogenicity and its prolonged persistence in the body. It is also contraindicated in patients with severe renal or hepatic impairment.[30,31]

Similarly, meglumine antimoniate requires careful consideration. Typically administered intravenously or intramuscularly over a similar treatment period to miltefosine, it demands cautious use in patients with preexisting cardiac, hepatic, or renal conditions because of risks such as antimony intolerance and arrhythmias. Like miltefosine, its use is contraindicated during pregnancy, and caution is recommended during breastfeeding despite limited clinical data.[32]

The pooled results showed superior early efficacy of miltefosine, particularly at the 2-month follow-up, aligning with findings from previous RCTs.In one study, 81.7% of

patients receiving miltefosine achieved lesion cure at two months, compared to 60% in the meglumine antimoniate group.[23] Similarly, another RCT reported apparent cure rates of 73.2% for miltefosine versus 60.7% for meglumine antimoniate at the same time point.[22] These findings underscore miltefosine's advantage in promoting a faster therapeutic response compared to traditional antimonial therapies.

However, while miltefosine demonstrates early efficacy benefits, differences in cure rates between miltefosine and meglumine antimoniate tend to diminish over time. No statistically significant differences were observed at 3-, 4-, 6-, or 12-months post-treatment, although miltefosine consistently maintained a slight numerical advantage at 3- and 6-months. Supporting these observations, a study on both Old World and New World CL by Iranpour et al. found that miltefosine was more effective than meglumine antimoniate at the 3-month follow-up, particularly when a high-weight study was excluded in sensitivity analyses. By the 6-month follow-up, pooled analyses revealed no significant difference in efficacy between the two treatments.[14]

In *L. braziliensis* infections, miltefosine achieved significantly higher cure rates at 2-months, but this advantage was not maintained at later follow-ups. Although miltefosine promotes faster initial healing, its long-term effectiveness appears comparable to that of meglumine antimoniate. Similar findings were reported by Soto et al. in 2007, who also evaluated *L. braziliensis* infections. In their study, miltefosine achieved higher cure rates than meglumine antimoniate at 2-months. By 4- and 6-months, however, the cure rates between the two treatments became comparable, with meglumine antimoniate slightly surpassing miltefosine at later time points.[28] This pattern further supports the observation that miltefosine's early benefit diminishes over time.

Although 2-month cure rates were reported in clinical trials, they reflect early treatment response rather than definitive cure. Olliaro et al., in a methodological guide for clinical trials in cutaneous leishmaniasis, propose a standardized framework in which outcomes are assessed at three key time points: 6–9 weeks for initial response, 3-months for initial cure, and 6–12 months for definitive cure, the latter being crucial to capture late relapses and ensure long-term efficacy.[33] Complementing this, the World Health Organization considers the absence of clinical relapse at 6-months a reliable indicator of sustained cure, as relapses may occur several months after initial lesion healing.[34] Therefore, while 2-month cure rates provide clinically relevant information on early lesion resolution, they should not be interpreted as definitive evidence of parasitological cure. Longer follow-up, preferably up to 6- or 12-months, is essential for reliable efficacy assessment.[34]

In terms of failure rates, this analysis showed no statistically significant difference in cure failure at 6-months. However, the analysis revealed considerable heterogeneity and sensitivity of the pooled estimate, largely driven by the influence of a single study. When this study was excluded in sensitivity analysis, the results shifted in favor of meglumine antimoniate, suggesting that the long-term efficacy of miltefosine may be less consistent in certain settings. Similar concerns have been raised in previous studies. One pilot study reported that although all patients showed initial clinical improvement after a 28-day course of miltefosine, only 48.7% achieved complete cure at 6-months, with a relapse rate of 32.3%.[35] These findings align with the trend observed in the meta-analysis, highlighting potential limitations of miltefosine in sustaining long-term outcomes despite its early efficacy. Nonetheless, other studies have reported contrasting results. A separate cohort study found that pentavalent antimonials were associated with higher relapse rates than miltefosine.[36] These discrepancies emphasize the need for further high-quality studies to better understand factors affecting long-term treatment success and relapse.

Safety profiles also differed between treatments. Meglumine antimoniate was associated with a higher incidence of systemic and musculoskeletal adverse events, including significantly increased rates of arthralgia and fever, both supported by high-certainty evidence, as well as elevations in hepatic enzymes (ALT and AST). Similarly, studies on systemic meglumine antimoniate treatment have highlighted its broad spectrum of side effects, ranging from mild symptoms, such as muscle and joint pain, gastrointestinal disturbances, fatigue, fever, and skin reactions, to severe, life-threatening complications like cardiovascular abnormalities and liver or pancreatic dysfunction.[2,37] The present study also found that miltefosine was linked to a higher incidence of gastrointestinal issues, particularly nausea and vomiting, consistent with a meta-analysis on interventions for CL and mucocutaneous leishmaniasis, which reported higher rates of nausea and vomiting with miltefosine compared to meglumine antimoniate.[16]

Beyond efficacy and safety, cost and accessibility are also critical considerations. A recent study compared the costs of meglumine antimoniate and miltefosine with caregiver directly observed therapy. It found miltefosine more cost-effective for patients and society due to lower travel and lodging costs compared to meglumine antimoniate. The study concluded that miltefosine is cost-saving for patients and society, with a minimal increase in government expenses.[38] Given miltefosine's early efficacy and safety, these cost benefits make a strong case for its wider use, especially in resource-limited areas where access to treatment is a challenge.

This meta-analysis has several important strengths. It includes eight RCTs conducted across diverse regions in Latin America, focusing exclusively on New World cutaneous leishmaniasis to ensure geographic and clinical relevance. The methodology adhered strictly to PRISMA guidelines, ensuring a transparent and rigorous selection and appraisal process. Risk of bias was systematically evaluated using the Cochrane RoB-2 tool, and the certainty of evidence was assessed with the GRADE approach. To address variability and strengthen the robustness of findings, leave-one-out sensitivity analyses and Baujat plots were employed to identify sources of heterogeneity and assess the influence of individual studies.

Nonetheless, some limitations should be considered. High heterogeneity was observed in certain outcomes, which may reduce the precision and generalizability of pooled estimates. Several studies had relatively short follow-up periods, potentially underestimating late relapses or long-term adverse effects. In addition, small sample sizes in some comparisons limited the power to detect rare adverse events and may have contributed to imprecision in safety outcomes. Finally, despite these efforts to standardize data collection, variations in treatment protocols, patient popu-

lations, and outcome definitions across studies could have influenced the results.

Notwithstanding these challenges, this systematic review and meta-analysis offer a comprehensive overview of the most robust evidence regarding the efficacy and safety of miltefosine compared to meglumine antimoniate for the treatment of CL in the New World.

Conclusion

This systematic review and meta-analysis demonstrate that miltefosine offers superior early treatment response compared to meglumine antimoniate for ACL, particularly at two months. However, this advantage diminishes over time, with cure rates becoming comparable at later follow-ups. Miltefosine was linked to more gastrointestinal side effects, while meglumine antimoniate had a higher risk of hepatic and systemic adverse events. The certainty of evidence, as assessed by GRADE, ranged from high for early efficacy and certain safety outcomes to very low for long-term efficacy and cure failure, primarily due to inconsistency and imprecision across studies. This variability limits confidence in sustained treatment effects over time. Considering its early efficacy, safety profile, and cost-effectiveness, miltefosine remains a valuable treatment option, particularly in resource-limited settings where oral administration is advantageous. Nonetheless, the inconsistent durability of cure and limited long-term data highlight the need for further high-quality studies with extended follow-up.

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Authors' contributions

Ana Carolina Putini Vieira: The study concept and design; critical review of literature; data collection, analysis and interpretation; preparation and writing of the manuscript; final approval of the final version of the manuscript.

Fernanda Cronemberger Lins: Critical review of literature; data collection, analysis and interpretation; preparation and writing of the manuscript; final approval of the final version of the manuscript.

Arianne Costa Baquião: The study concept and design; preparation and writing of the manuscript; effective participation in research orientation; manuscript critical review; 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.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.abd.2025.501253.

Editor

Luciana P. Fernandes Abbade.

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ORIGINAL ARTICLE

Diagnostic value of direct immunofluorescence in oral mucous membrane pemphigoid: a retrospective study☆

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Abstract

Background: Mucous membrane pemphigoid (MMP) is an autoimmune blistering disease with heterogeneous clinical manifestations that is hard to diagnose. Direct immunofluorescence (DIF) is critical, but its role in multimodal frameworks is unclear.

Objective: To assess DIF's diagnostic performance in MMP and explore factors affecting its positivity patterns in multimodal workflows.

Methods: We retrospectively analyzed 79 suspected MMP patients, categorizing them into confirmed and non-confirmed groups based on clinical, histopathological, and serological criteria. DIF of perilesional mucosal biopsies showed linear deposits of IgG, IgA, IgM, C3, and fibrinogen along the basement membrane zone (BMZ). Diagnostic efficacy was assessed via ROC curve analysis.

Results: 55 cases were confirmed. Histopathology demonstrated subepithelial blisters in 51, with 100% specificity, 92.73% sensitivity (AUC = 0.964, $p < 0.05$). DIF identified 47 cases, with C3 (63.64%) and IgG (60.00%) most common, showing 85.45% sensitivity, 100% specificity, and 97.87% concordance with histopathology. Disease duration independently predicted positive IgM ($p = 0.023$).

Study limitations: This study is a single-center retrospective study with a limited sample size, which has certain limitations.

☆ Study conducted at the Peking University Hospital of Stomatology, Beijing, China.

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Conclusion: DIF, 100% specific, aids histopathology in MMP diagnosis, especially with C3/IgG linear BMZ deposition. Notably, IgM positivity correlates with prolonged disease duration, suggesting DIF efficiency may link to disease stage.

Introduction

Mucous membrane pemphigoid (MMP), a chronic autoimmune blistering disease targeting the basement membrane zone (BMZ), poses significant diagnostic challenges due to its heterogeneous clinical presentations and overlapping features with other mucocutaneous disorders.[1–3] While oral mucosa involvement occurs in 85% of cases, extramucosal manifestations (e.g., ocular, cutaneous) often emerge later, complicating early diagnosis.[4–6] Current diagnostic criteria emphasize a multimodal approach integrating clinical, histopathological, and immunological evidence.[7–10]

Histopathology remains the cornerstone of MMP diagnosis, revealing subepithelial clefting and inflammatory infiltrates at the BMZ.[6] However, up to 30% of early-stage lesions may lack overt blistering, reducing its sensitivity.[11] Direct Immunofluorescence (DIF) remains the gold standard for confirming MMP by detecting linear deposits of IgG, C3, IgA, or fibrinogen along the BMZ.[12–14] Recent meta-analyses report pooled DIF sensitivity of 73%–89% in perilesional biopsies,[15,16] with C3 and IgG exhibiting the highest positivity rates.[17]

Despite its diagnostic utility, DIF interpretation is confounded by several factors. Pre-biopsy pharmacotherapy (e.g., corticosteroids) may reduce immunoreactant deposition,[18] while disease activity and sampling site variability (e.g., lesional vs. perilesional mucosa) impact positivity rates.[19,20] Debate continues over the optimal biopsy site, with some studies favoring non-lesional mucosa,[21] and others supporting lesional tissue.[22]

Serological tests for anti-BP180/BP230 using ELISA show high specificity (>90%) but low sensitivity (<50%) in MMP,[23] limiting their use as a standalone tool,[24] Recent guidelines thus recommend combined algorithms integrating DIF, histopathology, and serology to improve diagnostic accuracy.[6,25]

This study addresses critical gaps in MMP diagnostics by: 1) Systematically evaluating DIF's performance within a multimodal framework; 2) Quantifying the impact of pre-biopsy pharmacotherapy and disease activity on DIF positivity; 3) Proposing a standardized diagnostic algorithm to optimize DIF utility in clinical practice.

Methods

Participants

A total of 79 patients with suspected Mucous Membrane Pemphigoid (MMP), who had undergone Direct Immunofluorescence (DIF) testing at the Department of Oral Pathology at Peking University Hospital of Stomatology between January 2023 and December 2024, were retrospectively enrolled in this study. Inclusion criteria: 1) Clinical manifestations suggestive of MMP (e.g., oral mucosal blisters/erosions); 2) Availability of complete clinical, histopathological, and DIF data. Exclusion criteria: 1) Incomplete medical records; 2) Combining with other oral mucosal diseases. For patients with multiple visits, only the first-visit data were analyzed. Control samples (n = 24) derived from patients initially suspected of MMP but excluded after comprehensive evaluation as follows. Biopsies were obtained from perilesional oral mucosa using the same protocol as confirmed cases.

Diagnostic criteria

1 Clinical manifestations suspicious of MMP: Oral mucous membranes often present with blisters and erosions, most commonly involving the gingiva and palatal mucosa. Gingival lesions are often described as desquamative gingivitis. In addition, the lesions can involve the conjunctiva, pharynx, reproductive system, and skin, presenting with erythema, blisters, and scars.
2 Positive microscopic findings: Histopathological images show subepithelial splitting, accompanied by a non-specific mixed infiltration composed of lymphocytes, histiocytes, plasma cells, neutrophils, and eosinophils.
3 Positive serological antibody test: Positive for BP180/BP230 detected by ELISA.

According to the S3 guidelines for MMP diagnosis,[6] antibody testing should be performed for individuals with clinical manifestations suspicious of MMP. Those with positive serological antibodies are classified into the confirmed MMP group. For individuals with negative serological examination results, if the microscopic findings are positive, they are classified into the confirmed group; otherwise, they are classified into the unconfirmed group.

Specimen processing

Biopsy samples were submitted to the in-house pathology laboratory, embedded in OCT compound, and snap-frozen. Serial 5 μm-thick cryosections were cut using a cryostat. One section was stained with H&E for histopathological confirmation of the presence of epithelial lesions. Consecutive sections from confirmed cases were used for DIF analysis.

DIF

Primary antibodies against IgG, IgM, IgA, fibrinogen (F), and C3 (all purchased from commercial sources, dilution according to manufacturer's instructions) were applied to

separate sections. After incubation at 37 °C for 30 minutes, unbound antibodies were removed with three PBS washes. Fluorescein Isothiocyanate (FITC)-conjugated secondary antibodies were then applied, and sections were incubated in the dark at 37 °C for another 30-minutes. Following final PBS washes, sections were mounted with antifade mounting medium and visualized under a fluorescence microscope.

DIF results were interpreted by two experienced pathologists blinded to clinical data, following established criteria:

Positive DIF: Autoantibodies (IgG, complement component C3, IgM, IgA, and fibrinogen) linearly deposit along the BMZ, visualized as continuous linear green fluorescence.

Negative DIF: Absence of linear BMZ fluorescence.

Non-specific coloring: DIF revealed discontinuous punctate/granular or focal continuous linear green fluorescence along the basement membrane zone.

ELISA detection

Serum samples were collected at the time of biopsy. Anti-BP180 (NC16A domain) and anti-BP230 antibodies were quantified using ELISA kits (MBL International) following the manufacturer instructions. A threshold of $\geq$20 U/mL was defined as positive.

Diagnostic efficiency metrics

1 Sensitivity = (Number of true positives by the diagnostic method / Number of gold standard positives) $\times$ 100%
2 Specificity = (Number of true negatives by the diagnostic method / Number of gold standard negatives) $\times$ 100%
3 Overall Agreement Rate = [(True positives + True negatives) / Total cases] $\times$ 100%
4 Positive Predictive Value (PPV) = (True positives / Total positives by the diagnostic method) $\times$ 100%
5 Negative Predictive Value (NPV) = (True negatives / Total negatives by the diagnostic method) $\times$ 100%
6 Missed Diagnosis Rate = (False negatives / Gold standard positives) $\times$ 100%
7 Misdiagnosis Rate = (False positives / Gold standard negatives) $\times$ 100%

Statistical analysis

Statistical analysis was performed using SPSS24. Continuous variables with normal distribution and homogeneous variance were presented as mean $\pm$ Standard Deviation (SD) and compared using independent samples *t*-tests. Non-normally distributed data were reported as median and analyzed via Mann-Whitney *U* tests. Categorical data were expressed as percentages (%) and compared using Pearson's Chi-Squared (χ^2) test or Fisher's exact test when sample sizes were small. Diagnostic performance of clinical, histopathological, and DIF findings for MMP was evaluated using Receiver Operating Characteristic (ROC) curve analysis, calculating Area Under the Curve (AUC), sensitivity, and specificity. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Patient characteristics and serology

A total of 79 patients (22 males, 57 females; mean age 58.57 $\pm$ 11.74 years) were included. Among them, 55 patients (17 males, 38 females; mean age 61.36 $\pm$ 10.93 years) were definitively diagnosed with MMP. The oral mucosa was the predominant site of involvement (gingiva in 64.56%), with 61.82% of cases reporting a history of blistering. Disease duration ranged from 0.7 to 240 months (median 20.92 months). In MMP group, pre-biopsy medication history was documented in 61.82% of patients, with topical corticosteroids.

ELISA for BP180/BP230 showed limited utility: only 22/55 MMP patients (40.00%) tested positive for BP180, and 6/55 (10.91%) for BP230.

Histopathology

Histopathological examination revealed subepithelial blisters in 51/55 MMP participants and in 0/24 controls, demonstrating 92.73% sensitivity, 100% specificity, and 94.94% diagnostic agreement rate (Fig. 1).

Direct immunofluorescence findings

In the present data, the classic DIF fluorescence pattern typically presents as a continuous, homogeneous linear green deposit along the epithelial-connective tissue junction (Fig. 2). DIF analysis revealed BMZ deposition of immunoreactants in 47/55 MMP participants and in 0/24 controls. Among DIF-positive cases, 91.49% exhibited typical homogeneous linear staining along the BMZ, while regional linear or granular fluorescence patterns were observed in 8.51% of these cases.

Notably, C3 and IgG demonstrated the highest positivity rates (65.45% and 60.00%, respectively) among DIF-positive cases. Co-deposition of C3 and IgG was observed in 45.45% of cases, whereas isolated C3 or IgG positivity occurred in 20.00% and 14.55% each. Fibrinogen, IgA, and IgM all showed positivity rates below 50%, with IgM exhibiting minimal involvement (<10%).

The diagnostic efficacy of DIF is summarized in Table 1, with a sensitivity of 85.45%, a specificity as high as 100%, and a Youden's index of 0.8545. The AUC of DIF is 0.927 (95% CI 0.869–0.985, p < 0.001) (Fig. 3).

In the MMP cohort, 46 of 47 DIF-positive patients (97.87%) exhibited subepithelial blisters on histopathology, demonstrating a significant correlation between these results (p < 0.001). The single discordant case showed scattered inflammatory cell infiltration in the lamina propria without distinct blister formation. This patient presented with recurrent oral erosions on the bilateral buccal mucosa and tongue dorsum, supported by positive autoantibody testing (both serologically and via DIF), ultimately confirming the MMP diagnosis.

Analysis of potential factors influencing DIF positivity rates revealed a significant positive correlation between disease duration and IgM positivity (p = 0.023), but showed no significant correlations with IgG (p = 0.256), IgA (p = 0.607),

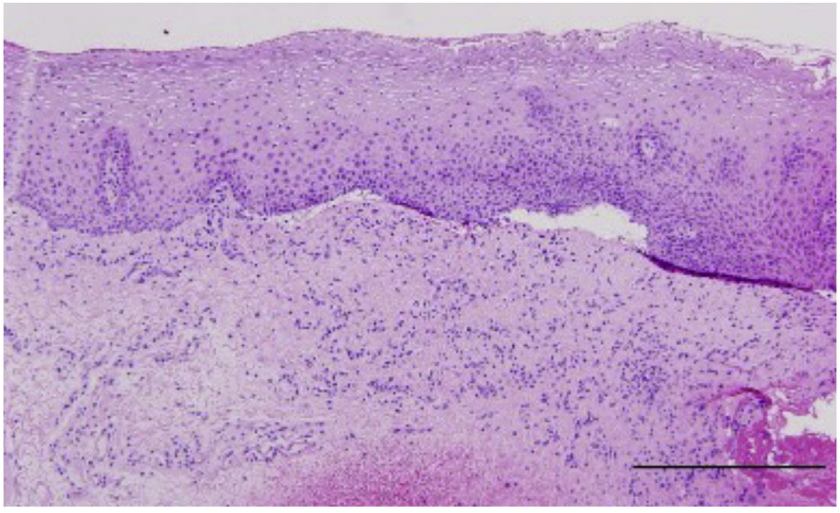

Fig. 1 Representative histopathological features of MMP under light microscopy. Epithelial separation from the lamina propria with partial denudation. The denuded connective tissue surface appears smooth, accompanied by subepithelial blister formation. The lamina propria demonstrates infiltration of lymphocytes, plasma cells, and eosinophils.

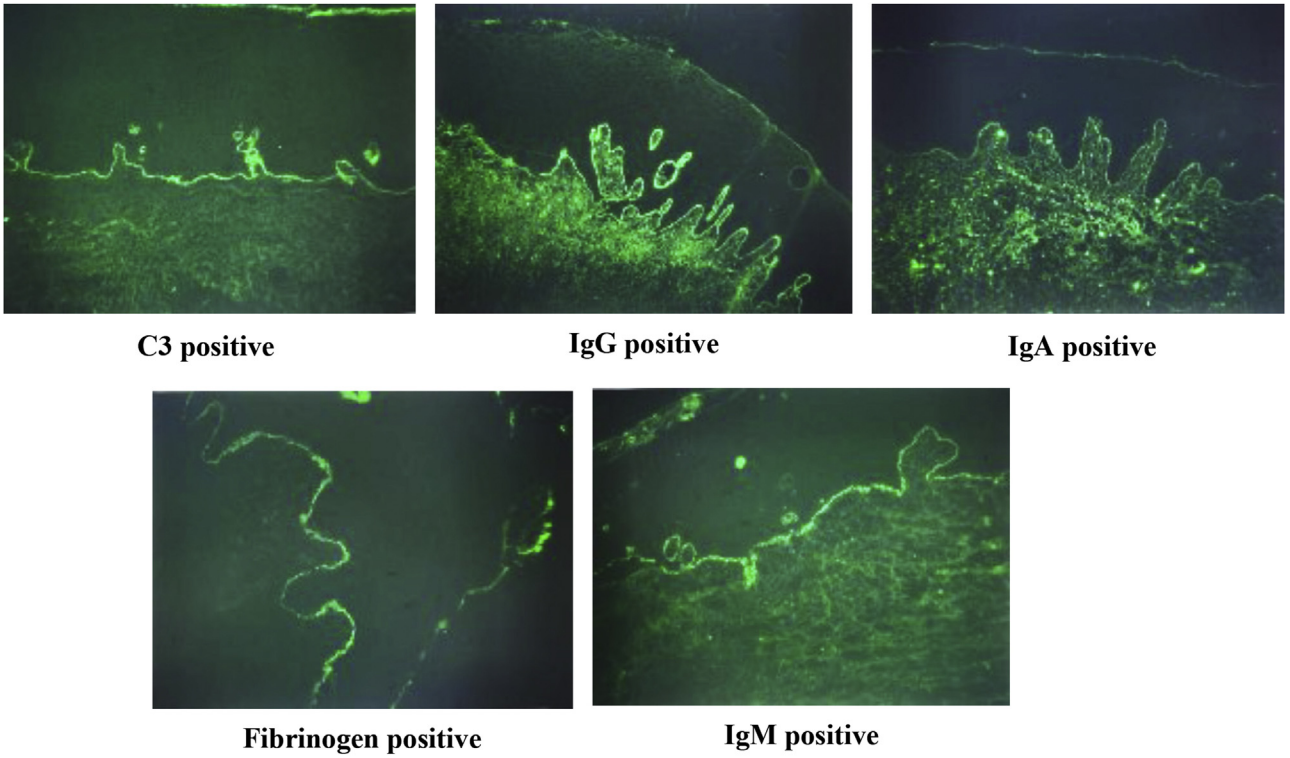

Fig. 2 Characteristic DIF fluorescence patterns. DIF demonstrated continuous and homogeneous linear green fluorescence for C3 and IgG along the BMZ, with positive linear staining for IgA, IgM, and fibrinogen observed in a subset of cases.

C3 ($p = 0.541$), or fibrinogen ($p = 0.256$). Longer disease duration correlated with IgM deposition at the BMZ (median duration: 24-months in IgM (+) vs. 3-months in IgM(-) cases; $p = 0.023$).

Among 55 confirmed cases, 8 patients tested negative for DIF. The clinical manifestations, histopathological features, and serological test results of these patients are presented in Table 2. The negative DIF results showed no significant correlation with the lesion sites, history of blistering, skin lesions, preoperative medication history, or disease duration ($p > 0.05$).

Discussion

MMP is an autoimmune blistering disorder primarily affecting the mucosa and skin. The present study's cohort demographics align with established MMP epidemiology,[10,20,26–29]

Table 1 Diagnostic efficacy of different DIF indicators in MMP.

Examination index	Sensitivity	Specificity	Agreement rate	Positive predictive value	Negative predictive value	Missed diagnosis rate	Misdiagnosis rate
IgG	60.00%	41.67%	54.43%	70.21%	31.25%	40.00%	58.33%
C3	65.45%	66.67%	65.82%	81.82%	45.71%	34.55%	33.33%
F	45.45%	83.33%	56.96%	86.21%	40.00%	54.55%	16.67%
IgA	21.82%	95.83%	44.30%	92.31%	34.85%	78.18%	4.17%
IgM	7.27%	95.83%	34.18%	80.00%	31.08%	92.73%	4.17%
DIF	85.45%	100.00%	89.87%	100.00%	75.00%	14.55%	0.00%

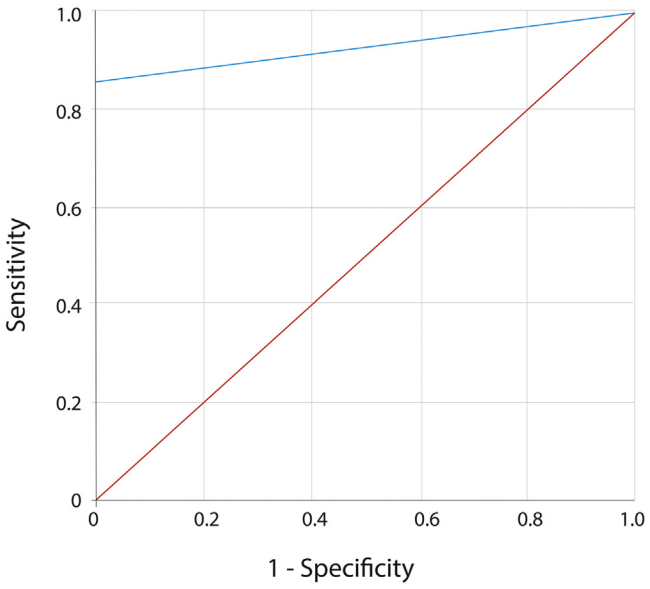

Fig. 3 ROC curve of DIF diagnosis in MMP. ROC curve of DIF diagnosis connects coordinate points with 1 − specificity (=false positive rate) as the x-axis and sensitivity as the y-axis at all cut-off values measured from the test results. The 45° diagonal line serves as the reference line, since it is the ROC curve of random classification.

affirming its predilection for elderly females and oral mucosa (gingiva > 80%).[29–32] Extramucosal involvement (e.g., ocular, skin) further complicates early diagnosis.[5,30]

The European S3 guidelines emphasize a sequential multimodal approach for MMP diagnosis; the present study reaffirms DIF's critical role, serving as a vital complementary diagnosis tool for MMP.[6,25,33,34] Serologically, BP180 antibodies are detected in 46% of oral MMP cases, while BP230 reactivity occurs in 0%–40%.[35–39] Histopathology may fail to detect subepithelial blisters due to technical limitations. Of particular note is the complementary role of DIF when conventional diagnostic methods yield negative results. DIF's performance corroborates meta-analyses confirming its role in multimodal diagnosis,[3] Its near-perfect specificity and synergy with histopathology critically reduce misdiagnosis risks:[6] it confirmed MMP in 1 histopathology-negative and 19 serology-negative cases, while excluding all non-MMP controls. This positions DIF as an indispensable adjunct to conventional methods in ambiguous presentations.

Some studies have shown that the positive rate of DIF indicators is affected by the disease course.[40,41] We propose a novel correlation: IgM deposition predicts prolonged disease duration ($p = 0.023$), potentially reflecting chronic antigen exposure or isotype switching in advanced MMP. This contrasts with dominant IgG/C3 responses in early stages, suggesting IgM as a candidate biomarker for disease chronicity – a hypothesis warranting longitudinal serology studies.

In this cohort, only 8 confirmed MMP cases exhibited negative DIF results, aligning with literature-reported positivity rates of 80%–95%.[3,42,43] False-negative DIF outcomes primarily stem from five categories:

(i) Sampling site selection: Biopsy site selection significantly impacts DIF positivity, though optimal biopsy sites remain contentious. Current guidelines recommend perilesional tissue (0.5–1 cm around the blisters/erosions) or unaffected normal mucosa when inaccessible.[6,44] While Carey et al. report equivalent positivity rates between sites,[14] a meta-analysis designates unaffected mucosa as optimal for MMP.[16] Moreover, whether sampling different oral mucosal sites (e.g., gingiva, tongue, buccal mucosa) influences false-negative DIF results remains inconclusive. Certain scholars found no oral site-dependent effects,[45] whereas others attribute this to regional variations in antigen expression and inflammatory cell distribution.[46]

(ii) Technical limitations: Suboptimal slide preparation causes false negatives, including tissue preservation failures during transport, delayed specimen processing, improper section thickness, low-quality fluorescent antibodies, or incorrect dilution ratios.[6]

(iii) Disease course: Stage-dependent immune complex dynamics lead to false-negative DIF results: insufficient deposition in early/remission phases, transient autoantibody reduction during disease fluctuations, or epidermal destruction in late-stage MMP.[41,47,48]

(iv) Treatment interference: Immunosuppressants (glucocorticoids or immunomodulators) suppress immune cell activity, reducing autoantibody levels, thus leading to false-negative DIF results.[40,41,47,49]

(v) Patients/Disease heterogeneity: Suboptimal autoantibody levels in patients' serum and localized disease (e.g., isolated ocular involvement) may contribute to false-negative results in DIF testing.[50,51]

Table 2 Other test results of DIF-negative patients in the MMP group.

N°	Clinical manifestations	Histopathological features	Serological test results
1	Recurrent blistering and erosions on the right posterior gingiva for 1–2 years	Subepithelial blisters	BP180(+)/BP230(+)
2	Recurrent gingiva ulcerations and erosions for over one year, with a history of blistering.	Subepithelial blisters	BP180(−)/BP230(−)
3	Recurrent ulceration and erosions on the buccal gingiva of teeth 24–25 for the past two months, with a history of blistering.	Subepithelial blisters	BP180(+)/BP230(−)
4	Gingiva ulcers for 3–4 years	Subepithelial blisters	BP180(−)/BP230(+)
5	Recurrent gingival ulcerations for over half a year	Subepithelial blisters	BP180(−)/BP230(−)
6	Recurrent pain and ulceration in both cheeks, lips, and tongue for over 6-years, accompanied by skin lesions on the abdomen and lower legs.	Mucosal inflammation, without evident formation of subepithelial blisters.	BP180(+)/BP230(+)
7	Recurrent buccal ulcers for three months	Mucosal ulceration with inflammation, without evident formation of subepithelial blisters.	BP180(+)/BP230(+)
8	Right buccal ulceration for over two months, with ulcers visible in the pharyngeal region.	Mucosal ulceration with inflammation, without evident formation of subepithelial blisters.	BP180(+)/BP230(−)

Therefore, repeat biopsy is recommended for initially negative cases to improve detection.[21,52]

While the protocol prioritized DIF, histopathology, and BP180/BP230 ELISA, the authors acknowledge the guideline's recommendation for IIF on salt-split skin and anti-laminin 332 testing in specific scenarios.[6] This is particularly relevant given that 19 serology-negative MMP cases were confirmed by DIF and histopathology in the studied cohort. Incorporating IIF on salt-split skin and anti-laminin 332 testing could potentially increase serological sensitivity. Future protocols should integrate these as per S3 guidelines to optimize risk stratification.[53–56]

This study has several inherent limitations that warrant acknowledgment. First, the single-center retrospective design inherently constrains the generalizability of findings, particularly regarding correlation analyses, treatment efficacy assessments, and long-term follow-up data. Furthermore, the limited sample size of DIF-negative cases (n = 8) precluded more robust statistical analyses, thereby restricting detailed investigation into potential confounders such as biopsy site selection or therapeutic influences.

Conclusion

In summary, DIF is a highly specific and valuable tool for diagnosing MMP, with optimal performance when integrated with histopathological evaluation. The present findings support current guidelines advocating for DIF as a first-line diagnostic modality in clinically suspected cases. Future multicenter studies with larger cohorts are needed to explore the impact of treatment regimens and disease progression on DIF outcomes.

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Pan Wei: Writing of the manuscript or critical review of important intellectual content; effective participation in the research guidance; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; final approval of the final version of the manuscript.

Zhixiu Xu: Data collection, or analysis and interpretation of data; Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases.

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Binbin Li: Study concept and design; statistical analysis; writing of the manuscript or critical review of important intellectual content; data collection, analysis and interpretation; effective participation in the research guidance; critical review of the literature; final approval of the final version of the manuscript.

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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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ORIGINAL ARTICLE

Frequency of HLA class I and II in an admixed Brazilian population with psoriasis☆

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Abstract

Background: Psoriasis is a chronic, immune-mediated disease with a significant genetic component. The HLA-*C**06:02 allele is one of the most strongly associated with the disease, particularly influencing early onset and severity. There are few current data on genetics in a Brazilian population with psoriasis.

Objective: This study aimed to investigate the genetic associations between human leucocyte antigen (HLA) alleles and psoriasis in a Brazilian admixed population.

Methods: We conducted HLA class I and II genotyping in 144 patients with psoriasis and compared the results with those of 720 controls. Additionally, we calculated the Psoriasis Area and Severity Index (PASI) and recorded whether the patient had current or previous systemic treatment for psoriasis and the age of disease onset.

Results: HLA-*B**13:02g, *B**15:01g, *B**37:01g, *B**38:01g, *B**57:01g, *B**57:02g, *B**13:02g, *C**01:02g, *C**06:02g, *C**12:03g, *C**18:01g, *DRB1**01:02g, *DRB1**04:08g and *DPB1**04:01g alleles were associated with an increased risk of psoriasis (after the Bonferroni correction factor, only the HLA-*C**06:02 remained significant). And HLA-*DRB1**15:03g conferred protection against psoriasis after Bonferroni correction. Alleles significantly associated with PASI score < 10 were *A**34:02g ($p = 0.037$) and *B**50:01g ($p = 0.037$), while the allele related to PASI > 10 was *DRB1**01:01g ($p = 0.049$). When comparing the age of disease onset, the following alleles were significantly associated with early onset psoriasis (before 30 years of age): *B**44:03g ($p = 0.010$) and *C**07:02g ($p = 0.022$).

☆ Study conducted at the University Hospital Pedro Ernesto, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

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Study limitations: The sample size was small compared with other international publications, and the subgroup of patients with mild disease was less represented; however, the combination of analytical approaches (univariate tests, PCA, and correction for multiple comparisons) reinforces the robustness of the work.
Conclusion: The present findings highlight the genetic complexity of psoriasis in a diverse population and suggest that it may not be directly linked to specific genetic factors. Further research is required to explore the environmental and genetic interactions that contribute to psoriasis pathogenesis.

Introduction

Psoriasis is a chronic, systemic, immune-mediated disease that involves both innate and adaptive immunity. In Brazil, the prevalence is estimated to be 1.31% (1.15% in females and 1.47% in males), with an average age of 52 years.[1] The prevalence varies regionally, being higher in the south and southeast, likely due to greater European ancestry and lower ultraviolet radiation exposure than in other areas.

Regarding the genetic background, it is well established that the HLA-*C**06:02 allele has the strongest association with psoriasis and plays a key role in immune response against melanocytes by presenting autoantigens such as the peptide ADAMTS-like protein 5,[2] potentially influencing early onset and severity.[3] Other HLA alleles, including HLA-*C**18:01, *a rare allele in Europeans*,[4] -*C**12:02 *and* -*C**07:04 in Japan,[5] -*C**01 in Asia,[6] -*C**12,[7] and HLA-B and HLA-A, are associated with psoriasis globally.[2,8,9] Class II HLA genes are less commonly associated with links to HLA-*DPB1**05:01 in China[10] and HLA-DQα1 amino acid position 53 in a cohort of 9,247 Europeans.[11]

In Brazil's admixed population, limited previous studies have linked psoriasis to HLA-*B**57, -*B**27, and -*C**06, with HLA-*A**02∼*C**06∼*B**57∼*DRB1**07∼*DQB1**03 as a common haplotype in patients and HLA-*B**07 appears to be protective against psoriasis.[12] Other studies have examined tumor necrosis factor (TNF) polymorphisms and HLA-C.[13–17]

The group also previously studied single-nucleotide polymorphisms (SNPs) in genes related to the IL17 inflammatory pathway and found no association between SNPs rs361525, rs4819554, and rs33980500 in a Brazilian population.[18] In this study, we compared the frequencies of class I and class II HLA genes between psoriasis patients, categorized based on the severity and age of disease onset, and healthy controls.

Methods

Psoriatic individuals

Between 2021 and 2023, patients diagnosed with psoriasis (based on medical history, physical examination and skin biopsy) were recruited from the Dermatology Department at University Hospitals in Rio de Janeiro, Brazil. All participants signed an Informed Consent Form (ICF) to confirm their willingness to participate. Inclusion criteria included age 18–70 years, sex, ethnicity, and disease duration of more than 10 years. Patients with psychiatric disorders, intellectual disabilities, or other visible skin diseases were excluded from the study. The Psoriasis Activity Score Index (PASI) was also completed during consultation.

All participants read and signed an informed consent form for inclusion in the study, which was approved by the Research Ethics Committee (CAAE: 41957320.3.0000.5259).

Samples

Peripheral blood samples were collected in 4 mL EDTA tubes (purple top) from all participants. The samples were transported to a thermal cooler using industrial ice packs.

DNA extraction

Genomic DNA was extracted from blood samples using the Biopur Mini Spin Plus Kit (Biopur, Biometrix, Curitiba, Brazil) (Catalog: BP100-50, Batch: 32200739). DNA concentration was measured using a NanoDrop spectrophotometer.

Patient samples

The authors included previous HLA-typed with medium resolution SSOP *HLA-A, -B, -C, -DRB1 and -DQB1* typed results.[12] The allelic level (4-digit resolution) was imputed by selecting the most common allele for each MAC code in the Brazilian population.[19] Samples of 85 patients included in the cohort after 2021 were HLA-typed (*HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1*) using a commercial NGS-based HLA kit (Holotype HLA™ NGS Assay; Omixon Inc., Budapest, Hungary) on an Illumina MiSeq sequencer (Illumina, Inc., San Diego, USA).

Control samples

Genotypic and allelic frequencies were assessed and compared with those in the general Brazilian population. Controls were randomly selected from the Brazilian Bone Marrow Donor Registry (REDOME) and matched to cases based on sex, self-reported color-race (ethnic descent), and geographic region at a ratio of 5:1. In total, 720 healthy controls were included.

HLA alleles within P or G groups were denoted by a lower case 'g'.[20]

Table 1 Sex, age, and ethnicity of control subjects and patients with psoriasis, as well as PASI scores and age at disease onset.

	Control (n = 720)	Psoriasis (n = 144)	p-value
Sex (F/M)	300/420	60/84	0.498
Age onset	26.5 ± 4.9 [18–47]	29.0 + 15.5 [5–68]	<0.001
Skin color			
White	245 (34.0%)	49 (34.0%)	
Black	100 (13.9%)	20 (13.9%)	
Brown	375 (52.1%)	75 (52.1%)	
Severity of psoriasis[a]			
Mild		25 (17.4%)	
Moderate to severe		119 (82.5%)	

Demographic and clinical characteristics of control subjects and patients with psoriasis. Data include sex distribution, age at disease onset, skin color, Psoriasis Area and Severity Index (PASI) scores, and disease severity classification. Patients with previous or current high PASI or undergoing systemic treatment were classified as having severe disease.

[a] Previous or current high PASI; patients with systemic treatment were considered to have severe PASI.

Statistical analysis

Allelic frequencies, as well as the Hardy-Weinberg balance test, and Class I haplotypes were determined based on conventional expectation maximization, analyzed for HLA class I and II results, and evaluated for their presence in psoriasis patients and controls using Arlequin 3.5.2.2.[21] The HLA frequencies and HLA Class I A∼C∼B haplotypes, with counts greater than 4 were compared: a) between patients with psoriasis and the control group, b) PASI score, and c) psoriasis age of onset was determined using the EpiInfo software. The odds ratio (OR) and confidence interval (CI; 5%–95%) were calculated, and p (significance level Fisher test, < 0.05), or analysis of variance (ANOVA) was applied when appropriate, the pC (p correction - Bonferroni factor)

The loading plots were created on the platform MetaboAnalyst 5.0 Website using $\log_{10}$ normalized data, auto-scale features, Euclidean distance measure, and Ward clustering method, with the top 10 different alleles selected after the *t*-test results.[22,23] The authors also sought to identify alleles among psoriatic patients with differences between mild vs. moderate to severe according to the PASI score (Psoriasis was defined as mild if PASI than 10 and moderate to severe if ≥ 10), and/or previous or current use of systemic treatment (classified as moderate to severe disease), and if the disease appeared before or after 30 years of age.

Results

HLA alleles in psoriatic patients and controls

The study included 144 patients with psoriasis (84 men and 60 women) and 720 healthy individuals (420 men and 300 women). The mean age of the disease group was 29 ± 15.5 (5–68) years-old and 34% self-declared as *branca* (white-European descent), 13.9% as *preta* (black -sub-Saharan African descent), and 52.1% as *parda* (admixed) in both the case and control groups (Table 1).

Psoriasis HLA loci pairwise population was significantly different from the control (FST = 0.03485, $p < 0.05$). When considering the Hardy-Weinberg equilibrium of the studied population (Table S1), HLA-*DQB1* was the only locus that was not in equilibrium. Linkage disequilibrium (LD) analysis among HLA loci (Table S2) demonstrated that, in the psoriasis group, most pairs of loci were in linkage disequilibrium, particularly across Class I regions (A∼C, A∼B, C∼B) and between Class I and Class II loci (A∼DRB1, B∼DRB1, C∼DRB1).

The alleles associated with disease protection (in crescent OR order) and risk were presented in Table 2. HLA-*DRB1**15:03 g was found to be protective, and C*06:02 g is the strongest risk allele for psoriasis. Allele frequencies in controls and in psoriasis patients are detailed in Tables S3 and S4, for class I (HLA- A, -B and C) and class II (HLA-DRB1, DQB1 and DPB1) alleles, respectively.

The present matrix data included 144 patients and 720 controls with 160 variables: sex, PASI, Onset age, self-reported color, and HLA alleles with a frequency greater than 4 HLA-*A* (n = 29), -*B* (n = 54), -*C* (n = 23), -*DRB1* (n = 35), and -*DQB1* (n = 15). The alleles were scored as 1 (absent), 10 (heterozygosity), or 100 (homozygosity) and log transformed. Principal Component Analysis (PCA) was performed to explore the contribution of HLA alleles to the genetic differentiation between psoriasis patients and healthy controls. The loading plot (Fig. 1) demonstrates that most alleles are clustered near the origin, indicating low discriminative power across groups. In contrast, specific Class II alleles, particularly *HLA-DRB1**07:01 g, *HLA-DQB1**02:01g, and *HLA-DQB1**03:01g, showed higher loading distances, suggesting a stronger influence in distinguishing psoriasis cases from controls.

Severity, age of onset of psoriasis and HLA alleles

Univariate analysis of the association between HLA alleles and psoriasis severity (Table 3) revealed that *A**34:02 g (p = 0.010) and *B**50:01 g (p = 0.011) were more frequently observed in patients with mild disease, suggesting a possible protective effect against moderate-to-severe forms. In contrast, the allele *DRB1**01:01 g (p = 0.062) was identified exclusively in patients with moderate-to-severe psoriasis, representing a risk marker for greater clinical severity. Regarding age at onset, A*23:01 g (p = 0.006), A*30:01 g (p = 0.003), B*15:03 g (p = 0.078), and *DQB1**03:03 (p = 0.026) were associated with late-onset psoriasis (>30 years),

Table 2 Protective and risk HLA alleles in controls and psoriasis individuals.

Alleles	Control		Psoriasis		OR [5%–95%]	*p*	pC
	n	%	n	%			
Protective							
*DRB1*15:03g*	83	11.5%	5	3.5%	0.27 (0.11–0.69)	0.001	**0.027**
*B*07:02g*	98	13.6%	8	5.6%	0.37 (0.17–0.78)	0.002	
*C*17:01g*	51	7.1%	4	2.8%	0.37 (0.13–1.05)	0.032	
*B*44:03g*	85	11.8%	8	5.6%	0.44 (0.20–0.92)	0.010	
*C*07:02g*	121	16.8%	14	9.7%	0.53 (0.29–0.95)	0.014	
*DQB1*06:02g*	171	23.8%	22	15.3%	0.57 (0.35–0.94)	0.011	
Risk							
*B*57:02g*	2	0.3%	3	2.1%	7.63 (1.26–6.13)	0.035	
*DRB1*04:08g*	5	0.7%	4	2.8%	4.08 (1.08–5.40)	0.047	
*B*13:02g*	18	2.5%	10	6.9%	2.91 (1.31–6.44)	0.007	
*B*38:01g*	30	4.2%	15	10.4%	2.67 (1.40–5.11)	0.003	
*C*01:02g*	19	2.6%	9	6.3%	2.46 (1.09–5.55)	0.021	
*B*37:01g*	16	2.2%	7	4.9%	2.24 (0.90–5.56)	0.049	
*C*06:02g*	110	15.3%	40	27.8%	2.13 (1.40–3.23)	0.000	**0.007**
*B*57:01g*	34	4.7%	13	9.0%	2.00 (1.02–3.89)	0.026	
*B*15:01g*	26	3.6%	10	6.9%	1.99 (0.93–4.22)	0.043	
*C*12:03g*	69	9.6%	25	17.4%	1.98 (1.20–3.26)	0.005	
*DPB1*04:01g*	37	8.22%	48	13.52%	1.75 [1.11–2.75]	0.008	
*DRB1*01:02g*	58	8.1%	18	12.5%	1.63 (0.93–2.86)	0.049	

Pc, p-value after Bonferroni correction, * - Fisher test.
Protective and Risk HLA alleles are presented in crescent and decrescent order of Odds Ratio, respectively. The number (n) and percentage (Perc) of samples with individuals presenting the alleles in controls and psoriatic patients (psoriasis) are depicted. Odds Ratio and confidence interval 5% and 95% (OR [5%–95%]) and p-level significance (p) were estimated with ANOVA with Fisher test when n < 5). Bonferroni correction was applied with a factor representing the number of alleles with n > 5 in each locus; only *DRB1*15:03 g* for protection and *C*06:02 g* for risk remained significant.

Table 3 HLA alleles, severity (PASI) and onset age.

Allele PASI	n Mild (<10)	%	n Moderate /Severe (≥10)	%	Odds Ratio [5%–95%]	p
*A*34:02g*	3	12.0%	2	1.7%	0.13 [0.02–0.79]	0.037
*B*50:01g*	3	12.0%	2	1.7%	0.13 [0.02–0.79]	0.037
*DRB1*01:01 g (risk)*	0	0.0%	15	12.6%	Undefined	0.049
Onset Age	**>30 y**		**<31 y**			
*A*23:01g*	10	15.4%	2	2.5%	0.14 [0.03–0.68]	0.003
*A*30:01g*	6	9.8%	1	1.2%	0.11 [0.01–0.95]	0.023
*B*15:03g*	6	9.8%	1	1.2%	0.11 [0.01–0.95]	0.023
*B*44:03 g*	0	0.0%	8	9.6%	Undefined	0.010
*C*07:02g*	2	3.3%	12	14.5%	4.99 [1.07–23.17]	0.022
*DQB1*03:03*	9	14.8%	3	3.6%	0.22 [0.06–0.84]	0.019

whereas *B**44:03 g (p = 0.009) and *C**07:02 g (p = 0.015) were more frequent in early-onset cases (<30 years), the latter being up to five times more common in this group, thus representing an important marker of risk for type 1 psoriasis (Table 3).

*HLA-C*06:02*, although strongly associated with psoriasis susceptibility, did not show significant differences between severity subgroups (Table 3), corroborating previous findings in the literature.

When the Principal Component Analysis (PCA) stratified by disease severity (PASI < 10 versus PASI ≥ 10) was made, it revealed that most HLA alleles clustered centrally, indicating minimal contribution to the differentiation between mild and moderate-to-severe psoriasis (Fig. 2). Nonetheless, *HLA-DRB1**07:01g, *HLA-DQB1**02:01g, and *HLA-C**06:02g, showed greater loading distances, suggesting a potential role in modulating disease phenotype and inflammatory intensity.

Class I haplotypes in psoriasis individuals and controls, PASI and age onset

Among the 81 *A∼C∼B* haplotypes with count greater than 4, *02:01g∼06:02g∼13:02g* (3.5% × 0.7% OR = 5.14 [1.47–18.91]), *02:01g∼06:02g∼57:01g* (3.5% × 1.0; OR-

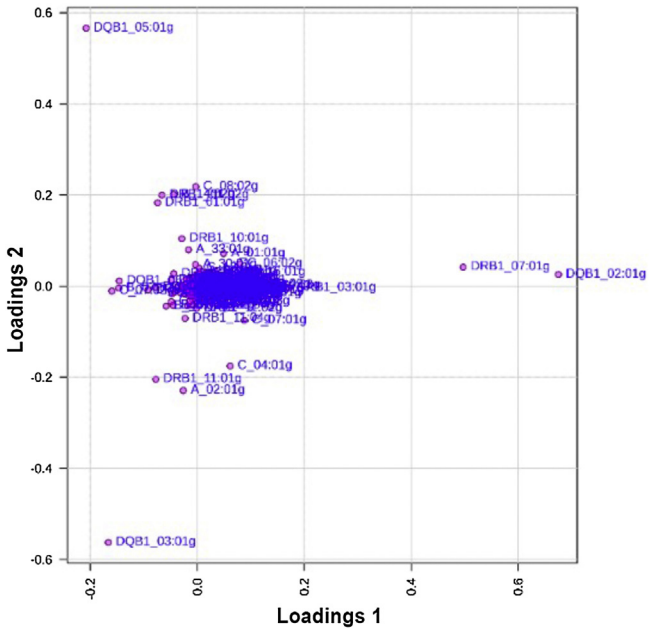

Fig. 1 Loading plot of Principal Component Analysis (PCA) applied to HLA alleles comparing psoriasis patients and healthy controls based on HLA frequencies. The loading plot displays the contribution of individual HLA alleles to the first two principal components. Most alleles cluster near the origin, indicating low discriminatory power between groups, while a few alleles – such as *HLA-DRB1**07:01 g, *HLA-DQB1**02:01 g, and *HLA-DQB1**03:01 g – show greater loading distances, suggesting stronger influence in distinguishing psoriasis cases from controls.

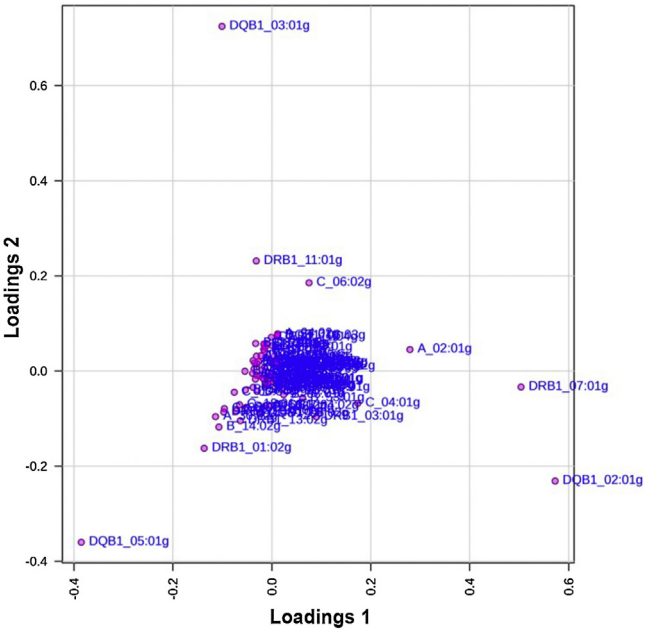

Fig. 2 Loading plot from Principal Component Analysis (PCA) comparing psoriasis patients with mild disease (PASI < 10) and those with moderate to severe disease (PASI ≥ 10). The PCA loading plot displays the contribution of HLA alleles to the genetic differentiation between psoriasis subgroups stratified by disease severity. Most alleles are concentrated near the center, indicating limited discriminative impact on clinical severity. However, *HLA-C**06:02 g, *HLA-DRB1**07:01 g, and *HLA-DQB1**02:01 g appear further from the origin, reflecting a stronger contribution to variance and suggesting potential modulation of disease phenotype. The dispersion pattern supports a complex genetic architecture in which certain Class II alleles may influence not only susceptibility but also the clinical expression of psoriasis.

3.66 [1.15–11.71]) and *26:01g∼12:03g∼38:01g* (4.9% × 1.1% OR = 4,55 [1.62–12.75]) were more frequent among individuals with psoriasis.

Discussion

This study provides valuable insights into the genetic landscape of psoriasis in an admixed Brazilian population, confirming a significant association between several HLA alleles and disease susceptibility. Consistent with previous research, the authors found that the HLA-*C**06:02g allele was one of the strongest genetic markers linked to psoriasis,[2,3] which aligns with global data on its role in determining the early onset and increased severity of the disease.

Additionally, the authors identified several other HLA alleles, such as *HLA-B*15:01g*, *B*57:01*, *B**57:02g, *B**13:02g, *B**38:01g, *B**37:01g, *C**01:02g, *C**18:01g, *C**12:03g, *DRB1**01:02g and *DRB1**04:08g which were associated with an increased risk of psoriasis.

In a previous study conducted in a Pakistani population, the *HLA-B*15:01* allele was associated with late-onset psoriasis.[24] However, no prior study has linked it to stress scores and psoriasis. *HLA-B*57* has been identified as a susceptibility allele for psoriasis in both Caucasian[25] and Asian populations[8] as well as in previous studies involving the Brazilian population.[12,16] However, the literature does not specifically mention HLA-*B**57:02g in psoriasis.

HLA-*B**13:02 has been reported as a susceptibility allele for psoriasis in the Chinese population[8] and has also been associated with cardiovascular disease.[26] HLA-*B**38:01 has been linked to an increased risk of developing psoriatic arthritis (PsA) among individuals with psoriasis.[27] Although HLA-*B**37:01 has not been well documented in the context of psoriasis, one study has associated its presence with treatment response.[28] HLA-*C**01:02 has been identified as a risk allele for psoriasis in a Chinese population,[29] whereas HLA-*C**18:01 has been associated with difficult-to-treat psoriasis in a Caucasian European population.[4] The remaining alleles have not previously been reported to be associated with psoriasis.

A previous Brazilian research group identified an association between HLA-*DRB1**15 and multiple sclerosis, but not psoriasis[30] or as a protective factor against the disease.

Interestingly, some alleles, particularly HLA-*DRB1**15:03g and HLA-*DQB1**02:02g exhibited protective effects against psoriasis in the Brazilian population, further emphasizing the complex link between genetic factors and disease susceptibility. Contrary to previous findings in the literature, where an association between psoriasis and HLA-*DQB1**02 was reported in a Slovak population,[31] the present results indicated that this allele confers protection against the disease.

The DRB1∼DQB1 pair analysis showed loss of LD, suggesting partial recombination or allelic heterogeneity within this segment in the psoriasis population. Such findings may reflect the impact of disease-associated selective forces or the unique genetic admixture of the Brazilian population on HLA haplotype distribution among psoriasis patients.

The HLA-*DQB1* locus deviation from Hardy-Weinberg equilibrium (Table S1) may be consequence of population substructures as allele frequencies may vary between subgroups, specifically in this locus and condition, moreover, in PCA analysis. DQB1 alleles appeared in extreme positions in both Loading 1 and Loading 2. The present results with PCA in loading plots1 and 2 discriminate predominantly class II alleles to differentiate controls for psoriasis patients, after Bonferroni correction, *DRB1**15:03g (Table 2), and risk with *DQB1**05:01g that also appeared in the loading plots.

Class II alleles are typically not associated with psoriasis. *DQB1**02:02 has previously been described as a pharmacogenetic marker and is associated with a better response to acitretin treatment.[32] In 2005, another Brazilian study also found an association between *DRB1**01:02/*DQB1**05 ($p < 0.05$, RR = 5.44) and *HLA-DRB1**07:01/*DQB1**03 alleles ($p < 0.02$, RR = 9.00), which correlated with early onset of the disease, as well as an association with the haplotypes HLA-*DRB1**01:02/DQB1*05 and HLA-*DRB1**07:01/DQB1:03.[33] *DQB1**05:01 is observed in the present study in Fig. 1.

*DRB1**07 (OR = 2.56) was previously reported to be associated with psoriasis in the Slovak population, and *DQB1**02 (OR = 1.09).[31] This is also observed (along with *DQB1**05:01) in Fig. 1.

In a Chinese Han population, the HLA-*DQA1**01:04 and *DQA1**02:01 alleles were associated with an increased risk of psoriasis, whereas the HLA-*DQA1**05:01 allele was found to have a protective effect against the disease.[34] However, the present results did not demonstrate the presence of these alleles.

On loading plot (Fig. 1), specific Class II alleles, particularly *HLA-DRB1**07:01 g, *HLA-DQB1**02:01g, and *HLA-DQB1**03:01g, showed higher loading distances, suggesting a stronger influence in distinguishing psoriasis cases from controls. These findings support the notion that, although the majority of alleles contribute minimally to total genetic variance, certain loci may exert disproportionate effects in defining disease susceptibility profiles within the Brazilian population. The alleles such as *DRB1**15:03g *and DQB1**02:02g, identified as protective, appear in peripheral positions because they contribute to differentiating patients from controls. Classical risk alleles, such as *C*06:02g and DRB1**07:01g, are also more distant from the center, confirming their weight in the plot. The central clustering of several alleles shows those with no significant impact on differentiation.

HLA and severity

HLA-*A**34:02g and HLA-*B**50:01g had lower frequencies in patients with moderate to severe PASI than in controls, whereas *DRB1**01:01g was detected only in cases of moderate to severe PASI. The discrepancy between these results and those in the literature may be due to the smaller sample size of mild disease cases (17.4%) compared to moderate to severe cases (82.5%).

Another Brazilian group found an association of more severe disease in male patients with alleles *B**37, *C**06, *C**12, and *DRB1**07, whereas *B**57 was associated with mild disease.[14]

A larger study in the Brazilian population with a larger sample size of mild disease cases is warranted for further research.

Nonetheless, on loading plot (Fig. 2), *HLA-DRB1**07:01g, *HLA-DQB1**02:01g, and *HLA-C**06:02g, showed greater loading distances, suggesting a potential role in modulating disease phenotype and inflammatory intensity. These alleles, previously associated with susceptibility in the overall cohort, also appear to influence the genetic structure of patients with more severe clinical forms. The pattern supports the hypothesis that while several loci contribute to disease risk, specific Class I and II alleles may further shape the phenotypic spectrum and therapeutic responsiveness of psoriasis in the Brazilian population.

HLA and age onset of psoriasis

Univariate analysis was performed and showed that alleles associated with psoriasis onset after 30 years of age (type 2 psoriasis) were: *A**23:01g (p = 0.006), *A**30:01g (p = 0.003), *B**15:03g (p = 0.078), and *DQB1**03:03 (p = 0.026), in contrast, *B**44:03g (p = 0.009) and *C**07:02g (p = 0.015) were detected mainly before 30y and *C**07:02g was 5 times more frequent in these young patients (14.5% × 3.3%).

Choonhakarn et al., in a Thai population, identified the alleles HLA-*A**01, *A**02:07, *A**30, *B**08, *B**13, *B**46:01, *B**57, *C**01, *C**06:02 (the strongest association), and *DRB1**07 as being associated with type I psoriasis (onset before 30 years of age), while higher frequencies of *A**02:07, HLA-*A**30, *C**01 and *DRB1**14:01 were significantly associated with psoriasis onset after 30 years of age.[35] In a Turkish population, Atasoy et al. found that alleles *B**57, HLA-*Cw6*, and *DRB1**07 are significantly associated with type I psoriasis.[36]

Kim et al. studied the Korean population and found that the haplotype HLA-*A**30-*B**13-*C**06:02-*DRB1**07-*DQA1**02-*DQB1**02 is a high-risk factor for the disease, particularly at an early age in females.[37] The haplotype HLA-*A**33-*B**44-*C**14:01-*DRB1**13-*DQA1**01-*DQB1**06-*DPB1**04:01 was identified as a protective haplotype for psoriasis, whereas the extended haplotype HLA-*A*1-*B*37-*Cw*0602-*DRB1**10-*DQA1**01-*DQB1**05 was found to be a high-risk factor for psoriasis in Koreans.[37] The Pakistani population previously discussed had HLA alleles *B**57, *C**06:02, and *DQB1**03:03:02 that were strongly associated with early-onset psoriasis, whereas alleles *B**15, *DRB1**13:02, and *DQB1**03:03:02 were associated with late-onset psoriasis.[24]

This study had some limitations that should be acknowledged. The relatively small sample size, particularly within the mild disease subgroup, may have limited the statistical power to detect subtle genetic associations and affected the generalizability of the findings. Additionally, the cross-sectional design precludes longitudinal assessment of disease progression and long-term outcomes associated with specific HLA alleles. The reliance on the self-reported age of onset introduces potential recall bias, and the use of a

single PASI assessment does not account for intra-individual variability over time. However, this limitation was mitigated by incorporating additional variables, such as previous or current use of systemic treatment, to classify patients with moderate to severe disease. Furthermore, given the high degree of admixture in the Brazilian population, undetected population substructures may have influenced allele frequency distributions, contributing to potential confounding factors. Despite these limitations, this study provides important and novel data regarding HLA associations in an admixed Brazilian cohort, a population that is underrepresented in global psoriasis research. The use of comprehensive statistical approaches, including univariate and principal component analyses, enhances the robustness of the findings and underscores the potential of certain HLA alleles to serve as biomarkers for disease susceptibility and severity in this unique population. Future larger, longitudinal studies are warranted to confirm these associations and further explore their clinical implications.

In conclusion, the findings of this study underscore the complexity and diversity of HLA allele associations in psoriasis across different populations. Although several alleles have been consistently linked to psoriasis in various populations, the present study adds to the growing body of evidence suggesting population-specific variations in genetic risk factors. The differences observed between the present results and those reported in other populations highlight the need for a more nuanced understanding of how genetic susceptibility varies across ethnicities.

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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.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.abd.2025.501258.

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ORIGINAL ARTICLE

Treatment response in chronic urticaria: analysis of clinical and laboratory predictors☆

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Abstract

Background: Chronic urticaria (CU) compromises quality of life, requiring escalated treatment with second-generation H1 antihistamines, omalizumab, and, in refractory cases, cyclosporine. Predictors of therapeutic response are not yet well established.

Objective: To evaluate clinical and laboratory factors associated with treatment response in patients with CU.

Methods: Cross-sectional study of 175 patients with CU followed at the Urticaria Reference Center (UCARE) of Complexo Hospitalar Universitário Professor Edgard Santos (HUPES/UFBA) between 2023 and 2024. Sociodemographic, clinical, and laboratory data were analyzed. Treatment response was assessed using the Urticaria Control Test (UCT), with responders being those with a score $\geq$12 or Angioedema Control Test (AECT) $\geq$10.

Results: Most patients were female (80.6%), with a mean age of 45.3 years. Chronic spontaneous urticaria (CSU) was predominant (86.3%). Higher body mass index (BMI), early onset, longer disease duration, and psychiatric disorders were associated with poorer response to second-generation H1 antihistamines. Responders to these drugs had shorter disease duration and a lower proportion of women compared to those requiring omalizumab. In omalizumab users, mental disorders remained associated with refractoriness. Total IgE, eosinophils, CRP, ESR, D-dimer, and anti-TPO did not correlate with therapeutic response.

Study limitations: Cross-sectional study and reliance on clinical records, information bias, and selection bias.

☆ Study conducted at the Universidade Federal da Bahia, Salvador, BA, Brazil.

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Conclusions: High BMI, female gender, early symptom onset, prolonged disease duration, and mental disorders were associated with poorer response to CU treatment. The evaluated laboratory tests did not demonstrate predictive value for treatment response.

Introduction

Chronic urticaria (CU) is characterized by erythematous and pruritic plaques, accompanied or not by angioedema, lasting more than six weeks. It can be classified as chronic spontaneous urticaria (CSU) when it occurs without a specific trigger, or chronic inducible urticaria (CIndU) when it occurs after a specific stimulus, primarily physical. Its course and duration are unpredictable, ranging on average from six months to five years.[1] It is estimated that CSU affects 0.5% to 1% of the global population, which is equivalent to two-thirds of CU cases, negatively impacting patients' quality of life.[2]

The pathophysiology of CU has not yet been fully elucidated, but the role of histamine, as well as some pro-inflammatory cytokines released by mast cells and basophils, is indisputable. The main mechanism associated with CSU is autoimmune, based on the presence of class G autoantibodies directed at high-affinity IgE receptors (FceRI) on mast cells and basophils or at circulating IgE molecules, in addition to IgE autoantibodies directed at various endogenous antigens.[3] The pathogenesis of CIndU is not yet fully understood, but the mechanisms involved in CSU also seem to play an important role.[4]

Therapeutic management is escalated according to severity and refractoriness to treatment and includes the use of second-generation H1 antihistamines at standard doses as recommended in the package insert up to quadruple doses, anti-IgE monoclonal antibody (omalizumab), and cyclosporine.[1]

Despite advances in treatment, CU management is still based on a trial-and-error approach, with little ability to predict which patients will respond to a given treatment phase, which contributes to a longer time to achieve symptom control and increases the costs associated with therapy.[5]

In recent years, several studies have sought to identify clinical and laboratory markers capable of predicting therapeutic response in patients with chronic urticaria, particularly regarding the second-generation H1 antihistamines, omalizumab, and cyclosporine. According to a systematic review by Fok et al.,[5] elevated Urticaria Activity Score (UAS7) values, as well as increased serum CRP and D-dimer levels, are associated with a lower response to second-generation H1 antihistamines. Regarding omalizumab, low IgE levels, a positive Autologous Serum Test (AST), and a positive Basophil Histamine Release Test (BHRA) were identified as possible predictors of poor or delayed response. In contrast, in the case of cyclosporine, there is evidence that a positive BHRA and reduced IgE levels may indicate a better response to treatment.

Complementarily, Giménez-Arnau et al.[6] also observed that high disease activity, increased CRP, ESR, and D-dimer levels are the main predictors of an absent or unsatisfactory response to second-generation H1 antihistamines. Furthermore, low or very low baseline IgE, a positive AST, a positive basophil activation/histamine release test (BAT/BHRA+), basopenia, eosinopenia, and elevated D-dimer were associated with an absence of response to omalizumab but a good response to cyclosporine. Conversely, normal or slightly elevated baseline IgE levels, as well as increased expression of the FcεRI receptor on basophils, seem to indicate a more rapid response to omalizumab.

Despite these findings, there is still little solid evidence in the literature on clinical and laboratory markers that can practically guide therapeutic choices, especially in specific contexts such as in Brazil. Therefore, further studies to validate these findings in different populations are needed.

Therefore, the present study aims to analyze possible clinical and laboratory predictors of treatment response in patients with chronic urticaria treated at a referral center, aiming to contribute to more personalized and efficient disease management.

Methods

Study design

This is a cross-sectional, observational study conducted with patients diagnosed with Chronic Urticaria (CU) and treated at the Urticaria Reference Center (UCARE), linked to Complexo Hospitalar Universitário Professor Edgard Santos (HUPES) of Universidade Federal da Bahia (UFBA), in Salvador, Bahia, between January 2023 and November 2024.

Patients of both sexes, without age restrictions, with a clinical diagnosis of CU, defined as the presence of wheals and/or angioedema for more than six weeks, according to the international guidelines of EAACI/GA^{2}LEN/EDF/WAO, were included.[1] In cases of CIndU, specific provocation tests were performed using standardized instruments such as the FricTest® and TempTest®.[7]

The sample was selected by convenience, and patient records were reviewed according to a standardized protocol to collect information on demographic data, clinical characteristics, laboratory results, administered treatments, and specificities of CU. No prior sample size calculation was performed, as the objective was descriptive and exploratory, with an analysis of all cases treated at the referral center during the proposed timeframe.

Patients with other urticarial lesions that did not correspond to CU, lack of follow-up, or those who did not consent

to participate in the study were excluded. Of the patients approached, only two declined to participate.

Data collection and laboratory tests

Data collected included sex, age, BMI, diagnosis (CSU, CIndU, or CSU + CIndU), disease duration, age at symptom onset, presence of angioedema, hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), associated comorbidities (metabolic, autoimmune, psychiatric, atopic, cardiovascular, and mental health), and laboratory tests.

The following tests were evaluated: total IgE (values < 40 IU/mL considered low),[5] eosinophils (<50 cells/μL defined as eosinopenia),[8] CRP, ESR, D-dimer, and anti-TPO. Tests were performed at the Immunology and Molecular Biology Laboratory of the Institute of Health Sciences at UFBA or at other services affiliated with the Brazilian Unified Health System (SUS, Sistema Único de Saúde) or private laboratories. In patients receiving omalizumab, only IgE values obtained before the first dose were considered.[9]

Response monitoring

Therapeutic response was assessed using the Urticaria Control Test (UCT), with a score ≥ 12 considered adequate control.[10] In cases of isolated angioedema, the Angioedema Control Test (AECT) was used, with a score ≥10 considered satisfactory.[11] The UCT was chosen because it is easier to apply and understand by patients during consultations and is administered under medical supervision at the time of care. Although the UAS7 was initially considered, its administration requires daily completion by the patient for seven consecutive days before the consultation, which proved difficult to adhere to and follow, and could compromise data reliability.

Treatment aspects

Patients were categorized into four treatment phases, according to current management: Phase 1, with second-generation H1 antihistamines at standard or double doses; Phase 2, with second-generation H1 antihistamines at triple or quadruple doses; Phase 3, with omalizumab; and Phase 4, with immunosuppressants. The minimum length of duration of each Phase (1 and 2) was four weeks, with variations depending on appointment availability and patient flow.

For the response to omalizumab, patients who achieved a UCT ≥ 12 were considered responders; partial responders were those who did not achieve this score but showed an increase of ≥ 3 points in the UCT (minimum clinically significant difference);[12] and non-responders were those who did not demonstrate improvement in the score after at least six months of continuous use of the medication.

Patients responding to omalizumab were further classified according to the time to response: early response, when improvement was observed after the first application; and late response, when improvement occurred only after subsequent applications.

Statistical analysis

Statistical analysis was performed using the chi-square test, Fisher's exact test, Student's *t*-test, Mann-Whitney test, or Kruskal-Wallis test, depending on the nature and distribution of the variables. ROC curves and effect size measures, such as Cramer's V, Cohen's d, and chi-square, were used, following recommendations in the literature. All analyses were conducted using R software version 4.3.3 (R Core Team, 2023) and considered a significance level (α) of 5%.

Ethical aspects

The study was approved by the Research Ethics Committee of Complexo Hospitalar Universitário Professor Edgard Santos (CAAE: 65818222.9.0000.0049). Patients were invited to participate during their scheduled appointments with their attending physician, at which time they were presented with the Informed Consent Form (ICF), authorizing both the collection of additional data and review of medical records.

Results

Sample characterization

A total of 175 patients with chronic urticaria were included, 80.6% of whom were female, with a mean age of 45.3 years. CSU was the most common subtype (55.4%), followed by a combination of CSU and CIndU (30.9%), and CIndU alone in 13.7%. Angioedema was present in 80% of cases, with the most common clinical presentation of CSU being a combination of urticaria and angioedema (73%; Table 1).

The most prevalent comorbidities were: metabolic disorders (47.4%), atopic disorders (40%), cardiovascular disorders (33%), NSAID hypersensitivity (31%), autoimmune disorders (23%), and mental disorders (18%; Table 1).

Regarding treatment, 66.9% were exclusively using second-generation H1 antihistamines, 29.7% were using omalizumab, and 3.4% were using immunosuppressants. The distribution by phase was: 26.9% in Phase 1, 40% in Phase 2, 29% in Phase 3, and 3.4% in Phase 4. Only approximately 10% of patients responded to the standard dose of second-generation H1 antihistamine. Among those who used omalizumab, 56.9% had an early response, 24% had a late response, 12% did not respond, and 6.8% had a partial response (Fig. 1).

Laboratory tests revealed abnormalities in part of the sample: elevated CRP in 21.9%, ESR in 47.3%, D-dimer in 24.2%, and anti-TPO in 19.6%. The mean eosinophil count was 196.8 cells/μL, with eosinopenia in 17% of cases. Total IgE averaged 272 IU/mL, with 73.8% of patients showing levels ≥ 40 IU/mL (Table 2).

Comparative analyses

The comparative analysis between patients who responded to the standard or doubled dose of second-generation H1 antihistamines and those who required increased doses revealed no statistically significant differences regarding

Table 1 Demographic and clinical data.

Variable	Results
Female sex, n (%)	141 (80.5)
Age in years (n = 175)	
Mean (SD)	45.2 (18.02)
Median (Q1; Q3)	47.14 (37.00; 59.50)
Range	6 – 85.77
BMI (KG/ BMI (kg/m^2), (n = 175*):	
Mean (SD)	27.92 (6.32)
Median (Q1; Q3)	27.60 (23.75; 32.05)
Range	13.30 – 47
BMI category (n = 175), n (%)	
Overweight	60 (34.29)
Obesity	58 (33.14)
Normal weight	50 (28.57)
Underweight	7 (4.00)
Age at onset in years (n = 171*):	
Mean (SD)	32.80 (18.08)
Median (Q1; Q3)	33.00 (19.00; 48.00)
Range	0 – 75
Disease duration in years:	
Mean (SD)	11.92 (12.60)
Median (Q1; Q3)	8.00 (3.00; 16.50)
Range	0–77
Angioedema (n = 175) – n (%)	141 (80.57)
Main diagnosis (n = 175) – n (%)	
CSU	97 (55.43)
CSU + CindU	54 (30.86)
CindU alone	24 (13.71)
Clinical manifestation (n = 175) – n (%)	
Urticaria alone	34 (19.42)
Urticaria + angioedema	129 (73.71)
Angioedema alone	12 (6.85)
CIndU specification (n = 78) – n (%)	
Dermographism	54 (69.23)
Pressure	17 (21.79)
Heat	11 (14.10)
Solar	4 (5.13)
Cholinergic	4 (5.13)
Cold	1 (1.28)
Comorbidities (n = 175) – n (%)	
Metabolic disorder	83 (47.43)
Atopic disorder	70 (40.00)
Cardiovascular disorder	57 (32.57)
Hypersensitivity to NSAIDs	55 (31.43)
Autoimmune disorder	40 (22.86)
Mental disorder	32 (18.29)

Source: Prepared by the author.
SD, Standard Deviation; Q1, First Quartile (25th percentile); Q3, Third Quartile (75th percentile); BMI, Body Mass Index; CSU, Chronic Spontaneous Urticaria; CIndU, Chronic Inducible Urticaria; NSAIDs, Nonsteroidal Anti-inflammatory Drugs.

Table 2 Laboratory data.

Variable	Results
High ESR (n = 150) – n (%)	71 (47.33)
Positive CRP (n = 160) – n (%)	35 (21.88)
High D-Dimer (n = 62) – n (%)	15 (24.19)
Eosinophils (n = 164):	
Mean (SD)	196.83 (189.96)
Median (Q1; Q3)	138.50 (68.96; 273.25)
Range	0–1.112
≥50 – n (%)	135 (82.31)
<50 – n (%)	29 (17.68)
Total IgE (n = 130):	
Mean (DP)	272 (448.4)
Median (Q1, Q3)	108.5 (39.1; 291.0)
Range	2–2.500
≥40 – n (%)	96 (73.8)
<40 – n (%)	34 (26.2)
High Anti-TPO (n = 153) – n (%)	30 (19.61)

Source: Prepared by the author.
SD, Standard Deviation; Q1, First Quartile (25th percentile); Q3, Third Quartile (75th percentile); ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; TPO, Thyroperoxidase.

demographic and clinical variables, presence of comorbidities, or laboratory tests evaluated (Table 3).

On the other hand, when comparing patients who responded to second-generation H1 antihistamines with those who required omalizumab, significant differences were observed in terms of sex and disease duration. The proportion of women was higher among those receiving omalizumab, while patients who responded to H1 antihistamines had a shorter mean disease duration. The other variables analyzed showed no statistical differences between the groups (Table 4).

When analyzed stratified by treatment phase, it was observed that among patients who responded to second-generation H1 antihistamines at standard or double doses (Phase 1), BMI was significantly lower compared to non-responders. No other variables showed significant differences (Table 5).

Among patients who required increased doses of second-generation H1 antihistamines (Phase 2), non-responders had earlier symptom onset, longer disease duration, and a higher prevalence of mental disorders. These factors stood out as possible markers of refractoriness in this therapeutic phase, while the other variables analyzed did not differ statistically (Table 6).

For patients who required omalizumab, the presence of mental disorders was also significantly more frequent among patients who did not respond to treatment (Table 7). The other variables also showed no statistical association with treatment response.

Regarding the type of chronic urticaria (CSU, CIndU, or CSU + CIndU), no significant differences were observed in the treatment response profile, whether with standard or increased doses of H1 antihistamines, or with omalizumab (Table 8). Similarly, no statistically significant associations were identified between the omalizumab response subtypes and serum total IgE or anti-TPO levels. Although the different subgroups did not differ overall regarding IgE levels, partial responders had significantly lower mean IgE levels compared to the other response types, with all cases in this group showing levels below 40 IU/mL. No differences were observed between IgE levels in patients with early or late responses, nor between anti-TPO levels in the different response profiles (Table 9).

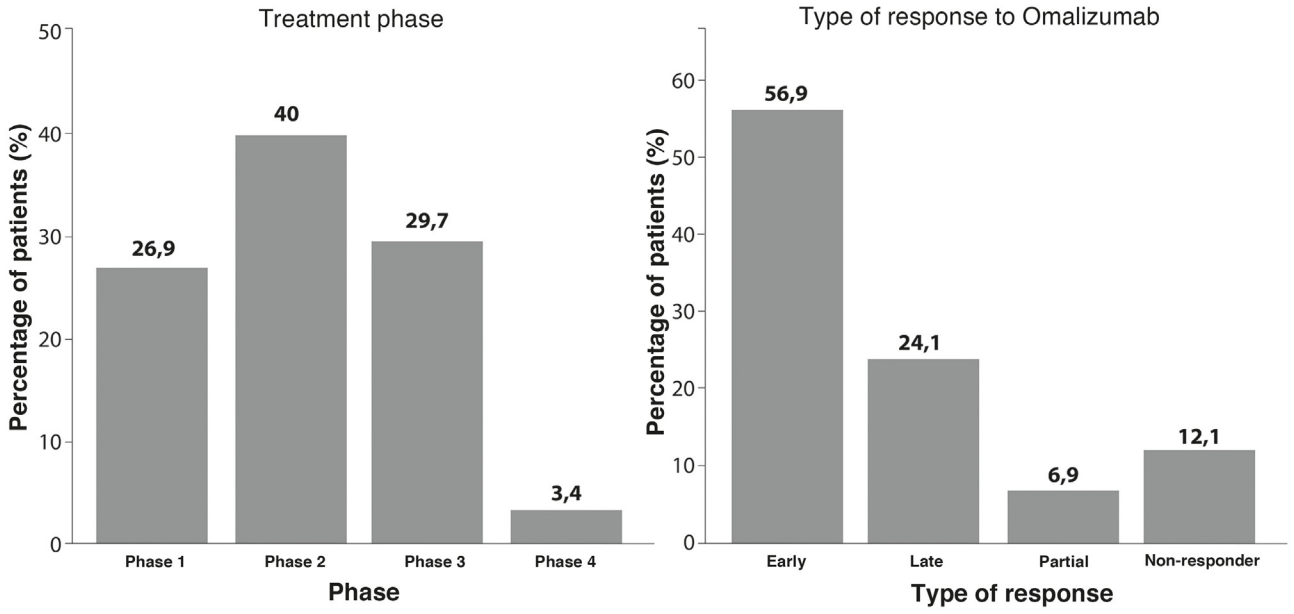

Fig. 1 Treatment data.

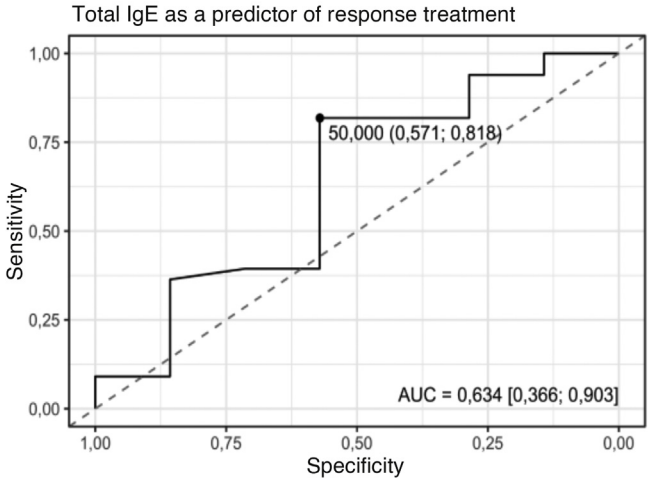

Fig. 2 ROC (Receiver Operating Characteristic) curve for Total IgE as a predictor of Response to Treatment. Note: AUC indicates the area under the curve. Values in brackets represent the 95% confidence interval. The highlighted point corresponds to the best cutoff point, according to the Youden index, which simultaneously maximizes sensitivity and specificity. The values in parentheses correspond, respectively, to the specificity and sensitivity for the highlighted cutoff point. The Yes group had, on average, higher Total IgE values than the No group. Source: Prepared by the author.

Finally, the ROC curve analysis evaluating the predictive ability of total IgE in omalizumab response demonstrated limited performance. The area under the curve (AUC) was 0.634 ($p = 0.327$), with a confidence interval including the 0.5 value, indicating a lack of statistically significant discrimination. The identified cutoff point was 50 IU/mL, with a sensitivity of 81.8% and a specificity of 57.1% (Fig. 2).

Discussion

This study evaluated clinical and laboratory predictors of treatment response in 175 patients with CU followed at a referral center. The analysis showed that clinical variables such as high BMI, female gender, early symptom onset, prolonged disease duration, and the presence of mental disorders were associated with a worse therapeutic response, especially in the initial phases of treatment with second-generation H1 antihistamines.

Among patients who responded or did not respond to low doses of H1 antihistamines, high BMI was significantly more common in nonresponders, reinforcing previous data associating obesity with greater CU severity, poorer symptom control, and longer disease duration, possibly due to chronic low-grade inflammation with higher concentrations of cytokines such as IL-6.[13,14]

Longer disease duration and early symptom onset were also markers of refractoriness, especially in patients taking increased doses of H1 antihistamines, which is consistent with data from Engstrom et al.,[15] which indicate worse clinical outcomes in these subgroups. Prolonged duration of chronic urticaria is associated with greater clinical severity, as demonstrated by Toubi et al.,[16] who observed that moderate to severe forms of CU persisted for significantly longer periods than mild cases. This association may reflect a more intense and sustained inflammatory process, possibly related to autoimmune mechanisms, such as the presence of autoantibodies against the IgE receptor (positive TSA) or antithyroid autoantibodies, both associated with longer disease duration. Additionally, a study showed that young patients with CU (18–40 years) had higher mortality, and that each additional year of disease increases the risk of developing mental disorders by 64% compared to controls.[17]

Furthermore, the higher proportion of women in the group requiring omalizumab may reflect the greater severity of CU in this group, which is also consistent with studies

Table 3 Comparison between patients responding to standard or double doses of H1 antihistamines and those requiring higher doses (n = 86).

Variable	Responds to standard or double dose (n = 39)	Responds only to higher doses (n = 47)	p	ES
Female sex, n (%)	28 (71.79)	35 (74.47)	0.973[a]	0.004
Age in years:				
Mean (SD)	44.37 (20.46)	46.01 (19.47)	0.591[b]	−0.058
BMI (kg/m^2):				
Mean (SD)	25.77 (5.51)	27.62 (6.84)	0.176[c]	−0.295
Age at symptom onset:				
Mean (SD)	30.86 (19.46)	37.26 (19.0)	0.151[b]	−0.158
Time of disease (years):				
Mean (SD)	12.22 (16.0)	9.02 (11.3)	0.174[b]	0.149
Presence of angioedema, n (%)	29 (74.4)	41 (87.2)	0.212[a]	0.135
Main diagnosis n (%)			0.959[a]	0.031
CSU	23 (59.0)	29 (61.7)		
CSU + CIndU	11 (28.2)	12 (25.5)		
CIndU alone	5 (12.8)	6 (12.8)		
Comorbidities n (%):				
Metabolic disorder	15 (38.5)	24 (51.1)	0.342[a]	0.103
Autoimmune disorder	12 (30.8)	13 (27.7)	0.938[a]	0.008
Mental disorder	4 (10.3)	3 (27.7)	0.907[a]	0.028
Atopic disorder	18 (46.2)	20 (42.6)	0.907[a]	0.013
Cardiovascular disorder	14 (35.9)	11 (23.4)	0.302[a]	0.111
Hypersensitivity to NSAIDs	13 (33.3)	14 (29.8)	0.905[a]	0.013
ESR – n (%):			0.433[a]	0.094
High	12 (44.4)	24 (57.1)		
Normal	15 (55.56)	18 (42.86)		
CRP – n (%):			0.169[b]	0.049
Positive	7 (19.4)	6 (13.3)		
Normal	29 (80.56)	39 (86.67)		
D-dimer – n (%):			1.000[d]	0.000
High	3 (21.4)	4 (28.6)		
Normal	11 (78.57)	10 (71.43)		
Eosinophils (cells/μL):				
Mean (SD)	151.4 ± 139.2	210.6 ± 192.4	0.169[b]	−0.152
Total IgE (UI/mL):				
Mean (SD)	230.5 (288.17)	332.9 (579.11)	0.834[b]	−0.026
< 40 UI/mL – n (%)	8 (29.63)	10 (23.81)	0.798[a]	0.031
≥ 40 UI/mL – n (%)	19 (70.4)	32 (76.2)	0.798[a]	0.031
Anti-TPO – n (%):			1.000[a]	0.000
High	7 (21.2)	8 (20.0)		
Normal	26 (78.79)	32 (80.00)		

Source: Prepared by the author.
SD, Standard Deviation; BMI, Body Mass Index; CSU, Chronic Spontaneous Urticaria; CIndU, Chronic Inducible Urticaria; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; TPO, Peroxidase.
ES, Effect Size. The following effect sizes were calculated: Cohen's d, for the independent *t*-test; r, for the Mann-Whitney test; Cramer's V, for the Fisher's exact test and chi-square test of independence.
[a] Chi-Square test of independence.
[b] Mann-Whitney Test.
[c] Independent *t*-test.
[d] Fisher's Exact Test.

that attribute the higher frequency of refractory forms of the disease to the female sex, possibly due to the higher prevalence of autoimmune diseases among women.[18]

The presence of mental disorders, in turn, was consistently associated with a worse response to both antihistamines and omalizumab. This finding reinforces the importance of neuroimmunoendocrine axes in the pathophysiology of CU and the impact of stress, anxiety, and substance P on mast cell activation.[19,20] Substance P, in particular, can bind to the MRGPRX2 receptor, present on the surface of mast cells, promoting their exacerbated activation, which may contribute to the persistence of symptoms in these patients.[21] It is worth noting that the study by Kolkhir et al.[17] revealed an increased risk of mortality among

Table 4 Comparison of the clinical and laboratory profile of patients responding to antihistamines and those responding to Omalizumab (n = 133).

Variable	Responds to antihistamines (n = 86)	Responds to Omalizumab (n = 47)	p	ES
Sex, n (%):			**0.009**[a]	0.226
Female	63 (73.26)#	44 (93.62)#		
Male	23 (26.74)#	3 (6.38)#		
Age in years:			0.596[b]	0.046
Mean (SD)	45.27 (19. 82)	45.37 (16. 40)		
Median (Q1; Q3)	49.50 (33.22; 60.00)	45.95 (38.37; 57.61)		
BMI (kg/m^2):			0.068[c]	−0.333
Mean (SD)	26.78 (6.31)	28.88 (6.28)		
Median (Q1; Q3)	27.55 (23.00; 30.42	45.95 (38.37; 57.61)		
Age at Onset in years:			0.097[b]	0.146
Mean (SD)	34.41 (19.36)	29.15 (15.75)		
Median (Q1; Q3)	40.00 (15.00; 49.50)	30.00 (17.50; 36.75)		
Time of disease:			**<0.001**[b]	−0.310
Mean (SD)	10.45 (13.62)	15.11 (11.35)		
Median (Q1; Q3)	7.00 (3.00; 10.00)	11.00 (6.00; 21.00)		
Angioedema n (%):	70 (81.40)	41 (87.23)	0.534[a]	0.054
Main diagnosis n (%):			0.668[a]	0.078
CSU	52 (60.74)	26 (55.32)		
CSU + CIndU	23 (26.74)	16 (34.04)		
CIndU alone	11 (12.79)	5 (10.64)		
Comorbidities n (%):			0.653[a]	0.653[a]
Metabolic disorder	39 (45.35)	24 (51.06)	0.106[a]	0.140
Autoimmune disorder	25 (29.07)	7 (14.89)	1.000[d]	0.000
Mental disorder	7 (8.14)	4 (8.51)	0.232[a]	0.104
Atopic disorder	38 (44.19)	15 (31.91)	0.255[a]	0.099
Cardiovascular disorder	25 (29.07)	19 (40.43)	1.000[a]	0.000
Hypersensitivity to NSAIDs – n (%)	27 (31.40)	14 (29.79)		
ESR n (%):			0.460[a]	0.070
High	36 (52.17)	19 (43.18)		
Normal	33 (47.83)	25 (56.82)		
CRP, n (%):			0.140[a]	0.132
Positive	13 (16.05)	13 (28.89)		
Normal	68 (83.95)	32 (71.11)		
D-Dimer, n (%):			1.000[a]	0.000
High	7 (25.00)	5 (25.00)		
Normal	21 (75.00)	15 (75.00)		
Eosinophils:			0.300[b]	−0.093
Mean (SD):	185.36 (173.26)	230.28 (238.30)		
Median (Q1; Q3):	137.00 (61.50; 255.75)	153.45 (92.88; 280.25)		
Total IgE:				
Mean (SD)*	292.85 (486.31)	331 (506.5)	0.740[b]	−0.033
Median (Q1; Q3)	111.0 (39.5; 313.0)	111.0 (64.8; 419.5)	0.740[b]	−0.033
< 40 – n (%)	18 (26.09)	6 (18.8)	0.579[a]	0.055
≥ 40 – n (%)	51 (73.91)	26 (81.2)	0.579[a]	0.055
Anti –TPO, n (%):			1.000[a]	0.000
High	15 (20.55)	9 (20.00)		
Normal	58 (79.45)	36 (80.00)		

Source: Prepared by the author.

SD, Standard Deviation; Q1, First Quartile (25th percentile); Q3, Third Quartile (75th percentile); BMI, Body Mass Index; CSU, Chronic Spontaneous Urticaria; CIndU, Chronic Inducible Urticaria; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; TPO, Peroxidase.

ES, Effect Size. The following effect sizes were calculated: Cohen's d, for the independent *t*-test; r, for the Mann-Whitney test; Cramer's V, for the Fisher's exact test and chi-square test of independence.

[a] Chi-Square test of independence.

[b] Mann-Whitney Test.

[c] Independent *t*-test.

[d] Fisher's Exact Test.

Table 5 Comparison of patients who responded versus non-responders to Phase 1 regarding their clinical and laboratory profile (n = 174).

Variable	No (n:135)	Yes (n:39)	p	ES
Sex – n (%):			0.187[a]	0.100
Female	112 (82.96)	28 (71.79)		
Male	23 (17.04)	11 (28.21)		
Age in years:			0.887[b]	0.011
Mean (SD):	45.53 (17.39)	44.37 (20.46)		
Median (Q1; Q3):	48.00 (38.00; 59.50)	47.00 (33.14; 59.50)		
BMI (kg/m^2)			**0.015**[c]	0.445
Mean(DP):	28.55 (6.44)	25.77 (5.51)		
Median (Q1; Q3):	27.90 (23.85; 32.50)	27.10 (22.60; 29.05)		
Age of onset in years			0.528[b]	0.048
Mean (SD):	33.26 (17.76)	30.86 (19.46)		
Median (Q1; Q3):	34.00 (20.00; 48.00)	29.00 (15.00; 47.00		
Time of disease in years:			0.711[b]	0.028
Mean (SD):	11.90 (11.58)	12.22 (16.00)		
Median (Q1; Q3):	8.00 (4.00; 17.00)	7.00 (3.00; 13.00)		
Angioedema – n (%)	112 (82.96)	29 (74.36)	0.329[a]	0.074
Main diagnoses– n (%):			0.899[a]	0.035
CSU	74 (54.81)	23 (58.97)		
CSU + CIndU	42 (31.11)	11 (28.21)		
CIndU alone	19 (14.07)	5 (12.82)		
Comorbidities, n (%):				
Metabolic disorder	68 (50.37);	15 (38.46);	0.259[a]	0.086
Autoimmune disorder	28 (20.74);	12 (30.77);	0.273[a]	0.083
Mental disorder	28 (20.74);	4 (10.26);	0.210[a]	0.095
Atopic disorder	51 (37.78);	18 (46.15)	0.450[a]	0.057
Cardiovascular disorder	43 (31.85);	14 (35.90)	0.779[a]	0.021
Hypersensitivity to NSAIDs	42 (31.11)	13 (33.33)	0.946[a]	0.005
ESR – n (%):			0.876[a]	0.013
High	59 (48.36)	12 (44.44)		
Normal	63 (51.64)	15 (55.56)		
CRP – n (%):			0.864[a]	0.014
Positive	28 (22.58)	7 (19.44)		
Normal	96 (77.42)	29 (80.56)		
D-dimer – n (%):			1.000[d]	0.000
High	12 (25.00)	3 (21.43)		
Normal	36 (75.00)	11 (78.57)		
Eosinophils:			0.119[b]	0.122
Mean (SD):	210.61 (200.32)	151.41 (139.23)		
Median (Q1; Q3):	144.50 (83.38; 278.00)	119.00 (59.50; 170.00)		
Total IgE:				
Mean (SD):	289 (482.2)	230.53 (288.17)	0.841[2]	−0.018
Median (Q1; Q3):	105,0 (40,4; 281,0)	109,0 (36,4; 309,5)	0,841[b]	−0,018
< 40 – n (%)	26 (25,2)	8 (29,63)	0,829[a]	0,019
≥ 40 – n (%)	77 (74,8)	19 (70,37)	0,829[a]	0,019
Anti –TPO– n (%):			1,000[a]	0,000
High	23 (19,33)	7 (21,21)		
Normal	96 (80,67)	26 (78,79)		

Source: Prepared by the author.
SD, Standard Deviation; Q1, First Quartile (25th percentile); Q3, Third Quartile (75th percentile); BMI, Body Mass Index; CSU, Chronic Spontaneous Urticaria; CIndU, Chronic Inducible Urticaria; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; TPO, Peroxidase.
ES, Effect Size. The following effect sizes were calculated: Cohen's d, for the independent *t*-test; r, for the Mann-Whitney test; Cramer's V, for the Fisher's exact test and chi-square test of independence.
[a] Chi-Square test of independence.
[b] Mann-Whitney Test.
[c] Independent *t*-test.
[d] Fisher's Exact Test.

Table 6 Comparison of patients who responded versus non-responders to Phase 2 regarding their clinical and laboratory profile (n = 128).

Variable	No (n = 81)	Yes (n = 47)	p	ES
Sex – n (%):			0.096[a]	0.147
Female	71 (87.65)	35 (74.47)		
Male	10 (12.35)	12 (25.53)		
Age in years:			0.280[b]	0.280[b]
Mean (SD)	44.58 (16.26)	46.01 (19.47)		
Median (Q1; Q 3)	44.00 (38.00; 55.23)	51.00 (34.98; 60.50)		
BMI (Kg/m^2):			0.203[c]	0.235
Mean (SD)	29.17 (6.43)	27.62 (6.84)		
Median (Q1; Q3)	27.60 (24.20; 34.00)	27.90 (23.20; 32.10)		
Age of onset in years:			0.036[c]	−0.393
Mean (SD)	30.42 (16.42)	37.26 (19.00)		
Median (Q1; Q3)	30.00 (19.75; 40.00)	42.00 (21.75; 50.00)		
Time of disease in years:			0.001[b]	0.285
Mean (SD)	13.38 (10.41)	9.02 (11.34)		
Median (Q1; Q3)	10.50 (5.00; 20.00)	6.00 (2.25; 8.00)		
Angioedema – n (%)	66 (81.48)	41 (87.23)	0.549[a]	0.053
Main diagnoses:			0.464[a]	0.109
CSU	41 (50.62)	29 (61.70)		
CSU + CIndU	28 (34.57)	12 (25.53)		
CIndU alone	12 (14.81)	6 (12.77)		
Comorbidities: n (%)				
Metabolic disorder	40 (49.38)	24 (51.06)	1.000[a]	0.000
Autoimmune disorder	14 (17.28)	13 (27.66)	0.245[a]	0.103
Mental disorder	23 (28.40)#	3 (6.38)#	0.006[a]	0.244
Atopic disorder	28 (34.57)	20 (42.55)	0.478[a]	0.063
Cardiovascular disorder	29 (35.80)	11 (23.40)	0.207[a]	0.111
Hypersensitivity to NSAIDs	25 (30.86)	14 (29.79)	1.000[a]	0.000
ESR – n (%):			0.336[a]	0.088
High	35 (46.05)	24 (57.14)		
Normal	41 (53.95)	18 (42.86)		
CRP – n (%):			0.075[a]	0.163
Positive	22 (29.33)	6 (13.33)		
Negative	53 (70.67)	39 (86.67)		
D-Dimer – n (%):			1.000[d]	0.000
High	8 (25.81)	4 (28.57)		
Normal	23 (74.19)	10 (71.43)		
Eosinophils:			0.845[b]	−0.018
Mean (SD)	207.20 (209.86)	210.63 (192.35)		
Median (Q1; Q3):	139.00 (83.50; 273.00)	145.00 (69.92; 276.50)		
Total IgE:				
Mean (SD)	246.4 (407.4)	332.9 (579.1);	0.498[b]	−0.068
Median (Q1; Q3)	139.00 (83.50; 273.00)	145.00 (69.92; 276.50)	0.498[b]	−0.068
< 40 – n (%)	15 (29.9)	10 (23.8)	1.000[a]	0.000
≥ 40 – n (%)	43 (74.1)	32 (76.2)	1.000[a]	0.000
Anti –TPO – n (%):			1.000[a]	0.000
High	14 (18.67)	8 (20.00)		
Normal	61 (81.33)	32 (80.00)		

Source: Prepared by the author.
SD, Standard Deviation; Q1, First Quartile (25th percentile); Q3, Third Quartile (75th percentile); BMI, Body Mass Index; CSU, Chronic Spontaneous Urticaria; CIndU, Chronic Inducible Urticaria; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; TPO, Peroxidase.
ES, Effect Size. The following effect sizes were calculated: Cohen's d, for the independent *t*-test; r, for the Mann-Whitney test; Cramer's V, for the Fisher's exact test and chi-square test of independence.
[a] Chi-Square test of independence.
[b] Mann-Whitney Test.
[c] Independent *t*-test.
[d] Fisher's Exact Test.

Table 7 Comparison of patients who responded versus non-responders to Phase 3 regarding their clinical and laboratory profile (n = 58).

Variable	No (n = 11)	Yes (n = 47)	p	ES
Sex – n (%):			1.000[a]	0.000
Female	10 (90.91)	44 (93.62)		
Male	1 (9.09)	3 (6.38)		
Age in years:			0.056[b]	−0.653
Mean (SD)	35.03 (12.88)	45.37 (16.40)		
Median (Q1; Q3)	39.00 (27.69; 42.50)	45.95 (38.37; 57.61)		
BMI (kg/m^2):			0.941[b]	−0.025
Mean (DP)	28.72 (7.63)	28.88 (6.28)		
Median (Q1; Q3)	28.90 (22.70; 32.50)	27.20 (24.40; 33.90)		
Age at onset in years:			0.494[b]	−0.231
Mean (SD)	25.55 (15.00)	29.15 (15.75)		
Median (Q1; Q3)	25.00 (19.50; 34.50)	30.00 (17.50; 36.75)		
Time of disease in years:			0.103[c]	−0.217
Mean (SD)	9.45 (6.44)	15.11 (11.35)		
Median (Q1; Q3):	7.00 (5.00; 16.00)	11.00 (6.00; 21.00)		
Angioedema – n (%):	9 (81.82)	41 (87.23)	0.639[a]	0.000
Main diagnoses			0.465[a]	0.153
CSU	4 (36.36);	26 (55.32);		
CSU + CIndU	5 (45.45);	16 (34.04);		
CIndU alone	2 (18.18)	5 (10.64)		
Comorbidities – n (%):				
Metabolic disorder	5 (45.45)	24 (51.06)	1.000[d]	0.000
Autoimmune disorder	2 (18.18)	7 (14.89)	1.000[a]	0.000
Mental disorder	8 (72.73)#	4 (8.51)#	**<0.001**[a]	0.567
Atopic disorder	4 (36.36)	15 (31.91)	1.000[a]	0.000
Cardiovascular disorder	3 (27.27)	19 (40.43)	0.507[a]	0.061
Hypersensitivity to NSAIDs	3 (27.27)	14 (29.79)	1.000[a]	0.000
ESR – n (%):			0.501[a]	0.056
High	3 (30.00)	19 (43.18)		
Normal	7 (70.00)	25 (56.82)		
CRP – n (%):			1.000[a]	0.000
Positive	2 (22.22)	13 (28.89)		
Normal	7 (77.78)	32 (71.11)		
D-Dimer – n (%):			0.481[a]	0.000
High	1 (50.00)	5 (25.00)		
Normal	1 (50.00)	15 (75.00)		
Eosinophils:			0.106[c]	−0.222
Mean (SD)	123.73 (119.26)	230.28 (238.30)		
Median (Q1; Q3)	91.15 (45.25; 130.25)	153.45 (92.88; 280.25)		
Total IgE:				
Mean (SD)	229.4 (319.4)	331.6 (506.5)	0.407[c]	−0.134
Median (Q1; Q3)	135.6 (24.0; 280.0)	111.0 (64.8; 419.5)	0.407[c]	−0.134
< 40 – n (%)	3 (37.5)	6 (18.8)	0.348[a]	0.105
≥ 40 – n (%)	5 (62.5)	26 (81.2)	0.348[a]	0.105
Anti –TPO – n (%):			0.668[a]	0.039
High	1 (10.00)	9 (20.00)		
Normal	9 (90.00)	36 (80.00)		

Source: Prepared by the author.
SD, Standard Deviation; Q1, First Quartile (25th percentile); Q3, Third Quartile (75th percentile); BMI, Body Mass Index; CSU, Chronic Spontaneous Urticaria; CIndU, Chronic Inducible Urticaria; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; TPO, Peroxidase.
ES, Effect Size. The following effect sizes were calculated: Cohen's d, for the independent *t*-test; r, for the Mann-Whitney test; Cramer's V, for the Fisher's exact test and chi-square test of independence.
[a] Chi-Square test of independence.
[b] Mann-Whitney Test.
[c] Independent *t*-test.
[d] Fisher's Exact Test.

Table 8 Analysis of the association between the pharmacological response profile and the type of CU (n = 175).

Variable	CSU (n = 97)	CSU + CIndU (n = 54)	CIndU (n = 24)	p	V
Responds to high-dose H1 antihistamines	29 (37.18)	12 (30.77)	6 (37.50)	0.927	0.058
Responds to low-dose H1 antihistamines	23 (29.49)	11 (28.21)	5 (31.25)	0.927	0.058
Responds to omalizumab	26 (33.33)	16 (41.03)	5 (31.25)	0.927	0.058

Source: Prepared by the author.
Chi-square test of independence; V, Cramer's V. CSU, Chronic Spontaneous Urticaria; CIndU, Chronic Inducible Urticaria.

Table 9 Comparison of serum IgE (n = 40) and Anti-TPO (n = 54) values of patients treated with omalizumab, according to their drug response subtype.

Variable	Early (n = 21)	Late (n = 11)	Partial (n = 2)	Non-responder (n = 6)	p	ES
Total IgE:						
Mean (SD)	268.5 (303.1)	452.1 (766.3)	16.8 (17.1)	300.3 (344.5)	0.295[a]	0.020
<40 – n (%)	4 (19.0)	2 (18.2)	2 (100.0)	1 (16.7)	0.122[b]	0.426
≥40 – n (%)	17 (81.0)	9 (81.8)	0 (0.0)	5 (83.33)	0.122	0.426
	Early (n = 33)	Late (n = 13)	Partial (n = 2)	Non-responder (n = 6)	p	V
Anti-TPO: n (%)					0.698	0.194
Normal	27 (81.8)	10 (76.9)	2 (100.0)	6 (100.0)		
High	6 (18.2)	3 (23.1)	0 (0.0)	0 (0.0)		

Source: Prepared by the author.
SD, Standard deviation; TPO, Peroxidase.
ES, Effect Size. The following effect sizes were calculated: $\eta 2[H]$, for the Kruskal-Wallis test; Cramer's V, for Fisher's exact test.
[a] Kruskal-Wallis Test.
[b] Fisher's exact Test.

patients with CSU, including higher rates of suicidal ideation and suicide attempts. This evidence reinforces the need for a multidisciplinary approach in the management of CSU.

Although previous studies[5,6] have shown that elevated CRP and D-dimer levels, as well as eosinopenia, are associated with poor response to H1 antihistamines, and that low total IgE, elevated CRP/ESR, eosinopenia, and increased D-dimer could predict a lower response to omalizumab and a better response to cyclosporine, none of these associations were confirmed in the present study in the evaluated therapeutic phases. These tests were requested based on the hypothesis that systemic inflammatory processes, reflected by markers such as CRP and ESR,[22,23] and coagulation activation, evidenced by D-dimer, play a role in the pathophysiology of chronic urticarial.[23,24] Eosinopenia, in turn, has been associated with increased migration of eosinophils into tissues, which contributes to local inflammation and may indicate increased disease activity, autoimmunity, and poor therapeutic response,[8,25] while total IgE is considered a possible marker of atopic phenotype and response to omalizumab.[26,27] However, the present results suggest that, taken alone, these biomarkers have limited predictive value in clinical practice, especially in the present sample. It is important to highlight that the number of patients with D-dimer measurements was small, which may have compromised the analysis. Furthermore, in the present population, eosinophil and total IgE levels may have been higher due to confounding factors, such as the presence of concomitant atopic diseases and intestinal parasitic infections, common in endemic regions.

The analysis of omalizumab response subtypes and IgE levels revealed no statistically significant association, although all partial responders had IgE levels <40 IU/mL. This finding differs from the meta-analysis by Chuang et al.,[28] but is consistent with studies that also failed to identify this correlation,[9,29,30] reinforcing the complexity of this relationship. IgE plays a central role in the pathophysiology of CSU, being involved in both autoallergic mechanisms (type I) and type IIb autoimmune forms, where low IgE levels often coexist with IgG autoantibodies against IgE or its receptor (FcεRI).[26] Therefore, the quantification of total IgE has been proposed as a predictive marker of response to omalizumab, with worse results observed in patients with lower IgE. However, in the present sample, the small number of non-responders and partial responders may have limited the detection of a statistically significant association.

Similarly, no association was observed between anti-TPO levels and response to omalizumab, a result similar to that described by Asero et al.,[31] but different from that by Kolkhir et al.[32] The association between thyroid autoimmunity and CU has been described, with several studies demonstrating a high prevalence of IgE and IgG autoantibodies against thyroid antigens (such as TPO and thyroglobulin) in patients with CSU. These autoantibodies can promote mast cell and basophil activation, contributing to the disease pathophysiology.[33] Although thyroid autoimmunity is associated with greater severity and poorer therapeutic response,[34] it is unclear whether isolated autoantibodies predict refractoriness. Biomarkers such as BAT, positive TSA, and elevated ANA have been associated with poor

response in other studies but were not included in this analysis.

ROC curve analysis for total IgE demonstrated limited performance, with an area under the curve of 0.634 (p = 0.327), confirming its low specificity as an isolated marker of response to omalizumab. Although higher IgE levels are associated with a more favorable response in some studies,[5,35] these data were not significantly replicated in the present sample, limiting its usefulness as an isolated predictor of response to treatment with this drug.

Therefore, the results reinforce the hypothesis that clinical and psychosocial characteristics are, to date, the main predictors of therapeutic response in chronic urticaria. The cross-sectional design, the small number of non-responders to omalizumab, and the lack of data on the duration of drug exposure are limitations that should be considered. In addition to these limitations, it is important to recognize that the study was conducted with a convenience sample recruited at a specialized tertiary center, which may have generated selection bias, limiting the representativeness of the general population with chronic urticaria. To minimize this bias, well-defined inclusion and exclusion criteria were used, with data collection performed in a standardized manner by a trained team using validated instruments (UCT and AECT). The potential information bias is also recognized, inherent to the use of medical record data, which was mitigated by systematically reviewing records and supplementing information during medical consultations, always with the patients' prior consent.

Regarding external validity, because this is a single-center study, extrapolation of the results to other populations should be done with caution, taking into account the specific clinical and epidemiological profile of the study sample. On the other hand, internal validity was ensured by adopting diagnostic criteria based on international guidelines (EAACI/GA^{2}LEN/EDF/WAO), using standardized therapeutic protocols, and by applying validated instruments to assess treatment response.

Prospective studies with standardized biomarker assessment are required to validate the findings and guide precision medicine in CU management.

Conclusion

The study aimed to analyze predictive markers of treatment response in patients with chronic urticaria. The research reinforces the complexity of CU and its management challenges, highlighting its predominance in women, adult onset, and long disease duration. The main predictors of poorer response to treatment were longer disease duration, female sex, high BMI, early symptom onset, and the presence of mental disorders. Eosinophils, total IgE, and the other evaluated laboratory markers (ESR, CRP, D-dimer, and anti-TPO) showed no significant association with therapeutic response.

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Research data availability

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

Conflicts of interest

Campos RA has declared receiving speaker fees from Novartis, Takeda, and Sanofi.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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REVIEW

The role of phototherapy in pediatric dermatology☆

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Abstract

Background: Phototherapy is one of the widely used therapeutic options in dermatology, and it has proven effective for many dermatological conditions. It includes various modalities such as heliotherapy, broad-band UVB, narrow-band UVB, excimer laser, UVA1, UVA with Psoralens (PUVA), among others. The mechanisms behind phototherapy's efficacy include proapoptotic, immunomodulatory, propigmenting, antifibrotic, and antipruritic effects. In this context, the effectiveness of this modality has been demonstrated in pediatric patients with various conditions; however, no consensus has yet been established regarding its use in this population.
Methods: A comprehensive literature review was conducted to identify the most recent studies and advancements in the use of phototherapy in the pediatric population.
Results: Phototherapy is a safe and effective therapeutic modality that can be used in multiple conditions, such as psoriasis, vitiligo, atopic dermatitis, mycosis fungoides, pityriasis lichenoides, and actinic prurigo, among others. The therapeutic outcomes depend on the condition being treated, the type of phototherapy used, and the appropriate selection of patients.
Conclusions: The phototherapy with NB-UVB is the most commonly use and preferred modality due to its efficacy and lower risk associated. Careful monitoring is recommended to assess long-term safety and optimize pediatric treatment protocols.

Introduction

Phototherapy is a treatment that involves delivering Ultraviolet (UV) radiation to patients to treat various dermatologic conditions[1] and has been highly effective in the management of epidermal and deep dermal diseases.[2] While it is an effective and safe treatment option for many skin disorders in adults, its use in children has been more restricted due

☆ Study conducted at the Hospital Clínico, Universidad de Chile, Santiago, Chile.

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to concerns about the potential long-term carcinogenic risks associated with UV exposure.[3] Nonetheless, there is substantial evidence supporting its use in pediatric dermatology for conditions such as vitiligo, Atopic Dermatitis (AD), psoriasis, alopecia areata, pityriasis lichenoides, mycosis fungoides, scleroderma, among others.[4]

Phototherapy has been practiced since ancient times, with records of heliotherapy and exposure to sunlight in ancient Egypt, China, and Hindu culture. The authors have the Ebers Papyrus (1550 BCE), which contains the treatment of vitiligo with Psoralen corylifolia and Ammi majus extract, and the after exposure of the person to sunlight. And many more records. In the 19th century, Nils Ryberg Finsen (1860–1904) started using electric carbon arc torch in the treatment of patients with lupus vulgaris, a chronic and progressive form of cutaneous tuberculosis caused by the bacterium Mycobacterium tuberculosis, becoming the father of modern phototherapy, and subsequently, the use of artificial light in phototherapy took place in the treatment of different skin diseases, till William Henry Goeckerman (1884–1954) began using UVB light to treat psoriasis. Since that, the field of phototherapy has been constantly growing and expanding to different areas of medicine such as neonatology, infectology, psychiatry, ophthalmology, rheumatology, and oncology.[5]

Photodermatology is a crucial part of the dermatological practice and requires appropriate knowledge and expertise for the correct implementation of this treatment.[2] The mechanism by which phototherapy works varies depending on the specific condition being treated and the modality employed. However, it is generally understood that UV light helps to modulate the immune response that underlies many inflammatory and autoimmune skin diseases, induces apoptosis, and modifies the cytokine environment.[6,7]

Phototherapy mechanisms of action that can occur simultaneously, among them are: proapoptotic effects (AD, psoriasis, T-cell lymphomas), immunomodulatory effects (AD, psoriasis, T-cell lymphomas), propigmenting effects (vitiligo), antifibrotic effects (scleroderma, GVHD), antipruritic effects (various dermatoses where pruritus is a predominant symptom), and, probiotic and prebiotic effects (AD, psoriasis).[2] Treatment options include heliotherapy (sunlight exposure), UVA1 (340–400 nm), UVA (320–400 nm), either alone or in combination with Psoralen (PUVA), broadband UVB (BB-UVB: 280–320 nm), narrowband UVB (NB-UVB: 311–313 nm), the excimer laser (UVB: 308 nm), as well as combination therapies that involve both UVA and UVB.[2,4,8]

Despite the existing body of evidence, there is a notable lack of randomized controlled trials on pediatric phototherapy, with most data coming from retrospective studies. As a result, treatment protocols and dosing regimens are often based on clinical experience rather than standardized guidelines. Additionally, special considerations must be considered when administering phototherapy to children, including the safe delivery of treatments, appropriate scheduling, and addressing long-term safety concerns.[4,9,10] This review aims to highlight the primary indications for phototherapy in children and explore the critical considerations involved in administering UV treatments within the pediatric population.

Material and methods

During November 2024 and February 2025, the authors conducted a narrative review of the literature by entering the terms ''phototherapy'', ''pediatric dermatology'', ''NB-UVB'', ''PUVA'', ''UVA1'', ''excimer light'', ''psoriasis phototherapy'', ''vitiligo phototherapy'' and ''atopic dermatitis phototherapy'' into PubMed and Google Scholar. The search was limited to articles in English and Spanish. All three authors participated in the search and subsequently selected the articles based on their relevance.

Indications

Principal indications, type and modality of phototherapy are summarized in Table 1.

Psoriasis

Psoriasis corresponds to a chronic multifactorial inflammatory skin disease, caused by a dysregulation of the immune system characterized by an activation of T-cells and proliferation of keratinocytes, affecting primarily skin, nails, and joints, with the presence of erythematous-desquamative plaques in the face, body, and extremities.[11] It has a prevalence of 2%–3% of the global population, and it represents 4% of all dermatoses in patients younger than 16-years-old.[12] The treatment is based on a step-wise approach, with the use of topical treatment in mild cases (topical corticosteroids, calcineurin inhibitors, and vitamin D derivatives) and systemic therapy in moderate and severe cases (systemic immunomodulators, biological agents, phototherapy, or photochemotherapy).[13] The evidence supporting the use of phototherapy in psoriasis primarily comes from retrospective reviews.[14] The American Academy of Dermatology (AAD) recommends phototherapy as a second-line treatment for children with psoriasis who do not respond to initial topical therapies or in cases of extensive disease.[15,16] NB-UVB is the preferred modality due to its proven efficacy, safety, and ease of administration in pediatric patients with psoriasis (Fig. 1A–B). In one of the largest studies to date, 88 children with psoriasis were treated using NB-UVB, with 92% of patients experiencing more than 75% improvement in their condition, with full clearance achieved in 51%.[17] A prospective study of 20 pediatric patients with recurrent guttate or plaque psoriasis showed an improvement of a minimum of 60% after 12-weeks of treatment, with remission rates of 90%.[18] Other treatment modalities include BB-UVB, excimer laser, and PUVA. In a study involving 30 patients with psoriasis (mean age 11 $\pm$ 3.6 years) treated with BB-UVB (mean number of treatments: 28.8 $\pm$ 13.3), 93.3% of subjects experienced more than 75% improvement. Another study that compared the safety and efficacy of the excimer laser in adults versus children evidenced efficacy and safety in both groups, with 12.5 sessions in children compared with the 9.7 sessions needed in adults.[19] Additionally, a small cohort of seven children with plaque or guttate psoriasis was treated with PUVA therapy, resulting in more than 75% clinical improvement in 83% of patients after an average of 28 treatment sessions.[20] To assess long-term efficacy, a retrospective study involving 75 pediatric

Table 1 Principal indications, type and modality of phototherapy in pediatric dermatology.

Indication	Modality used	Clinical comment
Psoriasis	UVB (nb-UVB, bb-UVB) Excimer laser PUVA.	High efficacy, well-tolerated, prolonged remission in some cases
Vitiligo	nb-UVB Excimer laser PUVA UVA1+UVB	NB-UVB is the most effective treatment, providing superior facial and neck repigmentation; its effects are enhanced when combined with topical steroids or tacrolimus.
Atopic dermatitis	NB-UVB UVA	Significant improvement; well-tolerated
Cutaneous T-cell lymphoma	nb-UVB PUVA	High remission rates; PUVA with longer remission duration
Actinic prurigo	UVB (nb-UVB, bb-UVB) PUVA	Temporary symptom relief: seasonal prophylactic use recommended
Pityriasis lichenoides	nb-UVB.	High remission rate
Alopecia areata	nb-UVB Excimer laser PUVA	Poor efficacy; excimer partially effective; not recommended as standard
Morphea / Localized scleroderma	nb-UVB UVA1 PUVA	Effective in superficial, non-progressive forms; preferred in children >12-years
Mastocytosis	nb-UVB PUVA	Reduced pruritus and serum tryptase
Langerhans Cell Histiocytosis	nb-UVB	Complete resolution of cutaneous lesions with no adverse effects
Graft-versus-host disease	nb-UVB PUVA UVA1	High response rates; NB-UVB with better safety profile
Prurigo nodularis	nb-UVB	Significant improvement; incomplete follow-up
Other conditions (urticaria pigmentosa, etc.)	nb-UVB PUVA	Used as photoprophylaxis and therapy for pruritic dermatoses

patients aged 3 to 17 years evaluated the durability of phototherapy. After 12-months, 52% of the 21 patients with psoriasis remained free of clinical symptoms.[1] Phototherapy can be used alone, or combined with other treatments such as emollients (e.g. mineral oil), topical corticosteroids, topical calcineurin inhibitors, coal tar (Goeckerman treatment), retinoids, among others.[13,14] Thus, both NB-UVB and PUVA can be safely and effectively administered to pediatric patients using the same treatment protocols as those applied in adults.[21]

Vitiligo

Vitiligo is an acquired chronic autoimmune disease that is characterized by the presence of white macules and patches, secondary to a progressive loss of melanocytes and alteration in their functions.[22] It has a prevalence of 0.1%–4% of the global population, and approximately 50% develop by 20-years.[23] Topical therapies are the first-line treatment for children with vitiligo, but phototherapy may be considered if these treatments fail or in cases of extensive or rapidly progressive disease.[24] Several phototherapy modalities have been used in pediatric vitiligo, including NB-UVB, PUVA, combined UVA1 and UVB, and the 308-nm excimer laser (Fig. 2). Historically, PUVA was frequently used to treat vitiligo; however, it has largely been replaced by NB-UVB due to its superior repigmentation outcomes and the potential risks associated with PUVA in children, such as an increased risk of malignancy.[25] The first study to explore NB-UVB use in childhood vitiligo was conducted by Njoo and colleagues, who found disease stabilization in about 80% of pediatric patients with generalized vitiligo treated with NB-UVB twice weekly. Over half of the patients experienced more than 75% repigmentation.[26] Response to therapy was positively correlated with the location of the lesions, with better improvement seen in lesions on the face and neck, and less improvement in acral lesions. This is thought to be due to the lower density of hair follicles in acral areas, which reduces the ability of UV light to stimulate residual follicular melanocytes.[27] For pediatric patients with treatment-resistant vitiligo, combination therapy using topical immunomodulatory agents alongside phototherapy may offer better results than phototherapy alone. One open-label study investigated the combination of NB-UVB and 0.03% tacrolimus ointment in children with symmetric vitiligo lesions. The study found a significant

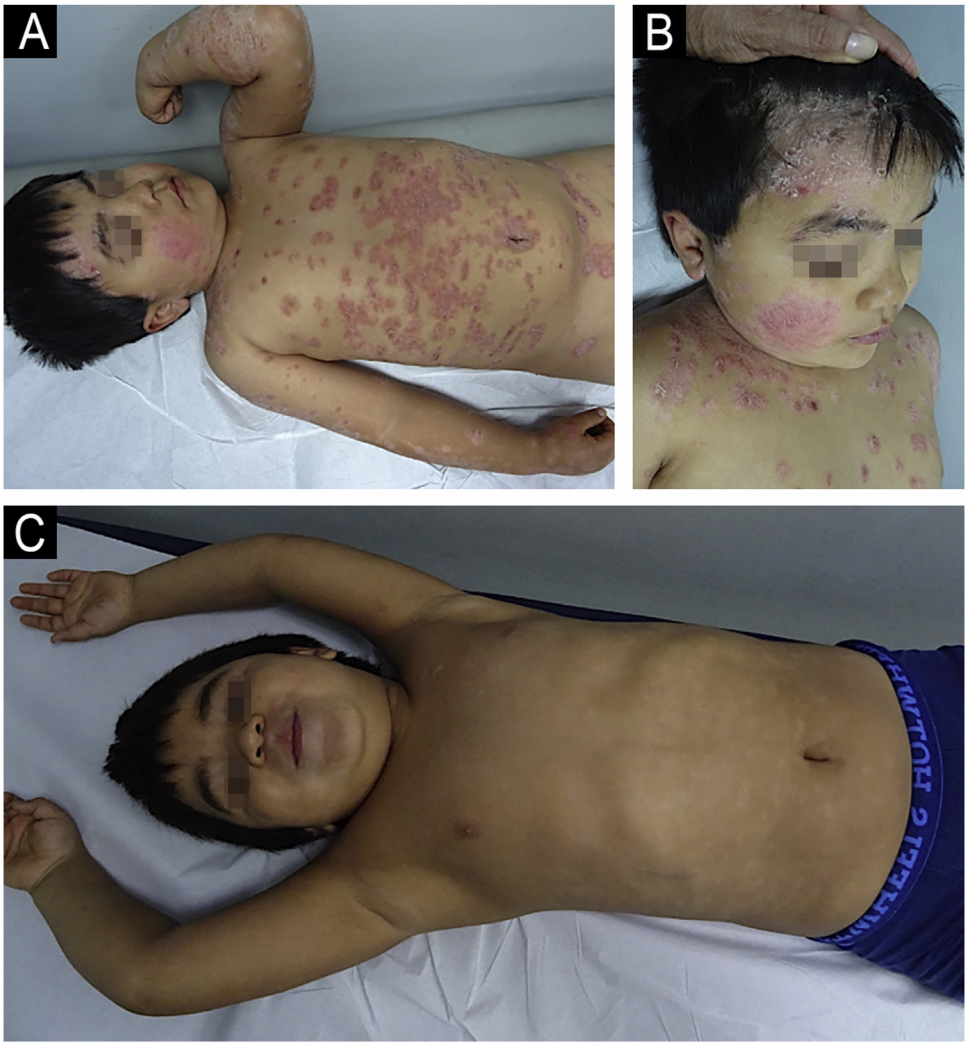

Fig. 1 (A) Six-year-old male patient diagnosed with psoriasis, presenting with intensely pruritic, erythematous, and scaly plaques on the face, scalp, and both anterior and posterior trunk. (B) Same patient after 22 biweekly sessions of nb-UVB phototherapy, showing significant clinical improvement with marked reduction in erythema, scaling, and pruritus.

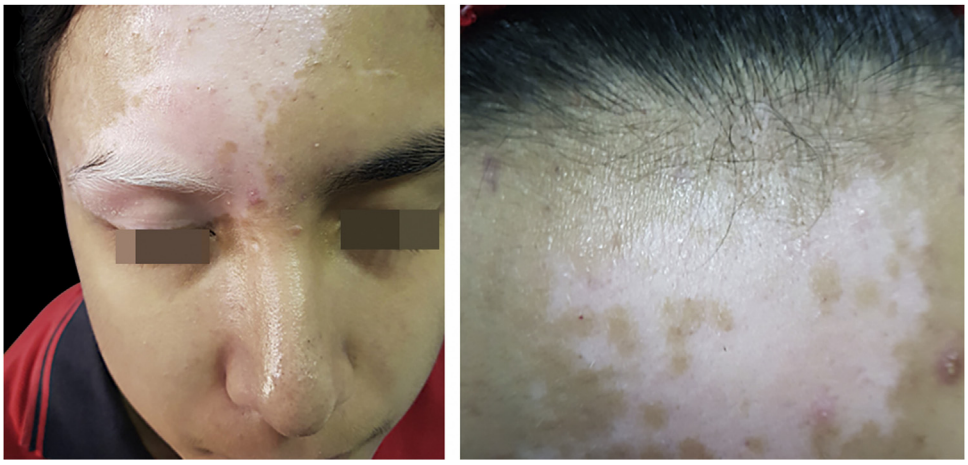

Fig. 2 (A) Fourteen-year-old male patient diagnosed with vitiligo, presenting with an achromic patch involving the glabellar region and extending to the right upper eyelid, associated with poliosis of the right upper eyelashes. (B) Same patient after 12 biweekly sessions of 308-nm excimer light phototherapy with good responses and signs of repigmentation.

increase in repigmentation at 4- to 6-months with combination therapy compared to phototherapy alone, and patients required fewer phototherapy sessions and lower cumulative doses to achieve clinically visible responses.[28] A retrospective review of 71 patients aged 5–15 years with vitiligo, more than half of whom had generalized vitiligo and over a third had segmental vitiligo, found that patients with generalized vitiligo had a better response to treatment than those with segmental vitiligo. The study reported the highest response rates for NB-UVB phototherapy (74% response rate), followed by targeted phototherapy combining UVA1 and UVB (67% response). 308-nm excimer lamp phototherapy and PUVA had marginally lower response rates (54% and 53%, respectively). Treatment duration ranged from 3- to 40-months, with the number of treatments ranging from 20 to 209 sessions. Side effects were generally mild and included itching, scaling, erythema, pain, sunburn, blistering, and phototoxicity.[29] In a retrospective chart review of 324 pediatric patients with vitiligo, 126 patients were treated with NB-UVB for a mean duration of 18-months, and Thirty-three patients (29%) experienced sunburn, including 10 (7.9%) who used home units; however, they were able to resume treatment after counseling.[30] Factors associated with improved or resolved vitiligo included nonsegmental disease, fewer signs of active disease, involvement of the face, head, neck, and extremities, and more areas of involvement.[30] Phototherapy should be considered for pediatric vitiligo unresponsive to topical agents with large body surface area involvement or advancing disease.[31]

Atopic dermatitis

Atopic Dermatitis (AD) is a chronic recurrent inflammatory disease that is characterized by the presence of pruritic eczematous patches in the skin. It is more frequent in childhood, affecting 10%–20% of the pediatric population.[32] Topical therapy with emollients, steroids, and/or calcineurin inhibitors is the first-line treatment for children with AD. However, phototherapy is recommended as a second-line treatment for patients with moderate to severe AD who do not respond adequately to topical therapies.[4,33] The AAD lists both UVA and UVB as safe and effective treatments for childhood AD (Fig. 3A–B), either as monotherapy or in combination with emollients and topical steroids.[34] NB-UVB is the most studied light modality for pediatric AD, with numerous studies supporting its safety and efficacy. In one of the largest retrospective studies, Clayton and colleagues found that 40% of children with AD treated with NB-UVB achieved complete clearance or minimal residual disease, while 23% showed significant improvement. The median time to remission was approximately 3-months.[35] Another study reported that more than half of their pediatric patients remained clear at one-year follow-up after completing NB-UVB therapy.[1] A prospective cohort study of children ages 3–16 years with moderate-to-severe AD showed a 61% reduction in mean SASSAD (Six Area, Six Sign Atopic Dermatitis) score in 29 patients who received phototherapy, compared to a 6% reduction in the 26 patients who deferred phototherapy. In addition, the mean surface area involvement at the end of treatment was 11% for the NB-UVB cohort, compared to 36% for the unexposed cohort.[36] A retrospective study of 62 patients, aged 4 to 16, with moderate to severe AD showed that 56.9% of patients experienced treatment success, as indicated by improvements in Investigator Global Assessment and Eczema Area and Severity Index (EASI) scores. Common side effects included xerosis, pruritus, erythema, and pain. Other reasons for discontinuing NB-UVB therapy included difficulties with time commitment (9.3%), hyperactivity (2.3%), and claustrophobia (2.3%).[37]

Cutaneous T-cell lymphoma

Mycosis Fungoides (MF) is the most common cutaneous T-cell lymphoma, but in the pediatric population, it is a rare disease, with a prevalence of 5%, but with an indolent course and with overall good prognosis.[38] Phototherapy in pediatric patients with MF is considered a first-line treatment, with studies supporting the efficacy of both NB-UVB and PUVA. There are no established treatment guidelines for pediatric MF, as the progression of the disease in children is extremely rare and typically follows an indolent course. MF is often diagnosed in early stages (IA, IB, IIA), and phototherapy, with a response rate greater than 80%, is considered an effective treatment in these cases. However, since recurrences are frequently seen after therapy is discontinued, a maintenance regimen and long-term follow-up are essential.[39] NB-UVB is recommended as first-line therapy for early-stage MF, particularly in younger patients with the hypopigmented form of the disease. In refractory cases, PUVA may be considered, but the potential long-term risks of PUVA should be carefully weighed against its benefits in managing this cutaneous malignancy on a case-by-case basis. While direct comparisons between NB-UVB and PUVA are lacking, some studies suggest that NB-UVB may be associated with more frequent recurrences than PUVA.[40] In a study by Brazzelli and colleagues, the mean remission period for patients aged 15–19 years was 11-months following NB-UVB treatment, compared to 30-months following PUVA. In those under 15-years-old, complete remission for a mean of 59-months was achieved with NBUVB alone.[32] A prospective study of 23 patients with MF found that hypopigmented MF was the most common clinical presentation (52.2%), followed by classical MF (30.4%) and folliculotropic MF (17.4%). All patients were treated with topical corticosteroids and phototherapy. Complete remission was achieved in 59.1% of cases, and partial response was seen in 40.9%. Two patients remained asymptomatic for five years.[41] NB-UVB has shown favorable outcomes in children with the hypopigmented variant of MF.[42]

Actinic prurigo

Actinic Prurigo (AP) is a rare photodermatosis characterized by the presence of an intense pruritic papulonodular dermatitis that affects sun-exposed areas, typically the face, neck, and upper extremities, and appears after UV exposure.[43] Its etiology is unclear, but 90% of the cases are associated with the HLA-DR4.[44] It mainly appears in childhood, and the main onset is before 10-years of age.[45] Topical corticosteroids, antihistamines, and systemic corticosteroids can be used to relieve symptomatic

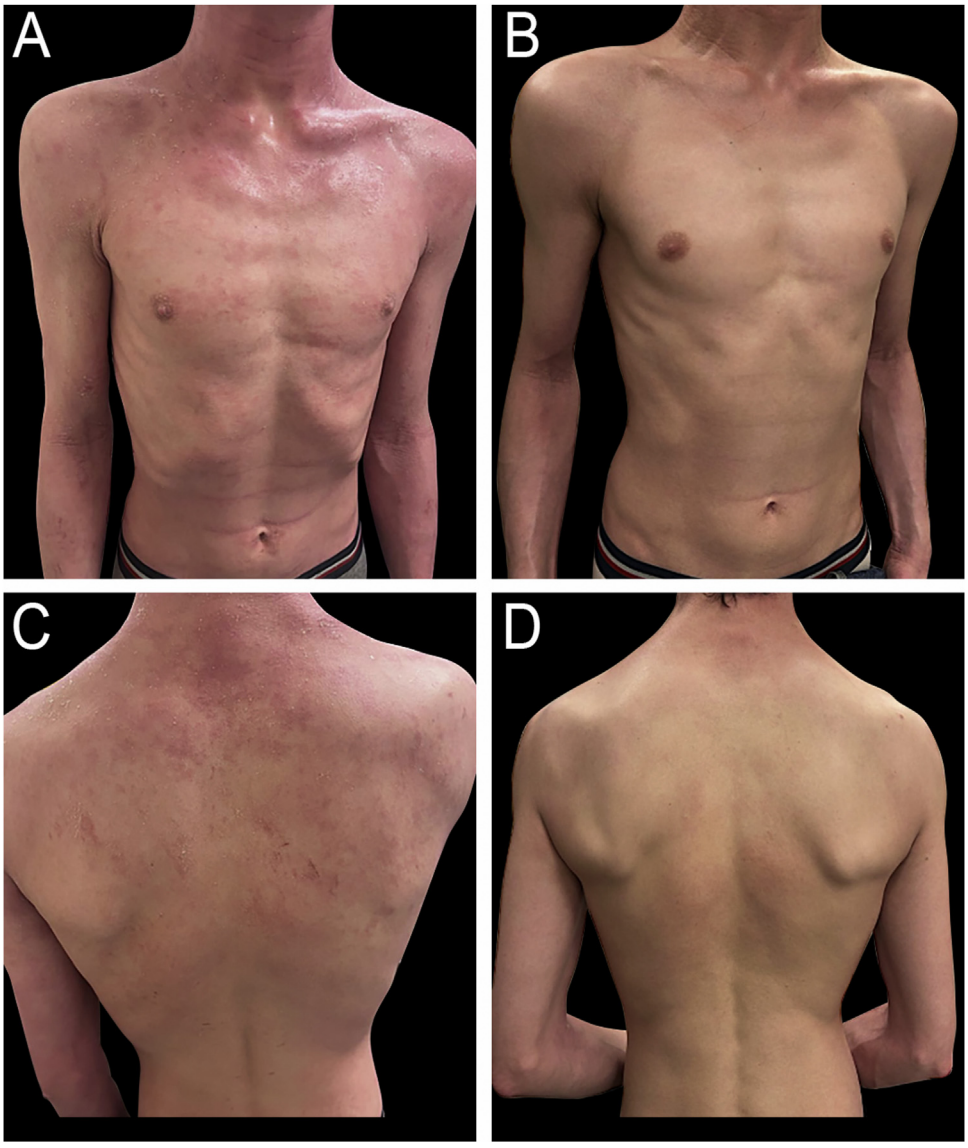

Fig. 3 (A) Seventeen-year-old male patient diagnosed with atopic dermatitis presenting with pruritic, erythematous, and scaly plaques on the body and lower limbs. (B) Same patient after 18 biweekly sessions of nb-UVB phototherapy, showing significant clinical improvement.

manifestations.[45] Most photodermatoses can be treated with preventive UV phototherapy and/or PUVA. The goal of these treatments is to increase the patient's tolerance to sunlight and prevent disease flare-ups.[46] Although the exact mechanisms through which UVB and PUVA promote tolerance remain unclear, factors such as pigmentation and skin thickening may contribute significantly to the protective effect.[46,47] A retrospective study of 21 patients with actinic prurigo also found some success with phototherapy. One patient received BB-UVB therapy during the spring and early summer, with eight treatments totaling 750 seconds (approximately 15 MED). This patient reported positive outcomes in preventing new lesions. NB-UVB therapy was used in two other patients: one received 48 treatments with a cumulative dose of 42.1 J/cm^2, and the other received 11 treatments with a cumulative dose of 2.7 J/cm^2. PUVA therapy was also used in one patient, with both treatments proving beneficial. However, the positive effects of UV phototherapy were temporary, and the protective benefits diminished during the winter months unless therapy was continued.[48] In a study involving five patients with actinic prurigo, PUVA treatment was administered twice weekly over 15-weeks. Before treatment, all patients exhibited heightened erythemal sensitivity to UVA and an abnormal enhancement of UVB erythema when treated with topical indomethacin. After undergoing PUVA therapy, all patients reported complete resolution of photosensitive symptoms, and the skin previously exposed to UVA showed normal erythemal responses.[49]

Pityriasis lichenoides

Pityriasis Lichenoides (PL) is a Papulosquamous inflammatory disease, with an acute form (PLEVA) that presents

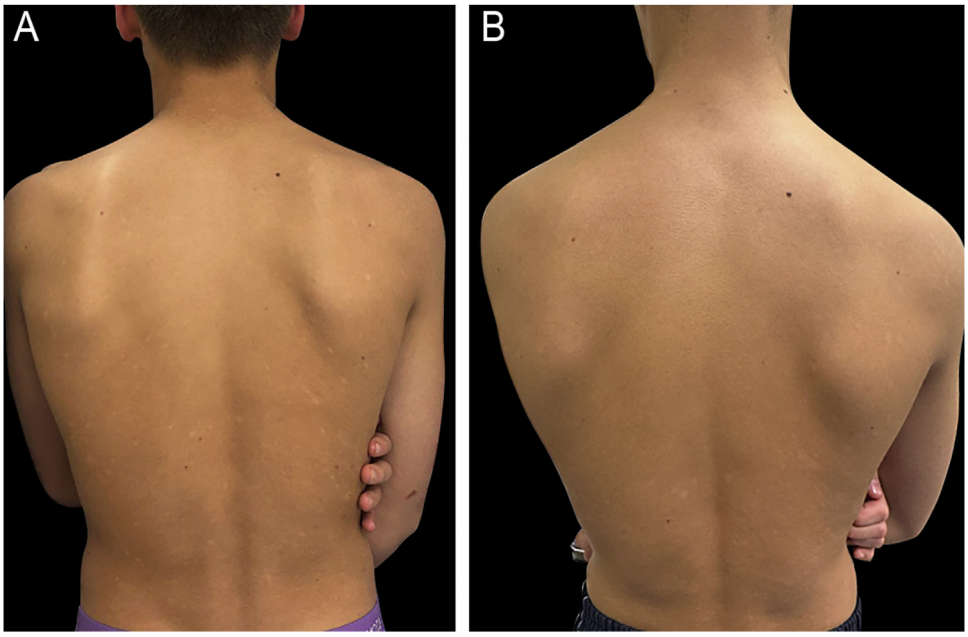

Fig. 4 (A) Sixteen-year-old male patient diagnosed with chronic lichenoid pityriasis presenting with lichenified, scaly plaques on the lower back. (B) Same patient after 24 biweekly sessions of nb-UVB phototherapy, showing marked clinical improvement.

erythematous macules and papules that can present ulceration and heal with varioliform scarring, and a chronic form (PLC), that presents erythematous papules and plaques with a central scale with periodical relapses.[50] The evidence for the use of phototherapy in treating PL comes from multiple small case series.[14] NB-UVB is the most studied treatment modality for pediatric PL, in both its acute and chronic forms, with strong evidence supporting its efficacy (Fig. 4). A review of five patients (two with PLEVA and three with PLC) treated with NB-UVB showed complete remission in all five patients following therapy after an average of 21 sessions (range 13–40 sessions), corresponding to an average duration of therapy of 4-months (range 2–8 months). Each patient maintained remission at follow-up visits at 3- and 6-months.[51] A systematic review of nine studies, involving 29 children treated with NB-UVB, found that 74% of patients achieved complete clearance, 13% had partial clearance, and 13% showed no improvement. On average, patients required 19 sessions to achieve a response.[6] It is important to consider that phototherapy does not modify the course of the disease or its tendency to relapse, and there is no established consensus regarding its position in the PL therapeutic ladder. However, the use of NB-UVB is effective and well-tolerated and can be considered a first-line treatment for diffuse types or recurrent PL.[50,52]

Alopecia areata

Alopecia Areata (AA) is an autoimmune disease that is characterized by nonscarring hair loss usually in patches that can affect any part of the body.[53] Its prevalence is approximately 2%, and in childhood, it has a prevalence of 0.11% and the peak is at 6–9 years.[54] The first line of treatment corresponds to the topical corticoids, followed by contact immunotherapy.[55] In a retrospective review, Ersoy-Evans and colleagues reported on 10 children, aged 1 4 to 16, with varying severities of alopecia AA who were treated with PUVA. Of these patients, only 2 (30%) experienced complete hair regrowth.[20] Similarly, another study assessing the use of NB-UVB for treating six children with AA found poor response rates, with 83% of patients reporting no improvement.[56] Based on these findings and the lack of strong evidence supporting its efficacy, phototherapy is not currently recommended as a standard treatment for AA in the pediatric population. In contrast, some studies have shown the 308-nm excimer laser to be an effective treatment option for pediatric AA. In a study involving 9 children with AA, those treated with the excimer laser twice weekly for 12-weeks reported hair regrowth in 41.5% of the treated areas of the scalp, while no growth was observed in the untreated control areas.[57] Additionally, a recent case report observed significant hair regrowth in a 5-year-old patient with extensive, refractory AA, treated with khellin and excimer laser.[58]

Morphea/Localized scleroderma

Morphea corresponds to a rare autoimmune and inflammatory disease that affects the skin and subcutaneous tissue. It has a wide spectrum of clinical presentations, but it is usually characterized by the presence of erythematous plaques that progress with inflammation and then sclerosis and depigmentation of the affected zone.[59] Itś more prevalent in Caucasians, and the mean age is between 7–11 years.[60] In most patients, the topical treatment can be enough, but in more widespread superficial disease, phototherapy (UVA1, UVA, PUVA, or UVB) and systemic treatment with MTX or MMF is indicated.[60,61] The current expert recommendation is the use of UVA1 or NB-UVB, preferably for children over 12-years of age with superficial, non-progressive morphea that does not involve joints or occur in ''non-cosmetically sensi-

tive areas'',[62] and the suggested dose of UVA1 is 60 J/cm^2 to a cumulative dose of 1460 J/cm^2.[60] Most of the available data supporting this approach comes from studies conducted on adults.[63] In a prospective study involving 13 patients, including those in the pediatric age group, treatments with systemic PUVA, topical PUVA, and NB-UVB were evaluated, and all patients responded effectively to the treatment, regardless of the modality chosen, with improvements evident both clinically and through ultrasound examination.[64]

Mastocytosis

Mastocytosis corresponds to a rare disorder characterized by the presence of abnormal accumulation and proliferation of mast cells in different tissues, and the most common is the skin, called ''Cutaneous Mastocytosis'' (CM). It is caused by mutations in the KIT gene.[65] In pediatric patients, the more frequent form of presentation is mastocytosis limited to the skin (CM) and is considered a myeloproliferative clonal disease with a benign course, favorable outcome, and a tendency to spontaneously resolve before puberty.[66] In a retrospective study of 20 patients with CM, 10 patients were treated with NB-UVB, and 10 with PUVA; both groups showed a statistically significant reduction in pruritus, along with a decrease in serum tryptase levels.[65] UVB light has been shown to have an inhibitory effect on mast cell degranulation, likely by causing noncytotoxic damage to membrane phospholipid metabolism.[67] Currently, there are no standard treatment guidelines for Systemic Mastocytosis (SM) in children. The primary treatment aim is to limit the release of mast cell mediators by avoiding potential triggering factors. The mainstay of systemic therapy consists of second-generation H1 and H2 antihistamines, which help reduce flushing, pruritus, and control wheal formation [68] and phototherapy (NB-UVB) can be considered a second-line therapy for refractory cases.[69]

Langerhans cell histiocytosis

Phototherapy, specifically NB UVB, has also been explored as a therapeutic option for Langerhans Cell Histiocytosis (LCH) with cutaneous manifestations. However, only isolated cases are reported in the literature. Ness MJ et al. reported the use of NB-UVB in a pediatric patient with cutaneous LCH lesions, showing a favorable response with minimal adverse effects.[70] Another report documented the successful treatment of a 10-month-old girl with cutaneous LCH using NB-UVB. Initially, the patient presented with an erythematous plaque on the chest, with the diagnosis confirmed after a biopsy. Since the lesion did not respond to triamcinolone injections, NB-UVB was chosen, resulting in complete resolution after 12-sessions with no adverse effects. These cases support the efficacy and safety of NB-UVB for managing cutaneous LCH lesions in children, avoiding the use of systemic treatments with potential side effects.[71]

Cutaneous graft-versus-host disease

Cutaneous Graft-Versus-Host Disease (GVHD) is a common complication in patients with allogeneic bone marrow transplantation and can affect multiple organs, making the skin the most frequently involved.[72] Typically, acute GVHD presents as a cutaneous rash, with erythematous, papular, or macular pruritic eruption.[73] There are multiple treatment options, such as topical therapy with corticoids or calcineurin inhibitors, systemic therapy, and physical therapies (phototherapy or extracorporeal photopheresis).[74] In a study of 10 pediatric patients with refractory response to first-line immunosuppressive treatment who were treated with NB-UVB achieved a complete remission was achieved in 80% of the patients.[75] In a recent systematic revision, the authors evaluated a total of 28 studies and 1304 patients, were patients treated with PUVA the response rate was 89.9%, with a mean of 33.2 treatments, patients treated with NB-UVB response of 94%, with a mean number of 26 treatments, patients treated with UVA1 presents a respond of 89.3% with a mean of 26.2 treatments, but with higher adverse events reported.[72] PUVA and UVA1 appear to be better for the treatment of sclerotic skin manifestations.[74]

Prurigo nodularis

Prurigo nodularis is a chronic skin disease that is characterized by the presence of multiple itchy nodules on the skin. For this disease, the authors found only one case of a patient with nodular prurigo treated with 25 sessions of NB UVB phototherapy, achieving a total cumulative dose of 18.0 J/cm^2. After treatment, significant improvement was observed, with skin that was virtually free of lesions according to the PGAS scale. However, the patient was lost to follow-up at 12-months.[1]

Other conditions

Phototherapy has also been used to treat other conditions in pediatric patients, such as urticaria pigmentosa, hydroa vacciniforme, and pruritic dermatoses.[4] Additionally, phototherapy may be used as photo-prophylaxis for light-sensitive cutaneous eruptions, such as erythropoietic protoporphyria and polymorphic light eruption.[76]

Practical considerations

According to the authors' experience and the publications on the subject, for proper selection of candidates, it is essential to conduct a detailed medical history and thorough physical examination and consider the presence of absolute contraindications. Once these have been ruled out, the most appropriate phototherapy modality and optimal treatment protocol should then be selected.[13] It is also critical to obtain written informed consent from the parents or guardians before initiating treatment, ensuring they understand the benefits, risks, alternatives, and expected course of phototherapy.

Dosing and frequency protocols for phototherapy in children can vary, as there are no established guidelines for treatment parameters. Typically, the treatment plan begins with calculating the Minimal Erythema Dose (MED), with the starting dose set at 70% of the MED or lower. Subsequent sessions usually increase by 20% per treatment. Some stud-

ies, however, suggest a more gradual escalation of 10% per session to minimize acute side effects such as erythema and burning and to improve overall tolerability.[1] It should be noted that the initial treatment dose can also be calculated based on the patient's skin type, with progressive increases. Adjustments may be required if there are long intervals between sessions. In the case of PUVA therapy, baseline, and follow-up laboratory tests such as liver function tests, renal profile, and complete blood count, among others, should be performed due to the systemic administration of psoralens. Additionally, psoralen formulations should be carefully selected for pediatric patients, with preference for low-dose or liquid preparations to ensure safe and accurate dosing.[77]

A retrospective study involving 98 pediatric patients with a mean age of 10.5 years and 122 adults receiving phototherapy showed no statistically significant differences in dosage, duration, or number of sessions between the two groups when treated with NB-UVB therapy or PUVA. A complete response was achieved in 35% of pediatric patients, and no differences were found between the pediatric and adult groups. This study concluded that NB-UVB therapy and PUVA are safe and effective for children and can follow the same treatment protocols used in adults. The most common conditions treated were psoriasis (48%), vitiligo (17%), and atopic dermatitis (16%).[78]

Administering phototherapy to children presents several challenges. One of the main difficulties is ensuring compliance with protective eyewear, especially in younger children, and ensuring that children remain still during treatment, which is crucial for targeting the affected areas and minimizing side effects.[4] Therefore, school-age children are often considered the most reasonable starting point for UVB therapy. It is also important to assess the child's behavioral development, including their ability to remain still and manage separation anxiety.[14] It is essential to implement comprehensive photoprotection measures both during and after phototherapy sessions, as the skin becomes more sensitive to UV radiation following treatment. Physical photoprotection, such as the use of protective clothing, including balaclavas or garments covering uninvolved areas, is particularly important during phototherapy to shield unaffected skin from unnecessary exposure.[4,7,14] In parallel, rigorous chemical photoprotection through the daily application of broad-spectrum sunscreens is strongly recommended outside of treatment sessions to reduce the risk of cumulative UV-induced damage. In this context, the importance of patient and family education and the value of obtaining written informed consent before initiating treatment are crucial.

Another challenge is the frequency of treatment sessions, which usually occur 2 to 3 times per week. This can be difficult for both the child and the parent, especially for school-aged children who may miss school time due to frequent treatments.[4] Adherence to treatment is one of the principal challenges in phototherapy, but studies suggest that in the pediatric population, adherence is higher than in adults. In a recent study, the main cause of incomplete treatment the school incompatibility.[78] In selected cases, home phototherapy may be considered to improve adherence and reduce logistical burdens. However, this approach requires rigorous training for caregivers, appropriate safety measures, regular medical supervision, and a clear understanding of the risks, such as burns or overexposure.[30]

To address these challenges, it is recommended that children and their parents familiarize themselves with the treatment unit. They should be allowed to enter and exit the unit as needed. During treatment, parents may stay nearby, with the option of keeping the door slightly ajar or standing outside to comfort the child. Over time, the goal is to transition to unaccompanied sessions.[14]

Adverse effects and safety considerations

The principal acute adverse effects of phototherapy, depending on the modality, include erythema, pruritus, xerosis, and tanning, and the long-term effects include the risk of photocarcinogenesis and premature skin aging.

For UVB and UVA phototherapy, short-term side effects include erythema (appears in the first 24-hs), blistering, xerosis, pruritus, photosensitive eruptions, and recurrent herpes simplex virus infections. Also, the risk of phototoxic reactions, such as tetracyclines, fluoroquinolones, voriconazole, azathioprine, amiodarone, and others should be considered. Anxiety may also arise in some patients and should be discussed before treatment. However, these side effects can be controlled with the education of the patient and correct selection of modality, dosing and dose adjustment, protection of the unevolved areas, monitoring of cumulative UV doses, and full-body skin examination.[7] There is no measurable evidence of increases in photocarcinogenesis in patients treated with NB-UVB and UVA1.[2,79,80]

In clinical practice, the decision to initiate phototherapy must be preceded by a careful evaluation of contraindications and precautionary conditions. These include absolute contraindications (e.g., photosensitivity syndromes, history of melanoma), relative contraindications (e.g., pregnancy, immunosuppression, pediatric age), and specific precautions (e.g., use of photosensitizing drugs, previous radiation exposure, ocular protection) that vary slightly depending on the modality used (NB-UVB vs. PUVA), a detailed summary of these conditions are provided in Table 2. This stratification is essential for optimizing safety and minimizing risk, particularly in vulnerable populations.[13,14,81]

Some studies have reported safe cumulative doses of up to 1985 mJ/cm^2 in dark-skinned populations without observing cutaneous malignancy during long-term follow-up. The AAD guidelines recommend maximum doses per session that vary according to phototype, reaching up to 5000 mJ/cm^2 for phototypes V–VI.[82] However, they do not establish an absolute limit for cumulative dose or number of sessions. In clinical practice, between 50 and 200 sessions are typically performed, and there are reports of patients treated with over 500 sessions without a significant increase in skin cancer risk.[34,83] On the other hand, it is known that the risk of melanoma increases significantly after more than 200 PUVA sessions, particularly after 15-years of follow-up.[82] Regarding cumulative dose, studies in dark-skinned populations have reported up to 2085 J/cm^2 of UVA without observing malignancy. However, in fair-skinned populations, it is recommended to limit cumulative exposure and the total number of sessions, ideally not exceeding 150–200 sessions over a lifetime.[84] For UVA1, protocols vary, but at least 8 ses-

Table 2 Contraindications and considerations of the use of UVB and PUVA phototherapy.[4,81]

Contraindication	UVB phototherapy	PUVA phototherapy
Absolute	• Genetic syndromes with photosensitivity or cancer risk (e.g., xeroderma pigmentosum, Bloom syndrome, Gorlin syndrome, Cockayne syndrome). • Photosensitive dermatoses (e.g., systemic lupus erythematosus, dermatomyositis). • Inability to follow or realize treatment protocol (e.g., severe claustrophobia, physical limitations).	• Genetic syndromes with photosensitivity or cancer risk (e.g., xeroderma pigmentosum, Bloom syndrome, Gorlin syndrome, Cockayne syndrome). • Photosensitive dermatoses (e.g., systemic lupus erythematosus, dermatomyositis). • Pregnancy and breastfeeding (oral PUVA). • Severe Hepatic or renal impairment (oral PUVA). • Hypersensitivity or intolerance to psoralen. • Untreated cataracts.
Relative	• History of melanoma or non-melanoma skin cancer. • Previous exposure to arsenic or ionizing radiation. • Use of photosensitizing agents (e.g., tetracyclines, retinoids, NSAIDs). • Photodermatoses (e.g., chronic actinic dermatitis, polymorphous light eruption, solar urticaria). • Immunosuppression (e.g., transplant recipients, systemic immunosuppressants). • Cataracts without adequate eye protection. • Significant systemic disease (e.g., liver/kidney failure).	• History of melanoma or non-melanoma skin cancer. • Current premalignant skin lesions. • Prior arsenic or radiation exposure. • Bullous pemphigoid/Pemphigus. • Immunosuppression. • Hepatic or renal impairment. • Allergy or intolerance to psoralens. • Uncontrolled epilepsy (risk of light-induced seizures).
Precautions	• Pregnancy (requires folate supplementation and UV dose control; and extra facial protection to prevent melasma). • Multiple atypical nevi / FAMMM (familial atypical multiple mole melanoma) syndrome. • Use of photosensitizing medications or herbs. • History of excessive UV exposure or photodamage. • Outdoor occupations (additional cumulative UV exposure). • Children under 16-years (use cautiously in ages 6–16).	• Ophthalmologic evaluation. • Over 200 lifetime PUVA sessions (increased risk of squamous cell carcinoma). • Genital Male protections (increased cancer risk). • Patients with cognitive or adherence difficulties. • History of excessive UV exposure or photodamage • Outdoor occupations (additional cumulative UV exposure). • Children under 10 (prefer NB-UVB in pediatric cases).

NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

sions with medium-to-high doses (up to 40 J/cm^2 per session) are generally required for a clinical response. No absolute limit for cumulative dose or maximum number of sessions has been established in the reviewed literature.[85]

For PUVA, oral psoralens can cause nausea and vomiting.[86] Short-term side effects of PUVA include erythema (which appears in 48–72 hours), swelling, and blister formation. Additionally, PUVA therapy can induce cataracts, and because the ocular lens is more permeable at a younger age, oral PUVA is relatively contraindicated in children younger than 12-years old.[87] Long-term effects of PUVA include photoaging, pigmentary changes, rhytides, xerosis, actinic damage, and PUVA lentiginosis (freckling).[14,81] Evidence has found that PUVA is associated with a significantly increased risk of developing Squamous Cell Carcinoma (SSC) and Actinic Keratoses (AK) principally, but also, in lower incidence, in melanoma and Basal Cell Carcinoma (BCC).[8,80]

Absolute contraindications for phototherapy include photosensitive and skin cancer-predisposing disorders, such as xeroderma pigmentosum, systemic lupus erythematosus, and Gorlin syndrome.[13] A family history of skin cancer should also be considered, although it is not necessarily a contraindication.[14]

A monocentric retrospective study of 90 children under the age of 16 who received a total of 790 phototherapy sessions (averaging three sessions per week) found that phototherapy was generally well tolerated. Among these patients, 52% were treated for psoriasis, with other indications including vitiligo (19%), atopic dermatitis (11%), pruritus/prurigo (9%), and alopecia areata (9%). Mild erythema occurred in 15% of the patients, and 32% of patients discontinued treatment, primarily due to difficulty balancing treatment schedules with parental employment or children's school hours.[3] A retrospective review of 100 children under 18 who received NB-UVB, BB-UVB, or PUVA photochemotherapy also found that treatments were well tolerated. Grade 2 erythema or higher occurred in 46% of children, but more severe reactions (Grade 3 and 4) were infrequent, and only three children stopped treatment due to burning.[10]

The primary long-term risk of phototherapy in children is the potential development of cutaneous malignancy due to repeated UV exposure. However, this potential risk must be weighed against the benefits of treatment. A retrospective cohort study involving 3,506 patients, 16 to 100 years, with a median age of 50-years at follow-up, treated with BB-UVB, NB-UVB, and/or combined UVA, with a mean follow-

up of 7.3-years, assessed the incidence of skin cancer. Most patients had psoriasis (60.9%) or eczema (26.4%), and the median number of treatments was 43 (ranging from 1 to 3,598). Overall, 170 skin cancers were reported, including 17 melanomas, 33 SCC, and 120 BCC. There was no significant difference in the incidence of these skin cancers compared to the general population, and no cumulative dose-response correlation between UVB exposure and skin cancer was observed.[88] However, this potential risk warrants special consideration in children due to their longer life expectancy and the possibility of increased carcinogenic risks that may become evident later in life.[4]

Phototherapy in the era of biologics

Phototherapy remains one of the most evidence-based and safest treatment modalities in dermatology for managing a range of skin diseases. Phototherapy is one of the most evidence-based and safe treatments in dermatology for managing various skin diseases. Its most common indications include psoriasis, vitiligo, and atopic dermatitis, among others. However, the emergence of new therapies, such as biological drugs, has raised questions about the continued role of phototherapy within the treatment landscape for these conditions. For example, in vitiligo, the combination of topical JAK inhibitors, such as ruxolitinib, with NB-UVB phototherapy may exert a synergistic effect on repigmentation. However, robust evidence is currently limited to adult populations, and further data are needed in pediatric patients.[89]

A comparative study that evaluated the clinical response of patients with psoriasis treated with oral PUVA versus biologic treatments showed that oral PUVA was comparable to the one treated with infliximab and superior to etanercept, efalizumab, adalimumab, and Ustekinumab.[90] A recent patient-reported study of patients with psoriasis treated with NB-UVB versus adalimumab versus placebo showed that both therapies improve skin-related quality of life and overall health-related quality of life after 12 weeks of treatment.[91]

The cost of a treatment is also an important factor to consider; an analysis made in 2010 estimated that biologic agents, such as adalimumab, cost at least twice that of NB-UVB and PUVA combined.[7,92] Despite significant advancements in the management of dermatological diseases, phototherapy remains the treatment of choice for patients with underlying conditions that preclude the use of systemic therapies, a history of toxicity, drug interactions, refractoriness to systemic treatments, or economic considerations.[93]

Conclusion

Phototherapy is an effective and well-tolerated treatment option for pediatric patients with various skin conditions, including psoriasis, atopic dermatitis, vitiligo, and others. The decision to initiate phototherapy in pediatric patients should be made on a case-by-case basis, considering factors such as the severity and extent of the condition, previous treatment responses, the child's age and behavior, as well as the family's ability to consistently adhere to the treatment regimen. NB-UVB is the widely used and preferred modality due to its efficacy and lower risk, is well tolerated in children, but there is a clear need for studies reviewing its long-term side effects. It is important to note that treatment protocols in this population often lack standardization and are frequently extrapolated from adult experiences, underscoring the urgent need to develop pediatric-specific guidelines. While current evidence supports the use of phototherapy in children, long-term studies are still needed to establish optimal dosing regimens, better define safety over time, and evaluate its true impact on quality of life. In this regard, the implementation of innovative strategies, such as home-based phototherapy, could represent a significant advance in accessibility and treatment adherence.

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Research data availability

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

Conflicts of interest

The authors declare that they have no conflicts of interest in this publication.

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REVIEW

Tirzepatide in dermatology: cutaneous adverse events, emerging therapeutic roles, and cosmetic implications – A comprehensive review☆

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Abstract Tirzepatide, a dual Glucose-dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) receptor agonist. Tirzepatide was first approved by the FDA for type 2 diabetes in May 2022 and subsequently for obesity in November 2023, and has demonstrated significant efficacy in glycemic control and weight reduction. Beyond its metabolic benefits, recent evidence highlights its relevance in dermatology. This review explores the dermatologic implications of tirzepatide, including its cutaneous adverse effects, therapeutic potential in inflammatory skin diseases, and cosmetic benefits. Cutaneous side effects such as hypersensitivity reactions, injection-site reactions, and rare severe dermatologic events have been documented. Across the SURPASS clinical trials, injection-site reactions occurred slightly more frequently, comparable to other GLP-1 receptor agonists as semaglutide. Meanwhile, tirzepatide's immunomodulatory properties suggest potential therapeutic roles in conditions like psoriasis and hidradenitis suppurativa; however, current evidence is limited to case reports and small studies. Additionally, its profound effects on fat distribution raise interest in its cosmetic implications. Tirzepatide's induced rapid weight loss may lead to aesthetic changes, including facial volume loss, which warrants cautious interpretation. This narrative review summarizes current data from clinical trials, case reports, and pharmacovigilance sources, based on a literature search of PubMed, Scopus, and Google Scholar up to May 2025, focusing on skin-related adverse events, therapeutic effects, and cosmetic outcomes of tirzepatide.

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Introduction

Tirzepatide is a new medication designed and approved by the US Food and Drug Administration (FDA) in May 2022 (Mounjaro) to treat type 2 diabetes and approved for obesity treatment in November 2023 (Zepbound).[1] It works by simulating the action of two natural gut hormones, GIP (Glucose-dependent Insulinotropic Polypeptide) and GLP-1 (Glucagon-Like Peptide-1), which are released after eating and are responsible for appetite, calorie intake control, and regulation of food intake and therefore they contribute to the regulation of blood sugar levels. Because it activates both receptors, tirzepatide is known as a dual incretin receptor agonist.[2]

Methodology

This narrative review was conducted through a comprehensive search of the literature from inception to May 2025 across PubMed, Scopus, and Google Scholar. Search terms included combinations of keywords and Boolean operators, such as (''tirzepatide'' OR ''Mounjaro'' OR ''Zepbound'') AND (''GLP-1 receptor agonist'' OR ''dual incretin'') AND (''dermatology'' OR ''skin'' OR ''cutaneous'' OR ''adverse effects'' OR ''hypersensitivity'' OR ''injection-site reactions'' OR ''cosmetic''). Medical Subject Headings (MeSH) were applied in PubMed where available (e.g., ''Skin Diseases,'' ''Drug-Related Side Effects and Adverse Reactions''). A representative search string in PubMed was: ("tirzepatide"[Mesh] OR "tirzepatide"[tiab]) AND ("Skin Diseases"[Mesh] OR "cutaneous"[tiab] OR "dermatology"''tirzepatide''[Mesh] OR ''tirzepatide''[tiab]) AND (''Skin Diseases''[Mesh] OR ''cutaneous''[tiab] OR ''dermatology''[tiab]. In Google Scholar, the first 200 results were screened, and only peer-reviewed articles were included. Eligible studies were English-language original research, reviews, clinical trials, and case reports addressing dermatologic adverse effects, therapeutic implications, or cosmetic outcomes. Duplicates were removed manually, and references were hand-searched for additional studies. Screening and extraction were performed by the author, and findings were synthesized narratively due to the limited scope of available evidence.

Chemical structure of tirzepatide

The molecule is a synthetic polypeptide made up of 39 amino acids, based mainly on the GIP sequence, with some modifications that allow it to also activate the GLP-1 receptor. To prolong its half-life and allow once-weekly dosing, a C20 fatty diacid side chain is conjugated to the peptide, promoting albumin binding.[3]

The difference between tirzepatide and other medications is its ability to act on two different receptors at the same time. GLP-1 receptor agonists, such as exenatide, liraglutide, dulaglutide, and semaglutide, which only stimulate the GLP-1 pathway, help lower blood sugar and reduce appetite, but their effect is limited to one pathway. In contrast, tirzepatide's dual action results in greater improvements in both blood sugar control and weight loss, as seen in recent clinical trials. It also appears to be better tolerated in some patients because the GIP part of the molecule may help reduce common side effects like nausea and vomiting. Overall gastrointestinal tolerability seems broadly comparable to GLP-1 receptor agonists; however, the suggestion that GIP receptor activation may attenuate nausea remains speculative and requires further validation.[3,4]

Mechanism of action of tirzepatide

Tirzepatide is a novel dual receptor agonist that targets both the glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors. Studies reveal a greater degree of engagement of tirzepatide for the GIP receptor than the GLP-1 receptor, so the molecule demonstrates higher affinity for the GIP receptor, with partial agonism at the GLP-1 receptor.[5] Upon subcutaneous administration, tirzepatide binds to and activates both receptors, leading to enhanced insulin release from the pancreas, suppression of glucagon release, slowing of gastric emptying, and promotion of satiety by central mechanisms, thereby improving postprandial and overall glycemic control. Furthermore, GIP receptor activation provides additional metabolic benefits, such as improved adipocyte insulin sensitivity, and may also counteract the gastrointestinal side effects often associated with GLP-1, thus enhancing tolerability and adherence to therapy; however, these hypotheses require further validation The synergistic action of these pathways results in significant reductions in HbA1c and substantial weight loss, compared to those observed with GLP-1 receptor agonists alone. Additionally, tirzepatide has also been shown to increase adiponectin levels, a protein hormone that regulates glucose and fatty acid oxidation. This may contribute to favorable effects on insulin sensitivity and lipid metabolism, but current evidence remains limited. In the SURPASS clinical program, tirzepatide achieved superior reductions in HbA1c compared with GLP-1 receptor agonists, while the SURMOUNT trials demonstrated substantial weight loss in individuals with obesity.[4,6] Although these results highlight the therapeutic potential of dual agonism, claims of cardiovascular risk reduction should remain cautious until dedicated Cardiovascular Outcome Trials (CVOTs) are fully published.[1,4,7,8]

Pharmacokinetics and efficacy of tirzepatide

Upon injection, tirzepatide is metabolized into single amino acids in different tissues, including the liver, where the polypeptide structure undergoes proteolytic cleavage, and the fatty acid side chain undergoes oxidation and amide hydrolysis. This fatty acid chain helps tirzepatide bind to albumin, slowing its degradation and clearance. Tirzepatide takes about 8–72 hours to reach a peak serum level. It has

a half-life of 5-days, which allows for the weekly subcutaneous injection. The drug metabolites are cleared in urine and feces.[9] The earlier reports categorized tirzepatide as a ''second-line'' therapy following GLP-1 receptor agonists.[10] However, current ADA (American Diabetes Association) 2024 and SBD (Sociedade Brasileira de Diabetes) 2024 guidelines support its early use in selected patients based on clinical characteristics and treatment goals rather than as an unconditional first-line agent.[11,12]

When comparing to placebo in SURPASS-1, there was a -2.11% reduction in HbA1c levels at 5 mg per week dosing with a 5.4 kg weight reduction compared to -0.86% with a placebo, which increased to a -2.34% reduction in HbA1c and 10.5 kg weight reduction when reaching the highest dose of 15 mg per week of tirzepatide.[4] In SURPASS-2 (head-to-head vs. semaglutide), tirzepatide produced superior reductions in both HbA1c and body weight.[13] In SURPASS-5, tirzepatide reduced HbA1c by up to -2.34% and body weight by -10.5 kg over 40-weeks in a dose-dependent manner. These effects are comparable to semaglutide for glycemic and weight management.[14] When administered to nondiabetic patients, in SURMOUNT-1 (obesity without diabetes), in a dose of 5 to 15 mg once weekly, tirzepatide produced remarkable reductions in weight, ranging from 16.5% to 22.4% over a period of 72-weeks.[7] Owing to the weight loss action, it is likely to have an indirect effect in the treatment of nonalcoholic fatty liver disease; however, this indication remains investigational.[15]

Dosage and adverse effects of tirzepatide

Tirzepatide is administered once weekly by subcutaneous injection, with the dose gradually increased based on HbA1c, weight response, and tolerability. The initial 2.5 mg dose is for tolerability rather than glycemic efficacy, so treatment typically starts at 2.5 mg once weekly, then after 4-weeks, the dose is increased to 5 mg, with further increases of 2.5 mg at $\geq$ 4-week intervals if needed. The maximum dose is 15 mg weekly. Evidence of dose modification in end-stage renal disease and advanced liver disease is limited, and use during pregnancy or lactation should be avoided due to insufficient safety data.[16]

Tirzepatide is generally well-tolerated, with most side effects being dose dependent. The most common side effects are gastrointestinal, including nausea, diarrhea, vomiting, constipation, and decreased appetite, particularly during the initial weeks of treatment, which improve over time. Hypoglycemia due to tirzepatide is rare unless tirzepatide is combined with insulin or sulfonylureas. Pancreatitis has been reported, but causality is unproven. Gallbladder disease (e.g., cholelithiasis) and acute kidney injury have been described as associations, often related to dehydration from GI losses. Overall, the safety profile of tirzepatide closely resembles that of GLP-1 receptor agonists, with careful monitoring recommended, especially during dose titration.[2,17]

Tirzepatide should not be used with other GLP-1 agonists and must be used cautiously with insulin to avoid hypoglycemia. It can reduce the effectiveness of oral contraceptives and affect the absorption of other oral drugs due to delayed gastric emptying. Contraindications include a personal or family history of medullary thyroid carcinoma, MEN-2 (Multiple endocrine neoplasia type 2), and known hypersensitivity to the drug. Routine monitoring should include HbA1c, weight, appearance of signs of adverse effects such as GI upset and pancreatitis, and new thyroid nodules on therapy.[13,18]

Due to its widespread global use and subcutaneous route of administration, there is a strong need to better understand the cutaneous adverse effects associated with tirzepatide. While tirzepatide's metabolic benefits have been well documented, adverse effects are also reported, with cutaneous reactions needing to be highlighted. These skin-related side effects range from mild injection site reactions to rare but potentially serious hypersensitivity responses. This review aims to provide a detailed overview of tirzepatide-induced cutaneous side effects, suggested underlying mechanisms, clinical implications, and management strategies. The reported skin-related side effects to tirzepatide are summarized in Table 1.

Injection site reactions

Injection Site Reactions (ISRs) are the most frequently notable tirzepatide-associated skin-related side effects.[14,19] These ISRs typically present as localized redness and erythema around the injection area, mild swelling or firmness and induration, pruritus, and discomfort or pain during and after the injection at the injection site. Across the SURPASS clinical trials, injection site reactions with tirzepatide were consistently reported in approximately 2%–6% of patients, compared to $\leq$ 1% with placebo or active comparators (semaglutide, dulaglutide, insulin degludec, or glargine).[4,13,14,19–21] Also, according to the FDA prescribing information, injection-site reactions were reported more frequently in patients who developed anti-tirzepatide antibodies (4.6%) compared to patients without antibodies (0.7%).[22]

Although incidence appeared slightly higher in patients who developed anti-tirzepatide antibodies, this represents a correlation rather than established causality. Mullin et al., reported that hypersensitivity and injection site reactions were more frequent in Treatment Emergent (TE) Anti-Drug Antibodies (ADA)+ than in TE ADA- patients, no consistent temporal association was detected between the time of the event reporting and ADA status, and most events resolved irrespective of ADA status.[19]

In the SURMOUNT obesity trials, ISRs rates were slightly higher, occurring in about 6%–8% of those patients who used tirzepatide for weight management, compared to 2% in the placebo group. Also, the reactions were usually mild and resolved on their own within a few days.[6,7,23] The risk of ISRs is consistent with other injectable incretin therapies. ISRs likely result from a localized immune or inflammatory response to the peptide, excipients, or injection trauma. Repeated injections in the same area can increase the risk of irritation.[19,24,25] The important differential diagnosis of ISRs includes cellulitis, which could be excluded by the self-limited course of the symptoms and the absence of fever and systemic symptoms.[24] Patient education on site rotation and aseptic technique is essential to minimize recurrence and complications.

Table 1 Reported dermatologic adverse events associated with tirzepatide.

Year	Study Type	Dermatologic Adverse Event	Number of Patients Affected	Dosage	Time of Onset	Management	Mechanism Explanation
2021[13]	SURPASS-2 (Phase 3 RCT)	Injection-site reaction and hypersensitivity reactions	Injection site reactions: 1.9% (5 mg), 2.8% (10 mg), 4.5% (15 mg) Hypersensitivity reactions: 1.7%–2.8%	5 mg, 10 mg, 15 mg weekly	Not specified	Symptomatic management, often self-limited	Possibly related to local immune response to subcutaneous injection and/or presence of anti-drug antibodies
2021[20]	SURPASS-3 (Phase 3 RCT)	Injection-site reaction and hypersensitivity reactions	ISRs: <1%–2% Hypersensitivity reactions: ~3% for all doses	5 mg, 10 mg, 15 mg weekly	Not specified	Often mild and self-resolving	Local immune response; similar rate to insulin degludec
2023[24]	Case Report	Injection site rash	1	2.5 mg weekly	10-days post-injection	Discontinuation of tirzepatide induced resolution within 1 month	Not specified
2024[25]	Cross-Sectional Analysis	Rash, pruritus, alopecia, urticaria, hyperhidrosis	Overall skin related side effects of tirzepatide (14.22%): Rash (17.7%), Pruritus (12.9%), Hyperhidrosis (6%), urticaria (14.9%) and Alopecia (22.7%)	Not specified	Not specified	Not specified	Not specified
2023[27]	Case Report	Biphasic anaphylactic reaction (diffuse urticarial rash and angioedema as well as respiratory and cardiovascular collapse), Recurrence of symptoms of anaphylaxis after an initial resolution	1	5 mg weekly	20 minutes post-injection	Epinephrine, methylpred-nisolone, diphenhydramine; observation in ER (It is suggested that patients with anaphylaxis to tirzepatide might benefit from desensitization therapy)	IgE-independent anaphylaxis (there was no prior exposure to tirzepatide)

Table 1 (*Continued*)

Year	Study Type	Dermatologic Adverse Event	Number of Patients Affected	Dosage	Time of Onset	Management	Mechanism Explanation
2024[29]	Case Report	Immediate-type allergic reaction to tirzepatide: A sudden onset of severe disseminated pruritus and a generalized urticarial rash on arms, hands, back, and entire body, excluding face and neck	1	Not specified (but occurred after the first injection of tirzepatide)	10–15 minutes post-injection	Antihistamines, symptoms resolved upon discontinuation	Possible IgE-mediated hypersensitivity
2025[32]	Retrospective Analysis	The most common: Eczematous reactions, pruritus, drug eruptions, hyperhidrosis, alopecia	Overall, 690 reactions (5.96%) of the total reported cutaneous adverse events: Eczematous reactions (183 cases), alopecia (155 cases), drug eruption (151 cases), pruritus (130 cases), hyperhidrosis (39 cases), skin discoloration (8 cases), life threatening reactions (7 cases), psoriasis (4 cases), acne (5 cases), nail changes (3 cases), photosensitivity (4 cases)	Not specified	Not specified	Not specified	Not specified

Hypersensitivity reactions

In addition to the local injection site reactions, tirzepatide may cause generalized skin rashes such as maculopapular eruptions, urticarial eruptions, and, in rare cases, more serious conditions like angioedema; despite being rare, but have been reported. Across the SURPASS studies, hypersensitivity reactions occurred in approximately 1%–2% of tirzepatide-treated patients, slightly higher than the 1% reported in placebo groups, and were generally mild to moderate in severity.[4,13,14] In immunogenicity analysis study by Mullin et al., that analyzed seven Phase 3 SURPASS studies, the rate was somewhat higher (∼3–4%), with greater incidence in antibody-positive patients (4.1% vs. 3.0% in antibody-negative), though this difference was not clinically meaningful and data on treatment-emergent antidrug antibodies and hypersensitivity remain inconsistent across studies, with no clear causal link established.[19] Furthermore, patients who developed treatment-emergent antidrug antibodies did not experience severe hypersensitivity or injection-site reactions, though comprehensive data were lacking.[19,26] Importantly, hypersensitivity is recognized as a class effect of GLP-1 receptor agonists, and vigilance is required.[25] Patients should be counseled on the signs of systemic reactions such as angioedema or anaphylaxis and instructed to seek urgent medical attention if these occur.[19]

Severe allergic reactions

Although extremely rare, severe allergic reactions, including anaphylaxis and serum sickness-like cutaneous and systemic symptoms, have been linked to tirzepatide. These require immediate medical attention. The FDA has issued warning labels for Mounjaro and Zepbound, highlighting these risks and advising patients to be vigilant for symptoms like facial swelling, breathing difficulty, or widespread rash.[22,27,28]

The exact mechanisms of tirzepatide-induced cutaneous side effects are not fully elucidated, but several hypotheses exist. Firstly, the immunogenicity of the tirzepatide synthetic peptide, as tirzepatide may be recognized as foreign by the immune system, triggering local or systemic immune responses.[25] Formation of anti-drug antibodies was more evident in patients who developed hypersensitivity and injection site reactions as described by Mullins et al.[19] Secondly, the injection itself can include minor tissue trauma, activating local inflammatory reaction and releasing mediators and cytokines. Thirdly, patients with pre-existing allergies or sensitivities to GLP-1 analogs or tirzepatide itself might be predisposed to IgE-dependent skin reactions when exposed again to tirzepatide due to structural similarities as a form of cross-reactivity.[27,29] Lastly, the preservatives or other inactive ingredients might stimulate allergic contact dermatitis or irritant reactions. However, mechanistic hypotheses such as immunogenicity, antidrug antibodies, or T−cell−mediated responses remain speculative. Antibody development is usually non-neutralizing and shows no consistent effect on pharmacokinetics, efficacy, or safety.[19] Reported hypersensitivity and ISR differences in antibody-positive versus antibody-negative patients are small and need further correlations.

Clinically, to differentiate, injection site reactions usually appear within hours, are usually localized and limited to areas like the abdomen, thigh, or upper arm, and they are self-limiting, resolving within 1–3 days, while tirzepatide-induced hypersensitivity reactions can occur days to weeks after starting therapy and may include generalized itching, urticarial rash, or angioedema. Severe cases may involve fever, malaise or breathing difficulty. Diagnosis is mainly clinical and based on the timing of symptom onset after drug initiation.[24,29] To reduce the risk of skin-related side effects of tirzepatide, patients should be aware of the common skin reactions. It is better to advise the patients to rotate injection sites and use the correct injection technique. Mild reactions can be treated with cold compresses, antihistamines, or topical corticosteroids. Severe reactions may require stopping the drug and starting corticosteroids. Systemic corticosteroids should be reserved for selected severe or prolonged reactions, while intramuscular epinephrine remains the first-line emergency treatment for anaphylaxis. Regular monitoring and reporting of skin reactions help improve understanding and safety of tirzepatide use.[24,27,30]

Skin side effect profile: Tirzepatide versus GLP-1 analogues

Regarding the skin-related side effects of semaglutide, a recent review analyzed 22 studies involving 255 patients. The common dermatologic adverse events included injection site reactions (3.5%), which were more frequent with placebo (6.7%), and higher rates of altered skin sensations such as paresthesia, dysesthesia, and burning sensation, especially with a high dose of oral semaglutide (50 mg weekly). Alopecia has been reported (up to 6.9% in one study of oral semaglutide), compared to 0.3% on placebo, though causality remains unproven, representing an emerging signal requiring further study. Two cases of keratinocyte carcinoma, squamous and basal cell carcinoma, were reported among 258 patients at risk receiving semaglutide, while no cases were observed in the placebo or the comparison groups. Rare but severe side effects included angioedema, bullous pemphigoid, leukocytoclastic vasculitis, and eosinophilic fasciitis, which led to discontinuation of the drug. The study highlights the need for awareness of these potential dermatologic reactions and calls for further research to understand their mechanisms and risk factors.[31] Therefore, similar injection site and hypersensitivity reactions are observed with GLP-1 receptor agonists like liraglutide, semaglutide, and dulaglutide, and tirzepatide does not appear to increase the incidence or severity of cutaneous side effects compared to these agents.[4,30]

In the SURPASS-2 and SURPASS-3 clinical trials, both hypersensitivity and injection-site reactions were observed with tirzepatide treatment, with some differences compared to semaglutide and insulin degludec. Injection-site reactions were more frequent with tirzepatide, particularly in the SURPASS-2 trial, where rates increased with dose (1.9% at 5 mg, 2.8% at 10 mg, and 4.5% at 15 mg) compared to only 0.2% with semaglutide.[13] In contrast, in the SURPASS-3 trial, the incidence of injection-site reactions with tirzepatide was lower (<1%–2%) and comparable to insulin degludec

(2%). Hypersensitivity reactions with tirzepatide occurred at rates of 1.7% to 2.8% in SURPASS-2, similar to semaglutide (2.3%), and consistently at 3% across all tirzepatide doses in SURPASS-3, higher than insulin degludec (1%).[20] These findings suggest that while tirzepatide may cause more frequent local injection-site reactions than semaglutide, its hypersensitivity risk appears mild and generally comparable to other injectable therapies.[26]

Furthermore, a cross-sectional analysis of adverse dermatologic events reported to the FDA after the use of GLP-1 agonists, including semaglutide and tirzepatide, found that dermatologic adverse events were reported in a percentage of 6.08% (4,896) of a total of 80,482 adverse events. Liraglutide accounted for the highest proportion of these skin-related events (45.85%), followed by semaglutide (40.18%) and tirzepatide (14.22%). Notably, there was a 186% rise in dermatologic reports from 2022 to 2023, aligning with the broader commercial use of these drugs. The most common dermatologic reactions were rash (21.79%), pruritus (17.95%), alopecia (13.97%), urticaria (11.09%), and hyperhidrosis (10.76%). While all three GLP-1 receptor agonists shared these top five reactions, their frequency varied. Tirzepatide is associated with a lower frequency of rash, pruritus, and hyperhidrosis, but a higher frequency of alopecia and urticaria compared to liraglutide and semaglutide. Reports of lipodystrophy and lipoatrophy were rare, with only five combined cases.[25] These findings highlight unique dermatologic safety considerations for tirzepatide, which may be relevant when counseling patients on treatment options. It should be noted that the FDA Adverse Event Reporting System (FAERS) data are subject to reporting bias and cannot establish incidence or causality.

The findings of Mullins et al., in their comprehensive analysis of patients treated with tirzepatide in seven Phase 3 studies, revealed that 51.1% of patients developed ADA during the treatment period. Notably, hypersensitivity reactions occurred in 4.1% of ADA-positive patients, compared to 3.0% in ADA-negative patients. Similarly, injection site reactions were reported in 4.6% of ADA-positive patients, versus 0.7% in those without ADA, suggesting that immunogenicity may contribute to these adverse events. These reactions were predominantly mild to moderate in severity and resolved independently of ADA status or titer levels. Importantly, the development of ADA did not impact the pharmacokinetics or efficacy of tirzepatide, indicating that immunogenicity did not adversely affect the drug's performance.[19]

In the same context, a retrospective review of cutaneous adverse events associated with semaglutide, dulaglutide, tirzepatide, lixisenatide, liraglutide, and exenatide found that the five most common cutaneous reactions associated with GLP-1 agonists were eczematous, pruritus, drug eruptions, hyperhidrosis, and alopecia. Life-threatening cutaneous adverse events accounted for 2.17% of all cutaneous reactions, with no statistically significant differences observed between drug types. Tirzepatide is associated with a lower overall rate of reported skin-related adverse reactions compared to other GLP-1 agonists, particularly exenatide, dulaglutide, and liraglutide. Tirzepatide accounted for 690 reactions, which is 5.96% of the total reported cutaneous adverse events, much lower than exenatide (42.4%), dulaglutide (20.1%), and liraglutide (16.9%). Regarding specific skin effects of tirzepatide, the most reported adverse reaction was eczematous reactions (183 cases), followed by alopecia (155 cases), drug eruption (151 cases), pruritus (130 cases), hyperhidrosis (39 cases), skin discoloration (8 cases), and life-threatening reactions (7 cases). Compared to other agents, tirzepatide had significantly fewer reports of pruritus, hyperhidrosis, and drug eruptions. Reports of rare cutaneous events such as psoriasis, acne, nail changes, and photosensitivity were anecdotal and extremely infrequent. These retrospective findings are suggestive of a relatively favorable cutaneous safety profile for tirzepatide, though not definitive.[32]

Aesthetic changes associated with tirzepatide use

Rapid or massive weight loss, induced by agents like semaglutide and tirzepatide, or after bariatric surgery, is associated with a significant reduction in subcutaneous fat tissue volume, predisposing to tissue laxity. This is caused by the loss of mechanical support provided by fat, which can lead to significant changes in skin structure, including decreased collagen synthesis and altered collagen fiber composition, and contribute to reduced skin firmness and increased laxity. Studies show a decrease in thick collagen fibers and an increase in thin collagen fibers, with a rise in elastic fiber density to maintain skin elasticity. The loss of underlying fat and impaired collagen cross-linking weakens the extracellular matrix, reducing mechanical skin stability and causing skin sagging and folds. Additionally, skin is directly affected by the diminished absorption of various nutrients and vitamins, such as vitamin A and D, that are crucial for collagen synthesis, and reductions in key enzymes involved in collagen production and persistent inflammation after weight loss further degrade skin integrity and elasticity, especially in areas like the abdomen, arms, and thighs.[33–35]

Facial lipoatrophy associated with GLP–1–induced weight loss (popularly termed 'Ozempic face') is described as the characteristic facial changes seen in some individuals using Ozempic (semaglutide). These changes typically include facial volume and fat loss, skin sagging, hollowing of the cheeks and temples, more prominent nasolabial folds and jawline, and an accelerated aging appearance. These aesthetic changes are secondary to rapid weight loss and not a direct pharmacologic toxicity of the drug, as patients on semaglutide can lose around 10.9% of their body weight in six months.[36–38] It is not a direct pharmacologic side effect of semaglutide, but it is a severely annoying dermatological cosmetic compromise.[38] Semaglutide-induced fat loss can significantly affect collagen synthesis, skin elasticity, alter dermal structure, and induce changes in general dermal health and skin appearance. Fat loss also alters adipokine levels and inflammatory responses, further impacting skin elasticity. However, mechanistic explanations, such as altered adipokines, inflammatory responses, and impaired collagen metabolism, remain speculative. Some studies observed regional fat loss in facial areas, resulting in noticeable aesthetic changes, but more studies are needed to fully understand semaglutide's direct effects on skin.[39,40]

Although the pharmacological treatments of obesity offer a balanced alternative to surgery and promote a gradual

fat loss, which helps maintain skin integrity, reduced food intake due to drugs like tirzepatide and semaglutide may still lead to nutrient deficiencies, such as vitamin D, B12, and protein, affecting skin health, making dietary support essential during treatment. Tirzepatide has been shown to produce greater weight loss compared to semaglutide. In clinical trials, patients treated with tirzepatide are more likely to achieve 10% or greater, and 15% or greater weight loss and experience larger reductions in body weight at 3-, 6-, and 12-months.[4,41] Therefore, tirzepatide is also suspected to cause facial fat loss and changes in skin elasticity and collagen synthesis due to rapid weight loss. Patients should be made aware of these potential side effects to better manage expectations and seek appropriate care if needed.

These aesthetic changes not only affect physical appearance but also have a profound psychosocial impact, including reduced self-esteem, dissatisfaction with body image, and emotional distress. Despite the focus on metabolic and weight-related outcomes, skin laxity remains an underrecognized consequence that can undermine treatment satisfaction and long-term adherence. To address this issue, an integrated therapeutic approach is essential, including the use of collagen biostimulators such as Poly-L-Lactic Acid (PLLA) and Calcium Hydroxyapatite (CaHA) to restore skin firmness by stimulating collagen production, complemented by energy-based devices like High-Intensity Focused Ultrasound (HIFU), fractional radiofrequency, and CO_2 laser. While no large-scale studies have yet combined tirzepatide therapy with anti-laxity treatments, clinical evidence supports their synergistic use in patients undergoing substantial weight loss. This multidisciplinary strategy ensures not only metabolic improvement but also preservation of aesthetic and psychological well-being.[40,42] These management strategies are extrapolated from bariatric surgery literature and represent expert opinion, as no controlled studies have evaluated them in tirzepatide-treated patients.

Dermatological therapeutic benefits of tirzepatide

Tirzepatide, by significantly improving glycemic control in patients with type 2 diabetes, may lead to a reduction in several diabetes-related cutaneous manifestations. Chronic hyperglycemia is known to contribute to a variety of skin conditions, such as diabetic dermopathy, necrobiosis lipoidica, acanthosis nigricans, and increased susceptibility to infections due to impaired immune response and poor circulation. With tirzepatide's dual GIP and GLP-1 receptor agonism, patients can achieve substantial improvements in HbA1c and insulin sensitivity, which can enhance skin barrier function, promote wound healing, and reduce the occurrence of skin infections. Clinical observations have noted improvements in conditions such as candidiasis and bacterial folliculitis with better glycemic control. Furthermore, improved metabolic profiles may also alleviate pruritus and reduce skin dryness, both commonly reported in diabetic patients. GLP-1 agonists are suggested to exert potential immunomodulatory effects, such as reducing proinflammatory cytokines and altering immune cell populations; however, these remain speculative rather than established. Therefore, tirzepatide's metabolic benefits can extend beyond glucose regulation and may positively impact skin health in individuals with diabetes.[7,43]

Anecdotal evidence from case reports has suggested possible dermatological benefits. A recent case report described significant hair regrowth with improvement in hair density within 6-months of tirzepatide at a dose of 2.5 mg weekly for the first 3-months followed by an increase of 5 mg weekly, in addition to improvement in insulin resistance and weight loss in a male patient with androgenic alopecia, suggesting that improved insulin sensitivity through tirzepatide might promote hair growth, control dihydrotestosterone levels, and release miniaturization of the dermal papilla of hair follicles.[44] Similarly, tirzepatide induced remarkable improvement in a male patient with a 30-year history of recalcitrant Folliculitis Decalvans (FD) with symptom relief and hair regrowth, following the initiation of tirzepatide for weight management. The case highlighted that tirzepatide could help to restore immune tolerance to follicular microbiota, and also pointed to the potential anti-inflammatory and immunomodulatory properties of tirzepatide in managing FD, a chronic and refractory dermatologic disorder. This single case highlights a potential anti-inflammatory and immunomodulatory effect, though causality remains unproven, and controlled studies are needed.[45] Additionally, a recent case report documented significant improvements in Hidradenitis Suppurativa (HS) severity and dermatology quality of life scores following combined treatment with tirzepatide, initiated at 2.5 mg/0.5 mL weekly and increased to 7.5 mg/0.5 mL weekly, and infliximab.[46] Given the anecdotal nature of these reports, their findings should be interpreted with caution. HS is a chronic skin disorder where obesity is prevalent in up to 75% of patients, aiding in the systemic inflammatory state and a higher body mass index is positively correlated with disease severity.[47]

GLP-1 receptor agonists are suspected to have a potential therapeutic role in inflammatory skin diseases such as psoriasis and HS. In psoriasis, these agents have been linked to significant reductions in Psoriasis Area and Severity Index (PASI) scores, likely through the downregulation of pro-inflammatory cytokines like TNF-α and modulation of immune pathways, including the enhancement of peripheral regulatory T-cell function. In HS, GLP-1 agonists have been associated with decreased systemic inflammation and improved patient quality of life. These findings support further exploration of GLP-1 agonists, including tirzepatide, as adjunctive treatments in dermatologic conditions characterized by chronic inflammation.[31,48,49] However, these observations remain preliminary, and controlled studies are essential before definitive conclusions can be drawn.

Lipodystrophy syndromes are characterized by visible lipoatrophy and abnormal fat redistribution, which manifest dermatologically as acanthosis nigricans, eruptive xanthomas, or impaired wound healing. These dermatologic manifestations often precede or accompany profound metabolic complications such as severe insulin resistance, hypertriglyceridemia, and hepatic steatosis.[50] Importantly, while metreleptin remains a cornerstone for generalized forms, its efficacy in partial lipodystrophy is limited, underscoring the relevance of alternative therapies. Dermatologists frequently encounter lipodystrophy within the context of connective tissue disease-associated forms (e.g., juvenile dermatomyositis–related acquired general-

Table 2 Dermatological therapeutic benefits of tirzepatide.

Dermatologic Condition	Proposed Mechanism	Clinical Evidence	Remarks
Diabetes-related cutaneous manifestations (dermopathy, necrobiosis lipoidica, acanthosis nigricans, infections, pruritus, xerosis)	Improved glycemic control, enhanced insulin sensitivity, better circulation, reduced proinflammatory cytokines, possible immune modulation	Observational data & indirect evidence from improved HbA1c, triglycerides, weight[7,43]	Improvement likely secondary to metabolic effects; immunomodulation still speculative
Hair disorders (androgenetic alopecia)	Improved insulin sensitivity, weight reduction, potential impact on dihydrotestosterone and release dermal papilla miniaturization	Case report: significant hair regrowth with improvement in hair density within 6-months of tirzepatide at a dose of 2.5 mg weekly for the first 3-months followed by an increase of 5 mg weekly, in addition to improvement in insulin resistance and weight loss in a male patient with androgenic alopecia[44]	Anecdotal; causality not proven
Folliculitis decalvans	Possible restoration of immune tolerance to follicular microbiota, anti-inflammatory and immunomodulatory properties	Case report: significant improvement and hair regrowth after tirzepatide initiation with symptoms relief[45]	Single case; controlled studies lacking
Hidradenitis suppurativa	Weight reduction, decreased systemic inflammation, improved metabolic profile; potential synergy with biologics (e.g., infliximab)	Case report: Marked improvements in HS severity and dermatology quality life scores following combined treatment with tirzepatide, initiated at 2.5 mg/0.5 mL weekly and increased to 7.5 mg/0.5 mL weekly, and infliximab[46]	Promising, but based on anecdotal data
Psoriasis	Downregulation of TNF-α, modulation of immune pathways, increased Treg activity	Evidence with GLP-1 agonists; limited but suggestive relevance to tirzepatide[49]	Preliminary; further studies needed
Lipodystrophy syndromes (with cutaneous stigmata: acanthosis nigricans, eruptive xanthomas, impaired wound healing, dermatomyositis-associated forms)	Dual GIP/GLP-1 agonism improves insulin sensitivity, reduces ectopic lipid accumulation, lowers triglycerides, suppresses glucagon	Observational cohort (n = 17): ↓BMI (-1.7 kg/m^2), ↓HbA1c (−1.1%), ↓TG (-65 mg/dL), ↓insulin use (-109 U/day); only mild GI effects[52]	Particularly relevant when metreleptin efficacy is limited; tirzepatide may alleviate secondary skin sequelae

ized lipodystrophy) and inherited syndromes with cutaneous stigmata.[51] Tirzepatide improves metabolic control by enhancing insulin sensitivity, stimulating glucose-dependent insulin secretion, suppressing glucagon, delaying gastric emptying, and reducing ectopic lipid accumulation. Recently, in an observational cohort of 17 patients with partial and generalized lipodystrophy, treatment with tirzepatide over a median of 8.7-months led to significant reductions in BMI (-1.7 kg/m^2), HbA1c (-1.1%), triglycerides (-65 mg/dL), and insulin requirements (-109 units/day), with only mild gastrointestinal side effects. These metabolic improvements are directly relevant to dermatology, as better glycemic and lipid regulation may alleviate secondary cutaneous sequelae of lipodystrophy, underscoring tirzepatide's promise as an adjunctive therapy within interdisciplinary management of lipodystrophy.[52]

Overall, dermatological benefits of tirzepatide, which are summarized in Table 2, remain an emerging area of investigation. Interdisciplinary collaboration between dermatology and endocrinology is encouraged to better define its potential role in skin disease management.

Conclusion and future perspectives

Tirzepatide is an effective therapeutic option for type 2 diabetes mellitus and obesity, used either as a first-line or add-on agent depending on patient characteristics in alignment with ADA and SBD guidelines. Cutaneous side effects, primarily injection site reactions, are common but usually mild and manageable, whereas hypersensitivity and severe allergic reactions are rare but require prompt recognition and intervention. Proper patient education, injection technique, and clinical monitoring are essential to mitigate risks and optimize therapeutic outcomes. Beyond its adverse effects, tirzepatide may also offer preliminary dermatologic benefits, including potential improvements in inflammatory skin diseases such as psoriasis, hidradenitis suppurativa, as well as androgenic alopecia. These observations remain anecdotal, and controlled dermatology-focused clinical studies and registries are needed to establish efficacy.

As tirzepatide use expands, real-world data will better define its safety profile, including cutaneous effects. Future research should focus on studies to understand immune reactions at the molecular levels, identifying patient risk factors for hypersensitivity, developing formulations with reduced immunogenicity, and exploring desensitization protocols for patients who benefit metabolically but have mild hypersensitivity.

Research data availability

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

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Authors' contributions

Heba Saed El-Amawy: Conceptualized the study, conducted the literature search and data analysis, wrote the original draft, reviewed and edited the manuscript, and approved the final version for submission.

Conflicts of interest

None declared.

Editor

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REVIEW

Update on novel acne treatments: a narrative review focused on microbiome modulation and non-pharmacological approaches☆

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Abstract Acne vulgaris is a chronic inflammatory condition with multifactorial pathogenesis. Despite the availability of numerous treatment options, there remains a need for safe, well-tolerated, and microbiome-preserving therapies. This narrative review explores recent advances in non-pharmacological acne treatments, focusing on various microbiome modulation strategies. It highlights emerging therapeutic modalities and their potential impact on clinical practice. Key findings from recent studies are summarized, providing insights for future research and practical applications in dermatology.

Introduction

Acne vulgaris is a chronic inflammatory skin condition with multifactorial pathogenesis, involving abnormal keratinization, sebum overproduction, inflammation of the pilosebaceous unit, microbial colonization by *Cutibacterium acnes*, and dietary influences.[1,2] Although numerous effective treatments are currently available, such as retinoids, antibiotics, and hormonal agents, they are often limited by adverse effects, antimicrobial resistance, and disruption of the skin microbiome. These limitations have intensified the search for alternative therapies that can restore microbial balance, modulate host-microbe interactions, and enhance safety and tolerability.[3]

The cutaneous microbiome plays a fundamental role in maintaining skin barrier integrity and regulating local immune responses. Its dysregulation can exacerbate inflammation, impair immune tolerance, and promote the overgrowth of pathogenic microorganisms, mechanisms that are increasingly associated with persistent or treatment-resistant acne.[4]

Consequently, microbiome-targeted approaches have emerged as a promising and innovative field in acne treatment. Advances in understanding the microbiome's role in

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cutaneous immunity and inflammation have opened new avenues for developing safer, more personalized therapies that address dysbiosis while preserving microbial diversity.[5]

This narrative review provides an overview of emerging non-pharmacological strategies, including topical probiotics, postbiotics, live biotherapeutic products, biotechnological phytocomplexes, bacteriophages, vaccines, gut-skin-axis interventions, and energy-based modalities such as photodynamic therapy. These strategies aim to achieve clinical efficacy while preserving or restoring microbiome balance, representing a paradigm shift in the contemporary management of acne vulgaris.

Methods

A comprehensive literature review was conducted to identify recent studies on non-pharmacological treatments for acne, focusing on microbiome modulation strategies. The review included articles published between 2022 and 2024, excluding those focused solely on scar treatments, while considering studies addressing all severities of inflammatory acne vulgaris. The search strategy prioritized clinical trials, Randomized Controlled Trials (RCTs), meta-analyses, and systematic reviews. To ensure relevance, filters were applied to include only studies published between 2022 and 2024. Searches were conducted on December 29, 2024, across multiple databases, including PubMed, Google Scholar, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. Additionally, a snowballing technique was employed to identify relevant studies cited in the reviewed literature. This review is based exclusively on previously published research and excludes any original studies conducted by the authors. Table 1[6–28] summarizes the key studies included in this narrative review.

Pathogenesis of acne vulgaris

Acne vulgaris is a chronic inflammatory skin condition affecting the pilosebaceous units, driven by multiple factors such as hyperseborrhea, follicular hyperkeratinization, localized immune-mediated inflammation, and dysbiosis of the skin microbiome, particularly involving *Cutibacterium acnes* (*C. acnes*).[4] The critical role of skin microbiome dysbiosis in the onset and progression of acne has reshaped therapeutic strategies. As our understanding of the interplay between the skin microbiome and host immunity deepens, the focus is shifting from traditional antibiotic treatments to innovative microbiome-targeted therapies.[29]

Skin microbiome and acne development

The skin microbiome is a dynamic ecosystem of microorganisms, including bacteria, viruses, fungi, and their surrounding environment, that plays an essential role in maintaining skin health.[29] Among these microorganisms, *C. acnes*, a Gram-positive anaerobic bacterium, predominates in sebaceous gland-rich areas.[30] Typically a commensal organism, *C. acnes* contributes to skin homeostasis by lowering pH through the release of free fatty acids and by inhibiting the growth of pathogens such as *Staphylococcus aureus* and *Streptococcus* spp.[31] However, under conditions of dysbiosis, *C. acnes* may adopt a pathogenic role, promoting skin inflammation through lipase-mediated sebum hydrolysis and free fatty acid release.[4]

The IA1 phylotype of *C. acnes* has been identified as particularly virulent due to its ability to form biofilms and activate inflammatory pathways via Th17-mediated immune responses, including Interleukin-17 (IL-17), a key cytokine in acne pathogenesis.[30,32] Additionally, *Staphylococcus* spp. have emerged as significant contributors to acne pathogenesis, acting as pathobionts or disease modulators.[33] Dysbiosis is further exacerbated by increased seborrhea, perpetuating a cycle of chronic inflammation and immune dysregulation.[3]

Impact of conventional acne treatments on the microbiome

Conventional acne treatments, such as topical retinoids, benzoyl peroxide, and oral antibiotics, primarily target *C. acnes* and modulate its associated inflammatory pathways. However, these approaches often disrupt the skin microbiome, leading to microbial imbalances that favor opportunistic pathogens and undermine cutaneous homeostasis.[34,35] The overuse of antibiotics has been linked to adverse effects such as resistance development and further microbial disruption.[34] This increasing awareness has shifted treatment strategies from solely eradicating *C. acnes* to restoring microbiome balance and diversity, highlighting the need for innovative therapeutic alternatives.[4,30] Consequently, microbiome-focused therapies, summarized in Fig. 1, have emerged as promising strategies. These approaches aim to address dysbiosis and modulate the skin microbiome without the negative consequences often associated with traditional treatments.[36] They emphasize restoring microbial equilibrium and reducing inflammation, representing a significant shift toward sustainable and targeted acne management.

Non-pharmacological microbiome-targeted approaches in acne treatment

Topical probiotics

Topical probiotics and postbiotics have emerged as promising alternatives to antibiotics by modulating the skin microbiota.[4] In a double-blind, placebo-controlled trial conducted in 79 patients wild mild-to-moderate acne vulgaris, Lebeer et al. (2022) evaluated a topical cream containing *Lactobacillus rhamnosus* GG, *Lactiplantibacillus plantarum* WCFS1, and *Lacticaseibacillus pentosus* KCA1 applied twice daily for eight weeks. The treatment significantly reduced *C. acnes* and *Staphylococcus* spp. colonization, while increasing *Lactobacillus* spp. abundance, likely due to decreased lipase activity and lactic acid production. Clinically, inflammatory lesion counts decreased significantly compared with placebo at weeks 4, 8, and 12, with a 34.4% reduction at week 4 in the active group versus 1.7% in the placebo group ($p < 0.001$). Although the exact Mean Difference (MD) was not reported, the reduction was statistically significant. Furthermore, the topical probiotic cream was well tolerated and improved skin hydration.[6]

Table 1 Comparative overview of key studies included in this narrative review.[6–28]

Authors / Year	Therapy	Study Design	Patients	Objective	Intervention	Key Findings	Safety	Conclusion
Lebeer et al. / 2022[6]	Topical Probiotics	Double-blind, placebo-controlled clinical trial.	79 patients mild-to-moderate acne.	To evaluate the efficacy and safety of a cream with lactobacilli in modulating the skin microbiome and improving acne.	Topical cream containing *L. rhamnosus* GG, *L. plantarum* WCFS1, *L. pentosus* KCA applied twice daily for 8-weeks.	Reduced *C. acnes* and *Staphylococcus spp.* colonization; increased *Lactobacillus spp.* abundance. Clinically, inflammatory lesions decreased and skin hydration improved.	Well tolerated, mild erythema in few patients.	Topical lactobacilli significantly improved acne and modulated microbiome composition. Findings suggest potential but require replication in larger RCTs.
Sathikulpakdee et al. / 2022[7]	Topical Probiotics	Single-blind RCT.	104 patients with mild-to-moderate acne.	To evaluate the efficacy and safety of probiotic-derived lotion compared to 2.5% benzoyl peroxide.	Lotion with cell-free supernatant of *L. paracasei* MSMC 39-1 vs. 2.5% benzoyl peroxide, applied twice daily for 4 weeks.	Both groups showed within-group reductions in inflammatory lesions, with no statistically significant difference between treatments ($p = 0.23$). Probiotic lotion reduced erythema from baseline ($p < 0.001$).	Well tolerated; fewer side effects (erythem, itching, scaling) in probiotic group.	Probiotic-derived lotion was safe, with comparable efficacy to benzoyl peroxide. Evidence remains preliminary and requires larger trials.
Casari et al. / 2022[8]	Topical Probiotics	Open-label pilot clinical study.	29 patients with mild-to-moderate acne.	To evaluate the efficacy and safety of a probiotic and hyaluronic acid-based serum.	Nightly application of serum with *L. paracasei* LiveSkin88 + hyaluronic acid for 28 days.	Significant reduction in papules/pustules at day 14 and 28 ($p < 0.0001$); erythema, skin hydration and affected facial area also improved ($p < 0.05$)	No adverse events; high patient satisfaction.	Probiotic serum improved inflammatory lesions and hydration. Preliminary evidence, requiring replication in controlled RCTs.

Table 1 (*Continued*)

Authors / Year	Therapy	Study Design	Patients	Objective	Intervention	Key Findings	Safety	Conclusion
Karoglan et al. / 2019[9]	LBPs	Open-label Pilot Study	14 patients with mild-to-moderate acne.	To evaluate safety and efficacy of applying non-pathogenic *C. acnes* strains.	Hydrogel formulations with specific non-pathogenic *C. acnes* strains; applied for 5 weeks.	Significant reduction in non-inflammatory lesions in both groups (p = 0.029 and 0.036). No effect on inflammatory lesions.	No severe adverse effects reported	Microbiome modulation through non-pathogenic *C. acnes* strains shows promise as a potential treatment for acne.
Knödlseder et al. / 2024[10]	LBPs	Preclinical (murine model + in vitro).	5 mice (genetically modified *C. acnes* group), 9 mice (control group).	To evaluate feasibility of engineered *C. acnes* expressing NGAL for sebum modulation.	*C. acnes engineered to express NGAL, applied to murine skin and sebocyte cultures.*	Sebum production was significantly reduced in sebocyte cultures treated with NGAL. No increase in pro-inflammatory cytokines (IL-1β, IL-6, TNF-α).	No adverse effects observed	Engineered *C. acnes* shows promise for targeted sebum modulation; evidence remains limited to in vitro and murine models.
AOBiome / published data 2022[11]	LBPs	Phase IIb RCT, double-blind, placebo-controlled.	358 adult patients with mild-to-moderate acne.	To evaluate efficacy and safety of topical *Nitrosomonas eutropha* B244.	*N. eutropha* B244 topical spray applied daily for 12 weeks.	Significantly higher proportion achieving IGA success (score 0–1) vs placebo (OR 2.45; 95% CI 1.08–5.56; p = 0.03); inflammatory lesions not significantly different.	Well-tolerated, with no treatment-emergent adverse events reported.	The topical application of *Nitrosomonas eutropha* significantly improved acne, presenting an alternative for managing mild-to-moderate acne.
Han et al. / 2022[12]	Topical Postbiotic	Randomized, placebo-controlled, split-face study.	20 patients with mild-to-moderate acne (IGA 2–3).	To evaluate the efficacy and safety of a lotion containing *Enterococcus faecalis* CBT SL-5 extract.	*E. faecalis* CBT SL-5 lotion applied to one side of the face; vehicle lotion to the other, twice daily for 4-weeks.	Significant improvement in global acne scores at all time points (week 2 p=0.009; week 4 p=0.005; week 6 p<0.001); reduced *C. acnes* density on treated side.	No serious adverse effects reported.	Topical postbiotics with *E. faecalis* CBT SL-5 extract improved acne and reduced *C. acnes* density. Promising results, but larger RCTs are required.

Table 1 (*Continued*)

Authors / Year	Therapy	Study Design	Patients	Objective	Intervention	Key Findings	Safety	Conclusion
Ho et al. / 2022[13]	Topical Postbiotic	RCT	20 patients with acne vulgaris.	To evaluate the efficacy of a co-fermented postbiotic with collagen in improving acne, reducing inflammation, and promoting skin healing.	Co-fermented topical gel (TYCA06/AP-32/CP-9 with collagen), applied twice daily for 4-weeks.	Significant improvement in skin hydration (+4.5%; $p<0.05$), reduced erythema (−7.1%; $p<0.01$) and brown spots (−8.7%; $p<0.001$); nonsignificant sebum reduction (−6.2%); downregulation of TSLP and IL-33.	Well tolerated, no adverse effects reported	The postbiotic formulation was safe and showed improvements in hydration, erythema, and pigmentation. Further validation in larger trials is needed.
Guerra-Tapia et al. / 2024[14]	Biotechnological Phytocomplexes	Open-label prospective study.	43 patients with truncal mild-moderate acne.	To evaluate the effect of a lotion containing a biotechnological phytocomplex, on bacterial diversity and clinical outcomes in truncal acne.	Lotion containing plant-based phytocomplexes (*C. sinensis* and *M. citrifolia* callus lysates), niacinamide 4%, succinic acid 2%, applied twice daily for 8-weeks.	Inflammatory lesions reduced by 52.1% (p = 0.006); IGA decreased by 27.6% (p < 0.001), with 60.5% of patients achieving ≥1-point improvement; *C. acnes* relative abundance decreased. Erythema reduced by 18.3% (p = 0.007); desquamation reduced by 63.8% (p = 0.02).	The treatment was well tolerated, with only two cases of mild itching reported.	Preliminary evidence of efficacy on inflammatory lesions and microbiota, but open-label design limit interpretation; RCTs are needed.
De Lucas et al. / 2024[15]	Biotechnological Phytocomplexes	Open-label, prospective study.	44 patients with mild-to-moderate acne.	To evaluate the effect of a facial cream gel containing a biotechnological phytocomplex on skin microbiota balance and clinical acne severity.	Topical application of a facial cream gel containing *C. sinensis* and *M. citrifolia* callus lysates, niacinamide 4%, succinic acid 2%, applied daily for 8-weeks.	Inflammatory lesions reduced by 47.3% (p < 0.001); non-inflammatory lesions reduced by 31.1% (p = 0.05); significant IGA improvement (p < 0.001). No 95% CI reported.	Well, tolerated with no severe adverse effects.	Phytocomplex improved both inflammatory and non-inflammatory lesions, but small open-label design and lack of CI limit conclusions; RCTs required.

Table 1 (*Continued*)

Authors / Year	Therapy	Study Design	Patients	Objective	Intervention	Key Findings	Safety	Conclusion
Kim et al. / 2019[16]	Bacteriophage therapy	Experimental preclinical, murine model	Nine Hairless 1 (HR-1) mice.	To evaluate the effect of bacteriophage therapy on *C. acnes*-induced inflammation in a mouse acne model.	HR-1 mice were injected intradermally with *C. acnes* (10^9 CFU/μL) followed by bacteriophage therapy in the treatment group.	Reduced inflammatory nodule size, decreased epidermal thickness and microcomedones; trends to lower CD8+ T-cells, neutrophils, IL-1β and MMP-3 (not statistically significant, no 95% CI reported).	No adverse effects observed	Early preclinical evidence that phages may reduce *C. acnes*-induced inflammation, but findings limited by lack of significant immunohisto-chemical effects.
Lam et al. / 2021[17]	Bacteriophage therapy	Experimental preclinical, murine model	24 male BALB/c mice with MDR *C. acnes* infection.	To evaluate the therapeutic effect of a newly isolated lytic bacteriophage (TCUCAP1) against *C. acnes*.	Intraperitoneal injection of *C. acnes*, followed by application of TCUCAP1 bacteriophage in a hydroxyethyl cellulose cream.	Significant reduction in inflammatory lesions; reduced IL-1β ($p < 0.05$) and caspase-3 ($p < 0.01$). No 95% CI reported.	No severe adverse effects reported	TCUCAP1 effectively reduced MDR *C. acnes*-induced inflammation, suggesting potential as an alternative for antibiotic-resistant acne.
Golembo et al. / 2022[18]	Bacteriophage therapy	Phase 1 randomized, double-blind, vehicle-controlled clinical trial.	75 patients with mild-to-moderate acne.	To evaluate the safety, tolerability, and ability of a topical bacteriophage gel (BX001) to reduce *C. acnes* burden on facial skin.	BX001 (three *C. acnes*-specific bacterio-phages) formulated into hydroxyethyl cellulose gel, applied once daily for 4-weeks.	High-dose BX001 significantly reduced *C. acnes* load vs. vehicle (from day 14–35, $p = 0.036$). No lesion counts, IGA, or relapse outcomes reported; no 95% CI provided.	Well tol-erated; no serious adverse events; pre-served micro-biome diversity.	BX001 showed targeted antibacterial effect, but clinical efficacy remains unproven; RCTs with standardized clinical endpoints are needed.
Eguren et al. / 2024[19]	Oral Probiotics	Randomized, double-blind, placebo-controlled clinical trial.	81 patients with mild-to-moderate acne (42 probiotic, 39 placebo).	To evaluate the efficacy and safety of an oral probiotic formulation in improving acne severity.	Daily capsule with *Lacticas-eibacillus rhamnosus* (CECT 30031) + *Arthrospira platensis* (BEA_IDA_0074B), 1×10^9 CFU/day for 12 weeks.	The probiotic group exhibited a significant reducion in non-inflammatory lesions (-8.06; 95% CI - 15.37 to -0.74; $p = 0.03$) and improvement in acne severity.	Well tol-erated, only mild digestive discom-fort reported.	Oral probiotic treatment was safe and effective, significantly improving acne severity and lesion reduction.

Table 1 (*Continued*)

Authors / Year	Therapy	Study Design	Patients	Objective	Intervention	Key Findings	Safety	Conclusion
Rinaldi et al. / 2022[20]	Oral probiotics	Randomized, double-blind, placebo-controlled clinical trial	114 patients with mild to moderate acne.	To assess efficacy and safety of a multi-strain probiotic + botanicals on acne and microbiome balance.	Dietary supplement containing probiotics (*Bifidobacterium breve* BR03, *Lacticaseibacillus casei* LC03, *Ligilactobacillus salivarius* LS03) and botanical extracts (*lupeol from Solanum melongena* and *Echinacea* extract).	Reduction in inflammatory lesions, along with improved erythema, desquamation, and sebum secretion in the supplement group compared to placebo. *C. acnes* and *S. aureus* levels decreased, while beneficial *S. epidermidis* increased on the skin.	Well-tolerated treatment, no serious adverse events reported	The combination of probiotics and botanical extracts reduced acne severity and improved skin microbiome, supporting its potential as an adjuvant therapy for inflammatory acne.
Da Rocha et al. / 2023[21]	Oral probiotics	Randomized, double-blind, placebo-controlled clinical trial	212 patients with mild-to-moderate acne (107 treatment, 105 placebo).	To assess the efficacy of an oral probiotic combined with fixed-dose topical treatment (benzoyl peroxide + adapalene) versus the same topical treatment with a placebo.	Oral probiotic (*Lactobacillus acidophilus, Bifidobacterium lactis*) + topical adapalene 0.1% + benzoyl peroxide 2.5% for 90-days, followed by 90 days of probiotic or placebo alone.	Higher proportion achieved IGA 0–1 in probiotic group vs topical alone ($p < 0.05$). Significant improvement in global acne severity. 95% CIs not reported	Well tolerated, mild gastrointestinal events in probiotic group.	Oral probiotics combined with topical therapy improved outcomes and should be considered as adjuvant for acne management
Huang et al. / 2024[22]	Omega-3 Fatty Acids	Randomized controlled clinical trial + animal model study.	40 patients with moderate-to-severe acne + 20 healthy controls.	To evaluate the role of ω-3 fatty acids in acne treatment and gut microbiota modulation.	Isotretinoin alone vs. isotretinoin + ω-3 fatty acids (2400 mg/day) for 12-weeks.	GAGS scores improved (15.1 ± 4.5 vs. 18.7 ± 4.9; MD = -3.6; $p = 0.02$).	Well tolerated; mild gastrointestinal discomfort in some patients.	Omega-3 fatty acids may serve as an effective adjuvant to isotretinoin, potentially modulating gut microbiota and reducing inflammation.

Table 1 (*Continued*)

Authors / Year	Therapy	Study Design	Patients	Objective	Intervention	Key Findings	Safety	Conclusion
Jung et al. / 2014[23]	Omega-3 Fatty Acids	Randomized, double-blind, controlled trial	45 patients with mild to moderate acne.	To evaluate the effects of ω-3 and GLA supplementation on acne lesion counts and severity.	Daily supplementation with ω-3 fatty acids (2000 mg/day EPA + DHA) or γ-linoleic acid (GLA, 400 mg/day) vs. control for 10-weeks.	ω-3 group: inflammatory lesions reduced 43% (from 10.1 ± 3.2 to 5.8 ± 3.4), non-inflammatory lesions reduced 20% (from 23.5 ± 9.2 to 18.9 ± 8.3). Cunliffe grade improved from 2.4 to 1.7. GLA group showed similar improvements. 95% CI not reported.	Well tolerated; some mild gastrointestinal discomfort.	Omega-3 and GLA supplementation appear safe and effective as adjuvant therapies for mild-to-moderate acne, though evidence is limited to small early-phase trials.
Yang et al. / 2021[24]	ALA-PDT	Prospective clinical study	15 patients with moderate-to-severe acne vulgaris.	To examine the effects of ALA-PDT on the skin microbiome, (impact on *C. acnes* and microbial diversity).	Four sessions of 5% ALA-PDT at two-week intervals. Skin microbiome samples were taken before treatment and before the final session.	Reduction in *C. acnes* abundance; increase in *Bacillus* and *Lactococcus*; improvement in overall microbial diversity. Shift toward a eubiotic profile. No 95% CI reported.	Well tolerated, only mild erythema observed	ALA-PDT modulated the skin microbiome by reducing *C. acnes* abundance and enhancing overall microbial diversity, supporting its role in microbiome modulation.
Guo et al. / 2023[25]	ALA-PDT	Prospective observational study	18 patients with severe acne + 8 healthy controls.	To evaluate the effects of ALA-PDT on microbiome composition.	ALA-PDT once a week for 3-weeks. Skin microbiome was analyzed before and after treatment using 16S ribosomal RNA sequencing.	Increase in microbial diversity; restoration of *Pseudomonas*, *Gordonia*, *Leptotrichia*, and *Mycobacterium* (genera often depleted in acne). *C. acnes* levels remained unchanged. No 95% CI reported.	No major adverse effects reported.	ALA-PDT modulates skin microbiota composition in severe acne patients, potentially contributing to its therapeutic effect.

Table 1 (*Continued*)

Authors / Year	Therapy	Study Design	Patients	Objective	Intervention	Key Findings	Safety	Conclusion
Zhang et al. / 2023[26]	M-PDT	Multicenter RCT	152 patients with moderate-to-severe acne (77 M-PDT vs. 75 ISO)	To compare the efficacy and onset of action of M-PDT versus low-dose ISO in patients with moderate-to-severe acne.	Up to 5-weekly sessions of M-PDT following manual comedone extraction vs. low-dose isotretinoin (0.5 mg/kg/day) for 6-months.	M-PDT achieved 50% clinical improvement after 1-week, compared with 8-weeks for isotretinoin. Comparable efficacy at 2, 4, and 6-months. No 95% CI reported.	M-PDT caused only local skin irritation, while ISO was associated with systemic side effects in 70.6% of patients.	M-PDT offers faster onset, fewer systemic adverse effects, and comparable efficacy, making it a promising alternative.
Kim et al. / 2023[27]	SJW- PDT vs. IAA-PDT	Randomized, double-blind, split-face, vehicle-controlled clinical trial	31 patients with mild-to-moderate acne	To compare the efficacy of SJW-PDT vs. IAA-PDT for acne treatment and assess their skin rejuvenation effects.	Split-face design: one side treated with SJW-PDT and the other with IAA-PDT.	SJW-PDT reduced acne lesions by 56.5% at 1-week and 65.9% at 4-weeks; sebum production decreased by 27.9%. IAA-PDT was also effective but less pronounced. No 95% CI reported.	No reported adverse effects in both groups.	Both protocols were effective; SJW-PDT provided stronger clinical and sebosuppressive effects.
Zheng et al. / 2024[28]	Curcumin-PDT.	Experimental in vitro study.	Tested on *C. acnes* bacterial cultures and biofilms.	To assess the effect of curcumin-based PDT on *C. acnes* biofilms.	25 clinical *C. acnes* strains were tested for antibiotic resistance and biofilm formation capabilities. Biofilms were treated with curcumin-PDT.	Curcumin-PDT significantly reduced the survival of antibiotic-resistant *C. acnes*. Biofilm structure was disrupted, with increased permeability and bacterial cell death. No 95% CI reported.	Not assessed in vivo	Curcumin-based PDT showed potent anti-biofilm and antibacterial activity against *C. acnes* in vitro, supporting its potential as a future photosensitizer; clinical efficacy remains untested.

C. Acnes: Cutibacterium Acnes; RCT, Randomized Controlled Trial; LBPs, Live Biotherapeutic Products; *S. Aureus*: S*taphylococcus Aureus*; *S. Epidermidis: Staphylococcus Epidermidis*; IGA, Investigator Global Assessment; GAGS: Global Acne Grading System; PDT, Photodynamic Therapy; MDR, Multi-Drug-Resistant; IAA, Indole-3-Acetic Acid; ALA, 5-Aminolevulinic Acid; SJW, St. John's Wort; ISO, Isotretinoin; M-PDT, Modified red light 5-aminolevulinic acid PDT; GLA, Gamma-Linolenic Acid.

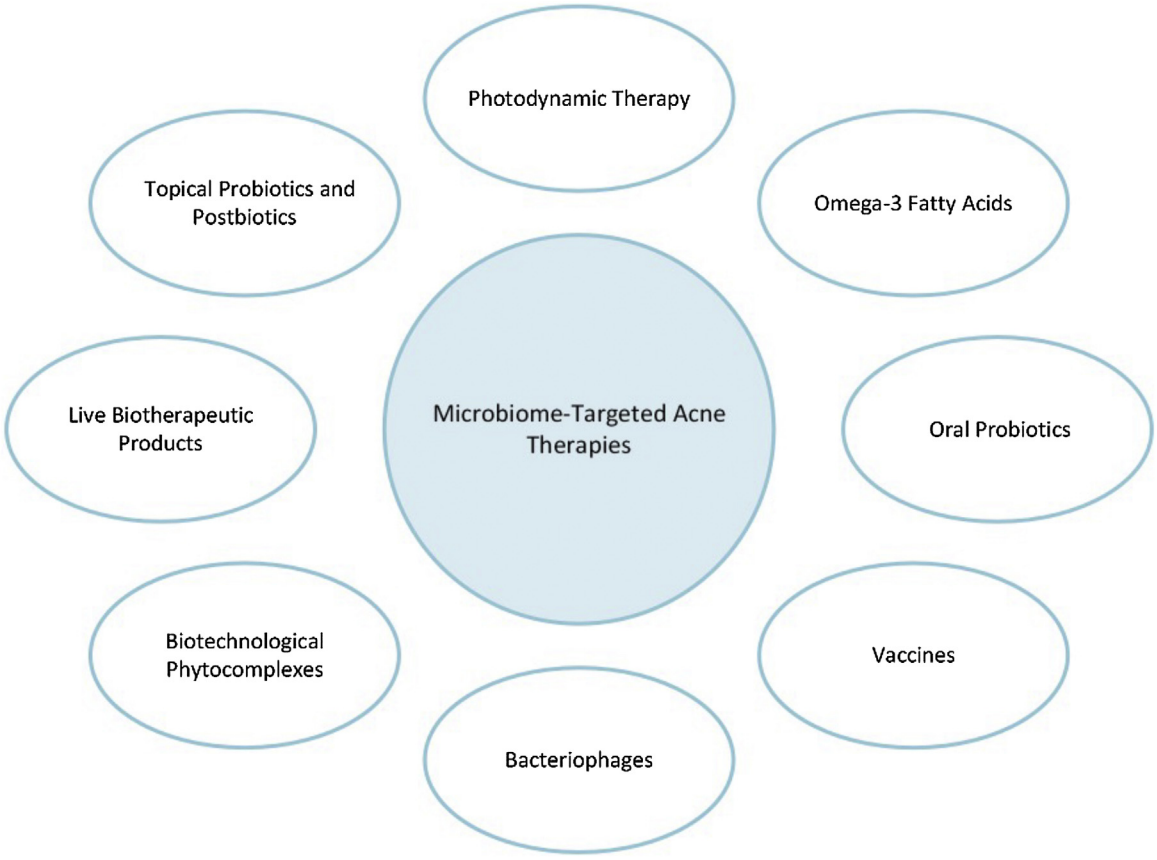

Figure 1 Different microbiome-targeted acne treatments.

Sathikulpakdee et al. (2022) conducted a single-blind RCT including104 patients to compare a probiotic-derived lotion containing the cell-free supernatant of *L. paracasei* MSMC 39-1 with 2.5% benzoyl peroxide. After four weeks, both groups showed significant within-group reductions in inflammatory lesion counts ($p < 0.001$ for both), with no statistically significant difference between treatments ($p = 0.23$). The probiotic lotion also significantly reduced erythema index from baseline (from 22.9 ± 1.9 to 21.4 ± 2.1 at week 4, $p < 0.001$), and showed a favorable tolerability profile, with fewer adverse events (7.69%) compared with benzoyl peroxide (26.92%).[7]

In a smaller open-label pilot study, Casari et al. (2022) evaluated a serum containing *Lactobacillus. paracasei* LiveSkin88 combined with hyaluronic acid in 29 patients with mild-to-moderate acne, applied nightly for 28 days. The treatment led to a statistically significant reduction in the number of papules and/or pustules ($p < 0.0001$). By day 14, the mean number of papules and/or pustules decreased from 7.9 ± 4.0 (mean value $\pm$ SD) at baseline to 4.7 ± 3.0 (95% CI), with improvements maintained through day 28 (mean 4.5 ± 3.8). Erythema also showed a a modest but significant improvement ($p < 0.0001$), while skin hydration increased from 53.5 ± 22.0 to 64.7 ± 19.9 arbitrary units ($p < 0.0001$; 95% CI). The facial area affected by acne significantly improved after 28 days ($p < 0.05$). No adverse events were reported, and patient satisfaction was high.[8]

Taken together, these trials underscore the strain-specific benefits of topical probiotics in acne management, ranging from reductions in inflammatory lesions to improvements in erythema and hydration. However, current evidence remains preliminary. Limitations include small sample sizes, short follow-up periods, heterogeneous formulations, and the fact that only one trial to date has been double-blind and placebo-controlled. Replication in larger, high-quality RCTs with standardized clinical outcomes, including lesion counts, Investigator's Global Assessment (IGA) scores, and relapse or recurrence rates, is essential to establish the efficacy, safety, and generalizability of topical probiotics in acne care.

Live biotherapeutic products

Emerging literature also highlights the potential benefit of Live Biotherapeutic Products (LBPs), a novel class of therapeutics incorporating live bacteria into topical formulations designed to modulate the skin microbiota and address localized dysbiosis.[37] Various LBP formulations using *C. acnes* strains have been investigated.

Karoglan et al. (2019) conducted an open-label pilot study in 14 patients with mild-to-moderate acne to assess whether non-pathogenic *C. acnes* strains could modulate the skin microbiome. Participants received one of two hydrogel formulations for five weeks. Non-inflammatory lesion counts decreased significantly in both groups: from 62 to 37 (mean reduction − 25 lesions; $p = 0.029$) and from 54 to 35 (mean reduction — 19 lesions; $p = 0.036$). Inflammatory lesion counts showed no significant changes ($p > 0.26$).

Microbiome analysis revealed colonization by the applied strains, with no irritation or flare-ups reported, supporting the safety and feasibility of this microbiome-modulating approach.[9]

Knödlseder et al. (2024) developed an engineered *C. acnes* strain expressing Neutrophil Gelatinase-Associated Lipocalin (NGAL), a protein involved in lipid regulation. In sebocyte cultures, NGAL reduced sebum production by approximately twofold within 48 hours, an effect comparable to isotretinoin 10 μM ($p < 0.0001$). NGAL produced by recombinant *E. coli* reduced sebum 1.7-fold but was less effective than the engineered *C. acnes*. Importantly, no cytotoxicity or apoptosis was observed. In murine models, the engineered strain colonized the skin and maintained NGAL expression without increasing pro-inflammatory cytokines such as IL-1β, IL-6, or TNF-α, underscoring its potential as a safe approach for targeted sebum modulation.[10]

AOBiome's Phase IIb trial (NCT02832063) investigated the topical application of *Nitrosomonas eutropha* B244, an ammonia-oxidizing bacterium, in 358 patients with mild-to-moderate acne. The randomized, double-blind, placebo-controlled design tested treatment for 12-weeks. Compared to placebo, B244 yielded a significantly higher proportion of participants reaching Investigator's Global Assessment (IGA) success, defined as a post-baseline score of 0 or 1 (Odds Ratio = 2.45; 95% CI 1.08–5.56; p = 0.03). Inflammatory lesion counts showed a numerical, but not statistically significant, improvement versus placebo. The formulation was well tolerated, with no treatment-emergent adverse events reported.[11]

These findings underscore the potential of LBPs to introduce a paradigm shift in acne therapy, focusing on microbial composition and host-microbe interactions. However, current evidence remains preliminary. Karoglan et al. provided only pilot open-label data without a control group (n = 14). Knödlseder et al. demonstrated promising effects, but only in vitro and in murine models. AOBiome's Phase IIb trial represents the most robust clinical evidence to date, though its primary outcome was not achieved in the intention-to-treat analysis. Larger, standardized, and controlled trials are warranted to confirm the clinical efficacy, durability, and safety of LBPs in acne management.

Topical postbiotics

Postbiotics, defined as preparations of inanimate microorganisms and/or their components that provide health benefits to the host, have demonstrated multiple benefits for the skin microbiome, including enhancing skin barrier function and promoting the growth of beneficial endogenous bacteria.[38] For acne management, various postbiotics have shown potential in restoring microbial balance and reducing acne severity through their anti-inflammatory and antimicrobial effects.[39]

Emerging evidence highlights the effectiveness of fermentation-derived products, such as *Enterococcus faecalis* CBT SL-5 extract, as a safe and well-tolerated topical option for reducing acne severity and addressing skin microbiome dysbiosis.[12] Han et al. (2022) conducted a randomized, placebo-controlled, split-face comparative study in 20 patients with mild-to-moderate acne. Participants applied a lotion containing *E. faecalis* CBT SL-5 extract twice daily for four weeks. The treated side showed significantly greater IGA improvement scores compared with the control side at all time points: week 2 (1.65 ± 0.81 vs 1.05 ± 0.51; p = 0.009), week 4 (1.80 ± 0.83 vs 1.15 ± 0.49; p = 0.005), and week 6 (2.15 ± 0.88 vs 1.05 ± 0.51; p < 0.001). Additionally, *C. acnes* density decreased significantly on the treated side, whereas no significant changes occurred on the control side. No treatment-related adverse effects were reported. Confidence intervals were not reported in the original publication.[12]

Similarly, Ho et al. (2022) performed a randomized clinical trial evaluating a co-fermented postbiotic formulation containing probiotic strains TYCA06, AP-32, and CP-9 combined with collagen in 20 patients with acne vulgaris. The formulation was applied twice daily for four weeks. The formulation significantly improved skin hydration (+ 4.5% from baseline; p < 0.05), reduced erythema intensity by 7.1% ($p < 0.01$), and decreased the number of brown spots by 8.7% ($p < 0.001$). Sebum production showed a non-significant reduction of 6.2%. In vitro assays demonstrated downregulation of Thymic Stromal Lymphopoietin (TSLP) and Interleukin-33 (IL-33) expression in human keratinocyte cultures, supporting an anti-inflammatory effect. The treatment was well-tolerated with no adverse events. Confidence intervals were not reported.[13]

Although these early-phase trials suggest potential benefits, clinical evidence supporting topical postbiotics in acne remains exploratory. Both Han et al. and Ho et al. relied on small samples and short follow-up durations, lacked standardized acne endpoints, and assessed heterogeneous formulations. The split-face design used by Han introduces observer bias, while Ho et al. primarily evaluated surrogate and cosmetic outcomes. To establish the translational applicability of topical postbiotics, future studies should employ adequately powered randomized controlled trials with standardized clinical and microbiome-informed outcomes.

Biotechnological phytocomplexes

Recent studies have evaluated biotechnological phytocomplexes in acne treatment, highlighting their antibiofilm and microbiota-modulating properties. These formulations combine metabolomes derived from plant stem cell cultures of *Camellia sinensis* and *Morinda citrifolia*. *C. sinensis* exhibits anti-inflammatory effects by reducing IL-6, IL-8, TNF-α, and CXCL levels, along with antiseborrheic and antibiofilm properties. Meanwhile, *M. citrifolia* inhibits biofilm formation and blocks bacterial communication, contributing to microbiota rebalancing.[14,15]

A novel phytocomplex lotion containing Canonia allysis©, niacinamide 4.00% and succinic acid 2.00% was evaluated in two open-label trials in patients with mild-to-moderate facial and truncal acne.[14,15] Guerra-Tapia et al. (2024) conducted a prospective open-label study in 43 subjects with mild-to-moderate truncal acne, treated for eight consecutive weeks (56 days). The application of this phytocomplex reduced inflammatory lesions by 52.1% (p = 0.006) and acne severity by 27.6% on the IGA scale, with 60.5% of patients achieving ≥ 1-point improvement (p < 0.001). Microbiome analysis showed a significant decrease in *C. acnes* relative abundance (66.4% to 58.1%, p = 0.009), indicating partial

microbial rebalancing. Erythema decreased by 18.3% ($p = 0.007$) and desquamation by 63.8% ($p = 0.02$). No serious adverse events were reported, supporting favorable tolerability.[14]

Similarly, De Lucas et al. (2024) conducted an open-label study in 44 patients with mild-to-moderate facial acne, treated for eight weeks. Inflammatory lesions decreased by 47.3% ($p < 0.001$), while non-inflammatory lesions decreased by 31.1%, with borderline significance ($p = 0.05$). IGA scores also improved significantly at day 56 ($p < 0.001$). No serious adverse events occurred.[15]

Despite these encouraging findings, the clinical evidence supporting biotechnological phytocomplexes remains preliminary. Both studies were open-label, non-randomized, with modest sample sizes ($n = 43$ and $n = 44$), lacked control groups, and did not report 95% Confidence Intervals, limiting interpretation of effect sizes. Moreover, both evaluated the same proprietary formulation and were industry-sponsored, raising concerns regarding potential conflicts of interest and publication bias. Although reported outcomes include statistically significant reductions in acne severity and microbial imbalance, the lack of independent, adequately powered randomized controlled trials with standardized clinical and microbiome-informed endpoints limits external validity and underscores the need for further research to establish their therapeutic role in acne care.

Bacteriophages

Controlling the inflammatory response is a primary goal in acne treatment, particularly given the rise of antimicrobial resistance. Bacteriophage therapy has emerged as a potential alternative due to its ability to specifically target *C. acnes* while preserving beneficial microbes. This strategy may help restore microbial balance and maintain skin microbiota homeostasis.[40,41]

Preclinical studies provide the initial evidence for this approach. Kim et al. (2019) tested *C. acnes*-specific phages in a murine acne model, showing a reduction in inflammatory nodule size compared to controls. Histological analyses revealed decreased epidermal thickness and fewer microcomedone-like cysts, while immunohistochemical results suggested reduced CD8+ T-cell and neutrophil infiltration, as well as lower IL-1β and MMP-3 expression. However, most of these changes were not statistically significant, and no 95% Confidence Intervals were reported, limiting the interpretation of effect sizes.[16] Similarly, Lam et al. (2021) evaluated the therapeutic phage TCUCAP1 in mice, observing significant reductions in nodule size and epidermal hyperplasia, together with decreased IL-1β ($p < 0.05$) and caspase-3 ($p < 0.01$). Only p-values were reported without confidence intervals.[17]

The only human evidence to date comes from Golembo et al. (2022), a randomized, double-blind, vehicle-controlled Phase 1 trial testing a topical gel containing the bacteriophage cocktail BX001 in patients with mild-to-moderate acne. The high-dose formulation significantly reduced *C. acnes* load compared with baseline and vehicle ($p = 0.036$), with effects observed from day 14 to day 35. The low-dose formulation did not show significant effects. Importantly, the study did not report lesion counts, Investigator's Global Assessment (IGA) scores, or relapse outcomes, and no 95% Confidence Intervals were provided. BX001 was well tolerated, with no serious adverse events, and did not alter overall microbiome diversity.[18]

Bacteriophage therapy for acne remains early-phase, with encouraging but limited preclinical and Phase 1 findings. Current evidence is restricted to microbiological and histological outcomes, without robust clinical endpoints. To establish their therapeutic potential, durability of effect, and relevance for acne management, independently conducted randomized controlled trials with standardized clinical and microbiome-informed outcomes, including lesion counts, IGA scores, and relapse or recurrence rates, are required.

Vaccines

Vaccines represent another innovative strategy targeting acne pathogenesis. By focusing on virulence factors such as the CAMP factor and sialidase, these approaches aim to neutralize *C. acnes* pathogenicity and reduce the inflammatory response while preserving commensal microbiota and minimizing side effects.[41–43] Sanofi is currently conducting a Phase I/II randomized, double-blind, placebo-controlled clinical trial (NCT06316297) evaluating the safety, immunogenicity, and efficacy of an mRNA acne vaccine targeting *C. acnes* virulence factors. This ongoing trial includes healthy participants aged 18–45 years with moderate-to-severe acne and is assessing different dose levels administered intramuscularly.[44]

Additionally, a completed Phase I trial (NCT05131373) investigated the safety, tolerability, and immunogenicity of ORI-A-ce001, an acne vaccine for treating moderate facial acne vulgaris in adults. This multicenter, randomized, double-blind, placebo-controlled trial evaluated various dose levels in adults aged 18-years and older. In addition to assessing safety and immune responses, the study collected preliminary data on the vaccine's efficacy, including its impact on inflammatory and non-inflammatory lesions, acne severity, and skin microbiome composition.[45] These findings provide valuable insights into the potential role of vaccines as a novel therapeutic approach for acne management.

Despite their conceptual appeal, acne vaccines remain in the early stages of clinical development. Both referenced trials are Phase I studies primarily focused on safety and immunogenicity, with no peer-reviewed efficacy results available to date. Larger, well-designed clinical trials are necessary to demonstrate meaningful improvements in acne severity, characterize immune durability, and assess real-world applicability.

Gut-skin-axis interventions

The gut-skin axis highlights the bidirectional relationship between the gastrointestinal system and skin health, mediated by immune regulation, the microbiota, and neuroendocrine pathways. The gut microbiota plays a pivotal role in acne development and overall skin health by modulating immune responses and systemic inflammation. Disruptions such as dysbiosis or impaired intestinal barrier function can exacerbate skin conditions, including acne. Although the contribution of the gut microbiota to acne pathogenesis remains underexplored, targeting gut health

through integrative approaches holds promising potential for improving skin outcomes.[46]

a) Oral probiotics:

Eguren et al. (2024) conducted a 12-week randomized, double-blind, placebo-controlled clinical trial evaluating an oral probiotic supplement containing *Lacticaseibacillus rhamnosus* (CECT 30031) and the the cyanobacterium *Arthrospira platensis* (BEA_IDA_0074B) at 1×10^9 CFU per daily dose in 81 individuals with mild-to-moderate acne vulgaris. Non-inflammatory lesions decreased significantly versus placebo group, with a difference of −8.06 lesions (95% CI −15.37 to −0.74; p = 0.03). Improvements were also observed in acne severity, with 50% of probiotic-treated patients improving by at least one Acne Global Severity Scale (AGSS) category, and 42.5% achieving ≥ 30% reduction in Global Acne Grading System (GAGS) scores (both p < 0,05). Inflammatory and total lesion counts showed no significant differences between groups (p = 0.040). The treatment was well tolerated, with only mild digestive events reported.[19]

Rinaldi et al. (2022) conducted an 8-week randomized, double-blind, placebo-controlled trial evaluating a dietary supplement containing *Bifidobacterium breve* BR03 (DSM 16604), *Lacticaseibacillus casei* LC03, and *Ligilactobacillus salivarius* LS03 combined with botanical extracts (lupeol and *Echinacea*) in patients with mild-to-moderate acne. The intervention significantly reduced inflammatory lesions (-56.7% vs. -18.9% in placebo; p < 0.05), decreased sebum secretion and desquamation, and favorably modulated the skin microbiota by reducing *C. acnes* and *S. aureus* while increasing *S. epidermidis*. However, 95% Confidence Intervals were not reported, limiting the interpretation of the magnitude of these effects.[20]

Da Rocha et al. (2023) conducted a 180-day randomized, double-blind, placebo-controlled trial in 212 patients with mild-to-moderate acne, evaluating an oral probiotic supplement (*Lactobacillus acidophilus* and *Bifidobacterium lactis*) combined with a fixed-dose topical regimen of adapalene 0.1% and benzoyl peroxide 2.5%. The combined approach significantly improved outcomes, with a higher proportion of patients achieving an IGA score of 0 or 1 compared with topical therapy alone (p < 0.05). The probiotic regimen was well tolerated, but as with the Rinaldi trial, no 95% Confidence Intervals were provided.[21]

Although the clinical evaluation of oral probiotics in acne has progressed, substantial variability in strain composition, outcome measures, and treatment duration limits external validity and reproducibility. Mechanistic endpoints and microbiome-informed outcomes were inconsistently assessed across studies. Despite these limitations, the consistent safety profile and randomized, placebo-controlled designs underscore their potential. Standardized protocols incorporating both clinical and microbiome endpoints, with clear reporting of effect sizes and 95% Confidence Intervals, are necessary to define the therapeutic role of oral probiotics in acne care.

b) Omega-3 fatty acids:

The fatty acids ω-3 and ω-6 are thought to have potential utility in acne through anti-inflammatory effects.[47] Huang et al. (2024) conducted a 12-week randomized trial in 40 patients with moderate-to-severe acne treated with isotretinoin with or without ω-3 fatty acids (2400 mg/day). The combination group achieved greater reductions in Global Acne Grading System (GAGS) scores (mean 15.1 ± 4.5) compared with isotretinoin alone (18.7 ± 4.9), with a mean difference of -3.6 points (p = 0.02).[22] These findings align with the results previously reported by Jung et al. (2014), who evaluated 45 patients randomized to ω-3 fatty acids (2000 mg/day EPA + DHA), γ-linoleic acid (GLA, 400 mg/day), or control for 10 weeks. The ω-3 group showed a 43% reduction in inflammatory lesions (10.1 ± 3.2 to 5.8 ± 3.4) and a 20% reduction in non-inflammatory lesions (23.5 ± 9.2 to 18.9 ± 8.3), both p < 0.05. Similar improvements were observed in the GLA group, while no significant changes occurred in controls. Acne severity (Cunliffe grade) improved from 2.4 to 1.7 in the ω-3 group and from 2.3 to 1.8 in the GLA group (p < 0.05).[23]

Collectively, these findings suggest that fatty acid supplementation may reduce acne lesion counts and severity; however, the lack of reported confidence intervals, small sample sizes, and short treatment durations limit interpretation of effect sizes and generalizability. In Huang et al., the concurrent use of isotretinoin precludes definitive attribution of effects to ω-3 fatty acids, and microbiome modulation was inferred rather than directly assessed. Similarly, Jung et al. lacked detailed reporting on blinding procedures and did not evaluate gut microbiota endpoints. Overall, although the anti-inflammatory role of fatty acids in acne pathophysiology remains biologically plausible, larger, independently replicated trials with standardized endpoints and reporting of 95% CIs are required to confirm their clinical efficacy and clarify underlying mechanisms.

Photodynamic therapy

Photodynamic therapy (PDT) is a non-invasive, targeted modality for inflammatory acne. It involves the application of a topical photosensitizer, most commonly Aminolevulinic Acid (ALA), followed by irradiation with a specific light source.[48] The most frequently used wavelength is red light (630 nm), which penetrates deeper into the skin and activates Protoporphyrin IX (PpIX), the metabolite of ALA. Upon activation, PpIX generates Reactive Oxygen Species (ROS), inducing selective cytotoxicity in sebaceous glands and reducing sebum production.[49] Beyond sebosuppression, ALA-PDT has demonstrated anti-inflammatory and microbiome-modulating effects, including disruption of *Cutibacterium acnes* biofilms and restoration of microbial diversity.[50,51] PDT has also been shown to downregulate Toll-Like Receptors (TLR-2 and TLR-4) and decrease pro-inflammatory cytokine production in sebaceous glands and the epidermis.[52]

a) ALA-PDT and microbiome modulation:

Yang et al. (2021) conducted a prospective study evaluating microbiome changes in acne patients before and after ALA-PDT. Treatment reduced *C. acnes* abundance (p = 0.037), increased *Bacillus* (p = 0.012) and *Lactococcus* (p = 0.022), and enhanced overall microbial diversity (p =

0.003), suggesting a shift toward an eubiotic environment resembling healthy skin.[24]

Guo et al. (2023) investigated ALA-PDT utilizing a 630 ± 5 nm LED light source in patients with severe acne. This intervention caused a gradual increase in the relative abundance of genera such as *Pseudomonas*, *Gordonia*, *Leptotrichia*, and *Mycobacterium*, microbes that were found at lower levels in severe acne patients compared to healthy individuals. Notably, the study found no statistically significant difference in the relative abundance of *C. acnes* among the healthy control, pretreatment, and posttreatment groups. These findings suggest that PDT's effects extend beyond bacterial suppression to include microbiome restoration.[25] Neither study provided 95% Confidence Intervals, limiting the interpretation of effect sizes.

b) Modified PDT protocols compared to standard therapy:

Zhang et al. (2023) performed a randomized multicenter trial comparing modified ALA-PDT (M-PDT) with low-dose isotretinoin in patients with moderate-to-severe acne. M-PDT achieved 50% clinical improvement after just 1 week, compared with 8-weeks for isotretinoin ($p < 0.001$). Adverse effects were limited to local skin irritation in the M-PDT group, while 70.67% of patients receiving isotretinoin experienced systemic side effects. Confidence intervals were not reported.[26]

c) Novel Photosensitizers:

Recent studies have explored natural photosensitizers as alternatives to ALA for acne management. Kim et al. (2023) conducted a randomized split-face trial comparing *St. John's Wort* (SJW)-PDT with Indole-3-Acetic Acid (IAA)-PDT. SJW-PDT reduced acne lesions by 56.5% at 1-week and 65.9% at 4-weeks (both $p < 0.001$), with sebum production decreasing by 27.9% ($p = 0.012$) and no adverse events reported; however, confidence intervals were not provided.[27] Zheng et al. (2024) evaluated curcumin-based PDT in vitro against *C. acnes* biofilms. The treatment demonstrated dose-dependent suppression of bacterial viability and potent anti-biofilm activity, highlighting curcumin's potential as a natural photosensitizer for acne vulgaris, particularly in cases involving antibiotic resistance.[28]

Although PDT shows promising antimicrobial, anti-inflammatory, and microbiome-modulating effects in acne, available studies are limited by small sample sizes, heterogeneity in photosensitizers, protocols, and endpoints, and the absence of reported confidence intervals. While early findings suggest efficacy and safety, robust multicenter randomized controlled trials with standardized clinical and microbiome-informed outcomes, including lesion counts, Investigator's Global Assessment (IGA), and relapse rates, are required to establish PDT's therapeutic role in acne care.

Conclusion

Acne management is undergoing significant advancements with the emergence of innovative therapies targeting microbiome modulation through non-pharmacological approaches. This strategy offers a promising avenue to restore microbial homeostasis, mitigate inflammation, and reduce reliance on conventional pharmacologic agents. The transition from traditional treatments to microbiome-focused interventions reflects a paradigm shift in acne care. These developments highlight the growing relevance of personalized, mechanism-driven therapies designed to enhance efficacy and improve patient outcomes.

Although preliminary data are promising, the evidence base remains limited by small samples, methodological weaknesses, and reliance on preclinical models. Well-designed, multicenter randomized controlled trials with standardized clinical and microbiome-informed endpoints are needed to establish the therapeutic value, long-term safety, and translational relevance of these interventions. Advancing this next phase of research is essential to move microbiome-modulating therapies from experimental innovation to standard-of-care options in acne management.

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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

Valentina Burckhardt-Bravo: The study concept and design; data collection, or analysis and interpretation of data; writing of the manuscript or critical review of important intellectual content; effective participation in the research guidance; critical review of the literature; final approval of the final version of the manuscript.

Rodrigo Funes-Ferrada: Writing of the manuscript or critical review of important intellectual content; effective participation in the research guidance; critical review of the literature; final approval of the final version of the manuscript.

Fernando Valenzuela: The study concept and design; data collection, or analysis, and interpretation of data; writing of the manuscript or critical review of important intellectual content; effective participation in the research guidance; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; final approval of the final version of the manuscript.

Conflicts of interest

None declared.

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LETTER - RESEARCH

Assessment of sexual function and its association with quality of life and disease severity in patients with atopic dermatitis☆

Dear Editor,

Atopic Dermatitis (AD) is a chronic inflammatory and pruritic condition that affects up to 25% of children and between 1% and 10% of adults, with no gender preference.[1] Although most patients experience resolution of symptoms in adulthood, between 10% and 30% continue to exhibit the condition, and a smaller portion develops the initial symptoms in adulthood.[2] This condition significantly impacts patients' quality of life, yet its effects on sexual function remain underexplored.[3]

We report preliminary findings from a cross-sectional study examining sexual function and health-related quality of life in patients with AD.

Between January 2022 and January 2024, we evaluated 70 patients with AD (40 women and 30 men; mean age 32.9 ± 13.6 years) at our university hospital's dermatology clinic. Eligible participants were aged 18 to 79 years, had a confirmed diagnosis of AD based on Hanifin-Rajka criteria, were sexually active, and literate.[1] Patients with chronic debilitating illnesses were excluded. Disease severity was assessed using the SCORAD index.[4] Sexual function was measured by the Female Sexual Quotient (QS-F) and the Male Sexual Quotient (QS-M) .[5,6] Health-related quality of life was evaluated using the EQ-5D-3L, a standardized instrument that measures perceived health status across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses are converted into a utility index ranging from 0 (equivalent to death) to 1 (perfect health).[7,8] Statistical analysis included Student's *t*-test, proportions' exact test comparisons (Fisher test), and Spearman's correlation analyses, with significance set at $p < 0.05$. In addition to significance testing, statistical power was estimated for each comparison to assess the reliability of the observed differences and to account for the probability of type II error (ability to identify a real significant difference). For Spearman's correlation coefficient, approximate power was calculated by converting the observed coefficient to its Pearson-equivalent.

Patients had a mean age of 32.9 ± 13.6 years and an average disease duration of 18.8 ± 11.0 years (Table 1). There were no significant differences between men and women in these parameters (power < 0.20 for both comparisons). The low power suggests these analyses had limited ability to detect meaningful differences if they existed. The mean SCORAD score was 29.7 ± 19.3, with 42.9% of patients presenting moderate disease and 41.4% classified as mild, again with no gender-based differences (power < 0.20). Again, the insufficient power limits confidence in ruling out clinically relevant differences. The average EQ-5D-3L index was 0.68 ± 0.20, with no significant differences between sexes and low power (below 0.20) (Table 1). Our overall EQ-5D-3L was significantly lower than Brazilian population norms (0.82 ± 0.17, $p < 0.001$, power = 0.99), indicating substantial impairment in perceived health status,[9] with a very high probability of identifying a significant difference (high statistical power). The most compromised dimensions were pain/discomfort, reported by 88.6% of participants, and anxiety/depression, reported by 82.9%.

Regarding sexual function, 77.1% of participants reported being sexually active, with no significant difference between women (75.0%) and men (80.0%; $p = 0.622$; power < 0.20), with insufficient power to rule out meaningful gender differences in sexual activity rates (Table 2). Women had a mean QS-F score of 64.8 ± 18.5, while men reported a significantly higher mean QS-M score of 77.9 ± 14.2, with a high statistical power ($p = 0.002$; power > 0.90). The high power supports the occurrence of this gender difference finding. Among women, 20.0% were classified as having good-to-excellent sexual function, 37.5% as regular to good, 35.0% as unfavorable to regular, and 7.5% as null or unfavorable. In contrast, 43.3% of men were very satisfied, 10.0% moderately satisfied, and 46.7% partially satisfied, with no men reporting dissatisfaction. These distributions showed a statistically significant difference between sexes in the highest satisfaction category ($p = 0.021$), but the power of associations was very low for some comparisons (< 0.20). The low power undermines confidence in this categorical comparison despite statistical significance.

☆ Study conducted at the Atopic Dermatitis outpatient Clinic, University Hospital Pedro Ernesto, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

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Table 1 Sociodemographic and clinical characteristics of the sample (n = 70).

Characteristic	Total (n = 70)	Women (n = 40)	Men (n = 30)	p-value (type I error)	Statistical power (1- type II error)
Age of the patient (years): mean ± SD	32.9 ± 13.6	34.5 ± 13.3	30.8 ± 13.8	0.260	0.204
Duration of disease (years): mean ± SD	18.8 ± 11.0	19.1 ± 11.7	18.5 ± 10.2	0.860	0.056
SCORAD (continuous): mean ± SD	29.7 ± 19.3	31.6 ± 19.8	28.3 ± 19.0	0.475	0.108
SCORAD (categorical): n (%)					
- Mild (< 25)	29 (41.4)	12 (40.0)	17 (42.5)	0.851	0.027
- Moderate (25–50)	30 (42.9)	14 (46.7)	16 (40.0)		0.049
- Severe (> 50)	11 (15.7)	4 (13.3)	7 (17.5)		0.037
EQ-5D-EL (continuous): mean ± SD	0.68 ± 0.20	0.65 ± 0.17	0.73 ± 0.23	0.061	0.361

SD, Standard Deviation; SCORAD, Scoring Atopic Dermatitis; EQ-5D-3 L, Health Questionnaire.

Table 2 Sexual activity and sexual function of men and women with atopic dermatitis (QS-F and QS-M scores).

Statistics and Categories	Women (n = 40)	Men (n = 30)	p-value (type I error)	Statistical power (1- type II error)
Reported Sexual activity: n (%)				
QS-F and QS-M: Mean score (± SD)	30 (75.0)	24 (80.0)	0.622	0.038
QS-F and QS-M: (categorical): n (%) (scores)	64.8 ± 18.5	77.9 ± 14.2	0.002	0.918
- Good to excellent (women) / Very satisfied (men) (82 to 100)	8 (20.0)	13 (43.3)	0.021	0.453
- Regular to good (women) / Moderately satisfied (men) (62 to 81)	15 (37.5)	3 (10.0)		0.661
- Unfavorable to regular (women) / Partially satisfied (men): n (%) (42 to 61)	14 (35.0)	14 (46.7)		0.112
- Null or unfavorable (women) / very unsatisfied/unsatisfied (men): n (%) (< 42)	3 (7.5)	0 (0.0)		0.115

SD, Standard Deviation; QS-F, Female Sexual Quotient; QS-M, Male Sexual Quotient.

Correlation analysis revealed that in women, higher QS-F scores were significantly associated with higher EQ-5D-3L index scores (r = 0.453, p = 0.003; power = 0.74), indicating that better sexual function was related to better perceived health. The moderate-to-high power (74%) supports this as a possible robust, clinically meaningful finding. Additionally, SCORAD scores correlated negatively with QS-F scores (r = -0.408, p = 0.008; power = 0.61), suggesting that increased disease severity was linked to reduced sexual satisfaction, but the power was only moderately high. In men, SCORAD was negatively associated with the satisfaction domain of the QS-M (r = -0.376, p = 0.041; power = 0.058), although no significant correlation was observed between total QS-M scores and EQ-5D-3L (power < 0.20). The very low power severely limits the interpretability of male findings.

These results highlight a psychosexual burden in patients with AD, particularly among women, whose sexual satisfaction was markedly lower than that reported in the general Brazilian population. The association between sexual function and overall health perception suggests that incorporating validated instruments such as the Sexual Quotients and EQ-5D-3L can enhance clinical understanding of disease impact.[10] The gender-specific patterns observed further support the need for tailored interventions in the management of AD.

It should be noted that some nonsignificant comparisons were accompanied by very low statistical power (< 20%), mostly due to small sample size, which limits the ability to draw firm conclusions and indicates a higher likelihood of type II error. Therefore, these results should be interpreted with caution.

Another important limitation of the present study is concerned to its external validity. The study was conducted in a single university hospital; hence, the findings are to be considered preliminary, and they would benefit from replication in larger and more diverse samples.

In conclusion, AD exerts a measurable impact on sexual function and health-related quality of life, with more pronounced effects in women. These results reinforce the importance of integrating sexual health assessments into routine dermatological care and adopting a gender-sensitive approach in both evaluation and treatment.

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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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Natalia Troncoso: Critical review of important intellectual content; final approval of the final version of the manuscript.

Carla Jorge Machado: Data collection, analysis and interpretation; critical review of important intellectual content; final approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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LETTER - RESEARCH

Association of oncogene mutations with clinical and histopathological characteristics in patients with metastatic melanoma☆

Dear Editor,

Melanoma is recognized as a highly aggressive form of skin cancer and exhibits the highest mutation rates of all solid tumors. Among the genetic alterations identified, mutations in specific oncogenes, particularly in the BRAF gene, are the most prevalent.[1] Characterizing the genetic profile of tumors is essential, as several approved and investigational therapies are effective only in the presence of specific mutagenic alterations.[2]

The clinical and epidemiological investigation of factors associated with metastatic melanoma can offer valuable insights into disease progression and inform preventive strategies and targeted therapeutic approaches. In this context, we retrospectively evaluated the mutational status of the BRAF, PDGFRA, and C-KIT genes in patients with metastatic melanoma treated at a Brazilian tertiary oncology hospital, correlating these findings with epidemiological and clinical parameters.

Medical records of 94 patients diagnosed with melanoma and treated between 2015 and 2022 at Hospital Amaral Carvalho (HAC), Jaú, São Paulo, Brazil, were reviewed. Clinical and histopathological data were collected. Exon 15 of the BRAF gene (codon 600 and adjacent regions) was sequenced in all cases. In selected samples, additional analyses for C-KIT and PDGFRA mutations were performed based on physician requests.

DNA was extracted using the QIAAMP DNA FFPE Tissue Kit (QIAGEN). PCR amplification employed primers previously described by Qiu et al.[3] and Braggio et al.[4] DNA sequencing was conducted on an ABI PRISM 3100 Genetic Analyzer-3130xl system.

Descriptive and inferential statistical analyses were performed using Pearson's chi-square test or Fisher's exact test, binomial logistic regression (variables included age, gender, patient status, primary tumor site, histological subtype, ulceration, Breslow thickness, and mitotic index), and Kaplan-Meier survival analysis. Cases with missing data were excluded from specific analyses. A significance level of 5% was adopted. This study was approved by the Ethics Committees of the Lauro de Souza Lima Institute and Hospital Amaral Carvalho (Protocol 58842922.0.3001.5434).

Table 1 summarizes the demographic and tumor-specific characteristics of the cohort. The most frequent site of metastasis was the regional lymph nodes (61.7%), followed by the lungs (13.8%), bones (6.4%), liver (4.3%), and other locations (13.8%) (Supplementary Table S1).

Among the 94 patients, 41 (43.6%) exhibited wild-type BRAF (BRAF-WT) and 53 (56.4%) harbored BRAF mutations: 48 (51%) had the V600E mutation, 4 (4.3%) had the V600 K mutation, and 1 (1.1%) had the L597Q mutation.

Nineteen patients underwent analysis for C-KIT mutations: 14 (73.7%) were wild-type, and 5 (26.3%) presented mutations (two in exon 17, and one each in exons 13, 11, and 9). Among five acral melanoma biopsies analyzed for C-KIT, 2 (40%) harbored mutations (in exons 9 and 13). The remaining C-KIT–mutated tumors were classified as nodular, polypoid-nodular, or superficial extensive melanomas.

Twelve patients were analyzed for PDGFRA mutations, all of whom were wild-type.

The association between BRAF mutational status and clinical-pathological variables is presented in Table 2. BRAF mutations were significantly associated with younger age at diagnosis (p = 0.0085).

In univariate logistic regression (n = 56), younger age was associated with BRAF mutation (p = 0.004, OR = 0.946, 95% CI: 0.910–0.983). The acral subtype was associated with wild-type tumors and superficial extensive cases with the BRAF mutation (p = 0.042, OR = 0.161, 95% CI: 0.0276–0.935). Breslow thickness was marginally related to WT tumors (p = 0.060, OR = 2.490, 95% CI: 0.964–6.432). In multivariate analysis, younger age remained the only independent factor associated with BRAF mutation (p = 0.003). No statistically significant associations were observed for C-KIT mutations (Table 3).

At the time of data collection, the median survival time was 62-months for patients with BRAF-mutated tumors and 50-months for BRAF-WT patients. The Hazard Ratio (HR) for death in the BRAF-WT group was 1.331. For KIT-mutated

☆ Study conducted at the Hospital Amaral Carvalho, Jau, SP, Brazil.

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Table 1 Clinical characteristics of the patients and anatomopathological variables of the primary tumor.

Variable	Category	n	%
Gender	Female	45	47.9
	Male	49	52.1
Age at diagnosis	<40 years old	17	18.1
	40–59 years old	37	39.4
	>60 years old	40	42.5
Primary tumor site	Head or neck	18	19.1
	Upper limb	09	9.6
	Trunk	26	27.7
	Lower limb	33	35.1
	Unidentified	08	8.5
Histological subtype	Superficial extensive	29	30.9
	Nodular	26	27.6
	Acral	11	11.7
	Lentigo maligno	01	1.1
	Others	03	3.2
	No information	24	25.5
Breslow index	<1 mm	13	13.8
	1.01 – 2 mm	06	6.4
	2.01 – 4 mm	22	23.4
	>4 mm	31	33.0
	No information	22	23.4
Ulceration	Yes	44	46.8
	No	50	53.2
Mitotic index	<1 mitosis/mm^2	15	15.9
	>1 mitosis/mm^2	45	47.9
	No information	34	36.2
LDH at diagnosis	Low	13	13.8
	Normal	41	43.6
	High	10	10.6
	No information	30	32.0
LDH at metastasis	Low	05	5.3
	Normal	29	30.9
	High	17	18.1
	No information	43	45.7
Patient Status	Alive	32	34.0
	Death	62	66.0
Overall survival	<5-years	45	72.6
	>5-years	17	27.4
Observed survival	>5-years	24	75.0
	<5-years after diagnosis	8	25.0

patients, the median survival was 38-months, compared to 70-months in KIT-WT patients (HR = 1.145) (Fig. 1).

A slight male predominance was observed, and the onset of melanoma was predominantly from the fifth decade of life onwards, consistent with previous reports.[5] Although the lower limbs were the most frequently affected primary site in this cohort, prior studies have more commonly reported the trunk and lower limbs.[5] This discrepancy may reflect cultural or behavioral differences in sun exposure patterns.

Survival analysis revealed that 72.6% of deceased patients (n = 62) had a survival time of less than 5-years, while 75% of survivors (n = 32) remained alive beyond five years. Prognostic factors influencing melanoma survival include tumor thickness, ulceration, mitotic index, and metastatic burden.[6]

The most prevalent histological subtype was superficial extensive melanoma (30.9%), followed by the nodular subtype (27.6%). These findings may be attributable to the association between these subtypes and chronic or intermittent sun exposure. Additionally, more than 60% of patients exhibited a high Breslow index, 50% had a mitotic rate >1 mm^2, and approximately one-third presented with tumors >4 mm in thickness – all features linked to poor prognosis.[6]

Younger age was significantly correlated with BRAF mutation, in line with previous studies.[7] The superficial extensive and nodular subtypes also demonstrated a higher frequency of BRAF mutations. Although not statistically significant, primary tumors located on the trunk and lower limbs tended to exhibit more BRAF mutations than those on the upper limbs or head and neck.

Table 2 Relationship between clinical-pathological variables and the presence of BRAF mutation.

Variable	Category	BRAF-MUT	BRAF-WT	Total	p-value[a,b]	Logistic Regression	
						OR (95% CI)	p-value
Gender	Female	26	19	45			
	Male	27	22	49	0.7938[b]		
Age at diagnosis, years	<40	14	03	17		0.946 (0.910–0.983)	0.004
	40–59	23	14	37	**0.0085**[b]		
	>60	16	24	40			
Primary tumor site	Head or neck	11	07	18			
	Upper limbs	04	05	09			
	Trunk	17	09	26	0.3891[b]		
	Lower limbs	15	18	33			
Histological type	Superficial extensive	19	10	29		0.161 (0.0276–0.935)[d]	0.042[d]
	Others	18	23	41	0.074[b]		
Breslow index	<1 mm	09	04	13		2.490 (0.964–6.432)	0.060
	>1 mm	32	27	59	0.3709[a]		
Ulceration	Yes	22	22	44			
	No	26	15	41	0.2126[b]		
Mitotic index, mitosis/mm^2	<1	08	04	12			
	>1	22	26	48	0.3334[a]		
LDH at diagnosis, U/L	Up to 480	30	24	54			
	Above 480	06	04	10	>0.9999[a]		
LDH at metastasis, U/L	Up to 480	19	15	24			
	Above 480	11	06	17	0.5461[b]		
[c]Survival	<5-years	24	21	45			
	>5-years	26	15	41	0.3439[b]		

[a] Fisher analysis.
[b] Chi-Square analysis.
[c] Three patients with BRAF mutation and five BRAF-WT patients who were diagnosed with the disease less than 5-years ago and are still being monitored were excluded.
[d] Significance was found in univariate analysis for the acral subtype and BRAF-WT.

Table 3 Relationship between clinical-pathological variables and presence of c-KIT mutation.

Variable	Category	KIT-MUT	KIT-WT	Total	p-value
Gender	Female	04	06	10	
	Male	01	08	09	0.3034[a]
Age at diagnosis	<60-years-old	00	06	06	
	>60-years-old	05	08	13	0.1280[a]
Primary tumor site	Head/neck/trunk	02	04	06	
	Upper and lower limbs	03	10	13	>0.9999[a]
Histological type	Superficial extensive	01	04	05	
	Others	04	06	10	0.6004[a]
Breslow index	<1 mm	01	02	03	
	>1 mm	04	07	11	>0.9999[a]
Ulceration	Yes	05	09	14	
	No	00	04	04	0.2778[a]
Mitotic index	<1 mitosis/mm^2	00	02	02	
	>1 mitosis/mm^2	05	08	13	0.5238[a]
LDH at diagnosis	Up to 480 U/L	04	06	10	
	Above 480 U/L	01	00	01	0.4545[a]
LDH at metastasis	Up to 480 U/L	01	06	07	
	Above 480 U/L	00	02	02	>0.9999[a]
*Survival	<5-years	03	06	09	
	>5-years	02	07	09	>0.9999[a]

[*] One KIT-WT patient who was diagnosed with the disease less than 5-years ago and is still being monitored was excluded.
[a] Fisher analysis.

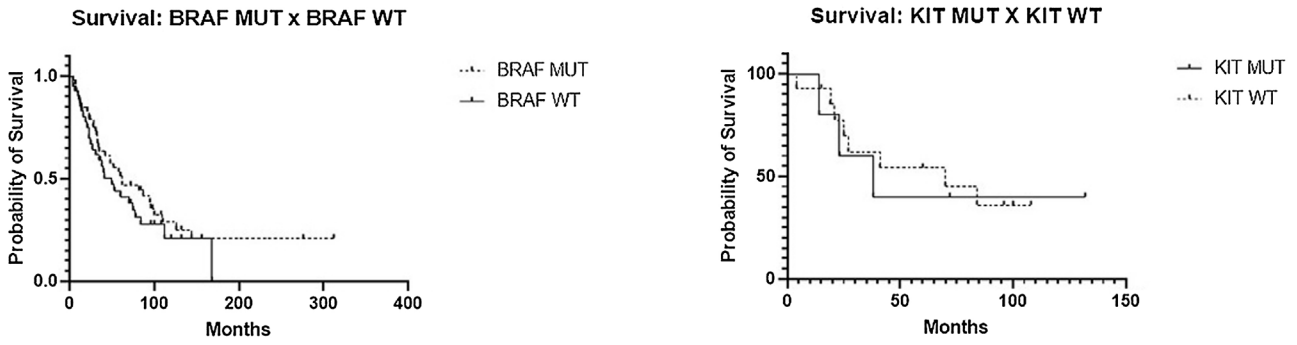

Fig. 1 Survival curve BRAF-MUT × BRAF-WT and c-KIT-MUT × c-KIT-WT.

While the majority of patients with lower Breslow thickness and lower mitotic index harbored BRAF mutations, the prognostic relevance of BRAF status remains controversial, as some studies report no consistent correlation between BRAF mutations and histopathological parameters.[8]

KIT mutations were more frequent in female patients aged over 60-years. All KIT-mutated tumors exhibited ulceration and a mitotic index >1 mm^2, both unfavorable prognostic markers.[6] Notably, KIT mutations were identified in 40% of acral melanoma cases, a subtype typically classified as ''non-solar'' melanoma, potentially associated with mechanical trauma rather than UV radiation. Acral melanomas generally demonstrate a lower frequency of point mutations but a higher rate of gene copy number variations.[9]

The median 5-year survival was higher in patients with BRAF mutations and slightly lower in those without mutations. Reports indicate that patients with BRAF mutations treated with selective BRAF inhibitors can achieve a 5-year survival rate of up to 60% in some cases.[10]

The median 5-year survival was higher in patients without c-KIT mutations. Of the 19 patients tested for KIT mutations in this study, only 5 (26.3%) had mutations in this gene. Previous studies have reported that less than 10% of melanoma cases involve KIT mutations.[11] Treatment with KIT inhibitors typically demonstrates lower therapeutic efficacy compared to other selective inhibitors, which may be associated with decreased survival.[2]

In this study, BRAF mutations were found to be associated with younger age and the superficial spreading subtype. No significant correlation was observed between KIT mutations and the examined variables. Our findings provide important insights into the clinical, pathological, and molecular characteristics of melanoma, offering valuable contributions to the development of future research focused on preventive and therapeutic strategies.

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Luiza Pinheiro-Hubinger-Stauffer: Study conception and design; collection, analysis and interpretation of data; statistical analysis; research guidance; 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.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.abd.2025.501260.

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LETTER – RESEARCH

Comparative analysis of the prevalence of histopathological findings between DRESS syndrome (drug rash with eosinophilia and systemic symptoms) and drug-induced maculopapular rash: a cross-sectional study

Dear Editor,

DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) is a serious adverse drug reaction characterized by fever, exanthema, and systemic involvement. Observed in 1930 in patients treated with anticonvulsants, the current term was proposed by Bocquet et al. in 1996, seeking to standardize the nomenclature and facilitate diagnosis. The estimated incidence is 1 case per 1,000 to 10,000 drug exposures, with mortality of up to 20%.[1–3]

Its etiopathogenesis involves hypersensitivity to drugs or their metabolites, with aromatic anticonvulsants, antidepressants, sulfonamides, nonsteroidal anti-inflammatory drugs, antibiotics, and allopurinol frequently being implicated.[2,3] The diagnosis is based on clinical-laboratory criteria, initially proposed by Bocquet et al. and subsequently refined by the European RegiSCAR score, which classifies cases as possible, probable, and definite.[4]

Skin biopsy can aid in diagnosis, although there is no single, specific pattern that clearly differentiates DRESS from other drug eruptions, such as maculopapular exanthema (MPE), which shares similar skin morphology but with less clinical severity.[5–7]

Given the scarcity of studies on the histopathological characteristics of DRESS in Latin America, this cross-sectional, retrospective, single-center study was conducted to compare the histopathological findings between confirmed and discarded cases of the syndrome, aiming to determine whether DRESS has specific pathological characteristics that allow it to be histopathologically differentiated from MPE. Forty patients hospitalized between 2008 and 2021 at Hospital das Clínicas, Faculty of Medicine, Universidade de São Paulo, were evaluated, all with clinical suspicion of drug-induced skin reaction and available skin biopsy. The medical records were reviewed for application of the RegiSCAR score, with 20 cases being classified as probable or definite DRESS (RegiSCAR > 3) and 20 as MPE (RegiSCAR $\leq$ 3). Additionally, a scoring system was proposed for the variables that showed a statistically significant difference between the groups, aiming to evaluate the sensitivity and specificity of the findings in distinguishing between DRESS and MPE.

Histopathological analysis was performed by two experienced dermatopathologists, and the criteria evaluated were parakeratosis, spongiosis, isolated keratinocyte necrosis, vacuolar interface dermatitis, papillary edema, pigmentary incontinence, red blood cell extravasation, eosinophilia, and inflammatory infiltrate.

The criteria were graded as described below:

Parakeratosis: Present or absent.

Spongiosis: Absent; mild (< 2/3 of the epidermis); moderate (> 2/3 and without vesiculation); intense (> 2/3 and with intraepidermal vesicles).

Isolated keratinocyte necrosis: Absent; mild (0-2/field); mild intermediate (2-5/field); moderate intermediate (5-10/field); intense (> 10/field).

Vacuolar interface dermatitis: Absent; mild (focal hydropic changes on $\times$400); intense (diffuse hydropic changes on $\times$200).

Papillary edema: Absent; mild (subtle); intense (intense with subepidermal blister formation).

Pigmentary effusion: Absent; mild (rare sparse melanophages); intense (melanophages clustered in the papillary dermis).

Hemorrhage: Absent; mild (restricted to the dermal papilla, evaluated at $\times$400); intense (hemorrhage extending beyond the dermal papilla, evaluated at $\times$200).

Eosinophilia: Absent; mild (0-10/field); moderate (10-20/field); intense (> 20/field).

Inflammatory infiltrate: Evaluated for density (absent, mild, moderate, and intense) and composition (lymphohistiocytic, neutrophilic, eosinophilic).

For the statistical analysis of these parameters, Fisher's exact test was used. Differences were considered significant if $p < 0.05$.

For the analysis of the proposed score, Matthews' correlation coefficient (MCC) was used, which ranges from -1 to +1, and the closer to 1, the more reliable the data obtained.

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Table 1 Comparative analysis of histopathological findings between the DRESS (n = 20) and drug-induced maculopapular exanthema groups. (n = 20).

Parakeratosis				
	Present	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	5	1.00	1.25	0.75
Maculopapular exanthema	4		(0.39–3.99)	(0.17–3.33)
Spongiosis				
	Mild	Moderate	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	8	5	1.00	0.93	1.26
Maculopapular exanthema	11	3		(0.60–1.43)	(0.33–4.73)
Isolated keratinocyte necrosis				
	Mild	Mild and moderate intermediary + Intense	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	6	11	0.007	2.13	0.12
Maculopapular exanthema	7	1		(1.20–3.75)	(0.03–0.54)
Interface dermatitis				
	Absent + Mild	Intense	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	8	12	0.002	6.00	0.07
Maculopapular exanthema	18	2		(1.54–23.44)	(0.01–0.41)
Papillary dermis edema				
	Mild	Intense	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	6	4	0.523	1.43	0.54
Maculopapular exanthema	7	0		(0.68–3.00)	(0.15–1.92)
Pigmentary incontinence				
	Mild	Intense	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	10	3	1.00	1.00	1.00
Maculopapular exanthema	13	0		(0.63–1.58)	(0.27–3.67)
Red blood cell extravasation				
	Absent + Mild	Intense	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	13	7	0.008	–	0.05
Maculopapular exanthema	20	0			(0.00–0.89)
Eosinophilia					
	Mild	Moderate	Intense	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	7	4	5	0.300	1.33	0.38
Maculopapular exanthema	9	1	2		(0.88–2.03)	(0.09–1.54)
Inflammatory infiltrate density					
	Absent + Mild	Moderate + Intense	p-value (Fisher)	PR (95% CI)	OR (95% CI)
DRESS	6	14	0.056	2.00	0.23
Maculopapular exanthema	13	7		(1.03–3.88)	(0.06–0.87)

Table 1 (*Continued*)

Inflammatory infiltrate composition		
Mean	DRESS	Maculopapular exanthema
Lymphohistiocytic	87.57	94.75
Neutrophilic	2.71	1.50
Eosinophilic	6.14	3.75

Table 2 Proposed scoring system for differentiating between DRESS and drug-induced maculopapular exanthema, based on three criteria: intense interface dermatitis (0 or 1-point), intense red blood cell extravasation (0 or 1-point), and keratinocyte necrosis (0 or 1-point – isolated or 2-points – extensive). The total score ranges from 0 to 4.

1-point rule					
	0	≥ 1	Total		
DRESS	4	16	20	Specificity	0.85
Maculopapular exanthema	17	3	20	Sensitivity	0.80
Total	21	19	40	PPV	0.81
				NPV	0.84
				Accuracy	0.83
				MCC	0.65
2-point rule					
	0	≥2	Total		
DRESS	10	10	20	Specificity	1.00
Maculopapular exanthema	20	0	20	Sensitivity	0.50
Total	30	10	40	PPV	0.67
				NPV	1.00
				Accuracy	0.75
				MCC	0.58

PPV, Positive Predictive Value; NPV, Negative Predictive Value; MCC, Matthews Correlation Coefficient.

Regarding the results, a significant association was observed between DRESS and the presence of isolated keratinocyte necrosis, intense vacuolar interface dermatitis, and extensive red blood cell extravasation (all with $p < 0.05$). The other parameters did not differ between the groups (Table 1).

Regarding the proposed score, when ≥ 1 it showed 80% sensitivity and 85% specificity for the diagnosis of DRESS, and ≥ 2 had 100% specificity. The MCC was 0.65 for a 1-point score and 0.58 for a 2-point score (Table 2).

The results obtained in this study corroborate previous findings in the literature that indicate that keratinocyte necrosis and interface lesions are frequent markers in DRESS. Overall, interface dermatitis is the most common histopathological presentation reported in the literature, having been found in more than three-quarters of patients with DRESS in previous studies.[7]

The presence of extravasation of red blood cells, possibly resulting from endothelial damage, also stood out as a discriminatory criterion, reinforcing the hypothesis that the dermal endothelium is a frequent target of DRESS.[5–8]

Although eosinophilia is an important diagnostic criterion in peripheral blood, eosinophilic tissue infiltration did not show correlation with the severity of the condition, both in the present study and in previous analyses; that is, more severe phenotypes did not show a higher density of eosinophilic tissue infiltrate.[5]

As for spongiosis, described in up to 80% of cases in other publications and correlated with favorable outcomes in DRESS,[7,8] was not statistically significant in the present sample, which may be attributed to the temporal variability between the appearance of lesions and the biopsy performance, and to the sample size.

The study by Cho et al.[7] demonstrated that the coexistence of three histological patterns (eczematous, interface dermatitis, and vascular damage) is more common in definitive cases of DRESS, being associated with greater clinical and hematological severity. The observation of multiple patterns was also present in part of the present sample, although it was not formally quantified.

Regarding the study limitations, it is a retrospective study, dependent on the analysis of medical records (which are not always complete); it has a medium sample size, which impacts the statistical analysis; and it has a variation between the time of lesion evolution and the biopsy performance, which affects the histopathological findings.

In conclusion, the present study demonstrated that, when comparing patients with DRESS and MPE, the presence of isolated keratinocyte necrosis, intense vacuolar interface dermatitis, and extensive red blood cell extravasation

was significantly higher in the first group. Furthermore, the proposed score has relevant discriminatory potential, but its diagnostic application requires validation in independent cohorts and in different centers.

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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

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João Avancini: Design and planning of the study; Effective participation in research orientation; Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; Approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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LETTER - RESEARCH

Comparing the genetic and serum expression of *LL-37* Antimicrobial Peptide in pemphigus vulgaris and pemphigus foliaceus patients☆

Dear Editor,

Pemphigus is an immunobullous disorder characterized by flaccid blisters and erosions of skin/mucous membranes with high morbidity if left untreated. Infections: resulting from fragile skin barrier, dysfunction of immunity, and systemic corticosteroid use, are the most frequent complications of patients with pemphigus and account for 22.6% of all deaths.[1] To cope with the microbial exposure, cells produce several Antimicrobial peptides (AMPs) which inhibit the invasion of pathogens. *LL-37* is the unique cathelicidin peptide that has piqued the interest of the research community because of its numerous immune system-modulating properties.[2] Indeed, dysregulation of *LL-37* is associated with the onset and progression of multiple autoimmune diseases.[3] The scarcity of studies in autoimmune bullous diseases was the rationale for the design of our study, aiming to offer a concise general view of the expression of *LL-37* and briefly discuss the role of this small peptide as a key factor in the development of pemphigus.

This study enrolled pemphigus foliaceus (PF) and pemphigus vulgaris (PV) patients, recruited at the Dermatology Department in the Hedi Chaker University Hospital of Sfax, Tunisia, as detailed in the flow chart (Fig. 1). Pemphigus diagnosis is confirmed according to international recommendations. Patients were classified, according to disease stage and treatment management, into 3 groups: newly diagnosed, untreated and treated patients with remittent pemphigus (PDAI $\leq$ 8) or chronic patients' group (PDAI $\geq$ 9). The *LL-37* mRNA expression in PBMC was assessed in 20 PV and 27 PF patients in comparison to 16 Healthy Controls (HC), by Quantitative-PCRusing Gene-specific primers (*F: 5'-TCGGATGCTAACCTCTACCG-3'/R: 5'-GGGTACAAGATTCCGCAAAA-3'*) and normalized to the average housekeeping gene *GAPDH*. Serum concentration of *LL-37* was measured with a Human Antibacterial Protein *LL-37* ELISA Kit from CUSABIO (*CSB-EL004476HU*). Data were analyzed with SPSS software 2.0, using adapted tests. A summary of demographic, clinical, and serological data is presented in Table 1.

Although PF and PV are clinically distinct, they share common immunological mechanisms. In our dataset, the biological markers and clinical parameters under investigation did not differ significantly between the two forms. Overall, the *LL-37* expression profile was differentially dysregulated in pemphigus. *LL-37* gene as well as serum expressions were significantly up-regulated in pemphigus patients compared to HC (Fig. 2A–B). In detail, *LL-37* mRNA gene expression was significantly enhanced in newly diagnosed PV and PF compared to HC ($p = 0.012$, $p = 0.048$; respectively) (Fig. 2A).

To understand the impact of short-term corticosteroid therapy on *LL-37* gene expression, six newly diagnosed patients were followed after 3-months of treatment. *LL-37* mRNA expression changes significantly after 3-months of treatment ($p = 0.023$) (Fig. 2C). Interestingly, a notable negative correlation was revealed between Dsg1-Abs level and *LL-37* mRNA expression ($r = -0.7$; $p = 0.020$) (Fig. 2D).

By stratifying PV and PF patients according to their clinical disease stage, *LL-37* gene expression was followed up in a group of six-year average treatment period. A notable down-regulation of *LL-37* expression was identified in remittent group compared to the chronic group (Remittent $group_{mean} = 0.025 \pm 0.077$ vs. Chronic $group_{mean} = 0.172 \pm 0.05$, $p = 0.006$). A similar profile was observed when studying *LL-37* serum expression, without any statistical significance (Remittent $group_{mean} = 9.57 \pm 1.8$ vs. Chronic $group_{mean} = 14.24 \pm 1.7$, $p > 0.05$) (Fig. 2B). This significance was maintained even when studying the two separate class of pemphigus (PV: $p = 0.039$ and PF: $p = 0.028$) (Fig. 2E–F). There was also a decrease in *LL-37* gene expression in remittent PF patients when compared to newly diagnosed ones ($p = 0.013$).

It seems that the over-expression of *LL-37* in peripheral blood cells of newly diagnosed pemphigus patients is important in the disease onset. Yet, there is a lack of studies analysing the *LL-37* expression on a systemic level; particularly on PBMC. An up-regulation was largely reported in various biological specimens. Previous stud-

☆ Study conducted at the Research Laboratory ''Autoimmunity, Cancer and Immunogenetics'' (LR18SP12), University Hospital Habib Bourguiba, Sfax, Tunisia.

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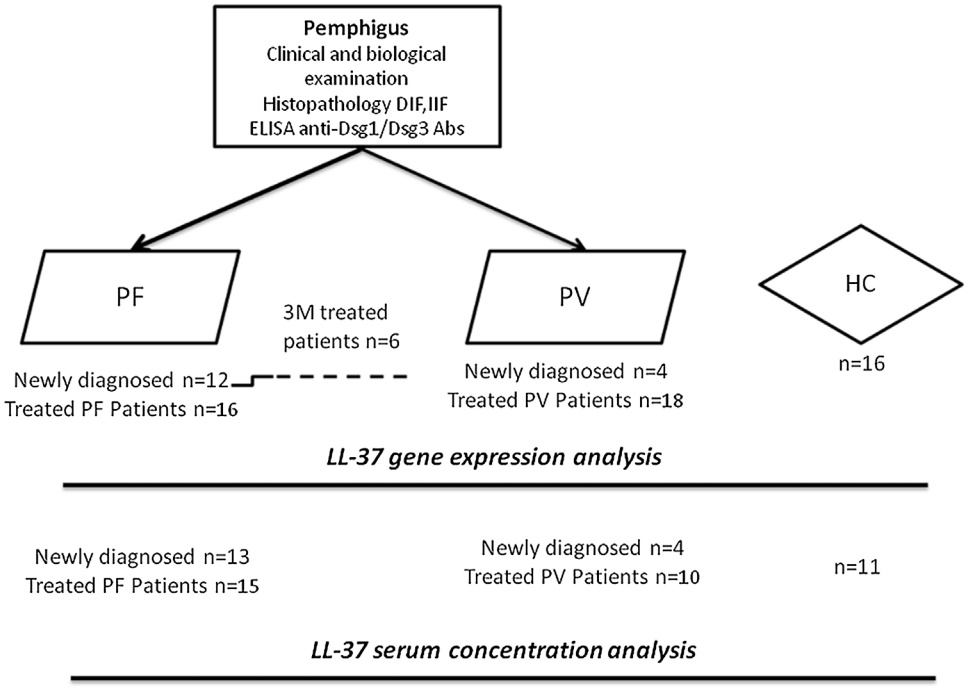

Figure 1 Flowchart for the studied groups. DIF, Direct Immunofluorescence; Dsg, Desmoglein; IIF, Indirect Immunofluorescence; PF, Pemphigus Foliaceus; PV, Pemphigus Vulgaris; HC, Healthy Control.

Table 1 Demographic, clinical and serological characteristics of pemphigus patients.

	Pemphigus Foliaceus patients (n = 29)		Pemphigus Vulgaris patients (n = 22)	
	Newly diagnosed patients (n = 13)	Treated Patients (n = 16)	Newly diagnosed patients (n = 4)	Treated Patients (n = 18)
Age mean	40	55	45	54
Sex ratio M/F	2/12	0/16	1/4	6/18
Disease duration (year)	–	7.6	–	4.7
Treatment	–	45.8% Corticosteroids 54.2% Corticosteroids + Immunosuppressors	–	41.6% Corticosteroids 58.4% Corticosteroids + Immunosuppressors
PDAI score mean	34.09	17.74	44.67	15.19
Anti-Dsg1	137.47 U/mL	93.3 U/mL	71.5 U/mL	56.13 U/mL
Anti-Dsg3	1.81 U/mL	2.4 U/mL	151.5 U/mL	72.9 U/mL

ies showed similar results in inflammatory skin disorders.[3] On the other hand, salivary concentration of *LL-37* was increased in inflammatory ulcerating diseases in both oral lichen planus.[4] Taken together, cathelicidin expression dysregulation appears to occur in pemphigus; PF and PV. However, the precise functions of *LL-37* in pemphigus remain elusive. Indeed, both pro- and anti-inflammatory functions have been assigned to *LL-37* in a dependent manner on the microenvironment and disease background. Actually, some studies have speculated that these AMPs may provide a protective effect from cutaneous infection in cutaneous lupus erythematosus patients.[3] However, a pro-inflammatory phenotype of *LL-37* on macrophages in systemic lupus was also suggested.[5]

The cornerstone of pemphigus treatment remains systemic corticosteroids due to their immunosuppressive and anti-inflammatory properties.[6] So, it seems logical to assume that corticosteroids impact the *LL-37* expression according to the disease context. The 3-months follow-up showed a significant up-regulation in *LL-37* gene expression, which was negatively correlated with anti-Dsg1 Abs in pemphigus monitored patients. Interestingly, chronic pemphigus groups exhibited a persistence of *LL-37* high levels in comparison to the remittent ones. Previous research indicated that the glucocorticoid promotes the production of *LL-37* and β-defensin.[7] Actually, corticosteroids play a critical role in remission induction; their interaction with the cytoplasmic corticosteroid receptor results in up-regulation

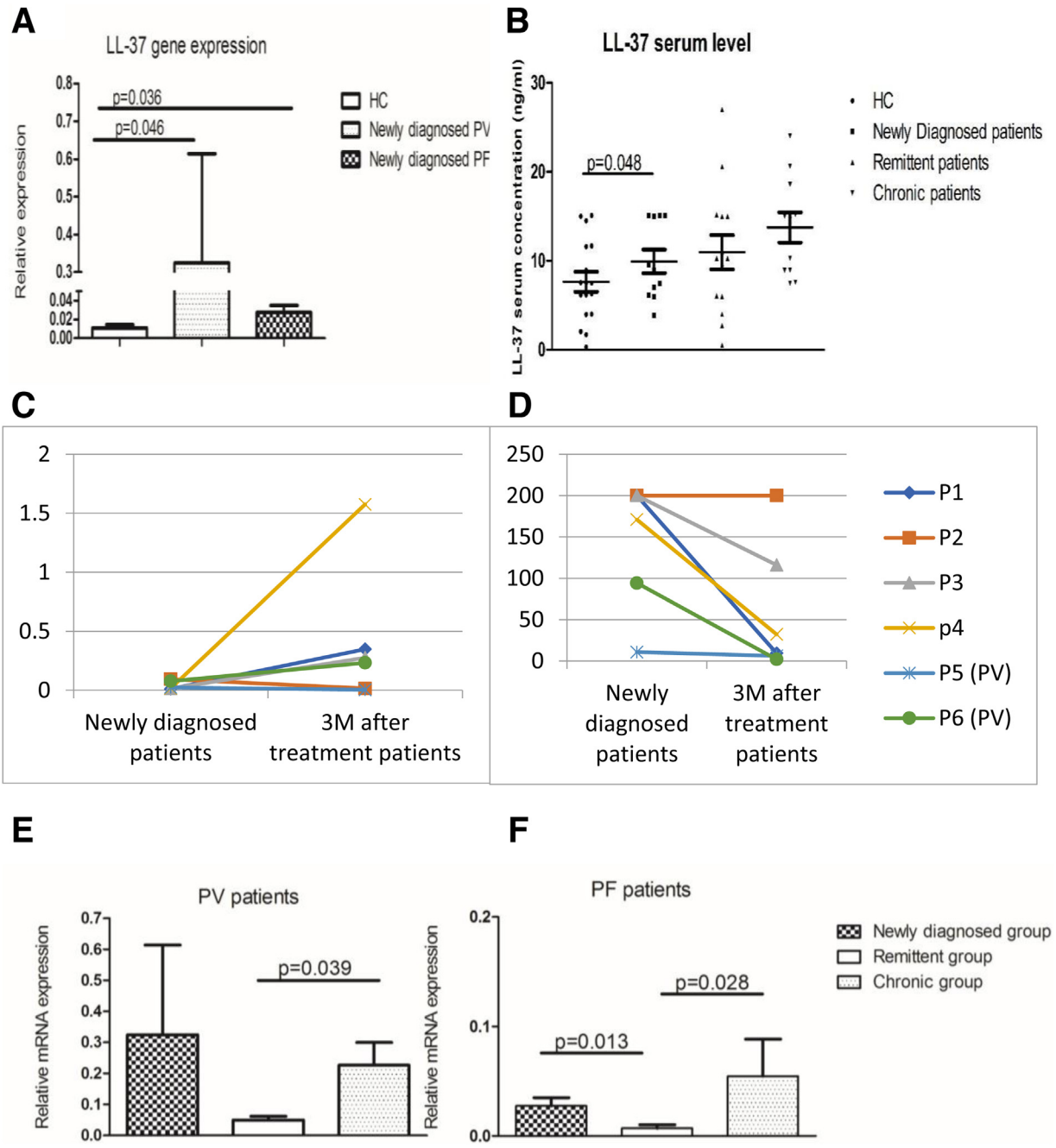

Figure 2 **LL-37 expression change in different studied groups.** (A) Differential expression level of LL-37 in newly diagnosed pemphigus patients (PV; n = 4, PF; n = 11) compared to HC (n = 16); (PV_{mean} = 0.324 ± 0.28, PF_{mean} = 0.027 ± 0.007 and HC_{mean} = 0.011 ± 0.003, with p = 0.046, p = 0.036; respectively). (B) LL-37 serum concentration comparison between Newly diagnosed patients (n = 15) and HC (n = 11) (Newly diagnosed $patients_{mean}$ = 10.06 ± 1 ng/mL, HC_{mean} = 6.22 ± 1.3 ng/mL, p = 0.048) and between remittent patients (n = 11) and chronic patients (n = 14) (Remittent $patients_{mean}$ = 9.5 ± 1.8 ng/mL, chronic $patients_{mean}$ = 14.2 ± 1.7 ng/mL, p > 0.05). (C) Differential expression of LL-37 and (D) Dsg1 values after 3 M of treatment. LL-37 mRNA expression changes significantly after 3-months of treatment (Newly diagnosed $patients_{mean}$ = 0.039 ± 0.014 vs. 3 M $treated_{mean}$ = 0.408 ± 0.24, p = 0.023) with a notable negative correlation between Dsg1-Abs level and LL-37 mRNA expression. (E) Differential expression level of LL-37 in chronic PV patients (n = 8) compared to remittent (n = 6) and newly diagnosed; (remittent PV_{mean} = 0.049 ± 0.011 vs. Chronic PV_{mean} = 0.225 ± 0.073, p = 0.039). (F) LL-37 mRNA expression changes in chronic PF patients (n = 6), compared to remittent (n = 8); (remittent PF_{mean} = 0.007 ± 0.003 vs. chronic PF_{mean} = 0.074 ± 0.034, p = 0.028; respectively) and newly diagnosed groups (p = 0.013). Comparison of two independent samples using the non-parametrical Mann-Witney test, p-value < 0.05.

of anti-inflammatory proteins and downregulation of those pro-inflammatory.[6] Therefore, *LL-37* up-regulation may contribute to suppressing the inflammatory responses and mediate tissue repair. Indeed, *LL-37* contributes to modulating cytokine production and chemoattracting various immune effector cells, leading to stimulation of angiogenesis and wound healing.[8] Alongside our results, the up-regulation of *LL-37* expression was suggested to be implicated in tissue repair in the recovery phase of sepsis.[9]

On the other hand, there was evidence that *LL-37* can perform two distinct functions in different tissues and different microenvironments. This peptide has been shown to regulate monocyte/macrophage differentiation[10] which can exhibit pro- and anti-inflammatory properties depending on the stimuli from their local microenvironment. In fact, *LL-37* exacerbated LPS-induced septic shock in rats when administered 2-hs after LPS treatment.[8] This is in line with the hypothesis suggesting that the persistence of *LL-37* high levels in chronic pemphigus can aggravate the damaging effects induced by inflammation. Thus, the timing and the cellular context could change the *LL-37* expression according to the disease severity. On the one side, *LL-37* seems to promote immune response and exerts its anti-inflammatory and wound healing effects for remission induction and persistence; on the other side, it seems to have the ability to stimulate inflammation and promote a pro-inflammatory response in the persistent chronic phase of pemphigus. In conclusion, the cellular environment and the timing appear to have an impact on *LL-37* expression. For a more comprehensive understanding, further functional studies on skin cell culture are needed.

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Ethical approval

The study was approved by the Human Research Ethics Committee of the Habib Bourguiba University Hospital of Sfax (protocol number of the ethical committee, 4/12).

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Research data availability

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

Conflicts of interest

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LETTER - RESEARCH

Eosinophilic annular erythema: report of four cases in adults and update of the literature☆

Dear Editor,

Eosinophilic annular erythema (EAE) is an uncommon, usually self-limited dermatosis, first described in infancy by Peterson in 1981.[1] The first adult case was reported in 2000 by Kahofer et al.[2] EAE belongs to both eosinophil-associated dermatoses and figurate erythemas as well.

The authors report four adult cases of EAE (Table 1) that were histologically proven and assessed at the same institution between 2017 and 2024. Two women and two men, aged 39 to 65 years (median age 53), presented clinically with lesions involving the trunk and extremities (Figs. 1 and 2). Intense itching was the main symptom. No vesiculation, scaling, or central punctum was present. Only Case 2 resolved with post-inflammatory hyperpigmentation. Laboratory tests, including complete blood count, C-reactive protein, erythrocyte sedimentation rate, VDRL, fasting blood sugar, renal and liver function, and direct immunofluorescence, were all normal or negative. On histological examination, all cases revealed similar findings, showing no epidermal involvement. The dermis showed an intense dermal edema, vasodilation, and a moderate mixed infiltrate with abundant eosinophils in a perivascular and interstitial distribution at superficial and deep levels. No flame figures were seen (Fig. 3).

Case 1

A healthy 39-year-old woman with no relevant past medical history presented with a five-month history of an intermittent skin eruption consisting of urticarial papules and annular plaques with erythematous borders, that enlarged centrifugally and each one disappeared without a trace, lasting up to 48 hours. There was no history of arthropod bites, exposure to pets, recent travel, or use of any medications. A skin biopsy confirmed the diagnosis of EAE. The patient received topical and oral steroids – prednisone 40 mg/od, plus a combination of three antihistamines. Prednisone was slowly tapered down to 4 mg/d over a month. The skin lesions faded gradually, and the pruritus score decreased from 10/10 to 6/10. Prednisone was stopped upon achieving complete remission. She suffered similar outbreaks over two years and finally went into remission.

Case 2

A 61-year-old man with no previous medical history presented with an acute, recurrent, intensely itchy skin rash on the trunk and extremities that affected his quality of life. Physical examination revealed widespread involvement sparing the face, genitalia, oral mucosa, scalp, palms, and soles. Individual lesions had become confluent, developing into large erythematous polycyclic configurations. Laboratory tests revealed eosinophilia of 18%, and an elevated IgE 400 Iu/mL. The patient failed to respond to topical corticosteroids and high-dose antihistamines. Topical and oral prednisone – 40 mg/day followed, with symptomatic relief but incomplete control of lesions. Hydroxychloroquine 200 mg/day was subsequently added with similar results. Finally, oral cyclosporine (3.5 mg/k/day) monotherapy was started, and after two weeks, the majority of the lesions resolved, with significant central post-inflammatory hyperpigmentation. Complete remission of skin lesions was achieved at 4-weeks (Fig. 4), and cyclosporine was gradually tapered and discontinued six months after initiation. At one-year follow-up, the patient has remained relapse-free.

Case 3

A 67-year-old man suffering from chronic eczema for many years presented with a pruritic eruption of erythematous macules and plaques. He had been receiving valproic acid for epilepsy for the past 20-years, lipid-lowering therapy for the past 7-years, and levothyroxine for hypothyroidism. Skin biopsy confirmed the diagnosis. The patient was started on prednisone – 40 mg/day over 40-days with a good response, tapering to 40/20 mg alternate days, then 20 mg/d over two more months, until he was free of lesions.

☆ Study conducted at the Instituto de Investigaciones Médicas Alfredo Lanari, Universidad de Buenos Aires, Buenos Aires, Argentina.

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Table 1 Clinical data.

Case nº	Age yrs/ Gender	Concomitant disease	Type of lesions	Location	Histology	Blood test	Treatment	Duration	Relapse
1	39 Female	None	Urticarial papules and erythematous annular plaques	Trunk and extremities	Dermal edema. Superficial and deep moderate perivascular eosinophilic infiltrate.	Normal	Prednisone + anti histamines with good response	2 years	Yes
2	61 Male	None	Urticarial papules and annular plaques	Trunk and extremities	Mild spongiosis.Perivascular and interstitial mixed infiltrate with numerous eosinophils	Eosinophilia IgE 400 IU/mL	Prednisone and hydroxychloro-quine were ineffective. Cyclosporine (3.5 mg/Kg/d) with good response. Post inflammatory hyperpigmenta-tion	6 months	No
3	67 Male	Chronic eczema Epilepsy Hypothyroidism	Erythematous macules and plaques	Trunk and extremities	Spongiosis, dermal edema. Moderate mixed perivascular infiltrate with numerous eosinophils	Normal	Prednisone with good response	2 months	No
4	45 Female	Atopic dermatitis Allergic rhinitis ANA+	Annular erythematous plaques	Trunk and abdomen	Moderate perivascular and interstitial mixed infiltrate with numerous eosinophils	Normal	Prednisone and antihistamines	After 6-months still continues	Yes

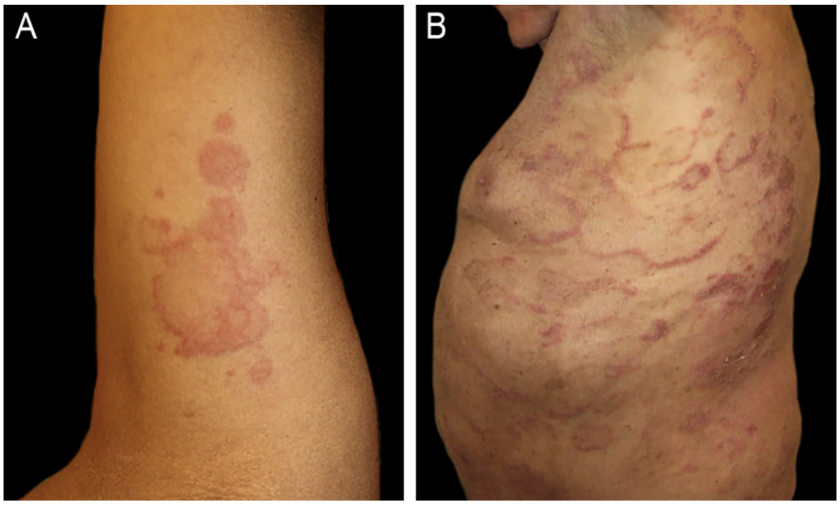

Fig. 1 (A) Case 1: Annular plaques with erythematous borders on the right armpit and upper extremity. (B) Case 3: Erythematous macules and plaques with the typical figurate erythema aspect, on the trunk.

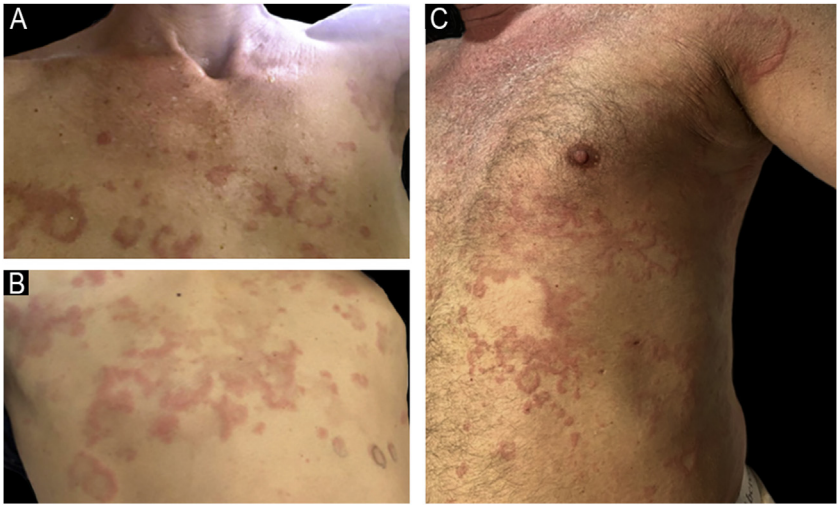

Fig. 2 (A and B) Case 4: Annular plaques with central healing and erythematous borders on the trunk. (C) Case 2: Urticarial papules and erythematous plaques on the trunk and extremities.

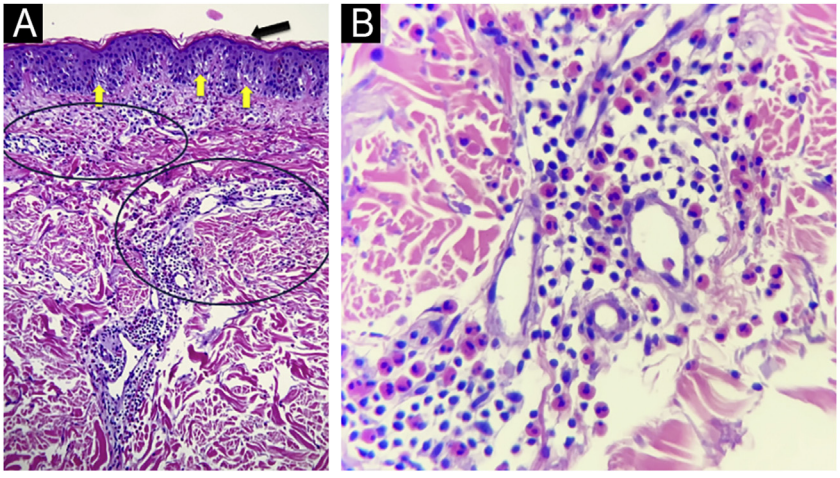

Fig. 3 (A) Hematoxilyn & eosin, 100×. Epidermis with orthokeratosis (black arrow) and mild spongiosis (yellow arrows). Dermis with moderate inflammatory infiltrates of perivascular and interstitial disposition. (circles) (B) Hematoxilyn & eosin, 400 ×. A close up of the dermal infiltrates on a perivascular and interstitial disposition made up of lymphocytes and numerous eosinophils.

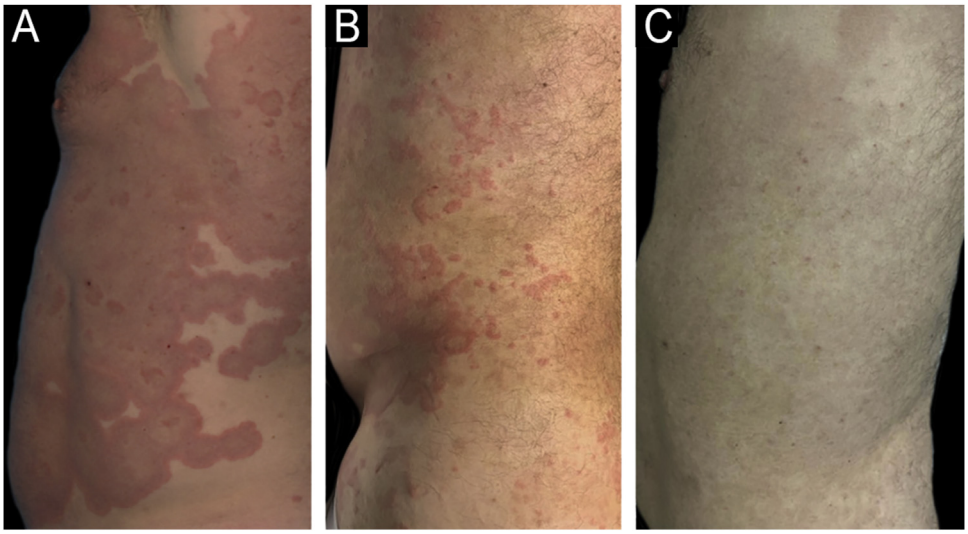

Fig. 4 Case 2 Pre- and post-treatment. (A) Baseline (cyclosporine 3.5 mg/k/day). (B) 9 days of treatment. (C) Complete remission at 4-weeks of treatment.

Case 4

A 45-year-old healthy woman presented with a 4-months history of an intermittent pruritic rash on her trunk and abdomen. As a possible trigger factor, the patient mentioned that the skin rash started after a bee sting during her holidays. There was no history of exposure to pets or use of any medications. Except for her atopic dermatitis, recurrent allergic rhinitis, and a positive Antinuclear Antibody (ANA) at a 1:320 dilution with a fine nuclear speckled pattern (AC-4), her personal medical history and family history were otherwise normal. The patient received oral prednisone 8 mg od and a combination of two second-generation antihistamines as maintenance therapy. This combination achieved pruritus control with lesional improvement. However, relapses occurred upon withdrawal of therapy. The authors have failed to achieve disease control to date.

EAE is an acute, benign, and intensely pruritic dermatosis characterized by recurrent annular, arciform, figurate, or polycyclic erythematous and edematous plaques with a centrifugal growth pattern. The lesions usually arise on the trunk and extremities and most individual lesions tend to disappear within 36–48 hours. The absence of vesiculation and residual scaling distinguishes it from other conditions. At least 82 adult cases have been reported in the literature, including atypical variants with vesiculobullous features or palmoplantar localization.[3,4] Although self-limited, relapses are characteristic of the disease. Regarding the two patients who experienced several relapses during a 2-year follow-up, the authors found no changes in their laboratory tests or other possible explanations for this course.

The pathogenesis remains unclear. Current hypotheses suggest an Interleukin-5 (IL-5) mediated eosinophil recruitment in response to unknown triggers, possibly allergic stimulus or insect bites, as suspected in Case 4. Although eosinophilia is occasionally reported, it is not a common finding.[5]

Histopathology typically shows dermal involvement with a perivascular and interstitial infiltrate with numerous eosinophils and some lymphocytes without granulomas or vasculitis. Flame figures, characteristic of wells syndrome (WS), are generally absent. Pigmentary incontinence and basal melanosis may lead to post-inflammatory hyperpigmentation, as seen in Case 2.[5]

Differential diagnoses (Table 2) include other annular dermatoses, such as generalized granuloma annulare, erythema annulare centrifugum, subacute cutaneous lupus erythematosus, erythema multiforme, erythema gyratum repens, and erythema migrans. Eosinophilic disorders to consider include WS, bullous pemphigoid, parasitic infections, arthropod bites, and eosinophilic vasculitis.[1]

There is an ongoing debate regarding whether EAE is a separate entity or a variant of WS. Some authors propose that EAE represents a chronic, treatment-resistant form of WS with higher relapse rates. However, the absence of flame figures, lack of blood eosinophilia, and distinct clinical features support the classification of EAE as an independent condition.[6]

Associations between EAE and systemic diseases such as autoimmune thyroiditis (Case 3), diabetes mellitus, and systemic lupus erythematosus have been described. El-Khalawany et al. observed that managing systemic comorbidities may contribute to longer remission periods and reduced recurrence.[7]

Treatment should be individualized based on symptom severity, lesion extent, and associated conditions. Therapeutic options include topical and systemic corticosteroids (0.5–1 mg/kg/day), oral minocycline or doxycycline, hydroxychloroquine (200–400 mg/day), dapsone (50–100 mg/day), low-dose cyclosporine, methotrexate, and antihistamines, alone or in combination. Clinical improvement usually occurred within 2–6 weeks. However, relapses after drug discontinuation are frequent. One case in the literature reported the successful use of narrowband UVB in a corticosteroid and hydroxychloroquine-resistant patient, achieving long-term remission.[8,9]

Recent reports have also described successful treatment of refractory cases with biologics such as dupilumab,

Table 2 Differential diagnoses of EAE.

Dermatosis	Clinical description	Histologic features
Generalized Granuloma Annulare	May occur in infancy and adulthood. Asymptomatic or occasionally pruritic, non-scaly erythematous papules and plaques with different morphology, annular, arciform, polycyclic. The etiology is unclear. It may be associated with Diabetes mellitus, thyroid diseases, infections (hepatitis B/C virus, HIV), malignancies, etc.	Pattern of either palisading granuloma with focal degeneration of collagen bundles surrounded by lymphocytes, histiocytes, and giant cells, or interstitial distribution of the infiltrate, in the upper and mid-dermis. Abundant mucin deposition
Erythema Annulare Centrifugum	Usually begins in middle age with erythematous papules and plaques that enlarge centrifugally to form rings and arcs with central hypopigmentation. On the inner part of the advancing edge, a fine collarette of scales is described. Each lesion lasts days to months. Face, trunk, extremities. Occasionally, it accompanies an underlying disease (infections, malignancies, etc.)	The epidermis often shows areas of mild spongiosis surmounted by focal parakeratosis. Dense perivascular lymphohistiocytic infiltrate in the superficial and deep dermis without eosinophils
Subacute lupus	Usually in adults. It presents with erythematous papulosquamous or annular plaques on photo-exposed areas. ANA + and Ro+	Interface dermatitis, edema, perivascular, peri-adnexal lymphocytic infiltrate. Positive Direct Immunofluorescence (DIF)
Erythema gyratum repens	Persistent concentric, arcuate, or polycyclic, scaling plaques, almost always associated with an underlying malignant neoplasm of the breast, lung, stomach, bladder, prostate.	Histologically, it shows both, epidermal (hyper and parakeratosis, focal spongiosis), and a dermal component composed by mild perivascular mononuclear infiltrate
Tinea corporis	Annular erythematous plaques with peripheral leading scale and central healing	Direct potassium hydroxide microscopy (KOH) and culture lead to the diagnoses of superficial fungal infection
Wells syndrome	Clinically, itś characterized by prodromal burning, painful edema, and peripheral induration. The classical description is a cellulitis-like plaque, but then, its clinical polymorphism with erythematous annular and figurate lesions have been described. The lesions usually resolved within a few weeks leaving a slate-grey morphea-like induration. The recurrent course and spontaneous healing after months or years, are features that both entities share.	Prominent papillary dermal edema, and interstitial infiltrate mainly eosinophils, are diffusely distributed, and can be localized at the superficial, mid and/or deep dermis and extending into the subcutis. Typical flame figures consisting of degenerated collagen fibers, due to deposits of the major basic protein of the eosinophil.
Erythema Gyratum Atrophicans	Occurs in newborns as a generalized eruption of erythematous plaques evolving to atrophy and hypopigmentation.	Epidermal atrophy, dermal edema, and a mononuclear cell infiltrate are present. DIF reveals granular deposits of IgG, C3, and C4 at the dermoepidermal junction and around the superficial capillaries
Erythema Multiforme	May occur at any age presenting as symmetrically distributed papules, annular plaques and target-like lesions typically fixed for a minimum of seven days.	Interface dermatitis characterized by epidermal basal cell damage, which may be manifested by cell death and/or basal vacuolar change, and a lichenoid distribution of inflammatory cells obscuring the dermoepidermal interface
Erythema Chronicum Migrans	There is often a history of an arthropod bite and a resulting central punctum. The non-scaly, usually unique plaque, expands centrifugally as a blue-red urticarial ring over several weeks or months.	Mononuclear peri-adnexal and perivascular dermal infiltrate is present.
Urticaria	Edematous papules that rapidly became large and irregular plaques intensely pruritic. Each lesion lasts no more than 6 -hs and they arise on different locations.	Edema and sparse perivascular inflammatory infiltrate in the upper dermis
Annular Erythema of infancy	Annular and figurate pruritic lesions with early age of onset (under 1-year of age) and spontaneous resolution on the trunk and extremities. No prodromes. Sparing the face, genitalia, palms and soles. No Eosinophilia in the majority of cases. Recurrent, chronic, with outbreaks.	Perivascular mononuclear infiltrate with few eosinophils; negative DIF; lack of mucin, ''flame figures'', vasculitis or granulomas

mepolizumab, benralizumab, and the JAK inhibitor baricitinib, though these remain off-label and are based on isolated cases.[10]

In conclusion, the authors propose that EAE is a distinct clinical entity, characterized by annular, pruritic, polycyclic plaques. This presentation differs from the more edematous, cellulitis-like lesions of WS, which commonly exhibit peripheral eosinophilia and flame figures on histology. Skin biopsy remains essential for diagnosis. Although therapeutic responses are usually favorable, relapses are common. Further studies are needed to clarify its pathogenesis, classification, and optimal long-term management.

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Authors' contributions

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Horacio A. Cabo: Intellectual participation in propaedeutic and/or therapeutic management of studied cases and approval of the final version of the manuscript.

Rosario Peralta: Manuscript critical review, critical literature review and approval of the final version of the manuscript.

Gabriel Salerni: Effective participation in research orientation and approval of the final version of the manuscript.

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Yolanda Gilaberte: Preparation and writing of the manuscript and approval of the final version of the manuscript.

Esteban Maronna: Data collection, analysis and interpretation and 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

The morbidity of systemic steroids: analyzing its use in bullous pemphigoid☆

Dear Editor,

Bullous Pemphigoid (BP) is the most common autoimmune bullous disease.[1] High-potency topical corticosteroids are accepted as first-line treatment in BP.[1,2] However, due to the chronic nature of the disease, which is often characterized by multiple relapses, or in moderate to severe/extensive cases, when topical therapies may be insufficient, systemic treatment is usually required to achieve disease control. Systemic steroids are typically prescribed after the failure of topical strategies[1,2] and are considered a second-line treatment according to most BP guidelines (doses of 0.5–1 mg/kg/day prednisone).[1,2] It is estimated that systemic steroids are used in 70%–80% of BP patients.[3]

However, their use has been classically associated with higher mortality and an increased risk of side-effects, particularly in elderly patients, who represent the majority of BP cases.[3,4] The aim of this study was to analyze the management of BP in our setting, with a specific focus on the outcomes of patients treated with systemic steroids.

A retrospective observational study was conducted, including all patients diagnosed with BP who were attended in our department between the year 2000 and the first semester of 2020. Diagnosis of BP was based on the updated diagnostic criteria.[1] All cases included had at least three out of the four criteria: clinical, histopathological, serological (including Indirect Immunofluorescence [IIF] and/or Enzyme-Linked Immunosorbent Assay [ELISA] and Direct Immunofluorescence [DIF]). Epidemiological (including comorbidities that were present at the time of BP diagnosis (neurological, neoplastic diseases, and diabetes mellitus type 2), clinical, immunological, histopathological, and therapeutic characteristics of all patients were recorded, including dosage, duration, lines of treatment, definitive treatment, need for hospitalization, and any adverse events if present.

AntiBP180 IgG antibodies detected were directed against the Noncollagenous 16A domain (NC16A) by BP180-NC16A ELISA assay.

A commercially available ELISA kit was used that includes the detection of IgG autoantibodies against desmoglein 1, desmoglein 3, BP180, and type VII collagen. Full-length BP180 autoantibodies detection was not performed.

Categorical variables were expressed as total numbers with percentages, and continuous variables were expressed as means, with standard deviation in symmetric distributions or medians and interquartile ranges in asymmetric variables. Demographic, clinical, histopathological, and serological characteristics were compared between deceased and non-deceased groups, using either the Chi-Square test (or Fisher's exact test when necessary) or Student's *t*-test (or Mann-Whitney *U*-test/Wilcoxon W-test when necessary). The bilateral F-test was used for the equal variance test. Statistical analysis was performed with Stata (version 16 StataCorp, College Station, Texas, USA).

A total of 257 patients were included; 154 were male (59.9%) with a global mean age (±SD) at diagnosis of 80.5-years (±10.4). In regard to comorbidities, diabetes mellitus type 2 was present in 106 cases (41.2%) and neurological and oncological diseases in 102 (39.7%) and 47 (18.3%) patients, respectively.

We classified BP in four groups depending on the Body Surface Area (BSA) affected: generalized (>50% BSA) in 81 patients (31.5%); trunk and extremities (< 50%, affecting extremities and trunk) in 122 (47.5%), trunk (<50%, affecting only trunk) in 13 (5.1%), extremities (<50%, affecting only extremities) in 39 (15.2%) and ''other'' (when not corresponding to prior criteria) in 2 cases (0.8%). Scalp and mucosal involvement were present in 22 and 16 patients, respectively. Due to incomplete information in the clinical records, we were unable to assess the presence of inflammatory versus non-inflammatory phenotypes or calculate any disease severity scores (BPDAI or IGA).

All skin biopsies showed a subepidermal blister with an eosinophilic inflammatory infiltrate and, except for 11 patients (4.3%), DIF revealed immunofluorescence patterns compatible with BP. In terms of serology, antiBP180 antibodies were found positive (>20 U/mL) in all cases in which these autoantibodies were tested (170 patients; 66.1%); the mean concentration (±SD) was 49.13 (±53.63).

☆ Study conducted at the Hospital General Universitario Gregorio Marañón, Madrid, Spain.

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Table 1 Therapeutic and management characteristics of BP patients included in the study.

Treatment	N = 257 n (%)	Definitive treatment, n (%) N = 257	Definitive treatment, n (%) N = Total of patients that received it
Topical corticosteroid	257 (100)	41 (16)	41 (16)
Systemic steroid (prednisone)	209 (81.3)	125 (48.6)	125 (59.8)
<0.5 mg/kg/day	178 (69.2)		
>0.5 mg/kg/day	28 (10.9)		
Azathioprine	63 (24.5)	50 (19.5)	50 (79.4)
Tetracyclines	29 (11.3)	12 (4.7)	12 (41.4)
Associated to nicotinamide	19 (7.4)	8 (3.1)	8 (42.1)
Methotrexate	21 (8.2)	16 (6.2)	16 (76.2)
Dapsone	11 (4.3)	7 (2.7)	7 (63.6)
Rituximab	6 (1.9)	6 (1.9)	6 (100)
Treatment duration of systemic steroids (prednisone) (months)			
Mean (±DS)	6.33 ± 1.77		
Median (p25–p75)	6 (3–9)		
Number of lines of treatments employed to achieve disease control [N = 257, n (%)]			
1	41 (16)		
2	127 (49.4)		
3	69 (26.8)		
4	14 (5.4)		
5	3 (1.2)		
6	3 (1.2)		
Number of flares/recurrences [N = 257, n (%)]			
0	198 (77)		
1	46 (17.9)		
2	9 (3.5)		
3	3 (1.2)		
4	1 (0.4)		
Hospitalization [N = 257 n (%)]			
Sí	93 (36.2)		
No	164 (63.8)		
Hospitalization time (days)			
Mean ± DS	5.91 ± 9.66		
Median (p25–p75)	5 (2–9)		

Definitive treatment was defined by the therapeutic strategy that led to achiev} complete remission. Percentages in the second column refer to the global study cohort (n = 257); in the third column, only patients who received the referred treatment were considered.

Of the 257 BP patients studied, all received topical treatment; 41 (16%) achieved complete remission after high/very high-potency topical corticosteroids as first-line treatment. Systemic steroids were prescribed in 209 cases. In 125 patients (48.6%) of the study cohort, systemic corticosteroids (with or without topical treatment) were the definitive treatment.

However, 91 patients required additional interventions to control the disease. In 234 cases (92.3%), remission was achieved with three or fewer lines of treatment. Among those receiving systemic steroid treatment, in 85.1% of cases, doses lower than 0.5 mg/kg/day (0.3–0.4 mg/kg/day) were prescribed. Mean steroid treatment duration was 6.33 (±1.77 SD) months (Table 1). None of the patients were treated with plasma exchange, intravenous immunoglobulin, or steroid pulse therapy.

By the end of the study period, 155 BP cases had died. There were no significant differences in terms of age, sex, neoplastic comorbidities, or BSA between deceased and non-deceased patients (Table 2).

However, neurological comorbidities were significantly more common in the group of deceased BP patients (50.3% vs. 23.5%, p = 0.000) (Table 2). No specific neurological disease, including vascular dementia, was more prevalent in the deceased group.

Although no differences were found in the detection rate of anti-BP180 autoantibodies, the concentration of these antibodies was higher in the group of patients who had deceased by the end of the study (p = 0.050) (Table 2).

Regarding therapeutic outcomes, there were no significant differences in definitive treatment, steroid doses, cumulative steroid doses or need for hospitalization (Table 2).

Additionally, higher steroid doses (>0.5 mg/kg/day) were not associated with a worse prognosis in terms of survival time (from BP diagnosis to death) compared to lower doses (median survival time: 5-years [95% CI 3.43–6.58] for higher doses vs. 6-years [95% CI 4.04–7.96] for lower doses). Mean survival time for other systemic treatments different from systemic corticosteroids found was 5-years (95% CI

Table 2 Analysis of the demographics, comorbidities, serological, therapeutics and hospitalization outcomes in deceased and non-deceased BP patients included in the study.

	Deceased N = 155, n (%)	Non-deceased N = 102, n (%)	p
Mean age (±SD) (years)	83.78 (± 8.25)	85.48 (± 11.39)	0.378
Sex			0.284
Female	58 (37.4)	45 (44.1)	
Male	97 (62.6)	57 (55.9)	
Neurological comorbidities	78 (50.3)	24 (23.5)	**0.000**
Senile dementia	22 (14.2)	4 (3.9)	
Alzheimer's Disease	19 (12.3)	7 (6.9)	
Vascular dementia	18 (11.6)	8 (7.8)	
Parkinson's disease	14 (9)	3 (2.9)	
Amyotrophic lateral sclerosis	3 (1.9)	0	
Multiple sclerosis	0	2 (2)	
Lewy body dementia	2 (1.3)	0	
Neoplastic comorbidities	29 (18.7)	18 (17.6)	0.839
Diabetes mellitus type 2	62 (40)	44 (43.1)	0.617
Body Surface Area (BSA)			0.532
Generalized (>50%)	49 (31.5)	32 (31.4)	
Trunk and extremities (<50%)	77 (49.6)	45 (44.1)	
Trunk (<50%)	6 (3.8)	7 (6.8)	
Extremities (<50%)	22 (14.1)	17 (16.7)	
Other	1 (1)	1 (1)	
Anti-BP180 antibodies			
Number of patients tested	102 (65.8)	78 (76.5)	0.358
Positivity (>20 U/mL)	56 (36.1)	59 (57.8)	0.692
Mean titer (±SD) (U/mL)	50.95 (±49.32)	41.93 (±56.48)	**0.050**
Definitive treatment			
Topical corticosteroids	155 (100)	102 (100)	–
Systemic steroids (prednisone)	130 (83.9)	79 (68.6)	0.196
Doses of systemic steroids			0.118
<0.5 mg/kg/día	108 (69.7)	72 (70.6)	
>0.5 mg/kg/día	22 (14.2)	7 (6.9)	
Treatment duration of systemic steroids (months)			0.235
Mean (± DS)	7.45 (± 1.03)	6.02 (± 2.41)	
Median (p25–p75)	6 (3–9)	6 (3–9)	
Mean steroid cumulative doses (mg/treatment/patient)	5369.54	4912.41	0.156
Azathioprine	34 (21.9)	29 (28.4)	0.236
Methotrexate	5 (3.2)	16 (15.7)	NS
Dapsone	1 (0.6)	10 (9.8)	NS
Tetracyclines [+ nicotinamide]	14 (9) [11 (7.1)]	15 (14.7) [8 (7.8)]	0.160
Hospitalization			
Need for hospitalization	62 (40)	31 (30.4)	0.117
Hospitalization time (days) [mean (±DS)]	5.58 (± 8.74)	6.47 (± 11.09)	0.891

3.02–6.98). No adverse events directly related to systemic steroids were observed.

Systemic corticosteroids have traditionally been linked to higher mortality and increased side effects, especially when employed at high doses (1 mg/kg/day).[5,6] Their use is generally recommended to be limited to younger patients, elevated BPDAI scores, and high concentrations of antiBP180 NC16A antibodies.[4–6] Lower doses (0.1–0.2 mg/kg) have also been associated with a higher risk of relapse.[3,4]

However, in agreement with our findings, several studies have reported no increase in mortality in patients treated with systemic steroids.[3,4,7,8] When investigating whether early initiation of corticosteroid-sparing therapy in BP patients resulted in better outcomes than late or no sparing, the rate of complications and 1-year mortality did not differ significantly among therapeutic strategies.[7]

Moreover, mortality in BP patients has been associated with older ages, presence of multimorbidity, higher concentration of anti-BP180 and anti-BP230 antibodies, greater disease activity, and higher levels of systemic inflammation.[3,8–10]

In conclusion, systemic corticosteroids, despite their classical association with increased mortality, may not necessarily elevate this risk. Doses of lower than 0.5 mg/kg/day of prednisone appear sufficient to control skin lesions in a significant number of patients while minimizing morbid-

ity in BP patients. The advanced age of most BP patients complicates efforts to improve quality of life and prevent recurrences when immunosuppressive drugs are required. Although treatment should always balance benefits and risk, patients with BP must be treated appropriately, and therapeutics must be adapted to disease severity, in order to reduce systemic inflammation and avoid poor outcomes

This study was reviewed and approved by the ethics committee of the Hospital General Universitario Gregorio Marañón (CEIC). Approval from our ethics institutional board was obtained prior to the design and production of this paper. This study was carried out in accordance with the Declaration of Helsinki.

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Authors' contributions

Lula María Nieto Benito: Study concept and design; data collection, analysis, and interpretation of data; statistical analysis; writing of the manuscript; critical review of important intellectual content; critical review of the literature; final approval of the final version of the manuscript.

Ricardo Suárez Fernández: Study concept and design; 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.

Editor

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LETTER - RESEARCH

Real-world experience with deucravacitinib in psoriatic patients: the Chilean perspective☆

Dear Editor,

We present the findings of a multicentre observational study evaluating the efficacy and safety of deucravacitinib (Sotyktu®) in a cohort of Chilean patients with moderate-to-severe plaque psoriasis. Psoriasis affects approximately 1.1% of the Chilean population, with an incidence of 22 per 100,000 inhabitants, highlighting the need to document the real-world performance of novel therapies.

From July 2023 to August 2024, 24 adults were recruited from four dermatology centres in Santiago. Deucravacitinib was prescribed at 6 mg orally once daily. Disease severity was assessed with the Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA), and quality of life with the Dermatology Life Quality Index (DLQI). Evaluations were performed at baseline and at 3-, 6-, and 12-months. Adverse Events (AEs) were summarized descriptively with R (v 4.3.2).

Seventeen participants were male; the mean ± SD age was 38.5 ± 9.3 years, and the mean disease duration 16.1 ± 11.99 years. Fifteen patients had at least one comorbidity, and most had previously received methotrexate and/or biologics. Baseline mean PASI was 18 ± 12.4, mean BSA 15 ± 0.13 %, and mean DLQI (n = 16) 24 ± 3.75 (Table 1).

At month 3 (n = 21), PASI-75, PASI-90 and PASI < 3 were achieved by 33.3%, 9.5% and 23.8% of patients, respectively, with DLQI falling to 7.3. At month 6 (n = 21), the corresponding proportions were 70.8%, 38.1% and 57.1%; at month 12 (n = 19), they were 78.9%, 31.6% and 78.9% (Fig. 1).

Reported AEs were mild: acneiform eruption (n = 1), self-limiting upper-respiratory infections (n = 2), and headache (n = 1). One patient discontinued treatment owing to loss of efficacy.

Table 1 Baseline characteristics of patients with psoriasis treated with Deucravacitinib (n = 24).

i. Demographic Data	
Male sex, n (%)	17 (70.83%)
Age (years)[a]	38.58 ± 10.56
Age of Psoriasis Onset (years)[a]	22.91 ± 14.25
Psoriasis duration (years)[a]	16.10 ± 11.99
ii. Clinical indexes	
Total PASI[a]	18.03 ± 12.44
BSA (%)[a]	15 ± 0.13
DLQI[a]	24.06 ± 3.75
iii. Comorbidities	
Total comorbidities (n)	15
Obesity	2
Hypertension	3
Type 2 Diabetes Mellitus	3
Psoriatic arthritis	1
Mood disorder	5
Other	8
No comorbidities	9
iv. Previous treatments	
Total previous treatments (n)	24
Topical treatments	20
Methotrexate	12
Phototherapy	14
Anti-IL23	2
Anti-TNFα	1
Anti-IL17	1
No prior treatment	0

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index.
[a] Data presented as mean ± standard deviation.

Two-proportion z-tests showed significant improvements from month 3 to 6 for all outcomes ($p < 0.05$). No further significant change occurred between months 6 and 12, indicating a clinical plateau. Compared with month 3, PASI-75 ($p = 0.0038$) and PASI < 3 ($p = 0.0005$) remained significantly higher at month 12, whereas the increase in PASI-90, although numerically greater, did not reach conventional significance ($p = 0.081$).

Deucravacitinib delivered rapid and durable clinical benefit with a favorable safety profile in this real-world Chilean

☆ Study conducted at the University of Chile Clinical Hospital, Universidad de los Andes Clinical Hospital, Clínica Alemana de Santiago, and two Private Dermatology Offices in Santiago, Chile.

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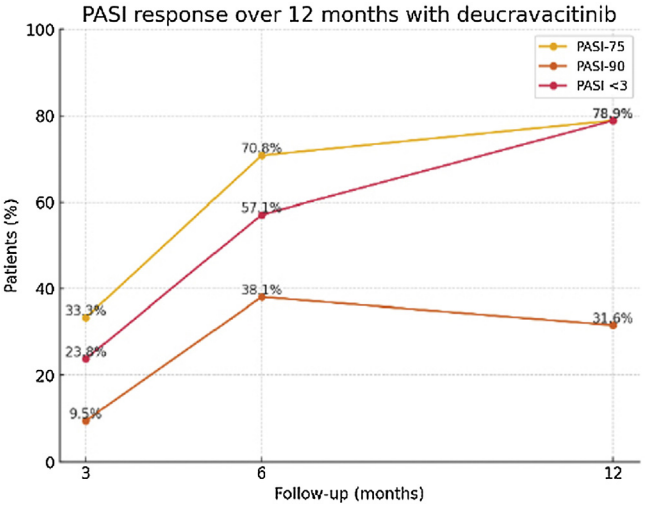

Fig. 1 Evolution of PASI at months 3, 6 and 12 in patients with Deucravacitinib: 21 patients were in follow-up at 3 months and 6 months, 19 patients were in follow-up at 12 months.

cohort, mirroring or exceeding the efficacy reported in pivotal trials.[1–3] The superior responses observed may reflect the permitted use of concomitant topical therapy. Our results also align with a recent Japanese series, which reported PASI-75 in 78.3% and PASI-90 in 52.2% of patients at week 16.[4] Continued assessment for 12 months is a notable strength of the present study.

These data support deucravacitinib as an effective first-line option for the management of moderate-to-severe psoriasis. Longer-term, larger-scale studies are warranted to refine its place in therapy within Latin-American and global populations.

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Research data availability

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

Conflicts of interest

Fernando Valenzuela has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by Pfizer Inc., AbbVie, Amgen, BMS, Janssen-Cilag, LEO, Lilly, Novartis, and Sanofi.

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Sílvio Alencar Marques

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LETTER – RESEARCH

Risk factors and surgical outcomes in periocular basal cell carcinoma treated with Mohs micrographic surgery

Dear Editor,

Periocular basal cell carcinoma (BCC) represents a therapeutic challenge due to its invasive behavior and proximity to critical anatomical structures. Few studies have evaluated its predictors of aggressiveness and recurrence treated with Mohs micrographic surgery (MMS).

A retrospective cohort study was conducted at a Brazilian multidisciplinary center by a single surgeon (maintaining the same surgical technique standard). Patients with periocular BCC treated with MMS between 2008 and 2018 were included.

Data were collected on sex, age, tumor location, aggressive histological subtype (micronodular, sclerosing, infiltrative, and metatypical/basosquamous) or non-aggressive (superficial, nodular), tumor diameter (> 10 mm or $\leq$ 10 mm), prior Mohs surgery recurrence (PMSR), MMS stages, type of reconstruction, follow-up, and postoperative recurrence. Cases with perineural invasion (two) and prior radiotherapy (none) were excluded because they are already established high-risk factors, for homogenization of the statistical sample, and because there were few cases. In cases with mixed subtypes, the most aggressive was considered. Reconstructions were classified based on non-standardized criteria as minor (primary closure, small flaps, canthotomy-cantholysis), moderate (Tenzel flap), and significant (Hughes or Mustardé flaps), according to the size of the defect and structures involved (up to 25%–30%, 30% to 60%, and above 60% of the eyelid margin, respectively). For cases without involvement of the eyelid margin, those requiring the Mustardé flap were considered significant, while the others were considered minor.

The statistical analysis included descriptive statistics, the Shapiro-Wilk test, the Wilcoxon test, Fisher's exact test, and the Kruskal-Wallis test ($p < 0.05$). Logistic regression models were used, with variable selection based on the calculation of Akaike's information criterion.

One hundred and eight patients were included, 57.1% female, mean age 66.3 years ($\pm$15.1; 27–91 years). The lower eyelid was the most affected site (55.5%) and medial canthus (29.7%), consistent with other literature studies on MMS in this location (51%).[1] Aggressive subtypes were present in 66.1%. Tumors with a diameter > 10 mm were observed in 49.1%, and 8% presented with PMSR. Recurrence after MMS occurred in 3.8% (n = 4), with a follow-up of 64.8 months ($\pm$31.6), similar to previous studies with recurrence of 3%–3.3% in similar cohorts.[2,3] The mean tumor area was 96 mm^2 and the mean final area was 398 mm^2. Reconstructions were minor (62%), moderate (13%), and significant (25%).

More stages of MMS were associated with PMSR (2.9 $\pm$ 1.5) vs. primary BCC (2.0 $\pm$ 1.1; $p = 0.002$), diameter > 10 mm (2.6 $\pm$ 1.4) vs. < 10 mm (1.9 $\pm$ 1.1; $p = 0.007$), and aggressive histology (2.4 $\pm$ 1.1) vs. non-aggressive (2.0 $\pm$ 1.5; $p = 0.005$).

Table 1, through univariate logistic regression, exemplifies that tumors > 10 mm were strongly associated with aggressive histology (OR = 7.33; $p < 0.001$) and larger defect area (OR = 1.008; $p < 0.001$). Tumors with PMSR showed a greater number of stages (OR = 1.72; $p = 0.002$), a larger defect area (OR = 1.008; $p = 0.001$), and more significant reconstructions (OR = 2.73; $p = 0.039$). Tumors with aggressive histology exhibited a greater chance of complex reconstructions (OR = 4.53; $p = 0.006$).

Table 2 using the multivariate model indicated that PMSR was associated with a larger defect area (OR = 1.002; $p = 0.001$) and significant reconstruction (OR = 3.77; $p = 0.0177$), as well as previous studies that demonstrated that lesions previously inadequately treated by conventional surgery tend to exhibit increased/more aggressive subclinical growth and behavior when recurring locally.[4,5] Tumors > 10 mm were associated with PMSR (OR = 8.02; $p = 0.0148$), aggressive subtype (OR = 8.41; $p = 0.0021$) and larger defect area (OR = 1.006; $p = 0.0017$). Aggressive histology was associated with a diameter > 10 mm (OR = 6.92; $p < 0.001$).

The anatomical distribution and cure rate (3.8%) after MMS are aligned with the literature, as in Shi et al. 4.2% (n = 167), with the lower eyelid and medial canthus being the most frequent sites.[1–3,6–8] The initial descriptive analysis revealed associations between a higher number of MMS stages and tumors with aggressive histology, diameter > 10 mm, and PMSR, as described in previous studies.[4,9]

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Table 1 Univariate logistic regression model of variables associated with the main surgical outcomes in periocular basal cell carcinoma. Pre-operative Mohs surgical recurrence (PMSR), Odds ratio (OR).

Outcome	Variable	p-value	Odds ratio (OR)	Confidence Interval
Diameter > 10 mm	PMSR	<0.001	5.875	2.413-15.635
	Stages	0.008	1.575	1.142-2.256
	Defect area	<0.001	1.008	1.005-1.012
	Aggressive histology	<0.001	7.333	3.093-18.848
	Moderate reconstruction	0.829	0.876	0.246-2.832
	Significant reconstruction	<0.001	6.938	2.494-22.807
PMSR	Diameter >10 mm	<0.001	5.875	2.413-15.635
	Stages	0.002	1.721	1.236-2.485
	Defect area	0.001	1.008	1.005-1.012
	Aggressive histology	0.158	1.873	0.8-4.623
	Moderate reconstruction	0.154	2.391	0.697-7.945
	Significant reconstruction	0.039	2.732	1.05-7.169
Aggressive histology	Diameter > 10 mm	<0.001	7.333	3.093-18.848
	Stages	0.072	1.364	0.988-1.954
	Defect area	0.066	1.001	1-1.002
	PMSR	0.158	1.873	0.8-4.623
	Moderate reconstruction	0.056	3.778	1.067-17.817
	Significant reconstruction	0.06	4.533	1.636-14.815

Table 2 Multivariate logistic regression for outcomes of diameter > 10 mm, prior Mohs micrographic surgery recurrence (PMSR), and aggressive histological subtype. Odds ratio (OR).

Outcome	Variable	Odds Ratio (OR)	Confidence Interval	p-value
Diameter > 10 mm	Defect area	1.006	1.003–1.010	0.0017
	PMSR	8.023	1.688–52.422	0.0148
	Aggressive histology	8.412	2.316–36.826	0.0021
PMSR	Defect area	1.002	1.001–1.004	0.0007
	Significant reconstruction	3.765	1.256–11.510	0.0177
Aggressive histology	Diameter > 10 mm	6.922	2.724–19.070	<0.001
	Moderate reconstruction	4.944	1.271–24.944	0.0305

The univariate analysis reinforced that larger tumors, aggressive histology, or those with PMSR exhibit a greater chance of subclinical growth and complex reconstructions.

The multivariate analysis confirmed these findings; however, it showed that tumors with PMSR and tumors > 10 mm were almost seven times more likely to have aggressive histology. Although modest, the differences in the area of the final defect were statistically significant, highlighting the impact of these tumor characteristics on surgical extent. The findings suggest that larger tumors with aggressive histology require wider excisions.

Significant reconstructions were associated with PMSR (OR = 3.76), suggesting that recurrent tumors require more complex approaches. However, reconstructive complexity may reflect tumor biology/behavior (size, histological subtype), without being an independent predictor. As shown above, BCCs with PMSR tend to be aggressive subtypes and have a diameter > 10 mm.

The association between size, PMSR, and tumor aggressiveness reaffirms MMS as the preferred technique in these cases, given the higher chance of subclinical growth.[4,5,9] Margin control is crucial, especially where conventional surgery is still common and access to MMS is limited, reducing the risks of invasive tumors.[2,3]

The study limitations include its retrospective and single-center design, which may limit its findings. Larger studies may validate these associations and support individualized surgical planning.

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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 - CLINICAL

Acitretin-induced psoriasis and Darier disease treated with adalimumab☆

Dear Editor,

The simultaneous occurrence of several dermatoses in the same patient supposes a diagnostic-therapeutic challenge for the dermatologist. Although the relationship of psoriasis with other entities is widely known, its association with Darier's disease is a rarity.

We present the case of a 44-year-old woman with a history of sulfonamide allergy, bronchial asthma, and Darier-White disease (Fig. 1) who started treatment with acitretin. The diagnosis of Darier-White disease was confirmed, with histopathology revealing acantholysis with dyskeratosis (numerous grains and corps ronds), as well as parakeratosis (Fig. 2A). After a few months, the patient presented with papules and erythematous-violaceous plaques with silvery desquamation on the extremities. The histopathology showed psoriasiform epidermal hyperplasia, regular acanthosis, parakeratosis, and hypogranulosis, as well as Munro-Sabouraud microabscesses and Kogoj pseudopustules (Fig. 2B), confirming the diagnosis of psoriasis (Fig. 3). Treatment with methotrexate was started, controlling the psoriasis, but recurrent outbreaks of brownish keratotic papules on the trunk made it necessary to maintain the acitretin. Given the insufficient clinical response, treatment was changed to adalimumab, resulting in almost complete clearing of both conditions (Fig. 4). Adalimumab was initiated using the standard induction dosing for psoriasis (80 mg in the first week, followed by 40 mg subcutaneously the following week). The patient showed lesion clearance at 8-weeks of treatment with a maintenance dose of 40 mg subcutaneously once weekly. The treatment remained effective during the subsequent 5-month follow-up period.

Darier disease (follicular dyskeratosis) is an autosomal dominant genodermatosis associated with a mutation of the ATP2A2 gene, altering intracellular calcium levels.[1] The estimated prevalence varies from 1:30,000–100,000.[2] It classically manifests in childhood or adolescence as erythematous-brown and keratotic follicular papules confluent in seborrheic and intertriginous areas.[2] The disease has a chronic course with exacerbations due to sun exposure, heat, friction, and infections.[2] Histology shows a characteristic acantholytic dyskeratosis.[2] Its association with psoriasis is exceptional in the literature, with 2 cases published to date.[3,4] The debut of psoriasis after initiation of acitretin is also unusual.

The pathophysiologic link between these two diseases has been the subject of several publications. It has been described that patients with psoriasis have a

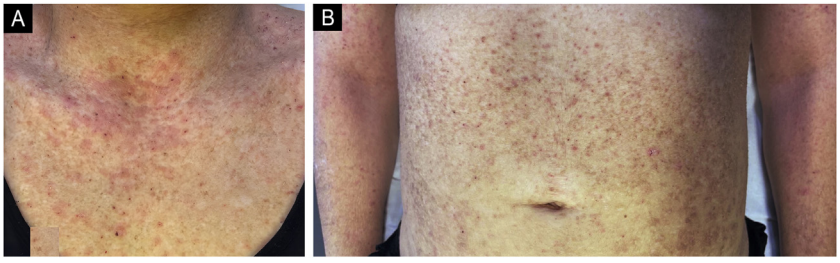

Fig. 1 Crusted erythematous papules on the neckline (A) and abdomen (B). Clinical findings are compatible with Darier-White disease.

☆ Study conducted at the Department of Dermatology, University Hospital of the Canary Islands, San Cristóbal de la Laguna, Santa Cruz de Tenerife, Spain.

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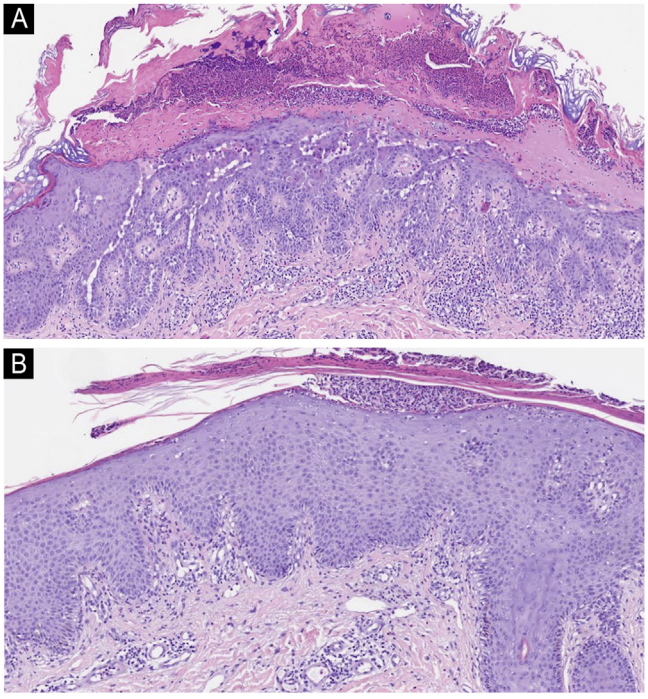

Fig. 2 Histological images with hematoxylin and eosin-stained sections (×40).
Acantholysis with dyskeratosis (numerous grains and corp ronds) as well as parakeratosis, findings suggestive of Darier's disease (A). Regular acanthosis with hypogranulosis and parakeratotic hyperkeratosis, as well as a Munro's microabscess, histologic findings suggestive of psoriasis (B).

down-regulation of the ATP2A2 gene.[5] In both diseases, endoplasmic reticulum stress and the consequent response to unfolded proteins are involved in the pathogenesis.[3] Abnormal expression of involucrin, a protein related to keratinocyte differentiation, was also observed.[6] Involvement of the Th17-23 axis has been demonstrated in patients with Darier disease.[7] However, these possible pathogenic associations contrast with the scarce joint report of both conditions.

Secondary psoriasis to acitretin is not documented in the literature. In our case, the Krach and Lasagna algorithm gave us a score of 7, considering probable causality. It has been described in the literature that this retinoid can worsen cases of previous psoriasis, even inducing erythrodermic forms.[8] Two hundred and seventeen cases of ''psoriasis'' have been reported with the use of acitretin to the EudraVigilance system of the European Medicines Agency (EMA)[9] to date. However, the history of the patients and whether the cases were associated with other drugs like biologics is unknown. A possible justification for this reaction could be the hyperproliferative effect that acitretin can have on healthy skin.

Interestingly, the patient was well controlled for follicular dyskeratosis with adalimumab alone. The latter has only been demonstrated for familial benign pemphigus. Only one case of Darier's disease has been published in a patient with rheumatoid arthritis who did not respond to anti-TNF-alpha treatment.[10]

The development of psoriasis in patients with Darier disease is exceptional. Both diseases seem to present common genetic and/or immunologic factors in their pathophysiology, which contrasts with the scarce joint report. Adalimumab could play a role in the treatment.

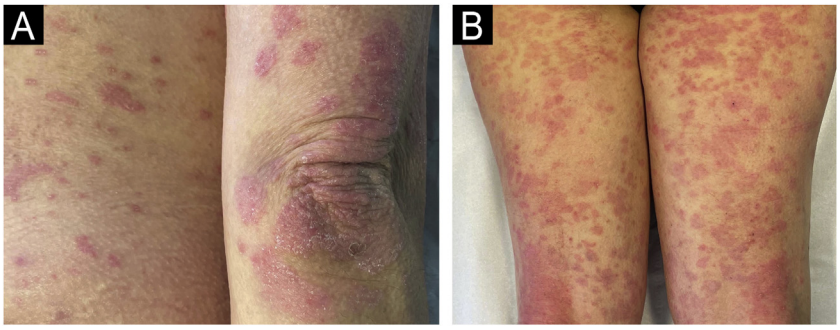

Fig. 3 Erythematous plaques with silvery-white scaling on elbows (A) and posterior aspect of both lower limbs (B) after initiation of acitretin. Morphologic findings that are compatible with psoriasis.

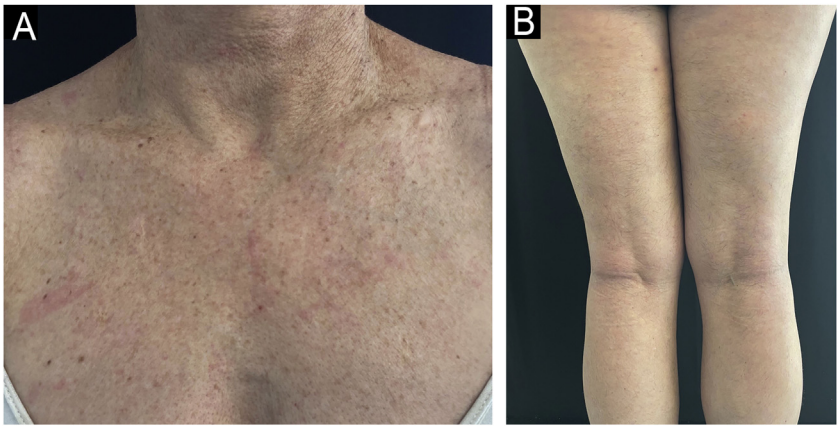

Fig. 4 Complete response of both dermatoses after initiation of adalimumab and discontinuation of acitretin at week-8 (A, pre-esternal region; B, legs).

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LETTER - CLINICAL

BLyS/APRIL dual inhibition by telitacicept for refractory pemphigus vulgaris combined with hepatocellular cancer☆

Dear Editor,

Pemphigus is a rare but potentially life-threatening autoimmune blistering disorder. Corticosteroids and immunosuppressive agents have been the conventional therapy. While some severe variants always fail to respond sufficiently.[1] Here, we presented a refractory pemphigus case combined with cancer, treated with telitacicept, a novel bioagent simultaneously targeting BLyS (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand),[2] achieving complete remission without tumor progression or secondary skin infections.

A woman in her 70 s had been diagnosed with pemphigus vulgaris from another hospital for 2-years, characterized by recurrent oral mucosal erosions, which had been effectively controlled with long-term oral prednisone (10 mg, Qd) treatment. Her skin histopathology and direct immunofluorescence were consistent with the diagnosis of pemphigus vulgaris, while indirect immunofluorescence using rat bladder epithelium didn't reveal IgG deposition (Fig. 1). She had a medical history of chronic hepatitis B, high blood pressure, diabetes mellitus, and multiple cavity effusions. Six months ago, she was given a diagnosis of hepatocellular carcinoma and received a curative left hepatectomy. The patient was doing well without any evidence of recurrence after surgery. Two months ago, she abruptly presented with severe blisters, erosions, exudations, and crusts, mainly affecting the waist, abdomen, inguinal, and vulva, and was admitted to our ward (Fig. 2). On admission, her pemphigus disease area index (PDAI) score was 21, and a culture of skin exudation revealed the presence of Proteus mirabilis. Given the patient's manifestations of infection, multiple antibiotics were administered. Despite receiving methylprednisolone (1.5 mg/kg/d), intravenous immunoglobulin (400 mg/kg/d, 5-days), meropenem, and plasma transfusion treatments for three weeks after admission, the lesions didn't improve. New blisters and purulent exudation appeared in her groin and back. As the initial therapy failed to control disease progression and combined with liver cancer, telitacicept (160 mg, once weekly) was added, which included systemic corticosteroids (methylprednisolone, 32 mg, Qd), but not anti-CD20 monoclonal antibodies mediated depletion of B-cells, considering that cancer and infections as its absolute contraindications. Following the addition of telitacicept, the patient's erythema, crusts, and exudation began to resolve, and the blister fluid was absorbed after three weeks of treatment. The disease activity was re-evaluated as mild (PDAI = 0) six weeks after being admitted to our ward. Furthermore, after four months of telitacicept treatment, no new blisters were observed, and the dose of methylprednisolone was gradually reduced to 12 mg/day, and telitacicept was reduced to a dose of 160 mg every two weeks. Enzyme-linked immunosorbent assay (MBL, Japan) revealed significantly reduced levels of both Desmoglein (Dsg) 1 and 3 (Fig. 3). No secondary skin infections or liver cancer progression were recorded.

In order to further interpret the reasons why the refractory case of pemphigus vulgaris responded positively to telitacicept without tumor progression or secondary skin infections, we analyzed the potential mechanisms of related drugs. The mechanism of telitacicept targets both BAFF and APRIL, largely eliminating long-lived plasma cells that have developed into potential autoantibody-producing cells and reducing autoantibody levels. However, the anti-CD20 antibodies mediate depletion of peripheral B cells but not long-lived plasma cells and may further exacerbate secondary infection.[3]

Unexpectedly, the lipid levels were found to be elevated, with LDL rising from 1.30 mmoL/L to 1.53 mmoL/L and TG level from 1.25 mmoL/L to 3.71 mmoL/L after telitacicept treatment. The same trend was seen in another two patients who also received telitacicept therapy (data not shown) and other literature published to date of which reported receiving telitacicept therapy (Table 1), although no adverse reactions causing elevated blood lipids were noted in Phase III clinical trials.[4] Further research is required to better understand the association between these findings.

As a new promising biological agent, telitacicept has expanded multiple therapeutic fields besides systemic lupus

☆ Study conducted at the Department of Dermatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

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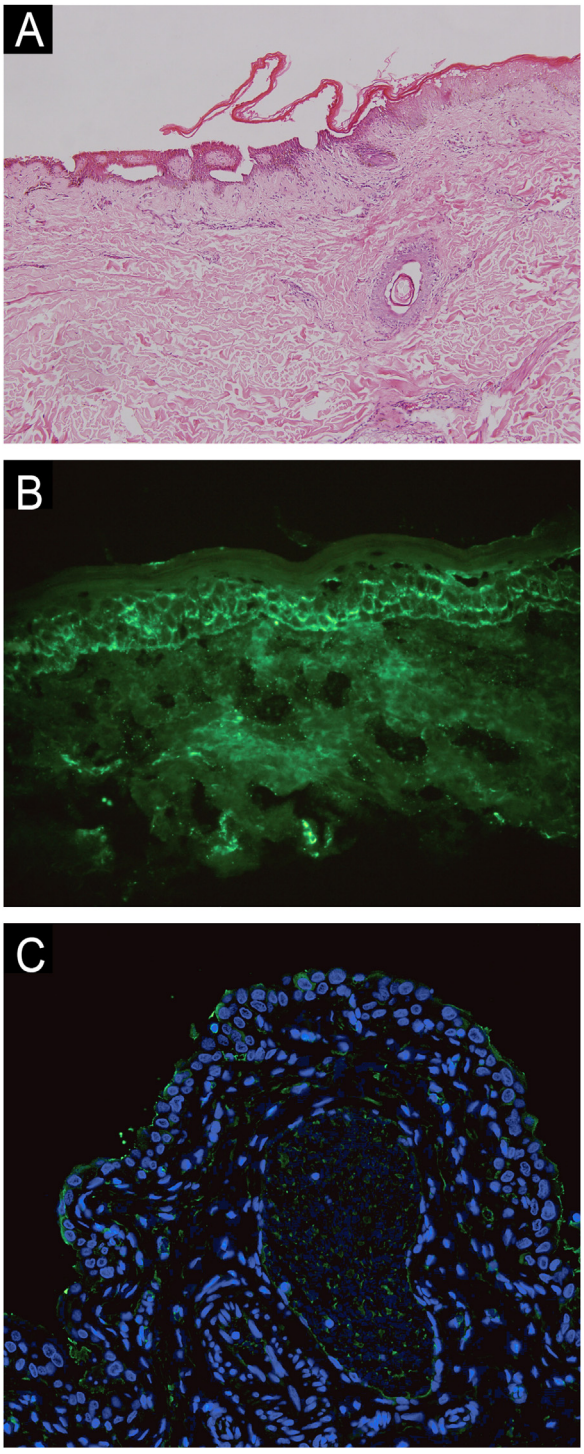

Fig. 1 (A) Histopathological examination on the abdomen lesions at first (Hematoxilyn & eosin, 100×). (B) Direct immunofluorescence showing intercellular deposition of IgG in the epidermis (400×). (C) Negative indirect immunofluorescence on a rat bladder epithelium (serum dilution 1:20, 40×).

erythematosus, and varied laboratory parameters were identified to predict its therapeutic response. To summarize clinical characteristics of patients after telitacicept therapy, we conducted a literature review, and the details were summarized in Table 1.[5–11] We found that some of the refractory cases whose pathogenesis are related to B-cells and autoantibody levels responded positively to telitacicept. Furthermore, in our case, a downward trend was noticed in her lymphocyte subsets and TNF-α level (Fig. 3), which can be released by B-cells,[12] and may contribute to the prediction of therapy response. Consistent with our results, in the IgG4-related disease, patients who presented with better therapeutic response to telitacicept had relatively higher levels of serum immunoglobulin and plasmablast at baseline. All the data indicated that B-lymphocyte subsets, inflammatory cytokine, and antibody secreted by B-cells provided a potential predictor for the therapy response, although more cases needed to be intaken.

To the best of our knowledge, this study represents the first exploration of the therapeutic potential of BLyS/APRIL-targeting biologics in treating refractory cases of pemphigus vulgaris accompanied by skin infection and cancer. It also showed a good safety profile for telitacicept, used to treat elderly patients with tumors. Larger sample size studies are necessary to optimize dosage and duration in the future.

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Ethics statement

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

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Authors' contributions

Yamin Zhang: Contributed to the conception and design of the study; Contributed to obtaining, analyzing and interpreting data; Engaged in intellectual participation in the propaedeutic and/or therapeutic management of the studied cases; Conducted a critical review of the literature; Provided final approval of the manuscript's final version.

Weiyu Chen: Participated in data collection, as well as the analysis and interpretation of data; Performed the statistical analysis; were involved in writing the article or critically reviewing its important intellectual content; Contributed to obtaining, analyzing and interpreting data; Effectively participated in supervising the research; Engaged in intellectual participation in the propaedeutic and/or therapeutic management of the studied cases.

Jian Xu: Participated in data collection, as well as the analysis and interpretation of data; Performed the statistical analysis; was involved in writing the article or critically reviewing its important intellectual content; Contributed to obtaining, analyzing, and interpreting data; Effectively participated in supervising the research.

Table 1 Reported cases in the literatures with the use of telitacicept.

Year	Diseases	Sample size	Age (y)	Sex (F/T)	Previous therapies	Concomitant therapies	Time for improvement (w)	Adverse events	Change from baseline in laboratory parameters to predict good prognosis			Ref.
									Cells subsets	Immunoglobulin	Others	
2023	IgG4-RD	9	51.5 median (ranged from 25 to 71)	2/9	A prospective single-arm clinical trial	None	4 (other 8 patients arrive a partial remission rate of 60%)	Injection site reaction, elevated LDL, elevated TG, lymphopenia	CD24- plasmablasts	IgG4, IgG, IgA, IgM, IgE	C3, C4, Cr, eGFR	[6]
2022	IgAN	44	37.0 (SD = 8.55)	21/44	Systemic corticosteroid therapy, other immunosuppressant therapy	Details unmentioned	4	Injection site reactions, upper respiratory tract infection	None	IgA, IgG, IgM	Proteinuria, eGFR	[7]
2023	GPA	1	64	0/1	Methylprednisolone sodium succinate, immunoproteins	CYC, prednisone	1	Upper respiratory tract infection	None	IgA, IgG, IgM	CRP, ESR, CREA, BUN	[8]
2023	MN	1	50	0/1	CYC, prednisone, rituximab, MMF, tacrolimus	Prednisone	4	Unmentioned	CD20 cells	None	Proteinuria, eGFR, serum albumin	[9]
2023	pSS	42	49.4 median	40/42	Hydroxychloroquine sulphf	Details unmentioned	4	Local injection reaction, acute pyelonephritis, leukopoenia, infection	None	IgA, IgG, IgM	C3, C4	[10]
2024	MG	2	64–70	1/2	IVIg, plasma exchange, prednisone, tacrolimus, pyridostigmine, thymectomy	Prednisone, tacrolimus, pyridostigmine	2	Unmentioned	Memory B cells, plasmablasts, plasma cells	IgG	APRIL, BLyS, BCMA, AChR-Ab	[11]
2023	NF155 + AN	1	14	1/1	MMF, rituximab, plasma exchange, steroid, immunoadsorption	Details unmentioned	1	Unmentioned	Plasmablasts	None	anti-NF155	[12]

y, year; F, Female; T, Total; w, week; Ref., Reference; IgG4-RD, IgG4-Related Disease; IgAN, IgA Nephropathy; GPA, Granulomatous Polyangiitis; MN, Membranous Nephropathy; pSS, Primary Sjögren's Syndrome; MG, Myasthenia Gravis; NF155 + AN, NF155+Autoimmune nodopathy; CYC, Cyclophosphamide; MMF, Mycophenolate Mofetil; IVIg, Intravenous Immunoglobulin; LDL, Low Density Lipoprotein; TG, Triglyceride; eGFR, Estimated Glomerular Filtration Rate; Cr/CREA, Creatinine; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; BUN, Blood Urea Nitrogen; BCMA, B-Cell Maturation Antigen; AChR-Ab, Acetylcholine Receptor Antibody.

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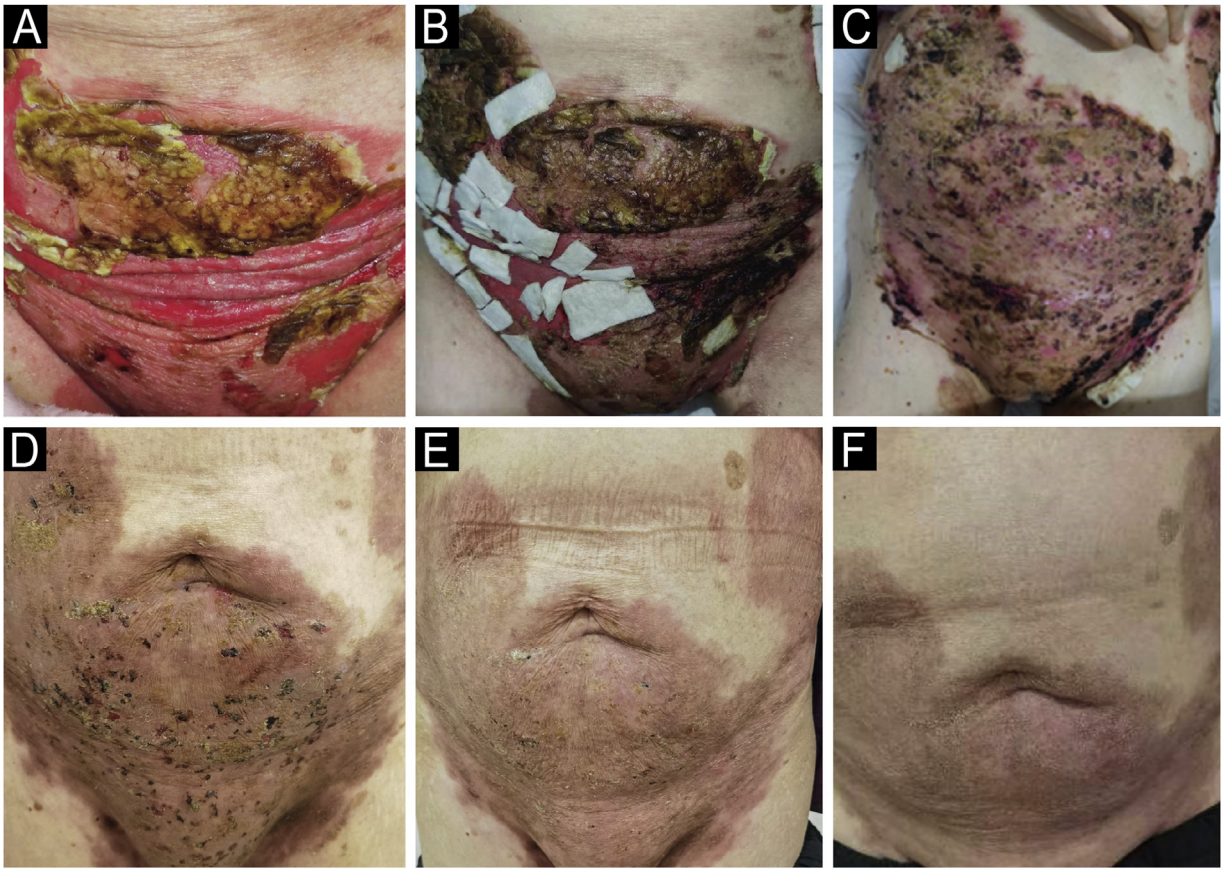

Fig. 2 Clinical presentation in refractory patient of pemphigus vulgaris before and after telitacicept therapy. (A) On admission, (B) 2-weeks, (C) 3-weeks, (D) 6-weeks, (E) 10-weeks, (F) 18-weeks.

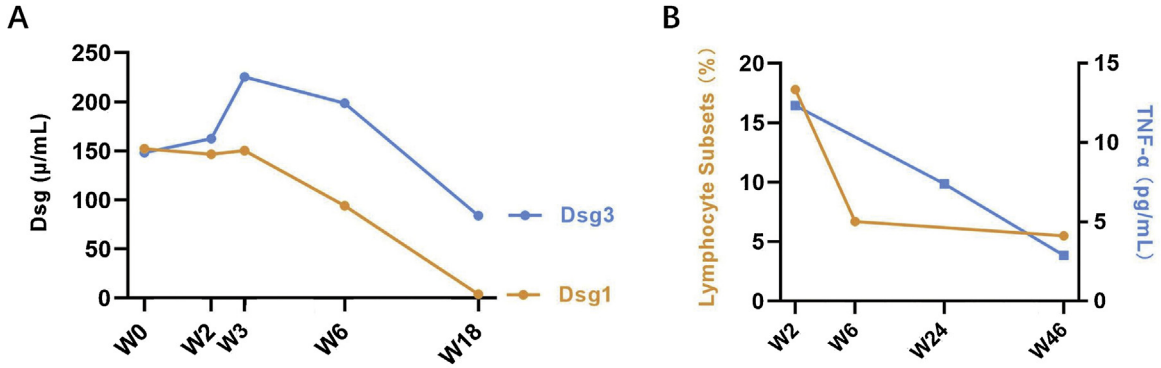

Fig. 3 (A) Serum Dsg1 and Dsg3 levels in refractory patient of pemphigus vulgaris treated with telitacicept (Enzyme-Linked Immunosorbent Assay, MBL, Japan). (B) Lymphocyte subsets and TNF-α levels in refractory patient of pemphigus vulgaris treated with telitacicept. The quantification of lymphocyte subsets were done with Automated Hematology Analyzer (mindray, C-760 CS). The TNF-α level was detected by human TNF-α (Tumor Necrosis Factor Alpha) ELISA Kit.

Research data availability

Does not apply.

Conflicts of interest

None declared.

Editor

Ana Maria Roselino.

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LETTER – CLINICAL

Cocaine-induced midline destructive lesion with extensive cutaneous involvement☆

Dear Editor,

It is described in the literature that cocaine use is responsible for the development of an entity called cocaine-induced midline destructive lesion (CIMDL).[1] This report describes the case of a 34-year-old female patient, a chronic cocaine user, who developed CIMDL with extensive cutaneous involvement over a period of eight months, presenting with symptoms such as rhinorrhea and local pruritus before the appearance of a well-defined, painful necrotic ulcer, located from the nasal columella to the philtrum (Fig. 1). After one month of evolution, the ulcer showed involvement of the orbicularis oris muscle, extending to the semi-mucosa of the upper lip (Fig. 2). The patient used cocaine occasionally. Initially, the hypotheses of Wegener's granulomatosis, cutaneous leishmaniasis, and nasal NK/T-cell lymphoma were raised. Complementary tests showed negative p-ANCA and c-ANCA tests. Kidney and liver function tests and blood count were normal. No imaging tests were performed. Histopathology revealed extensive necrosis affecting the epidermis and subcutaneous planes, without signs of vasculitis or malignancy (Fig. 3). After complementary examinations, the diagnosis of this pathology was made. A multidisciplinary approach was carried out with psychiatry and stomatology, and hospital admission was performed, with debridement of the ulcer, in addition to supportive measures and cocaine abstinence, with the patient showing significant clinical improvement of the lesion (Fig. 4).

Cocaine is a psychoactive drug; its use can become abusive and trigger numerous consequences for the human body through a mechanism of inflammation and nasal necrosis of multifactorial cause, involving a local ischemic vasoconstrictor effect, with one of its complications being the emergence of CIMDL.[1] Therefore, there is greater susceptibility to structural damage to the mucosa and bone and cartilage structures, with involvement of the nasal septum, hard palate, maxillary bone, and anterior base of the skull.[2] Consequently, these extensive deformities of the nose and midface can cause chronic damage and loss of structural support of the facial midline.[2] The prevalence of CIMDL in cocaine users is 4.8%.[3] However, its cutaneous dissemination is rare. The case described here stands out from the others due to the extensive cutaneous involvement. The literature review showed only one similar case described, reported by Sevinsky in 1995.[4] The case reported herein exhibited extensive and deep cutaneous involvement, evolving with destruction of the nasal septum.

In 1995, Sevinsky et al. reported a case of a male patient, a chronic cocaine user, who developed CIMDL after intranasal use of the substance.[4] In the reported case, there

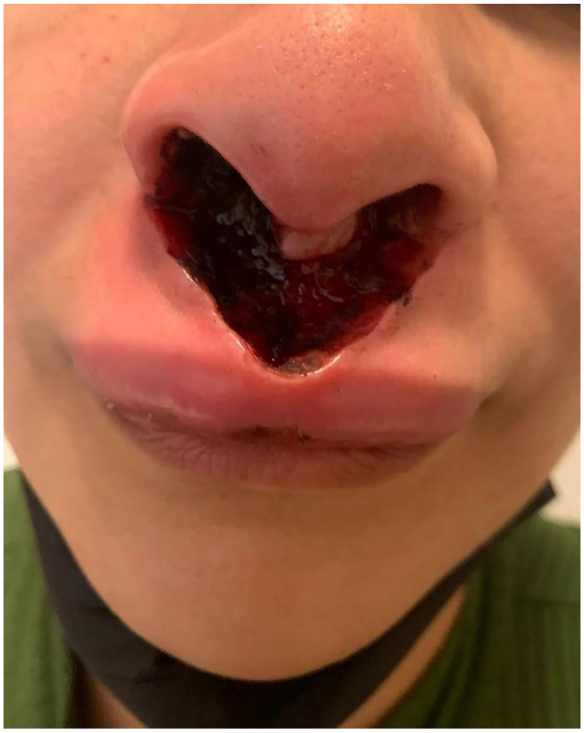

Fig. 1 Well-defined necrotic ulcer, located from the nasal columella to the philtrum.

☆ Study conducted at the Centro de Estudos Dermatológicos do Recife, Santa Casa de Misericórdia, Recife, PE, Brazil.

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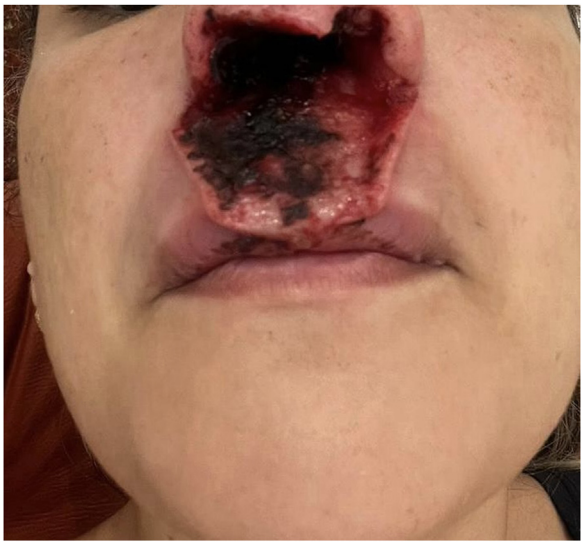

Fig. 2 Necrotic ulcer affecting the orbicularis oris muscle and extending to the submucosa of the upper lip.

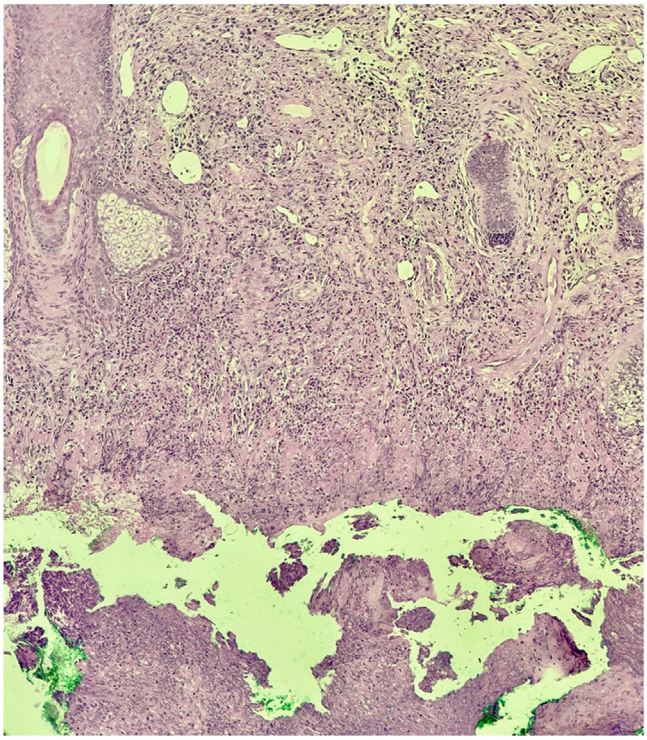

Fig. 3 Necrotic area evident in the deep dermis. (Hematoxylin & eosin, ×100).

was significant cutaneous involvement with total destruction of the nasal septum.

In 2022, Nitro et al. published a systematic review in which they systematized the prevalence of CIMDL involvement sites; 17 studies with a total of 127 patients were eligible. Destruction of the nasal septum occurred in 99.2% of cases. The prevalence of distribution decreased from the lower third of the nasosinusal complex (nasal floor and inferolateral nasal wall, respectively, 59% and 29.9% of

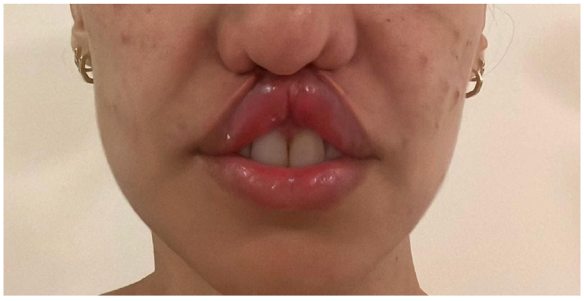

Fig. 4 Significant retraction of the upper lip with loss of the philtrum and relevant aesthetic impairment after hospitalization.

patients) to the middle third (middle turbinate and ethmoid; 22.8% of patients) and, finally, to neurocranial structures (7.9% of patients). The authors also proposed a classification based on the distribution patterns of CIMDL. For this purpose, the nasosinusal district was ideally subdivided into four parts that are progressively less involved by cocaine-related lesions, thus allowing grading of the extent of CIMDL. The prevalence of univocal lesions observed is most frequent at the level of the nasal septum (corresponding to Grade 1). The prevalence of invasion progressively decreases in the lower portion of the nasosinusal cavities (palate and/or inferior turbinate, maxillary bone and nasolacrimal duct (Grade 2); therefore, the prevalence reduces even further towards the ethmoid structures (Grade 3) and reaches its lowest prevalence for neurocranial invasion (lamina papyracea, orbit and/or base of the skull; Grade 4).

Given the extensive involvement, it is essential to broaden the understanding of the pathology and to publish reports similar to this case to have a better understanding of this entity, and consequently, an increasingly early diagnosis and, therefore, improve the clinical outcome for those with this condition.

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orientation; approval of the final version of the manuscript.

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Daniela Mayumi Takano: Conception, analysis, and interpretation of data; approval of the final version of the manuscript.

Research data availability

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Conflicts of interest

None declared.

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LETTER - CLINICAL

Cutaneous metastasis of primary urothelial ureteral cancer: an exceptional case with atypical presentation☆

Dear Editor,

Cutaneous metastases are an infrequent manifestation of internal malignancies, with an estimated incidence of 2.9%.[1] Skin involvement in urothelial carcinomas is exceptional, occurring in approximately 1% of cases, either concomitantly with or up to one year after the diagnosis of the primary tumor. Its relevance lies in the ominous survival prognosis it implies if confirmed.[1]

We report the case of an 87-year-old man with a history of right testicular seminoma treated with orchiectomy and underlying alcoholic liver cirrhosis, who presented with one year of recurrent hematuria. A CT urogram revealed a dilatation and an emptying defect in the proximal third of the left ureter, which was suggestive of urothelial carcinoma. Due to the COVID-19 pandemic, the patient returned two years later with a painful, progressively enlarging mass in the left pubic region adjacent to the base of the penis, without bleeding or discharge.

He was referred to the Dermatology Department, where physical examination revealed a pink, exophytic tumor with well-defined borders and surface scaling, measuring 2.5 × 2.0 cm (Fig. 1A). Dermoscopic evaluation showed a central keratin mass on a pink, structureless background, accompanied by white clods, erosions, and sparse fine irregular linear vessels (Fig. 1B). Based on these features, a provisional diagnosis of squamous cell carcinoma was made. However, excisional biopsy followed by histopathological examination revealed an undifferentiated carcinoma (Fig. 2), with positive immunohistochemical staining for GATA-3 (clone L50-823; Fig. 3) and negative staining for CK7 (clone SP52), CK20 (clone SP33), vimentin (clone V9), S-100 (clone 4C4.9), and OCT-4 (clone MRQ-10), findings consistent with a urothelial origin. A subsequent radi-

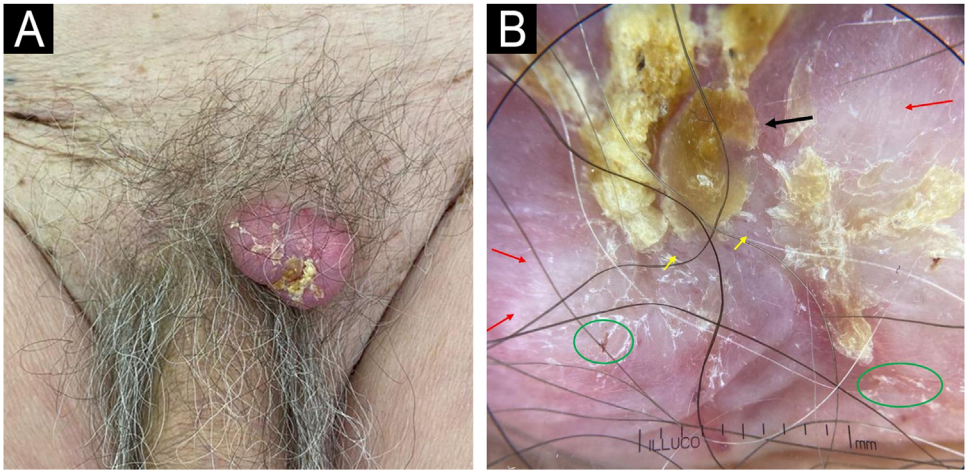

Figure 1 (A) Clinical image: Erythematous tumor with surface scaling located in the pubic region. (B) Dermoscopic image: Central keratin mass (black arrows), whitish areas (red arrows), erosions (green circle), and irregular, fine linear vessels (yellow arrow). (Illuco IDSfe-1100, 10×, polarized mode).

☆ Study conducted at the Hospital del Salvador, Santiago, Chile.

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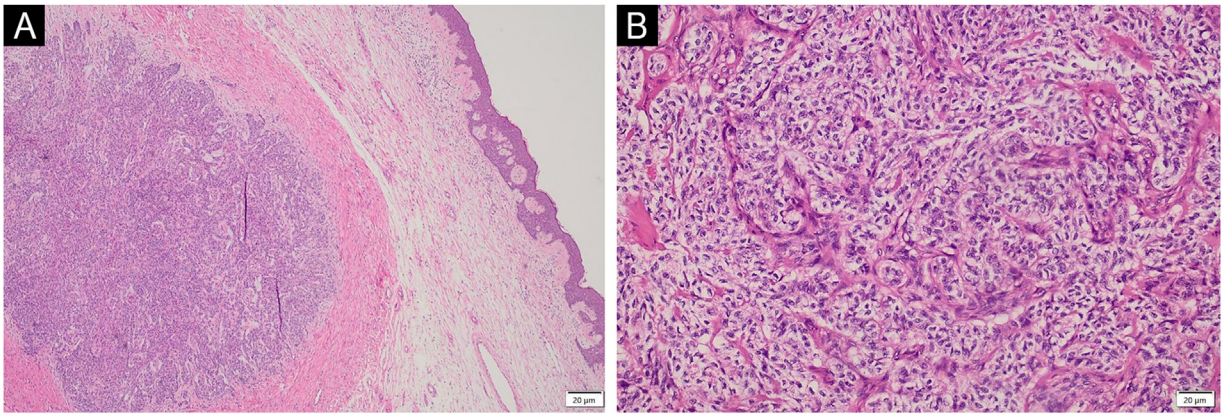

Figure 2 Histopathological study: (A) The epidermis shows hyperkeratosis and parakeratosis. A neoplasm arranged in nests infiltrates the dermis and hypodermis (Hematoxylin & eosin, 4×). (B) The neoplasm is composed of large cells with a high nucleus-to-cytoplasm ratio, moderate pleomorphism, and irregular nuclei. Up to five mitotic figures are observed per 10 high-power fields (Hematoxylin & eosin, 20×).

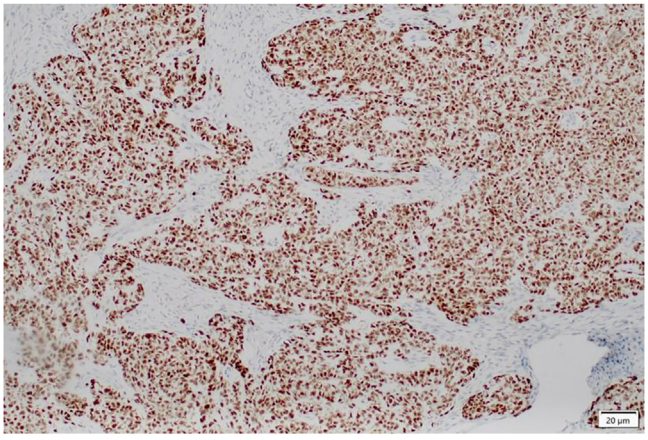

Figure 3 Immunohistochemistry: tumor cells show positive staining for GATA-3.

cal nephroureterectomy confirmed a high-grade papillary urothelial carcinoma with probable lamina propria invasion, thus confirming the primary tumor.

Bladder cancer is the ninth most common cancer worldwide and the thirteenth leading cause of cancer-related mortality, with an incidence rate of 5.6 per 100,000 individuals.[2] Approximately 90% of urothelial carcinomas arise from the epithelium lining the urethra, bladder, ureters, and renal pelvis. The 5-year survival rate reaches 96% when diagnosed in early stages, but drops dramatically to 4.6% in the presence of metastases.[3] These occur in about 5% of cases and typically affect the lymph nodes, bone, liver, and lungs.

Cutaneous metastases from urothelial carcinomas are rare, with bladder cancer accounting for approximately 0.84% of all cutaneous metastases.[4,5] Dissemination may occur via direct extension, lymphatic or hematogenous spread, or iatrogenic implantation during surgery – the latter being the most frequently reported mechanism.[3,6] Risk factors include muscle invasion, high histologic grade, poor differentiation, and large tumor size.[7] Clinically, three patterns of presentation have been described: infiltrative plaques or nodules, sclerotic lesions, and inflammatory-appearing lesions.[8] The classic manifestation is a multinodular plaque on the anterior abdominal wall.[9]

Diagnosis is confirmed by histological examination with immunohistochemical support, with GATA-3 serving as a reliable marker of urothelial origin. Coexpression of CK7 and CK20 is observed in 89% of cases,[7] while Uroplakin III positivity has been reported in 50%–80% of cutaneous metastases from urothelial carcinomas.[1] First-line treatment is surgical, when possible, and the first-line chemotherapy typically consists of gemcitabine/cisplatin-based chemotherapy, with methotrexate/vinblastine/doxorubicin/cisplatin as a second-line option.[6,10]

In conclusion, reports of cutaneous metastases from urothelial carcinoma are scarce and mostly limited to bladder cancer. To our knowledge, no previous cases of cutaneous metastasis originating from a ureteral urothelial carcinoma have been reported. Clinical presentation is often nonspecific and can mimic primary skin malignancies, inflammatory conditions, or other dermatoses.[9] Accurate identification of these lesions and other potential metastatic sites is essential, as the prognosis remains poor regardless of the treatment, which is typically palliative.[6,9]

This case represents the first report of a cutaneous metastasis from a primary ureteral urothelial carcinoma. Notably, its clinical presentation mimicked a squamous cell carcinoma, diverging from the classic description of anterior abdominal wall multinodular plaques.

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Jonathan Stevens Gonzalez: Data collection; writing of the manuscript and critical review of important intellectual content; intellectual participation in the therapeutic conduct of the studied case; critical review of the literature; final approval of the final version of the manuscript.

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Cecilia Jeraldo Romero: Data collection; writing of the manuscript and critical review of important intellectual content; intellectual participation in the therapeutic conduct of the studied case; critical review of the literature; final approval of the final version of the manuscript.

Conflicts of interest

None declared.

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LETTER - CLINICAL

Dermoscopic rainbow pattern in malignant blue nevus☆

Dear Editor,

A 74-year-old female patient presented with a 5-cm diameter grayish-blue nodule on her left buttock (Fig. 1). Dermoscopy revealed a bluish background, rainbow pattern, and bright white structures surrounding an ulcerated area. Polymorphic vessels and white, black, and red coloration were observed. The patient reported that the lesion had been present since birth, with accelerated growth over the past two years (Fig. 2). Histopathological examination revealed mitotic figures, including atypical mitoses, and involvement of nerve fibers in the deep reticular dermis (Fig. 3). Intense cellularity was observed, represented by the proliferation of atypical dendritic melanocytes, marked nuclear polymorphism, and hyperchromasia (Fig. 4).

The term ''malignant blue nevus'' (MBN) refers to a rare and aggressive subtype of melanoma described by Allen and Spitz in 1953. This type of melanoma can originate from a pre-existing blue nevus (BN), particularly a cellular BN, although less frequently it can arise from a common BN. In addition, the MBN can manifest *de novo*, with an appearance similar to a BN.[1]

MBN occurs in typical BN areas: scalp, face, and buttocks. It is more common in the elderly, with a predominance in males. Clinically, it presents as blue or black nodules or plaques and may ulcerate as it evolves. Late diagnosis is a determining factor for the aggressive behavior of MBN, which translates into a greater likelihood of metastasis and mortality.[2,3]

In a retrospective epidemiological study on MBN conducted in 2023, Yumeen et al. reported this aggressive behavior with a predisposition to metastasis, especially to lymph nodes and lungs. This finding corroborates initial studies of the tumor but diverges from the results of a case series published in 2009, which found no significant differences in the behavior of MBN and melanoma.[3,4]

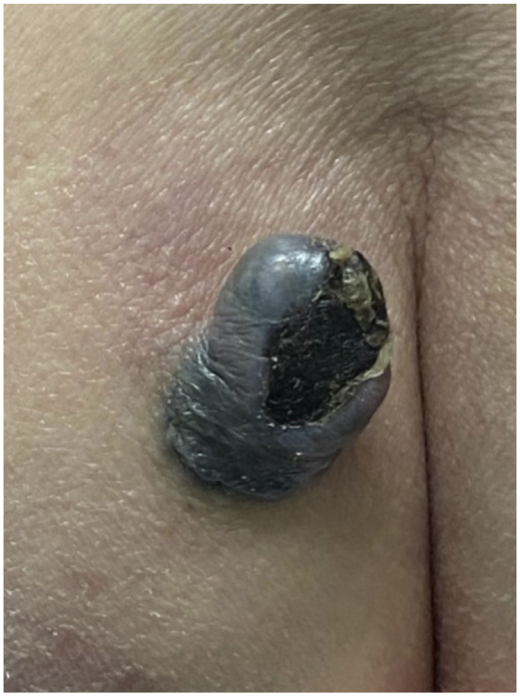

Fig. 1 Exophytic nodule, bluish in color, with central ulceration and a discrete area of irregular, blackened spot at the base, measuring approximately 5 cm in diameter at its longest axis, located on the left buttock. Erythema is also observed at the upper left pole of the lesion.

Although the dermoscopic findings of MBN are not widely described in the literature, it shares characteristics of melanoma and BN. This makes dermoscopic differentiation from pigmented lesions challenging.[1] The presence of bright white lines, polymorphic vessels, asymmetrical distribution of blue coloration, bluish globules at the lesion periphery, gray color, blue-gray veil, multiple colors, and chaotic pattern (which may reflect asymmetry in structures or color) is indicative of malignancy.[5,6]

The ''blue and black'' rule described by Argenziano et al., originally formulated to facilitate the diagnosis of nodular melanoma, states that the presence of both colors in at least 10% of the lesion extent has a positive predictive value of 90% for malignancy. The clinical case

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

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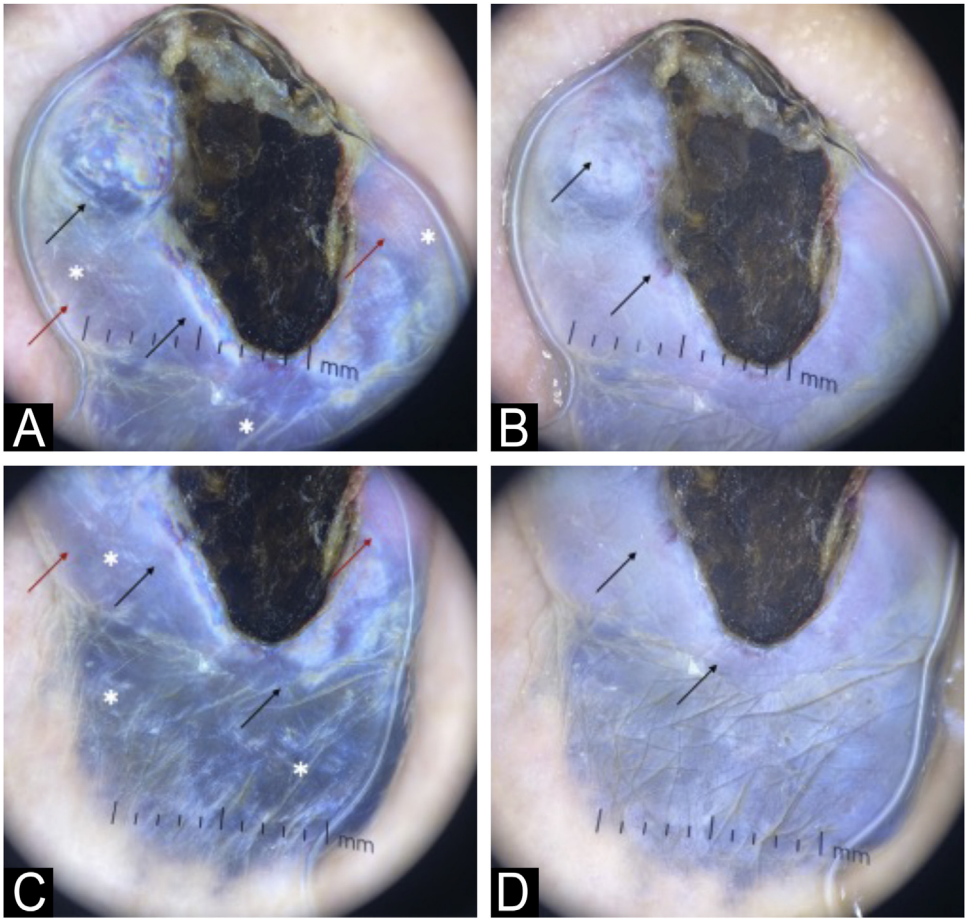

Fig. 2 (A) Dermoscopy (×10) with polarized light: Upper pole of the lesion showing a diffuse, exuberant rainbow pattern (black arrow) over a bluish area interspersed with reddish-white areas (red arrow). Bright white structures (white asterisk) are present throughout the region. A serohematic structure is observed in the center. (B) Dermoscopy (×10) with immersion, non-polarized light: Upper pole of the lesion showing a bluish area, with evident polymorphic vessels (black arrow). (C) Dermoscopy (×10) with polarized light: Lower pole of the lesion showing a diffuse, exuberant rainbow pattern (black arrow) over a bluish area interspersed with reddish-white areas (red arrow). Bright white structures (white asterisk) are present throughout the region. A serohematic structure is observed in the center. A poorly defined and irregular area is observed in the most distal portion. (D) Dermoscopy (×10) with immersion, non-polarized light: Lower pole of the lesion showing a bluish area, with polymorphic vessels (black arrow) and in the most distal portion of the lesion, a poorly defined and irregular area.

described, in addition to fitting the ''blue and black'' rule, shows polymorphic vessels, which strengthens the suspicion of malignancy.[7]

The histopathological correlate of the rainbow pattern on dermoscopy is not yet fully elucidated. It is suggested that it is related to the heterogeneity of the dermal layers, which interfere with the absorption, reflection and transmission of polarized light, resulting in the observed color spectrum.[8–10] In cases such as the present one, intense cellularity may contribute to this phenomenon.

The rainbow pattern was initially described in Kaposi's sarcoma, characterized by the presence of multiple colors visible under polarized light dermoscopy. Its origin is attributed to the phenomenon of light diffraction, that is, the ability of waves to bend around obstacles. However, this finding has been identified in several other conditions, such as stasis dermatitis, lichen planus, hemosiderotic dermatofibroma, blue nevus, and melanoma. Although it may be present in invasive melanomas, the rainbow pattern, alone, is not indicative of malignancy. However, when associated with specific dermoscopic criteria, it may suggest tumor invasion.[8–10]

The most recent theory proposes that the rainbow pattern observed in dermoscopy is related to the phenomenon of dichroism. Unlike diffraction, dichroism is the property of certain substances to absorb polarized light differently depending on the direction of incidence. This results in different colors depending on the angle of observation. In dermoscopy, this effect can occur in structures with heterogeneous organization and specific orientation, which interact unevenly with polarized light, generating the multicolored spectrum characteristic of the rainbow pattern.[9]

The history of congenital lesions suggests that the MBN arose as a malignant transformation of a previous BN. The case described illustrates an unusual dermoscopic finding, reinforcing the importance of thorough evaluation of pigmented nodular lesions.

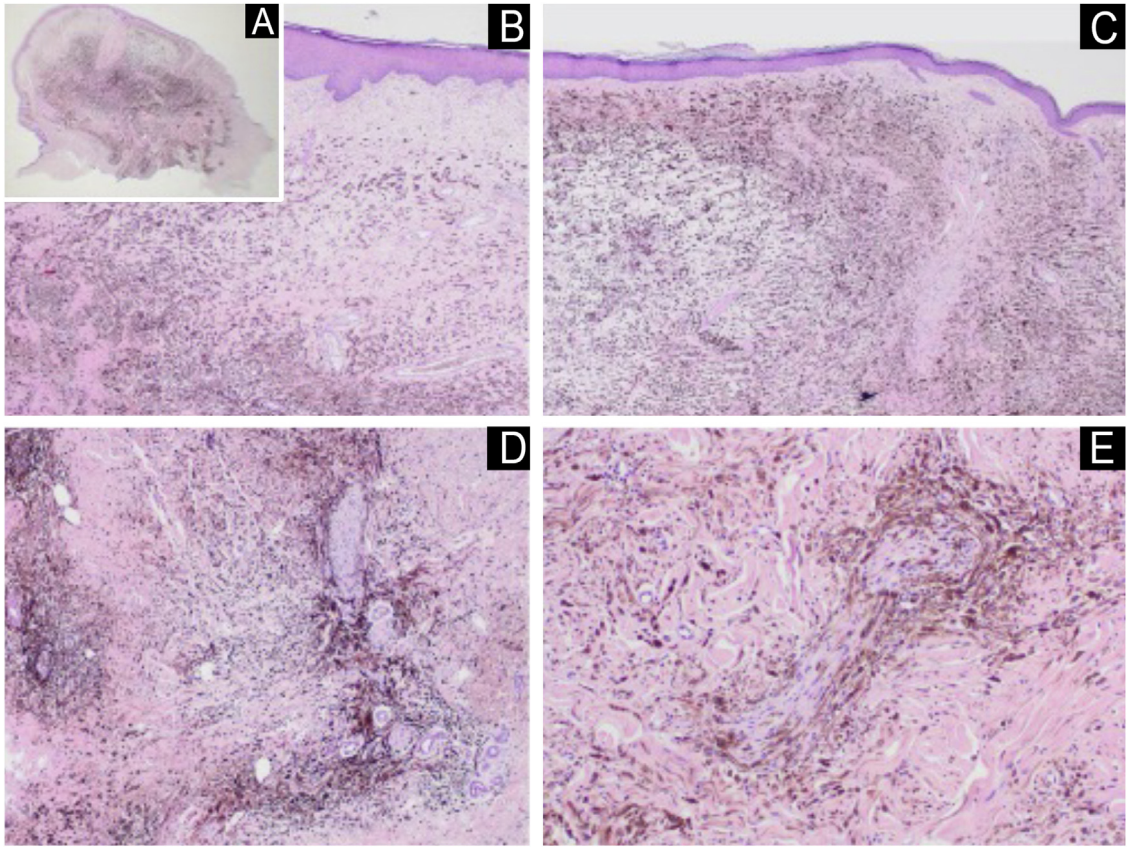

Fig. 3 (A) Panoramic view of the lesion showing its polypoid aspect. (B and C) They show diffuse proliferation of isolated dendritic melanocytes, distributed in an isolated manner among collagen fibers or forming bundles, occupying the entire dermis, without compromising the epidermis and with a compromised deep margin. (D) Proliferation of melanocytes involving cutaneous appendages, diffuse proliferation of isolated dendritic melanocytes, distributed in an isolated manner or forming bundles, without compromising the epidermis and with a compromised deep margin (Hematoxylin & eosin, ×20). (E) This melanocytic proliferation compromises nerve fibers of the deep reticular dermis (Hematoxylin & eosin, ×20).

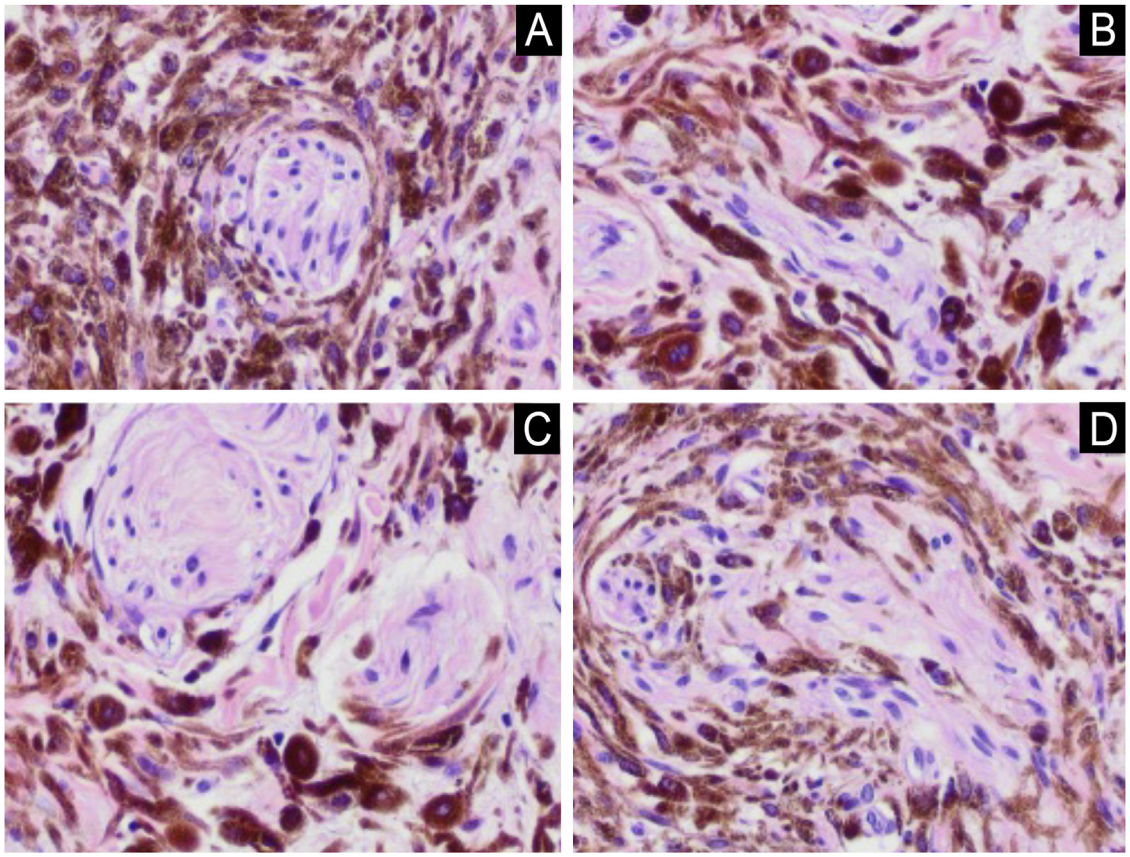

Fig. 4 In detail, atypical dendritic melanocytes are noted, with a marked degree of nuclear polymorphism and hyperchromasia, and infiltrating nerve fibers in Figures A, B, C and D (Hematoxylin & eosin, ×100).

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LETTER - CLINICAL

Encephalocraniocutaneous lipomatosis: a rare and sporadic phakomatosis☆

Dear Editor,

Encephalocraniocutaneous Lipomatosis (ECCL), also known as Haberland Syndrome, is a rare and sporadic genetic condition characterized by congenital alterations that simultaneously affect the skin, eyes, and central nervous system.[1,2] This association of manifestations in different systems reflects its inclusion in the group of phakomatoses, a heterogeneous set of genetic diseases that share cutaneous, ophthalmological, and neurological anomalies, frequently accompanied by developmental dysplasias and a predisposition to the emergence of tumors.[3]

The pathogenesis is attributed to post-zygotic somatic mutations in genes such as FGFR1, KRAS, and NRAS, which promote aberrant activation of the RAS-MAPK signaling pathway. This process results in mosaicism and ectodermal dysgenesis, explaining the asymmetrical distribution and heterogeneity of clinical manifestations.[2] Genetic alterations also compromise vasculogenesis, favoring the presence of dysmorphic intracranial vessels, in addition to predisposing to the development of mesenchymal tumors, such as lipomas. One of the most characteristic skin lesions is nevus psiloliparus—a patch of softened alopecia, prefer-

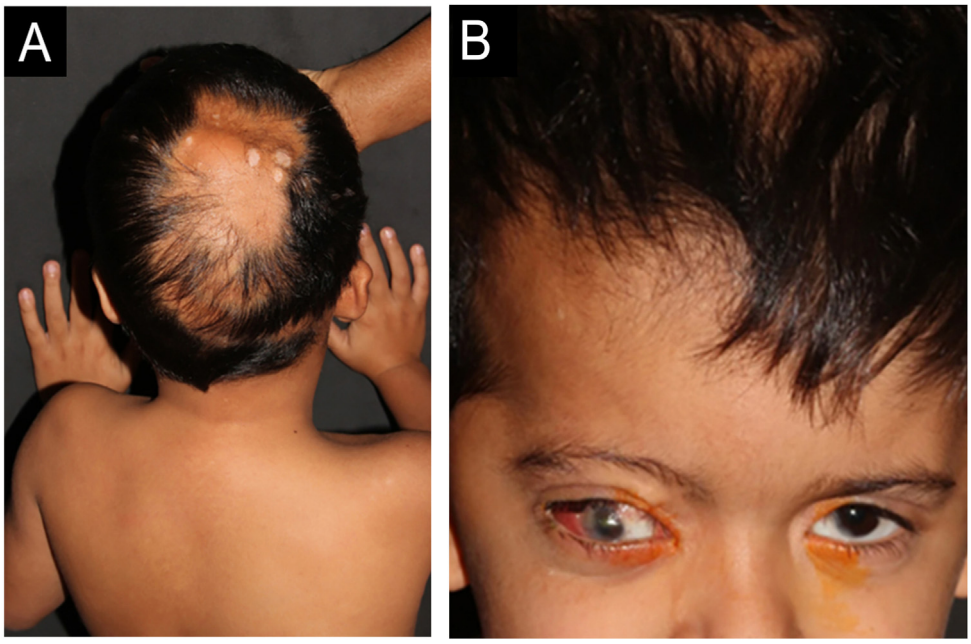

Fig. 1 (A) Aplasia cutis over a normochromic alopecia patch in the vertex region; (B) Ipsilateral ocular lipodermoids and low-set right ear.

☆ Study conducted at the Department of Dermatology, Faculdade de Medicina, Hospital das Clínicas, Universidade de São Paulo, São Paulo, SP, Brazil.

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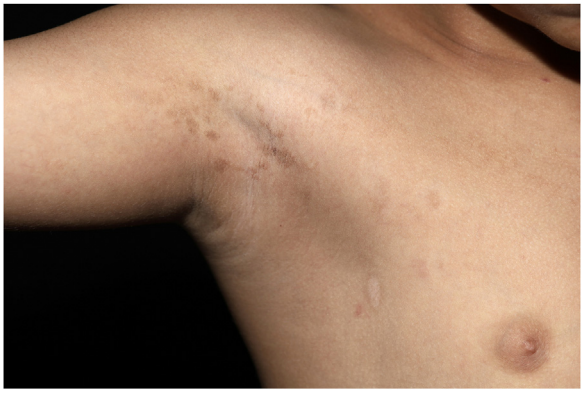

Fig. 2 Axillary freckles ipsilateral to ocular and neurological findings.

entially located on the scalp, consisting of ectopic mature adipose tissue in the dermis and absence of hair follicles and cutaneous appendages.[2,4] Due to the sharing of the RAS-MAPK pathway with other RASopathies, such as Neurofibromatosis type 1 (NF1), it is possible to observe some similar cutaneous findings in ECCL, such as café-au-lait spots.[1,2] This report identified axillary freckles, a finding not yet documented in cases of ECCL, but which can be explained by the same pathogenic mechanism. The diagnosis of ECCL is challenging due to the wide spectrum of clinical presentations and the rarity of the condition, often requiring a high degree of clinical suspicion and a multidisciplinary approach for confirmation.

A five-year-old male patient was referred to the pediatric dermatology clinic with patches of alopecia on the scalp, especially in the vertex and right parietal regions, accompanied by ocular anomalies present since birth. There was also a history of delayed neuropsychomotor development, episodes of seizures, behavioral changes, and a diagnosis of hydrocephalus at three months of age, requiring a ventriculoperitoneal shunt. In addition, the patient was under ophthalmological follow-up, having already undergone ocular surgery for partial excision of epibulbar lipodermoid—a benign congenital ocular choristoma, that is, a malformation consisting of normal tissue in an anomalous location, in this case, ectopic adipose tissue in the bulbar conjunctiva (Fig. 1).

On physical examination, a heterogeneous alopecic plaque was identified on the scalp, located in the vertex region, with areas of atrophy and others with a softened consistency, similar to adipose tissue, with a clinical appearance compatible with nevus psiloliparus (Fig. 1). The histopathology of one portion of the lesion was suggestive of aplasia cutis. The presence of freckles in the axillary region ipsilateral to the ocular and neurological findings was also observed (Fig. 2). Other anomalies, such as craniosynostosis of the sagittal suture, short stature, low hairline in a V̈shape in the posterior cervical region, low-set right ear with a folded helix, thin lips with eversion of the upper lip, and overlapping fingers, compatible with clinodactyly, were also evidenced. Magnetic resonance imaging (MRI) revealed multiple intracranial lipomas, as well as thickening of the tissue corresponding clinically to the area of alopecia (Fig. 3) in the right frontoparietal region. Based on the clinical picture, histopathological findings, and MRI results, a diagnosis of ECCL was made.

ECCL represents a distinct clinical and genetic neurocutaneous phenotype, characterized by dermatological, ocular, and neurological alterations. Definitive diagnosis of the disease is based on major and minor criteria, distributed among the three affected systems (Table 1).[5,6] The condition belongs to the group of RASopathies, a set of genetic syndromes caused by mutations in genes that regulate the RAS-MAPK signaling pathway.[2] These conditions share similar molecular mechanisms and may show overlapping clinical manifestations. Café-au-lait spots, already described in cases of ECCL, are also present in other RASopathies, such as NF1 and cardiofaciocutaneous syndrome.[7] Additionally, axillary freckles were observed, a manifestation not yet documented in association with ECCL, but which could be explained by the same pathogenic mechanism. This pattern is observed in other RASopathies, such as Neurofibromatosis-Noonan syndrome, NF1, and Legius syndrome, reinforcing

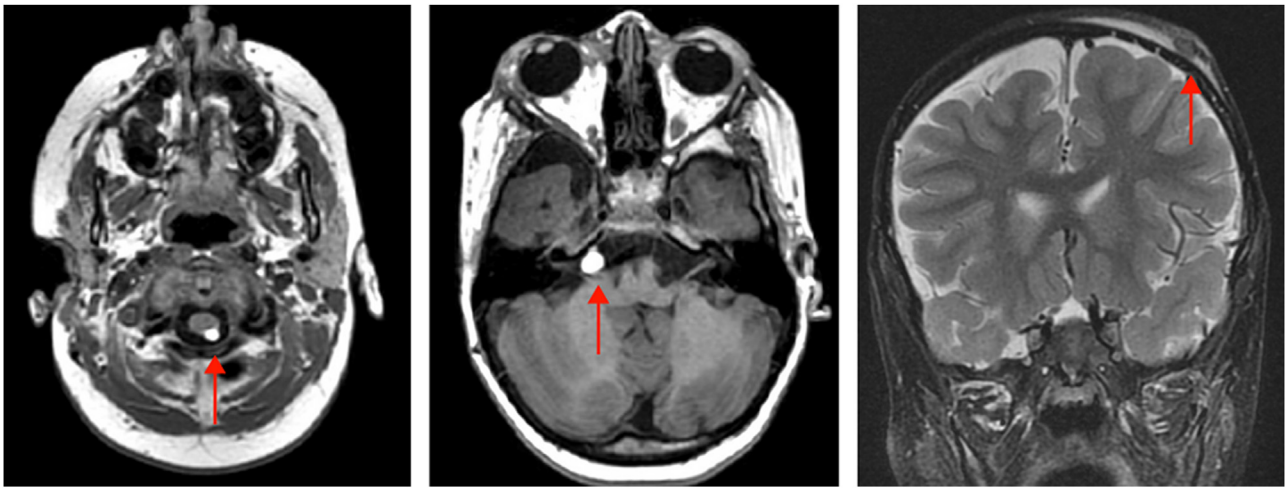

Fig. 3 MRI demonstrating a lipoma in the right pontocerebellar cistern and a lipoma posterior to the cervical spinal cord. Subcutaneous tissue thickening is also observed in the right frontoparietal region, clinically corresponding to the alopecia area.

Table 1 ECCL.

System	Major Criteria	Minor Criteria	Patient Findings
Eyes	1 Choristoma, with or without associated anomalies.	2 Corneal or other anterior chamber anomalies 3 Ocular or palpebral coloboma 4 Calcification of the eyeball	Choristoma (major), coloboma (minor)
Skin	1 Confirmed nevus psiloliparus (NP) 2 Possible NP and ≥ 1 of the minor cutaneous criteria (criteria 2–5) 3 ≥2 minor criteria among criteria 2–5	1 Irregular or banded alopecia, non-scarring 2 Subcutaneous lipoma(s) in the frontotemporal region 3 Focal aplasia/hypoplasia of the skin on the scalp 4 Small nodular lesions on the skin of the eyelids or between the outer corner of the eye and the tragus	Possible NP (major), subcutaneous lipomas in the frontotemporal region, non-scarring alopecia, focal skin aplasia (confirmed by biopsy)
Central Nervous System (CNS)	1 Intracranial lipoma 2 Intraspinal lipoma 3 ≥2 minor criteria	1 Abnormal intracranial vessels 2 Arachnoid cyst or other meningeal abnormality 3 Complete or partial atrophy of a cerebral hemisphere 4 Porencephalic cyst 5 Asymmetrically dilated ventricles or hydrocephalus 6 Calcifications (except in the basal ganglia)	Intracranial lipoma (major), volumetric reduction of the right frontal and temporal lobes, diffuse prominence of cerebrospinal fluid spaces on the right side, small arachnoid cyst in the right middle cranial fossa.
Others	1 Jaw tumor (osteoma, odontoma, or ossifying fibroma) 2 Multiple bone cysts 3 Coarctation of the aorta	N/A	N/A

Definitive Case.
1. Involvement of 3 systems, with major criteria in ≥ 2 of them; or.
2. Involvement of 3 systems, with confirmed or possible nevus psiloliparus (NP) and ≥ 1 of the minor cutaneous criteria (criteria 2–5); or.
3. Involvement of 2 systems with major criteria, one of which must include confirmed or possible nevus psiloliparus and ≥ 1 of the minor cutaneous criteria (criteria 2–5).

the possibility of phenotypic overlap mediated by activation of the RAS-MAPK pathway.[7,8]

Differential diagnoses include Oculocerebrocutaneous Syndrome (Delleman Syndrome), Proteus, Epidermal Nevus and Schimmelpenning Syndrome.[7,9,10] The therapeutic strategy depends on the symptoms. Endoscopic ventriculostomy of the third ventricle is generally preferred for relief of intracranial hypertension in cases of hydrocephalus.[11] Surgery is recommended for symptomatic spinal lipomas, aiming to preserve neurological function, with follow-up being essential to monitor the progression of lipomatous lesions and prevent vertebral deformities.[11]

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Milene Tiburcio Narenti Ferradoza: Analysis and interpretation of data; drafting and editing of the manuscript; approval of the final version of the manuscript.

Luciana Paula Samorano: Clinical intervention in the case; critical review of the manuscript; approval of the final version of the manuscript.

Maria Cecilia Rivitti-Machado: Clinical intervention in the case; critical review of the manuscript; approval of the final version of the manuscript.

Zilda Najjar Prado de Oliveira: Research orientation; critical review of the manuscript; approval of the final version of the manuscript.

The study was conducted in accordance with the institution's ethical standards, and informed consent was obtained from the patient's legal guardian.

All authors read and approved the final version of the manuscript.

Written informed consent was obtained from the patient's legal guardian for the publication of this case report and corresponding images.

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Research data availability

Not applicable.

Conflicts of interest

None declared.

Editor

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LETTER - CLINICAL

Familial multiple discoid fibromas: clinical features and a brief overview of the literature

Dear Editor,

Familial Multiple Discoid Fibromas (FMDF) is an extremely rare genodermatosis (OMIM 190340) presenting clinically with multiple, skin-coloured, dome-shaped papules located mainly on the face, neck, trunk and especially on pinna.[1] Although FMDF resembles Birt-Hogg-Dubé (BHD) syndrome (OMIM 135150) clinically, it has been recognized as a distinct entity based on its specific clinical characteristics and genetic profile.[1,2]

The index patient is a 25-year-old man who presented with multiple asymptomatic papules on his face, ears, trunk, and extremities. The lesions had begun in early adolescence and increased in number and size since then. Dermatological examination revealed multiple, firm, skin-coloured small papules on his central face, most prominently on the pinna (Fig. 1), trunk, and lower extremities. Histopathological examination revealed well-circumscribed discoid fibrovascular proliferation compatible with discoid fibroma (Fig. 2). No mutations were detected in genetic analysis of FLCN, PTEN, TSC1 and TSC2 loci. Radiological imaging of lungs, kidneys and brain was normal. When the family of the patient was evaluated, there was no parental consanguinity; the patient had only one brother. Similar multiple papules on the central face and the pinnae (Fig. 3) of his mother (47-year-old), and fewer papules on the face, pinnae and the neck of his younger brother (22-year-old) were detected. Their lesions had also begun in early adolescence. Histopathologic, genetic, and radiologic results of his mother and brother were similar.

The literature review and patient characteristics are summarized in Table 1. Clinical differential diagnoses of multiple skin-coloured papules include BHD syndrome, multiple fibrofolliculomas, trichoepitheliomas, tuberous sclerosis complex, Cowden syndrome, and Brooke-Spiegler syndrome.[1–4] FMDF differs from these conditions by its characteristic early age of onset, preferential involvement of the pinna, distinct histopathology compatible with discoid fibroma, absence of systemic manifestations, and its different genetic profile.

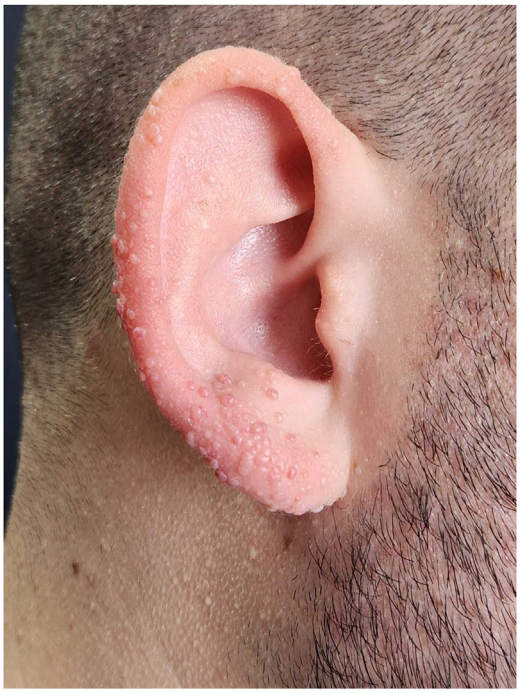

Figure 1 Discoid fibromas in Patient nº 1. Multiple skin-coloured small papules on the pinna.

Genetically, FMDF is defined by the absence of FLCN mutations, though a recent study suggests a possible link with a locus on chromosome 5 including the FNIP1 gene.[4] Although it is not exactly settled, autosomal-dominant inheritance has been described for most of the patients. Also, in the family we reported, the fact that the mother and both of her male children were affected, despite no affected individuals in the ancestors, suggests that a de novo mutation in the mother was inherited in an autosomal dominant manner. The observation that the number and size of discoid fibromas were highest in the oldest patient – the mother – and lowest in the youngest patient – the brother – suggests that the disease burden accumulates progressively over time.

Regarding treatment, surgical destructive methods may be used in the treatment of discoid fibromas. Topical rapamycin was reported to be beneficial in a case report.[3]

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Table 1 Overview of familial multiple discoid fibroma cases in literature.

Reference	Nº of Families and Patients	Age at Onset	Lesion Distribution and Morphology	Histopathology	Genetic Findings	Systemic Findings	Management and Outcomes
Starink et al. (J Am Acad Dermatol, 2012)	9 families (27 patients)	Childhood or adolescence (some as early as 1–3 years)	Mostly on the ear pinnae and central face (nose, cheeks). Lesions are 1–4 mm, dome-shaped fibrous papules, often with telangiectasia.	Well-circumscribed fibrovascular proliferations (''discoid fibromas''). No follicular epithelial proliferation as seen in fibrofolliculoma. Often a bent hair follicle at the periphery.	No pathogenic FLCN mutations. Linkage to BHD locus excluded by segregation analysis.	Rare sporadic renal cysts but no renal tumors. No pneumothorax.	Primarily surgical or destructive methods (eg, excision, curettage) for cosmetic reasons. Benign course without organ involvement. Emphasizes clinical/genetic distinction from BHD.
Wee et al. (Br J Dermatol, 2013)	2 siblings (no other affected relatives)	Brother at age 5; sister in adolescence.	Face (nose, malar area) and ear pinnae. Fewer lesions on trunk and limbs. Multiple firm papules.	''Discoid fibroma'' architecture. Some lesions exhibit a unique ''keloidal-like'' pattern: thick hyalinized collagen bands surrounded by spindle or histiocyte-like cells. No fibrofolliculoma-like epithelial strands.	FLCN negative. TSC1/TSC2 negative.	No pulmonary or renal lesions. No evident familial pattern (possible autosomal recessive or germline mosaic).	Surgical approaches yielded suboptimal cosmetic outcomes. Topical rapamycin (1 mg/mL) once daily led to marked papule regression.
Tong et al. (Cureus, 2017)	15 families (44 patients), 1 de novo 39-year-old patient	Typically childhood or early adulthood (variable among families)	Mostly on the face (cheeks, nose) and ear pinnae, sometimes trunk. Small firm papules, occasionally telangiectatic.	Benign fibrous lesions, described as ''trichodiscomas'' or ''discoid fibromas''. No central epithelial strands typical of fibrofolliculoma; peripheral hair follicle may be present.	FLCN mutation usually negative or benign variants. No pathogenic folliculin changes found.	Simple renal cyst in one case. No pneumothorax or renal tumors. No systemic malignancy.	Benign lesions; excisional or ablative treatments mainly for cosmetic reasons. No malignant transformation reported.
van de Beek et al. (J Hum Genet, 2023)	10 families	Not specifically stated.	Face, ear pinnae. Multiple ''trichodiscomas'' clinically described as FMDF.	Reported as consistent with ''trichodiscoma/discoid fibroma'' spectrum. No fibrofolliculoma-type epithelial strands.	FLCN negative. Linkage analysis reveals a locus on chromosome 5 (including FNIP1) in 9/10 families. A FNIP1 frameshift variant detected in most families; also a rare missense variant in PDGFRB co-segregating.	No mention of organ involvement.	No specific management details.

BHD, Birt-Hogg-Dubé syndrome; FLCN, Folliculin Gene; FMDF, Familial Multiple Discoid Fibroma; FNIP1, Folliculin Interacting Protein 1; mTOR, mammalian Target of Rapamycin; PDGFRB, Platelet-Derived Growth Factor Receptor Beta; TSC, Tuberous Sclerosis Complex.

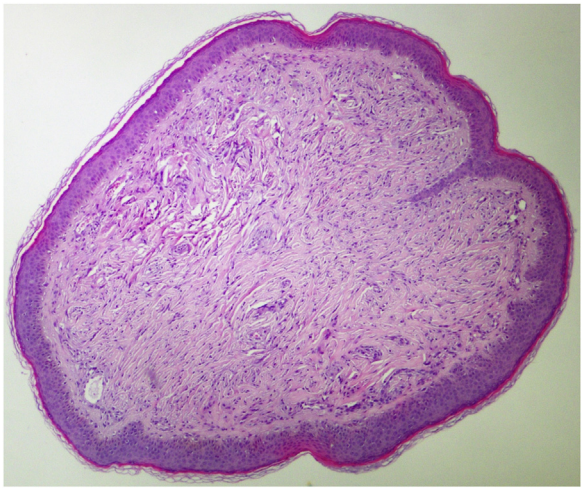

Figure 2 Histopathological examination of discoid fibroma. Well-circumscribed discoid fibrovascular proliferation (Hematoxylin & eosin, ×40).

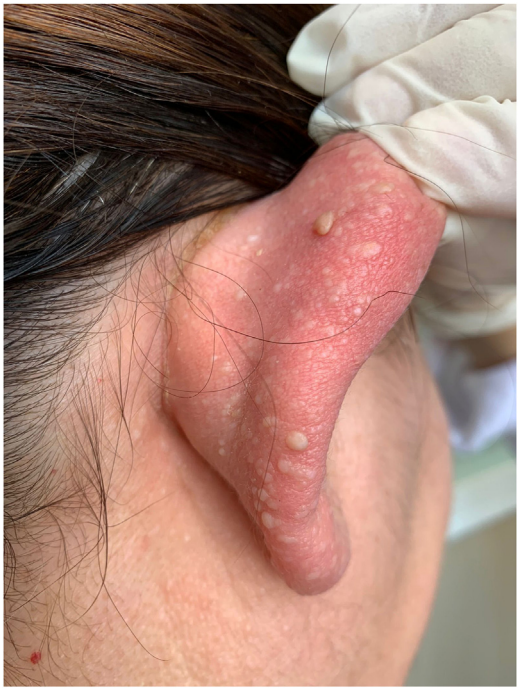

Figure 3 Discoid fibromas in his mother. Multiple skin-coloured papules on the pinna.

We performed electrosurgery for the lesions on the pinnae in our patients. However, during follow-up, the lesions showed a tendency to recur.

In conclusion, our findings emphasize that clinical recognition and careful genetic characterization remain key challenges in FMDF. A better understanding of its genetic background could improve diagnosis, counseling, and therapeutic strategies for this rare entity.

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Research data availability

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Authors' contributions

Ece Gokyayla: Contributed to the study conception and planning; effective participation in research orientation; critical literature review; data analysis and interpretation, and preparation and writing of the manuscript. She also performed a manuscript critical review and gave approval of the final version of the manuscript.

Kamer Gunduz: Contributed to the critical literature review; data collection, analysis and interpretation; preparation and writing of the manuscript, and performed manuscript critical review. She also gave approval of the final version of the manuscript.

Peyker Temiz: Contributed to data collection, analysis and interpretation and gave approval of the final version of the manuscript.

Conflicts of interest

None declared.

Editor

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LETTER - CLINICAL

Hemorrhagiectatic carcinoma: an uncommon clinical presentation of cutaneous metastasis from pulmonary adenocarcinoma☆

Dear Editor,

Cutaneous Metastases (CM) are rare and occur in 1%–5% of patients with internal malignancies. Although they can sometimes be the first manifestation of a primary cancer, they are typically detected in patients with a known history of malignancy. On average, the interval between the primary tumor diagnosis and the appearance of cutaneous metastases is 2.9 years.[1] The most common primary tumors that give rise to CM are melanoma and adenocarcinoma of the breast and lung.[1–3] In lung cancer, adenocarcinoma is the subtype with the highest frequency of cutaneous metastases (2.95%), surpassing squamous cell carcinoma (1.16%) and small cell carcinoma (0.81%).[1] CM can present pleomorphic, with dermal nodules being the most common manifestation. A rare subtype is hemorrhagic carcinoma, characterized by violaceous, indurated plaques with tumor infiltration in blood vessels and lymphatics.[1,3,4]

We present a case of a 58-year-old woman with a diagnosis of primary pulmonary adenocarcinoma and brain metastases in stage IV. She received combined treatment with surgery, radiotherapy, and conventional chemotherapy. Due to lymph node progression during follow-up, Nivolumab was started, completing 8 cycles with poor response. She developed progressively extensive violaceous-purpuric plaques with some infiltrated areas on the left hemiface, neck, sternum, shoulders, breasts, and axillae, associated with pruritus and burning (Fig. 1A–D). She was referred to the dermatology-oncology service with a suspected adverse reaction to Nivolumab, and an incisional biopsy showed dermis infiltrated by nests of atypical epithelial cells with extensive permeation in blood vessels and lymphatics (Fig. 2A–B). Immunohistochemistry showed strong positivity for cytokeratin 7, TTF1, and NapsinA (Fig. 2C–E), confirming the diagnosis of cutaneous metastasis from poorly differentiated lung adenocarcinoma. Brachytherapy (BT) was performed, leading to a significant reduction in lesion extent, infiltration, and symptoms. The patient underwent multiple courses of radiotherapy throughout the disease course. Initially, Whole-Brain Radiotherapy (WBRT) was administered at 30 Gy in 10 fractions, followed by a boost to the surgical bed of 36 Gy in 10 fractions after resection of brain metastases. For painful cervical lymphadenopathy, palliative External Beam Radiotherapy (EBRT) was delivered at 20 Gy in 4 fractions. Cutaneous metastases involving the hemiface, neck, thorax, shoulders, and axillae were treated with surface brachytherapy using a custom-made mold, delivering 20 Gy in 4 fractions, resulting in significant clinical improvement. Additionally, symptomatic thoracic bone metastases received a single-fraction palliative dose of 8 Gy via teletherapy. No electron-based teletherapy was used for skin lesions. Subsequently, Erlotinib was prescribed, and the cutaneous lesions continued to improve (Fig. 3A–C). The disease remained stable temporarily for a few months before progressing with bone metastasis and progressive deterioration, leading to the patient's death.

Cutaneous metastases, although rare, indicate systemic dissemination and are usually associated with a poor prognosis, with a median survival of less than one year.[1] CM is developed primarily by vascular invasion (lymphatic or hematogenous), caused by a complex phenomenon that occurs simultaneously with the development of the primary tumor.[5] The most frequent tumor that metastasizes to the skin is melanoma, followed by breast tumors (24%), Kidney (4%), ovary (3.8%), bladder (3.6%), lung (3.4%), colorectal (3.4%), and prostate (0.7%) cancer.[6] Regarding lung cancer, its main localizations of CM are the anterior thorax, abdomen, face and neck.[7] Clinically, CM can exhibit a pleomorphic presentation, with dermal nodules being the most frequently observed manifestation.[1,3] They generally tend to appear near the primary tumor site, although this is not always the case.[1,3] They can mimic benign and malignant tumors, multiple dermatoses, and vascular lesions, debuting as inflammatory plaques, fibrotic, sclerodermiform, vasculitis-like lesions, keratoacanthomas, and telangiectatic granulomas, among others.[3] A special and very unusual type of CM is hemorrhagic carcinoma. This is an inflammatory subtype of CM characterized by violaceous, purpuric, and indurated plaques that, upon histology,

☆ Study conducted at the National Cancer Institute, Santiago, Chile.

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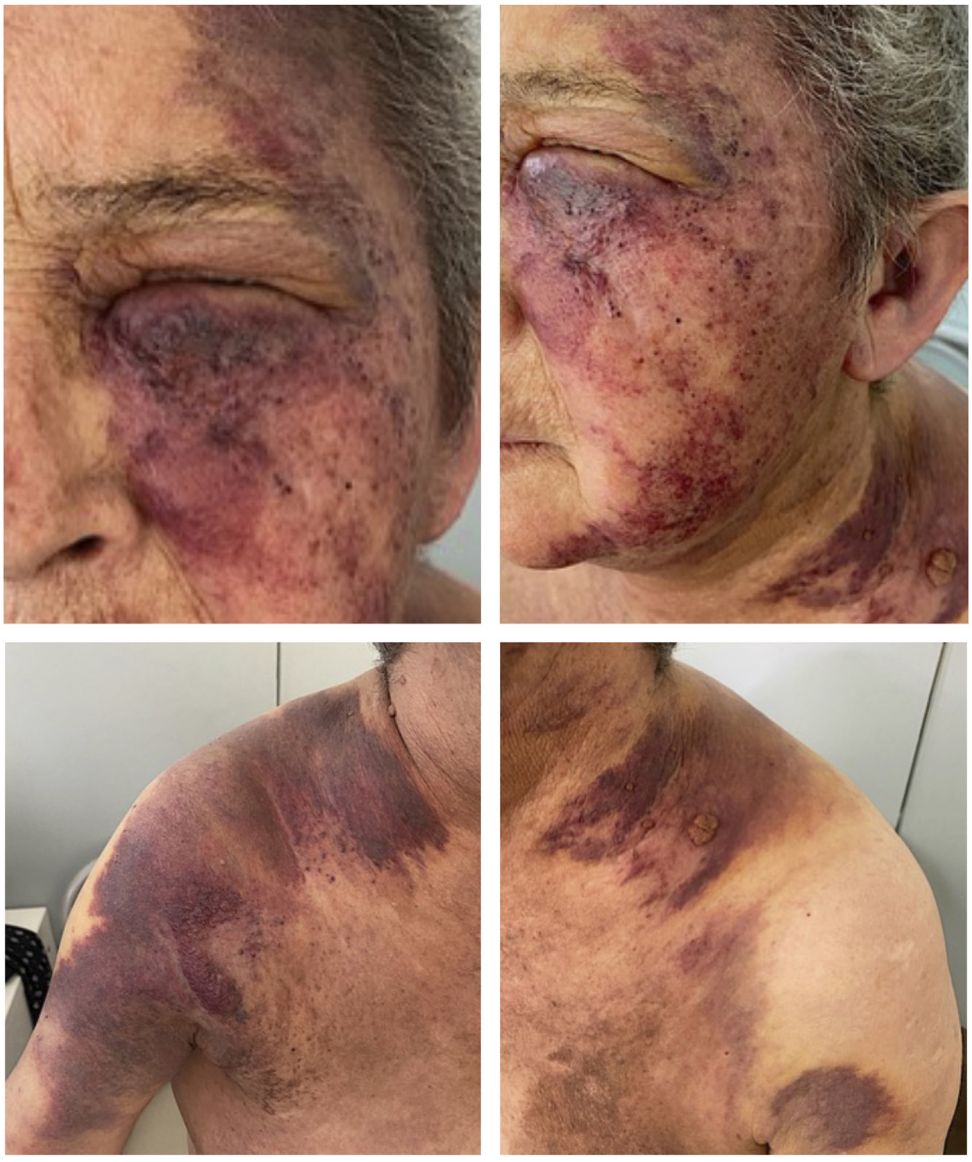

Figure 1 Presence of an extensive violaceous-purpuric plaques with some infiltrated areas on the left hemiface, neck, sternum, shoulders, breasts and axillae.

show infiltration of tumor cells in blood vessels, lymphatics, or both.[4] To date, it has only been described in a limited number of patients with primary tumors in the breast and salivary duct.[4] When possible, surgical resection is the treatment of choice, as it reduces tumor burden, improves functionality, quality of life, and even, partially, survival.[3] In cases where surgery is not feasible, a combination of therapies applied directly to the skin and immunotherapy has proven to be more effective than each treatment alone.[3] A meta-analysis by Spratt and colleagues reported high response rates and low recurrence rates following the use of skin-directed therapies.[8] Among the available modalities, which include electrochemotherapy, photodynamic therapy, radiotherapy, intralesional therapy, and topical therapy, electrochemotherapy stands out as the most effective.[3,8] In our case, the use of BT alone yielded excellent results, reducing lesion extent, infiltration, and symptoms. Following the introduction of Erlotinib, a therapeutic synergy was achieved, optimizing the response. To our knowledge, this is the first reported case of cutaneous metastasis from pulmonary adenocarcinoma with hemorrhagic morphology. This case is important because it underscores the need for dermatologists to be aware of the various manifestations of cutaneous metastases, which could improve clinical management and therapeutic response.

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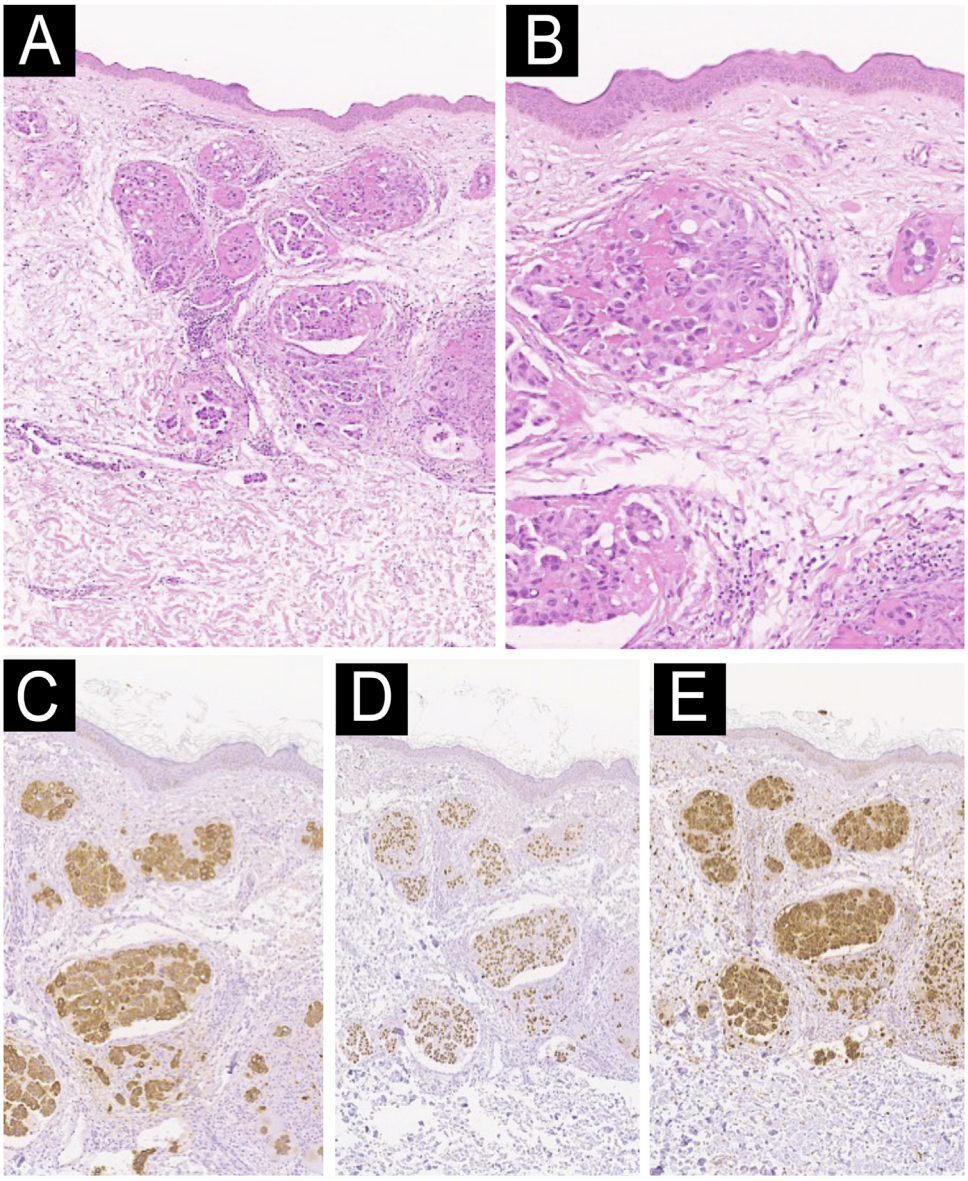

Figure 2 (A) Hematoxylin and eosin staining reveals extensive malignant infiltration of the dermis and subcutaneous tissue by atypical epithelial cells arranged in irregular glandular structures, some of which demonstrate intravascular permeation. (B) At higher magnification (200×), the tumor cells display marked pleomorphism, prominent nucleoli, and increased mitotic activity. (C–E) Immunohistochemical staining demonstrates strong and diffuse positivity for Cytokeratin 7 (CK7), Thyroid Transcription Factor 1 (TTF-1), and Napsin A, supporting the diagnosis of metastatic adenocarcinoma of pulmonary origin.

Research data availability

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Authors' contributions

Nelson Lobos-Guede: Approval of the final version of the manuscript; critical literature review; intellectual participation in propaedeutic and/or therapeutic management of studied case; manuscript critical review; preparation and writing of the manuscript.

Dan Hartmann: Approval of the final version of the manuscript; critical literature review; manuscript critical review; preparation and writing of the manuscript.

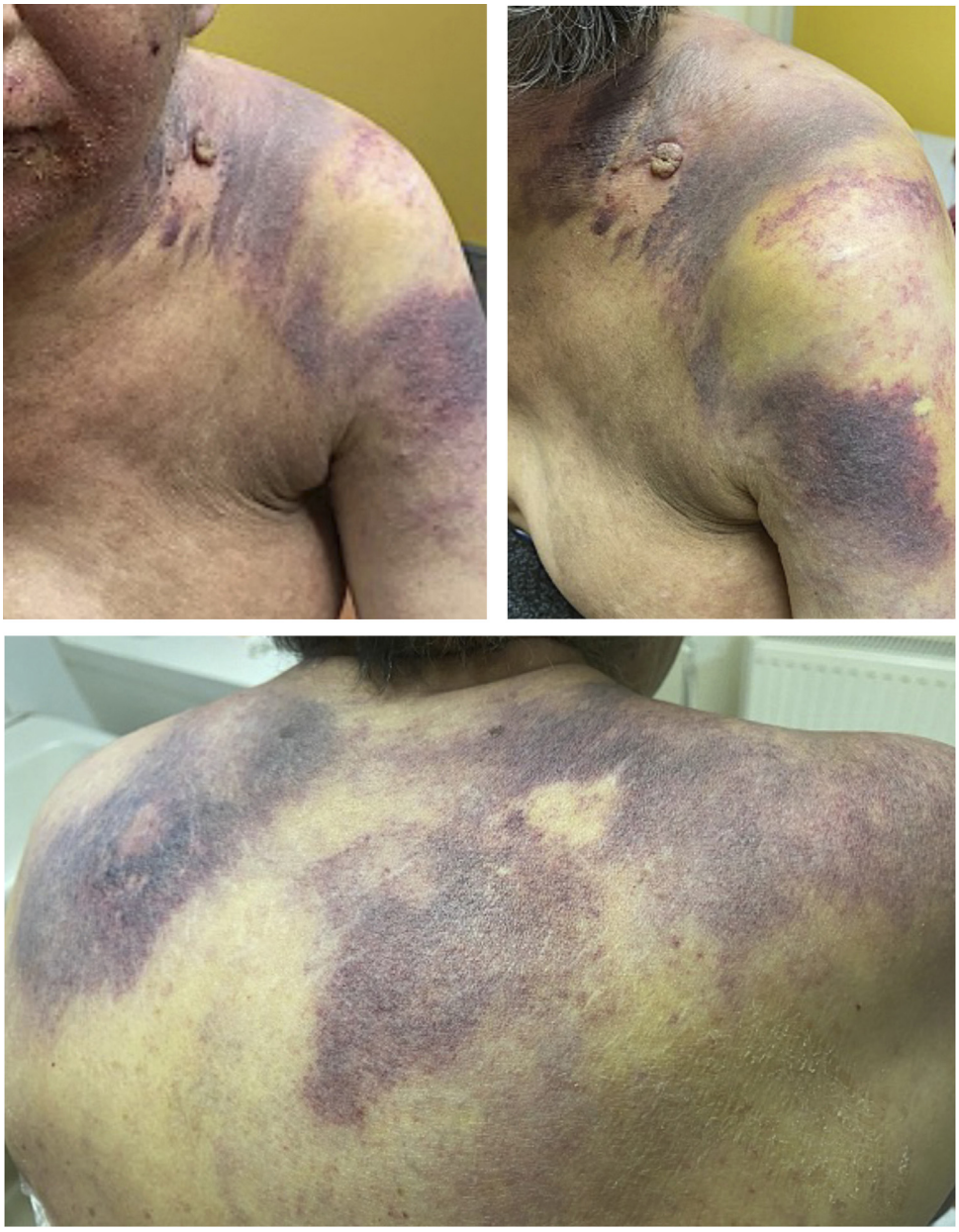

Figure 3 Cutaneous improvement with diminution of the violaceous plaques in the upper body and face after starting Erlotinib.

Felipe Carvajal Villarroel: Intellectual participation in propaedeutic and/or therapeutic management of the studied case; manuscript critical review; preparation and writing of the manuscript.

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Catalina Silva-Hirschberg: Intellectual participation in propaedeutic and/or therapeutic management of the studied case; manuscript critical review; preparation and writing of the manuscript.

Magdalena Delgado Barros: Intellectual participation in propaedeutic and/or therapeutic management of the studied case. Manuscript critical review; preparation and writing of the manuscript.

Conflicts of interest

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LETTER - CLINICAL

Novel sporadic c.2687G>T (p.Gly896Val) CYLD mutation in multiple trichoepitheliomas☆

Dear Editor,

Multiple trichoepithelioma (MTE) is a rare autosomal dominant neoplasm characterized by multiple skin-colored papules, primarily on the face.[1] It is associated with mutations in the CYLD tumor suppressor gene and originates from the pilosebaceous unit.[2] Variant mutations in the CYLD gene are associated with diseases in the CYLD cutaneous spectrum, such as Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma.[3] While familial cases predominate, de novo CYLD mutations are rarely documented, limiting genotype-phenotype correlations and genetic counselling guidance. Here, we report a case of multiple trichoepithelioma presenting with a new sporadic missense mutation in the CYLD gene.

A 31-year-old woman presented with asymptomatic papular lesions on the nasolabial folds, nose, and forehead, which had first appeared during the first month of life and progressively increased in number over time (Fig. 1). Lesions began perinasally and later involved the scalp and extremities. No additional skin tumor, such as cylindroma or spiradenoma, was detected. The patient denied a family history of similar lesions, and there was no known consanguinity. Physical examination revealed multiple, firm, asymptomatic, skin-colored papular lesions of 0.2–0.4 cm in diameter on bilateral nasal margins and forehead (Fig. 1). Multiple soft nodular lesions were observed on the occipital region and scalp (Fig. 2), along with a 1.4 cm nodule on the extensor surface of the right elbow and hyperkeratotic papules on the dorsum of the left toes. Dermatoscopic examination revealed a regular architecture with regular borders, thin, irregular vessels located peripherally, and opaque white areas on the lesion, which were suggestive of trichoepithelioma (Fig. 3). No dermoscopic signs of basal cell carcinoma (BCC) or sebaceous adenoma were present. Laboratory investigations showed no abnormalities. A punch biopsy was obtained from a lesion on the nasal margin with clinical differential diagnoses including adenoma sebaceum, syringoma, and trichoepithelioma. Histopathological examination disclosed features consistent with trichoepithelioma, characterized by basaloid cell islands, papillary mesenchymal structures, and cysts containing lamellar keratin within the dermis. DNA sequence analysis covering all coding exons (9–20) and exon-intron boundaries of the CYLD gene was performed using bidirectional capillary Sanger sequencing,

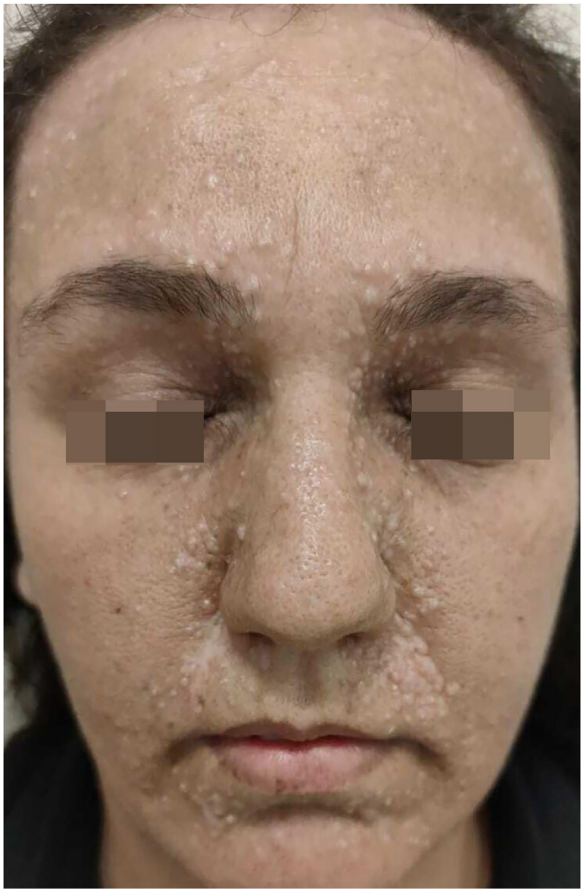

Fig. 1 Multiple skin-colored papules (0.5–2 mm) symmetrically distributed over the central face, consistent with trichoepitheliomas.

☆ Study conducted at the Department of Dermatology, School of Medicine, Pamukkale University, Denizli, Turkey.

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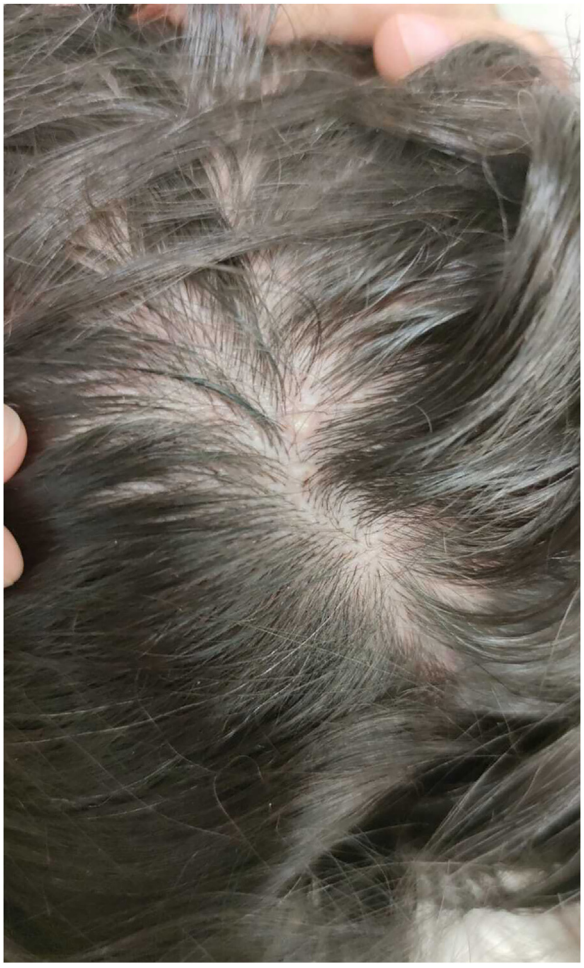

Fig. 2 Multiple soft nodules on the occipital region, clinically consistent with multiple trichoepitheliomas.

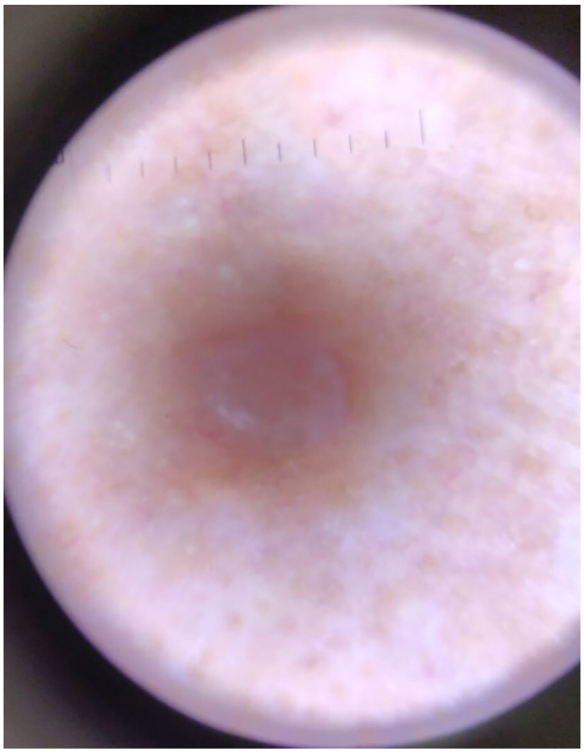

Fig. 3 Dermoscopy demonstrating regular lesion architecture with well-defined borders, peripheral thin irregular vessels, and central opaque white areas.

as previously described.[2,3] This analysis revealed a heterozygous variant, NM_015247.2:c.2687 G > G>T (p.Gly896Val), located in exon 20, with other previously reported mutations also shown in Fig. 4.[4,5] The patient was referred for genetic counselling. Due to financial constraints, laser treatment was not performed. Instead, selected lesions were treated with cryotherapy and electrocautery; however, these interventions were discontinued due to unsatisfactory cosmetic results. The patient continues to be under regular clinical follow-up.

CYLD encodes a deubiquitinase regulating NF-κB and other pathways; loss-of-function mutations underlie several adnexal tumor syndromes.[4,6] Mutations in the CYLD gene usually occur between exons 9 and 20 and have different phenotypic consequences.[5] Various CYLD gene mutations, such as splicing, frameshift, missense, and nonsense, which have been identified in recent years, have contributed significantly to the understanding of the phenotypic diversity of diseases such as Multiple Trichoepithelioma and Brooke-Spiegler syndrome in the CYLD-associated cutaneous syndrome spectrum.[2,3] Generally, missense mutations of the CYLD gene have been linked to less phenotypic variation compared to other mutation types, and the majority of these are multiple familial trichoepithelioma cases.[5] Although several mutations have been reported in exon 20 of the CYLD gene located at 16q12−q13, only a single substitution at nucleotide position c.2687 − namely c.2687 G > G>C (p.Gly896Ala) − has previously been described by España et al., in a familial case of multiple trichoepithelioma from Spain.[7] CYLD gene mutations, which have a well-defined autosomal dominant inheritance pattern, can also be seen sporadically, albeit rarely.[8,9]

In conclusion, to our knowledge, this is the first sporadic report of the NM_015247.2:c.2687 G > G>T (p.Gly896Val) variant; prior familial reports were limited to a Spanish pedigree. Although parental testing could not be performed and de-novo status therefore remains unconfirmed, this finding extends the known mutational spectrum of CYLD-associated cutaneous tumours and underlines the potential value of CYLD genetic testing even in non-familial cases. Reporting such cases not only contributes to the development of genetic counselling but also improves our understanding of the molecular pathogenesis of CYLD-associated skin diseases. Further molecular research is required to clarify the functional impact of novel CYLD variants in skin tumourigenesis and to confirm the pathogenicity of the p.Gly896Val substitution.

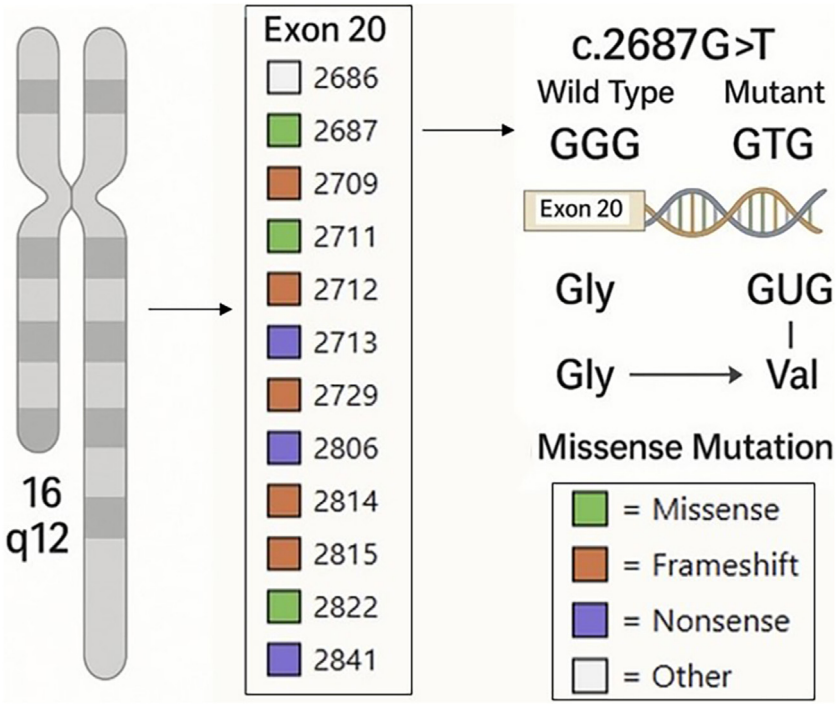

Fig. 4 Schematic of CYLD exon 20 showing the novel NM_015247.2:c.2687 G > G>T (p.Gly896Val) missense mutation identified in our patient (GGG → GTG; Gly → Val). Previously reported MTE-associated mutations at this exon are also displayed.[4,6] Mutation types are color-coded: Green, Missense; Orange, Frameshift; Purple, Nonsense; Grey, Other (Large deletions and rearrangements). Gly, Glycine, Val, Valine, MTE, Multiple Trichoepithelioma.

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LETTER - CLINICAL

Ulcerated necrobiosis lipoidica: clinical and histopathological presentation of two cases☆

Dear Editor,

Necrobiosis lipoidica (NL) is a rare granulomatous disease that affects more women than men. Its etiopathogenesis remains unexplained. Although it is most commonly associated with insulin-dependent diabetes, NL can coexist with thyroid dysfunction, sarcoidosis, rheumatoid arthritis, and metabolic syndrome. It presents as circumscribed, atrophic, yellowish-brown plaques with telangiectasias and violaceous borders, usually located in the pretibial region. About one-third of cases may progress to ulcerations, often resulting from minor trauma.[1,2]

The present report describes two cases of ulcerated NL to demonstrate the diagnostic and therapeutic challenges. The first case is a 70-year-old woman with type 2 diabetes, good glycemic control, and non-insulin-dependent, with high blood pressure and heart disease. She was followed for 28 years in the dermatology outpatient clinic, due to NL in the lower limbs with the formation of recurrent ulcers, initially diagnosed as venous ulcers (Fig. 1). Doppler ultrasound showed no pathological changes in the deep and superficial venous system. Histopathological examination showed changes characteristic of NL (Fig. 2A and B). Superficial surgical debridement, anti-stasis measures, dressings for exudative and colonized lesions (e.g., hydrofiber with silver), oral use of pentoxifylline, colchicine, gabapentin (for pain control), and sulfamethoxazole-trimethoprim (for control of recurrent infections) were performed. She

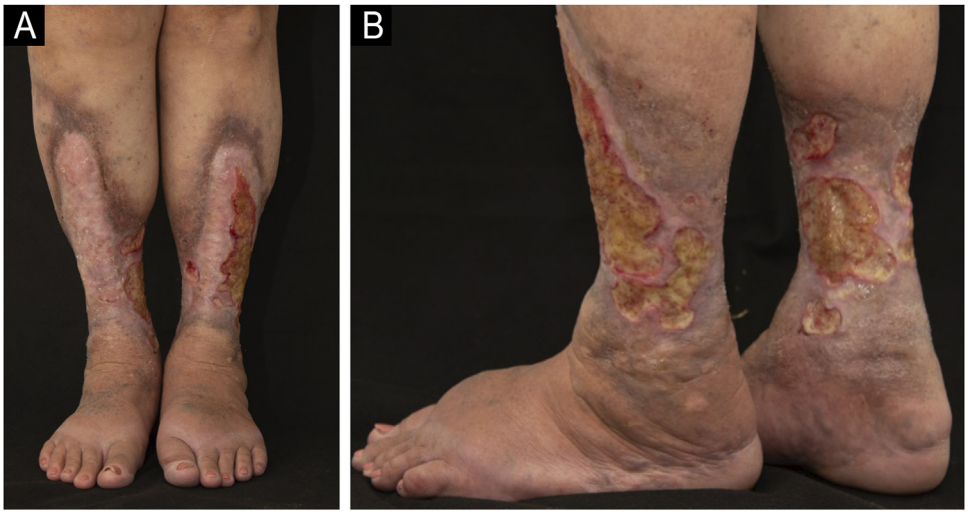

Fig. 1 (A and B) Case 1. Ulcerated Necrobiosis lipoidica simulating venous ulcers. Ulcers are observed on the anterior, lateral, medial, and posterior aspects of the lower limbs, with fibrinoid tissue over an extensive atrophic plaque with a slightly yellowish center, brownish and purplish borders, affecting the entire distal circumference, associated with bilateral edema.

☆ Study conducted at the Department of Infectology, Dermatology, Imaging Diagnosis and Radiotherapy, Faculty of Medicine, Universidade Estadual Paulista, Botucatu, SP, Brazil.

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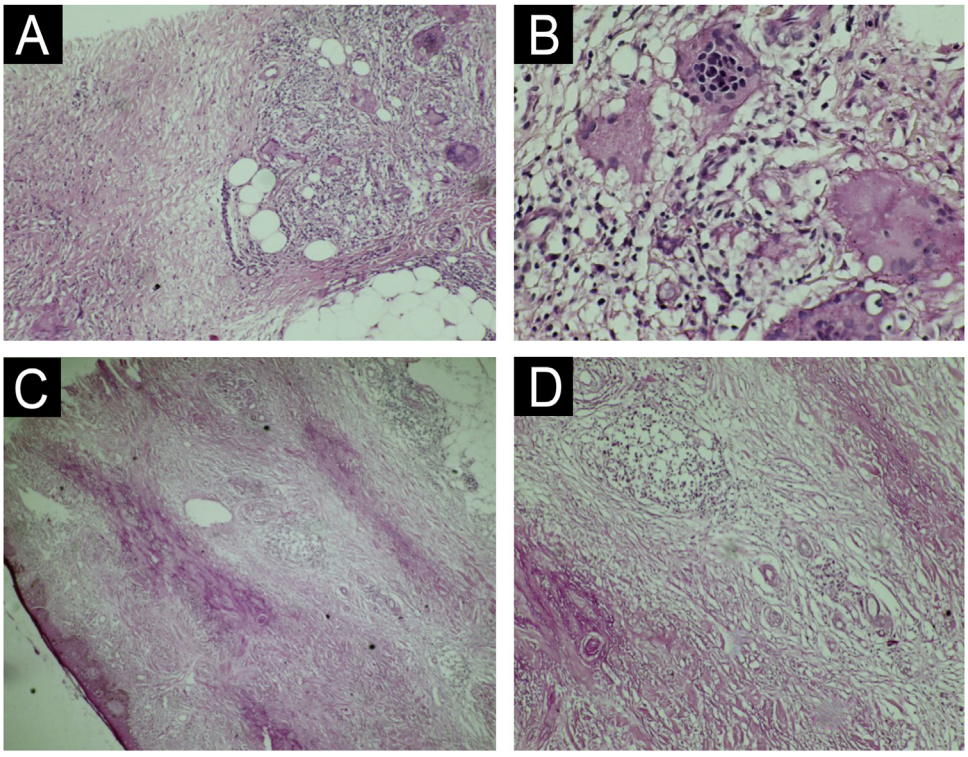

Fig. 2 (A and B) Anatomopathological examination of Case 1 highlights multinucleated giant cells and the granulomatous arrangement around necrotic connective tissue (A – Hematoxylin & eosin, ×100; B – Magnified image; Hematoxylin & eosin, ×400). (C and D) Anatomopathological examination of Case 2 reveals alternating bands of necrotic connective tissue and areas of chronic inflammatory infiltrate in a palisade pattern, rich in lymphocytes, multinucleated giant cells, and plasma cells. Inflammatory cells are also distributed around appendages and vessels. The typical alternating architectural pattern resembles the layers of a cake (C – Hematoxylin & eosin, ×40; D – Hematoxylin & eosin, ×100).

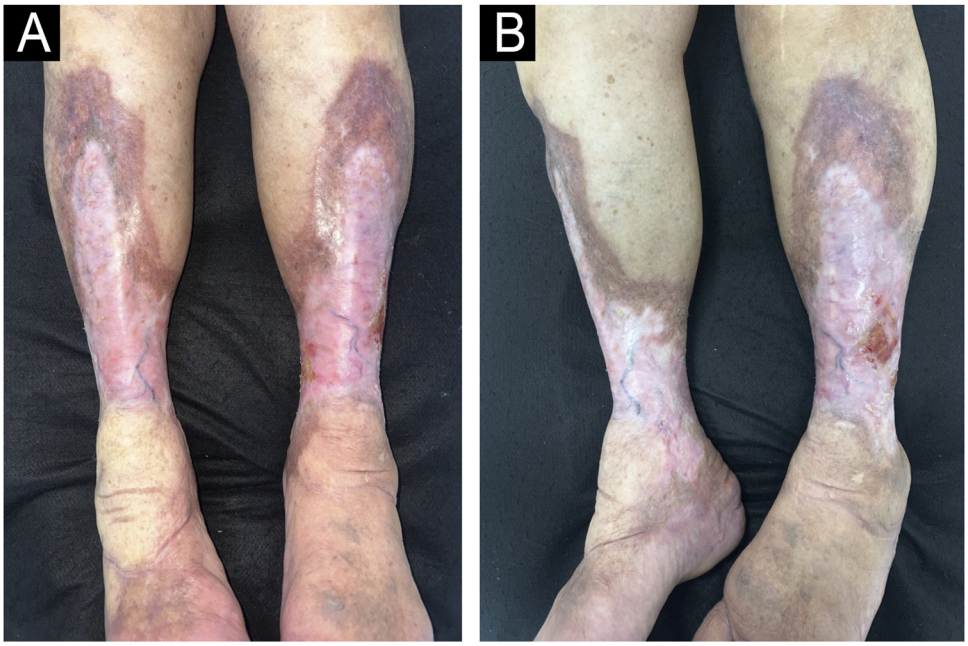

Fig. 3 Case 1. Necrobiosis lipoidica with ulcers evolving towards healing. (A) Observe an extensive atrophic plaque with visualization of blood vessels, a slightly yellowish center, and brownish and purplish edges, affecting the entire distal circumference. (B) The single ulcerated lesion on the lateral aspect of the left leg is evident, superficial, and with good granulation tissue.

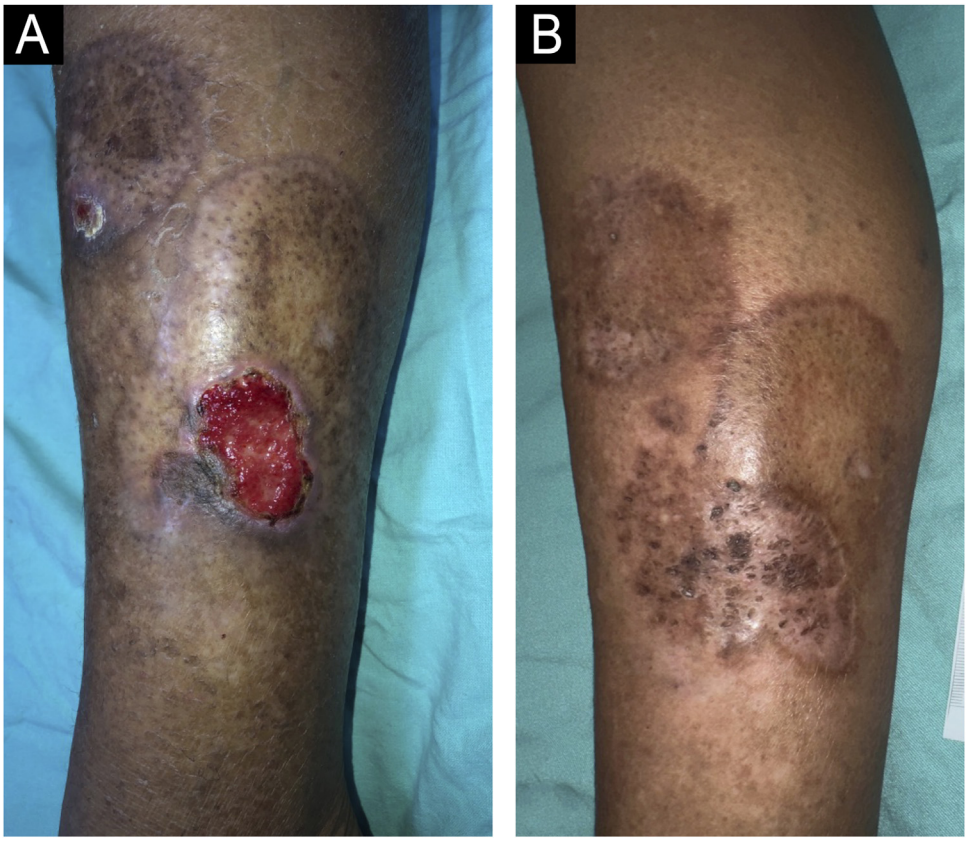

Fig. 4 Case 2. (A) Chronic ulcer on the left lower limb over necrobiosis lipoidica. At this stage, a hydrocolloid dressing was used to maintain a moist environment and promote healing. (B) Healed ulcer.

progressively improved in healing after the start of this antibiotic with maintenance for three months, although active NL lesions were still present (Fig. 3).

The second case is a 61-year-old woman, insulin-dependent diabetic, high bood pressure, dyslipidemic, with hypothyroidism, who underwent adrenalectomy due to adrenal carcinoma, being followed for five years in the dermatology outpatient clinic with the onset of hyperchromic plaques, with an atrophic and yellowish center, and well-defined and brownish borders in the pretibial region of the left lower limb associated with pruritus, with periods of ulceration and spontaneous healing (Fig. 4A). The histopathological examination was compatible with NL (Fig. 2C and D). She underwent surgical debridement, high-potency topical corticosteroid use when active lesions were present in the peri-ulcer skin, and anti-stasis measures, in addition to dressings depending on the healing stage. The lesions healed about a year ago without recurrence (Fig. 4B).

NL requires attention and early recognition by dermatologists, endocrinologists, and clinicians in general, being a warning sign for diabetes screening in affected patients.[1] Diagnosis requires the integration of clinical and histopathological findings. In histopathological examination, NL is characterized by granulomatous inflammation consisting of histiocytes and dispersed giant cells with dermal fibrosis and necrobiotic connective tissue, arranged in a ''layer-cake'' pattern. The blood vessels surrounding the necrobiotic connective tissue often show edema, fibrosis, and hyalinization of endothelial cells. The epidermis is usually not affected, but it may be atrophic or ulcerated.[3]

Ulcerated NL has differential diagnoses with other causes of chronic lower limb ulcers, mainly venous ulcers.[4,5] The NL plaque in the present case was initially confused with extensive lipodermatosclerosis; however, the patient did not have venous disease as evidenced by venous ultrasound, and the histopathology of the peri-ulcer lesion confirmed the diagnosis of NL. Late identification and delayed diagnosis can lead to disease progression, making it recalcitrant, particularly when ulceration occurs.[6]

NL treatment is challenging, and relapses occur frequently. Control of glycemic levels is recommended, although its relationship with disease control is controversial. The first line of treatment is topical and occlusive high-potency corticosteroids. In extensive and refractory cases, systemic corticosteroid therapy may be used, but evaluation of adverse events in diabetic patients is necessary. There are also reports of treatment with hydroxychloroquine, immunobiologicals (anti-Tumor Necrosis Factor-alpha – TNF-α), and Janus Kinase inhibitors (anti-JAK). According to the literature, about 20% of lesions show spontaneous resolution.[7–9]

In the case of ulcerated NL, the challenge is even greater. Treatment of possible secondary infections, serial debridement of devitalized tissues, compression therapy, and appropriate dressings are indicated. Anti-TNF-alpha and anti-JAK immunobiologicals represent promising ther-

apeutic strategies for disease refractory to conventional treatments.[7–9]

To date, it remains a challenging condition since the evidence for treatments is based primarily on case reports, given the multiple therapeutic modalities available and the rarity of cases. It is of paramount importance to conduct controlled primary studies aimed at proposing a first-line treatment and thus avoid NL refractoriness. It is noted that chronic cases, such as the one reported, require constant monitoring due to the risk of malignant transformation, mainly to squamous cell carcinoma on areas of chronic ulceration.[10]

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LETTER - DERMATOPATHOLOGY

Extensive discohesive melanoma: additional challenges beyond the Breslow Index☆

Dear Editor,

Discohesive,[1] bullous,[2–4] or acantholytic-like[5] are terms that have been applied to the uncommon finding of variable morphological patterns of epidermal detachment[6] associated with melanoma and referred to as the bullous variant.[2] The main practical pathological problem associated with bullous melanoma regards the evaluation of the Breslow index. The authors argue about nomenclature and additional histopathological difficulties in a case qualified as an extensive discohesive melanoma.

A 64-year-old female patient, phototype II, was referred for evaluation of an asymptomatic lesion in the left scapular region. An asymmetrical multicolored brownish, blackened, grayish macular lesion with reddish areas, irregular edges, and approximately 6 centimeters was observed (Fig. 1). Dermoscopy showed atrophy, ulceration, irregular peripheral network, and globules.

The histopathological exam revealed atypical melanocyte proliferation along the dermal-epidermal junction. Most lesional segment was associated with clefts of varying length and width (Fig. 2), covered by intact or ruptured epidermis. Proliferated melanocytes were stellate with an expanded cytoplasm and enlarged, rounded and hyperchromatic nuclei seen in suprabasal position, along adnexal epithelium or located in the papillary dermis. Atypical melanocytes were variably present on the floor of the clefts (Fig. 3), on the roof, and/or floating inside the blister space, grouped or not. Other findings included two areas of true superficial ulceration (Fig. 3), an intense dermal lymphocytic inflammatory infiltrate with melanophages, focal fibroplasia, and mild solar elastosis. The diagnosis of extensive discohesive melanoma, superficial spreading type, with a Breslow index of 1 mm, ulceration, and incomplete regression was considered.

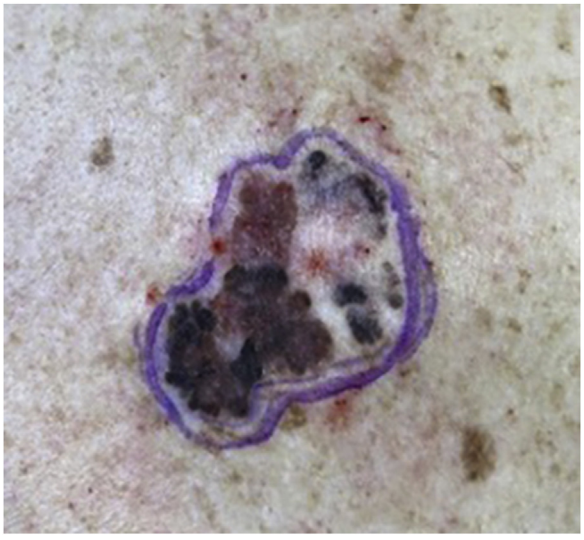

Figure 1 Asymmetrical multicolored brownish, blackened, grayish macular lesion with reddish areas and irregular edges.

Immunostaining with Melan-A was performed to better assess the histopathological findings (Fig. 4).

Discohesion among proliferating melanocytes and clefts are clues to the diagnosis of melanoma as compared to benign melanocytic proliferation.[6] Loss of adhesion of the neoplastic cells is attributed to the downregulation of receptors like E-cadherin and altered expression of integrin family molecules.[7] Meanwhile, melanoma with large, wide, or extensive clefts, with or without clinical expression, can be qualified as discohesive melanoma.[1,3–5] In the present case, despite no clinical observation of bulla, varying degrees of epidermal detachment composed most of the lesion length. Discohesive, isolated, round malignant cells could be referred to as acantholytic-like, but the finding was not so prominent as previously reported,[5] and the designation ''bullous'' was avoided. In addition, a Hailey-Hailey disease-like pattern, considering attached melanocytes floating in the clefts, was focal.[1,4]

Melan-A immunostaining was useful in the visualization of melanocytes in the roof of ruptured clefts, particularly when the denuded dermis lacked both melanocytes and

☆ Study conducted at the Faculty of Medicine, Universidade Federal de Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

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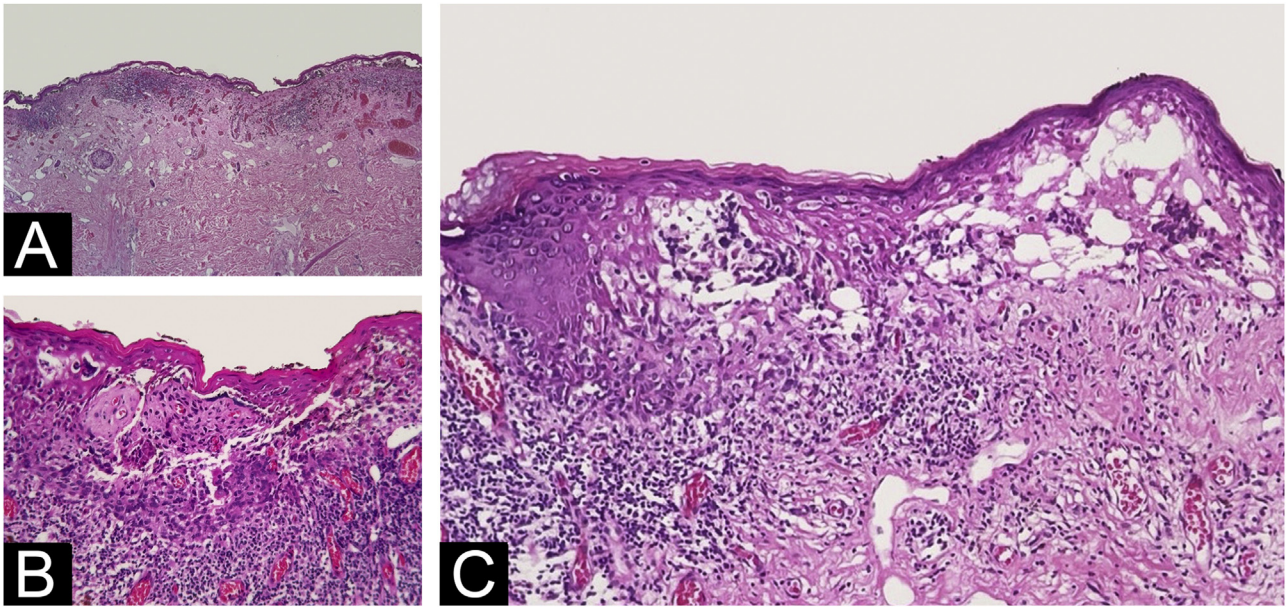

Figure 2 Varying degrees of dermal-epidermal detachment along almost de whole lesion (A – Hematoxylin & eosin, ×4); intact epidermis and grouped malignant melanocytes in the bottom, where superficial dermal infiltration is present (B – Hematoxylin & eosin, ×10); intraepidermal (on the left) and subepidermal (on the right) multilocular cleft with pagetoid dissemination of isolated cells that reached the granulosa layer (C – Hematoxylin & eosin, ×10).

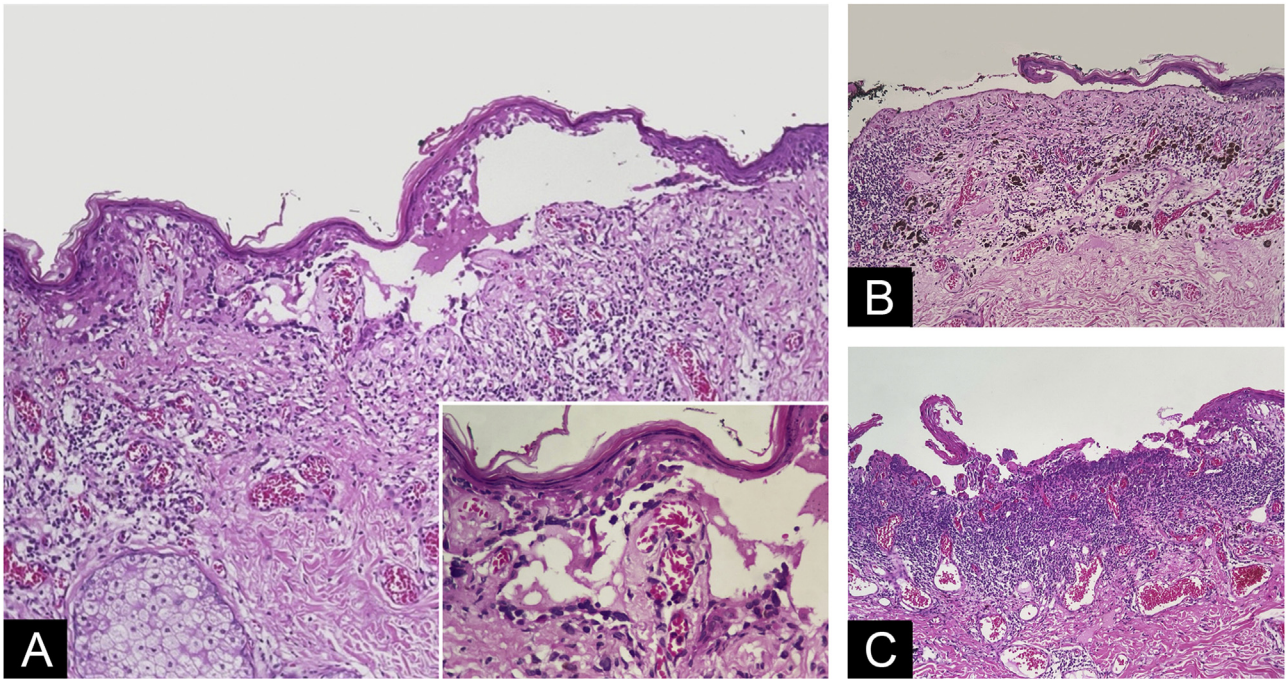

Figure 3 Blister with melanocytes present on the floor of the cleft, sometimes carpeting the dermis (A – Hematoxylin & eosin, ×10; Insert: detail of carpeting melanocytes – Hematoxylin & eosin, ×40); subepidermal ruptured bulla devoid of melanocytes at the bottom above dermal regressive changes (B – Hematoxylin & eosin, ×10); necrotic basophilic material covering papillary dermis together with juxtaposed inflammatory infiltrate. Some discohesive melanocytes can be seen in the lateral border of necrotic tissue (C – Hematoxylin & eosin, ×10).

keratinocytes, and the picture can mimic a primary blister disorder.

Extensive epidermal detachment, distorting epidermal architecture, made it difficult to histologically classify the lesion. It was considered a superficial spreading melanoma due to a high-level pagetoid spread observed in the short segments where the epidermis was still intact and attached to the dermis, and the absence of

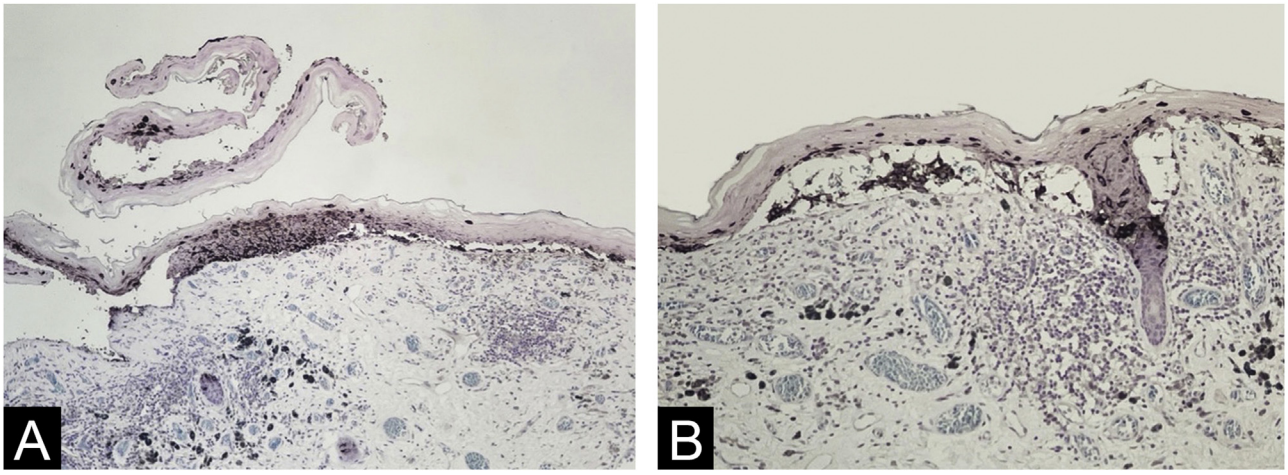

Figure 4 Melanocytes occupying almost the whole epidermal thickness at the lateral border of a ruptured blister devoid of melanocytes seen only on its roof (on the left) and carpeting melanocytes in the bottom of a narrow cleft (on the right) (A – Melan-A immunostaining, Giemsa counter-staining, ×10); melanocytes floating in cleft space and among keratinocytes at the roof. Notice epithelium-stroma detachment in follicular infundibula. (B – Melan-A immunostaining, Giemsa counter-staining, ×10).

dermal changes that characterize significant chronic sun damage.

The Breslow index is the main practical problem posed by melanomas with clefts. While some have included the bulla space in the Breslow index,[5,8] others suggest excluding the area.[4] The inclusion of the cleavage area resulted in a thickness of 1 mm, while its exclusion resulted in 0.9 mm, thus not affecting the pathological staging (pT1b/AJCC, 2018) in this case. The question is not addressed in recent guideline publications[9,10] and the Breslow index measured in the context of extensive discohesive melanoma will imply a probable over- or under-measurement to be declared in the pathological report.

Additional histopathological challenges account for the evaluation of ulceration. Detached segments with a ruptured roof, with melanocytes present only in their handedness or in the overlying epidermis, leaving behind a smooth papillary dermis devoid of cells and juxtaposed inflammation, were not considered true ulceration. On the other hand, consistent with dermoscopy findings, two areas were interpreted as actual superficial ulceration based on projections of degenerated papillary dermis or necrotic aspect of the floor along with a greater accumulation of inflammatory cells, including neutrophils, and fibrin.[10]

Melanoma clefts and blisters may create exceptional difficulties in the evaluation of several histopathological parameters that are not restricted to the measurement of Breslow's index but also concern the classification of the *in-situ* component of the lesion and the indication of ulceration, all aspects linked to clinical evolution, prognosis, and staging.

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Conflicts of interest

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LETTER - DERMATOPATHOLOGY

When comedones mislead: a dermoscopic and histological clue to follicular dowling-degos disease☆

Dear Editor,

Dowling-Degos Disease (DDD) is a rare, inherited skin condition characterized by a distinctive pattern of dark, lacy (reticulate) pigmentation, particularly in flexural sites. It typically presents in females during the third or fourth decade of life.[1]

A 26-year-old female presented with multiple asymptomatic dark lesions over the face, axillae, groin, inframammary folds, buttocks, and extremities since childhood. The lesions initially appeared in the axillae and gradually progressed to involve other body sites. A positive family history was noted, as similar lesions were observed in her mother. There was no history of itching, photosensitivity, or any systemic complaints.

On examination, numerous folliculocentric brown-to-black macules and comedone-like papules were widely distributed over the body with a predilection for flexural involvement (Fig. 1A–C). Multiple hyperpigmented atrophic macules and follicular pits were also present over the face (Fig. 1D). Nails, mucosae, palms, and soles were spared. No typical non-follicular, reticulate flexural hyperpigmentation was present.

Dermatoscopy (polarized mode, 10× magnification) over the upper back revealed folliculocentric, irregular star-shaped, and Chinese letter-like brown pigmentation, multiple discrete dark brown follicular plugs with a surrounding faint reticulate pigment network (Fig. 2A–B). Based on clinical and dermoscopic findings, a provisional diagnosis of follicular Dowling-Degos Disease (DDD) was considered.

Histopathologic examination from a buttock lesion showed characteristic antler-like elongation of rete ridges, basal layer hyperpigmentation, and follicular plugging with preservation of the suprabasal layer (Fig. 3A–B). No dyskeratosis, corps ronds, or grains were noted.

Dowling-Degos Disease (DDD) is a rare pigmentary disorder caused by mutations in the KRT5 gene, inherited in an autosomal dominant pattern or occurring sporadically. It typically presents in females during the third or fourth decade of life.[1] The KRT5 gene, located on chromosome 12, is essential for maintaining keratinocyte structure and participates in melanosome transfer, which explains the pigmentary anomalies seen in DDD, and its mutation leads to abnormal proliferation of the pilosebaceous unit.[1]

Follicular DDD, first described by Singh et al. in 2013, is a distinct variant of Dowling-Degos disease characterized by punctate, folliculocentric hyperkeratotic and hyperpigmented papules, macules, pits, and comedo-like lesions.[1] Lesions commonly affect the face, back, extremities, and flexures. Unlike classical DDD, follicular DDD lacks the typical reticulate pigmentation of flexures and shows histological changes confined to the follicular infundibulum, sparing the interfollicular epidermis.[2]

Dermatoscopy in follicular DDD reveals star-shaped or linear, thready pigmentation in a Chinese letter-like pattern, often centered around follicular openings, serving as a distinguishing feature of follicular DDD.[3]

In follicular DDD, histological changes are confined to the follicular infundibulum, showing features such as follicular plugging and horn cyst formation, while the interfollicular epidermis remains unaffected.[1] Treatment options for Dowling-Degos disease include topical agents like retinoic acid and hydroquinone, as well as procedural interventions such as erbium-YAG laser and a combination of Q-switched Nd: YAG and fractional carbon dioxide lasers.

The differential diagnoses of follicular Dowling-Degos Disease (DDS) include classical dowling degos, Galli-Galli disease, familial dyskeratotic comedones, and comedonal Darier's disease. Clinically, DDD begins as reticulate hyperpigmentation in intertriginous areas such as the axillae, groin, and inframammary folds, with gradual extension to sites like the trunk, inner thighs, upper arms, and face.[1]

Familial Dyskeratotic Comedones (FDC) is a rare autosomal dominant genodermatosis characterized by symmetrically distributed, hyperkeratotic, comedone-like papules.[4] It typically begins around puberty, with lesions first appear-

☆ Study conducted at the Faculty of Medical Sciences, Maulana Azad Medical College, University of Delhi, Delhi, India.

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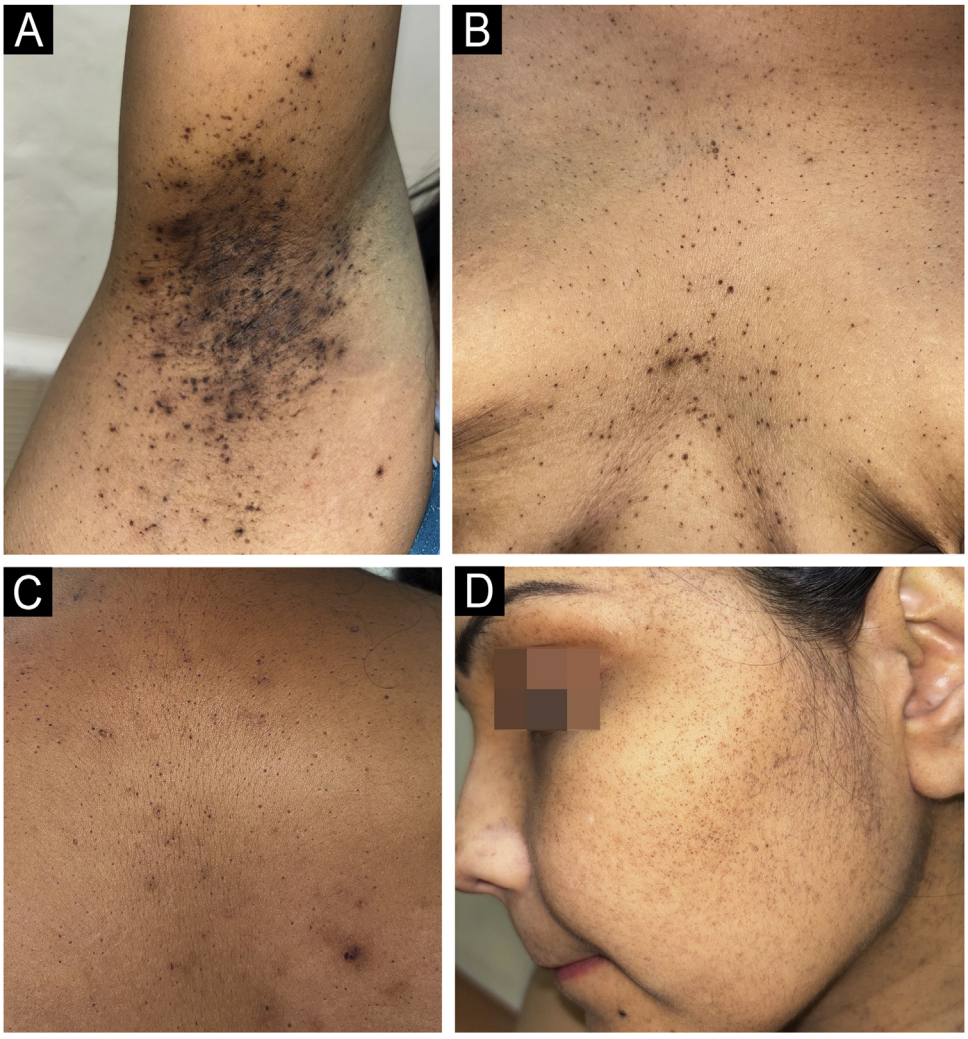

Fig. 1 Multiple follicular hyperpigmented macules and comedo-like papules distributed over the axillae (A), intermammary region (B), and upper trunk (C), Facial involvement with scattered atrophic macules and follicular pits (D).

ing on the trunk or extremities and gradually spreading while sparing the palms, soles, and mucosal surfaces.[4] FDC is suspected based on clinical resemblance to comedones, positive family history, and histological evidence of dyskeratosis. Lesions may also involve the face, scalp, and occasionally the genital area.[5] Dermatoscopy has not been well described, but this report identified brownish follicular papules with central keratin plugs.[4] Histopathology shows follicular invaginations filled with keratin-containing parakeratotic cells and melanin, along with dyskeratotic changes in deeper epithelial layers and occasional perivascular lymphocytic infiltration.[5]

Comedonal Darier's disease is clinically distinct from the classic form due to its pronounced follicular involvement, leading to the development of large comedo-like lesions, primarily affecting the face and scalp, often accompanied by subtle features of classic Darier's disease and poor response to therapy.[6] The lesions are typically persistent and minimally symptomatic.

Clinically, it may present as either nodular lesions or multiple large comedo-like blackheads, particularly on the face, scalp, and upper trunk.[7] Histopathologically, it demonstrates numerous dyskeratotic cells and occasional acantholytic cells confined to the follicular epithelium, along with dilated follicular ostia and distinguished from classic Darier's disease by prominent follicular involvement and the presence of elongated dermal villi and papillary projections.[7] Although usually minimally symptomatic and persistent, histopathology aids in diagnosis by revealing characteristic acantholytic and dyskeratotic cells within the follicular adnexal epithelium and dilated hair follicles.[6]

Follicular Dowling-Degos disease is a rare variant that can clinically mimic comedonal disorders, making diagnosis challenging. Dermoscopy and histopathology are essential in distinguishing it from its mimickers. Early recognition aids in accurate diagnosis, appropriate management, and genetic counseling.

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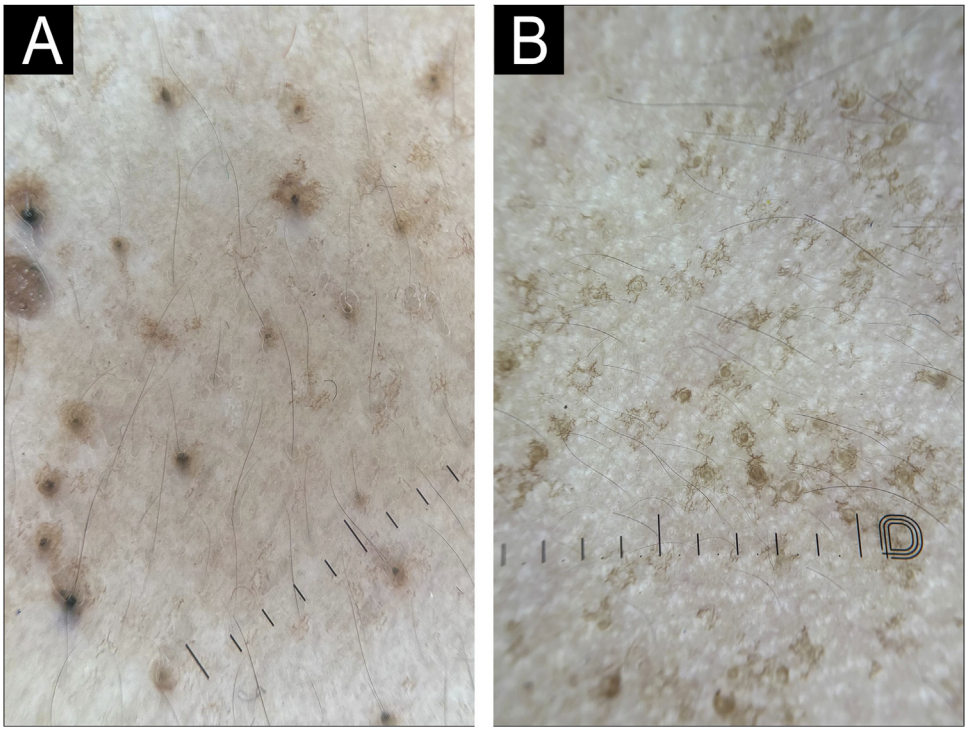

Fig. 2 Dermoscopy (polarized, 10× magnification) demonstrating central dark brown follicular plugs surrounded by irregular star-shaped and Chinese letter-like brown pigmentation (A). Dermoscopy (polarized, 10× magnification) demonstrating Chinese letter-like pigmentation centered around a follicular opening (B).

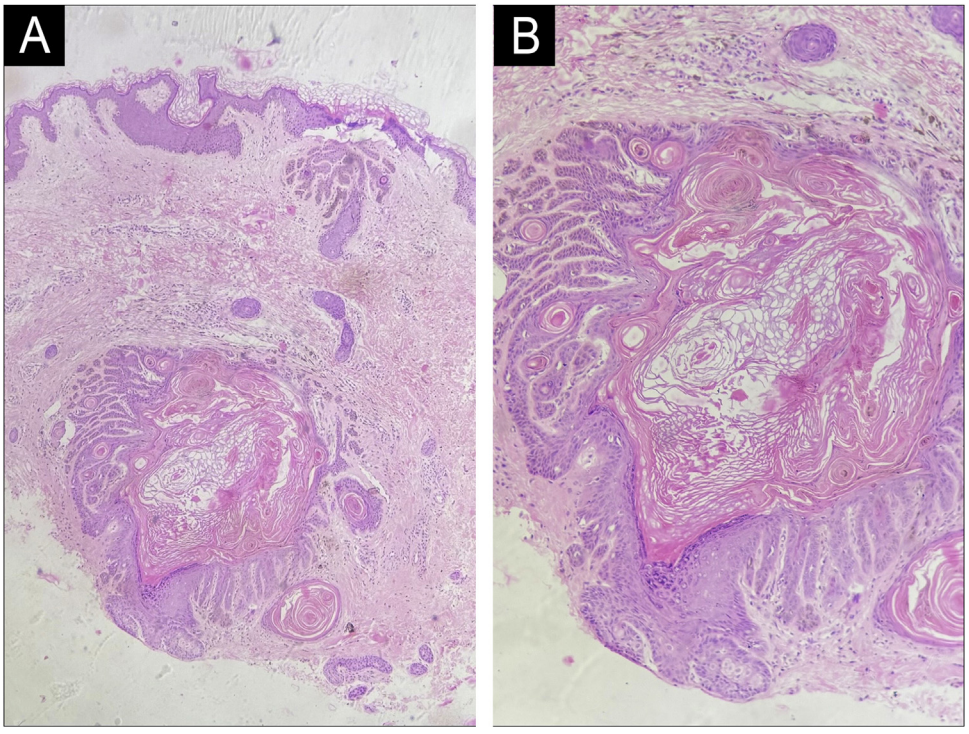

Fig. 3 Histopathological image showing elongated, branching (''antler-like'') rete ridges, basal hyperpigmentation, and follicular plugging, with sparing of the interfollicular epidermis (A – Hemaxitolyn & eosin, 40×), (B – Hemaxitolyn & eosin, 100×).

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Authors' contributions

Sonika Garg: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Anuja Yadav:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Gajanand M. Antakanavar:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Meeta Singh:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Zoya Hasan:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft.

Conflicts of interest

None declared.

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LETTER - TROPICAL/INFECTIOUS AND PARASITIC DERMATOLOGY

Sarcoidosis-like cutaneous lesions in paracoccidioidomycosis: four case reports and review of the literature☆

Dear Editor,

Paracoccidioidomycosis (PCM) is a deep mycosis caused by the thermo-dimorphic fungi *Paracoccidioides brasiliensis* complex and *Paracoccidioides lutzii*. Although common in Latin America, its true prevalence is underestimated due to the lack of mandatory reporting. The clinical manifestations often develop many years after inhalation of conidia from soil due to the reactivation of endogenous latent foci.[1]

PCM can involve any organ, but its clinical presentation is typically classified into acute/subacute and chronic forms.[1] Skin involvement occurs in up to 30% of patients with chronic PCM. The oral mucosa typically presents with ulcers featuring hemorrhagic dots (*moriform stomatitis*), whereas cutaneous lesions are polymorphic, predominantly ulcerative.[1,2]

We describe four Brazilian patients with sarcoidosis-like skin lesions caused by PCM (Figs. 1 and 2) and discuss the relevant literature. The female-to-male ratio was 3:1, with ages ranging from 25 to 51-years (average age of 38). The duration of skin lesions before diagnosis varied from 4-months to 4-years, and the most common misdiagnosis was leprosy (in 2 patients). The face was the first site involved in all patients, with systemic manifestations observed in the lungs (1 patient) and lymph nodes (2 patients). Skin biopsies showed granulomas with very few yeast elements, none exhibiting multi-sporulating characteristics. Culture and serology for Paracoccidioides sp. were positive in only one patient. All patients responded well to treatment with itraconazole or trimethoprim-sulfamethoxazole.

A literature search using the MeSH terms ''*paracoccidioidomycosis*'' AND ''*sarcoidosis*'' and ''*paracoccidioidomycosis*'' AND ''*sarcoid*'' in the PubMed and SciELO databases (August–September 2024) identified 12 articles describing sarcoidosis-like skin lesions in PCM. All publications were case reports or case series, dating from 2008 to 2024 (Table 1). A total of 13 patients were reported, primarily from the Southeast, South, and Central-West regions of Brazil.[3–14]

Sarcoidosis-like cutaneous lesions in PCM present as brownish or reddish papules and plaques, which may or may not be infiltrated. The balance between immune defense and fungal infection determines the lesions' morphology and distribution, with the sarcoid-like form of PCM being associated with a predominant Th1 immune response. This presentation is typically paucifungal and classically resis-

Table 1 Summary of narrative review cases.

Total of patients	13
Sex	
Women	6
Men	7
Age (average, in years)	33
Affected sites (%)	
Head	100%
Trunk	30.8%
Limbs	7.7%
Diagnostic delay (average, in years)	2.8
Lung involvement	
Positive	0
Negative	10
Unknown	3
PCM serology	
Positive	4
Negative	3
Unknown	6
Previous wrong diagnosis (%)	
Granulomatous rosácea	5 (38%)
Leprosy	4 (30%)
Sarcoidosis	1 (7.6%)
Lupus erythematosus	1 (7.6%)
Treatment	
Itraconazole	7
Trimethoprim sulfamethoxazole	5
Amphotericin B	2
Unknown	2

☆ Study conducted at the Faculty of Medical Sciences, Universidade Estadual de Campinas, Campinas, SP, Brazil.

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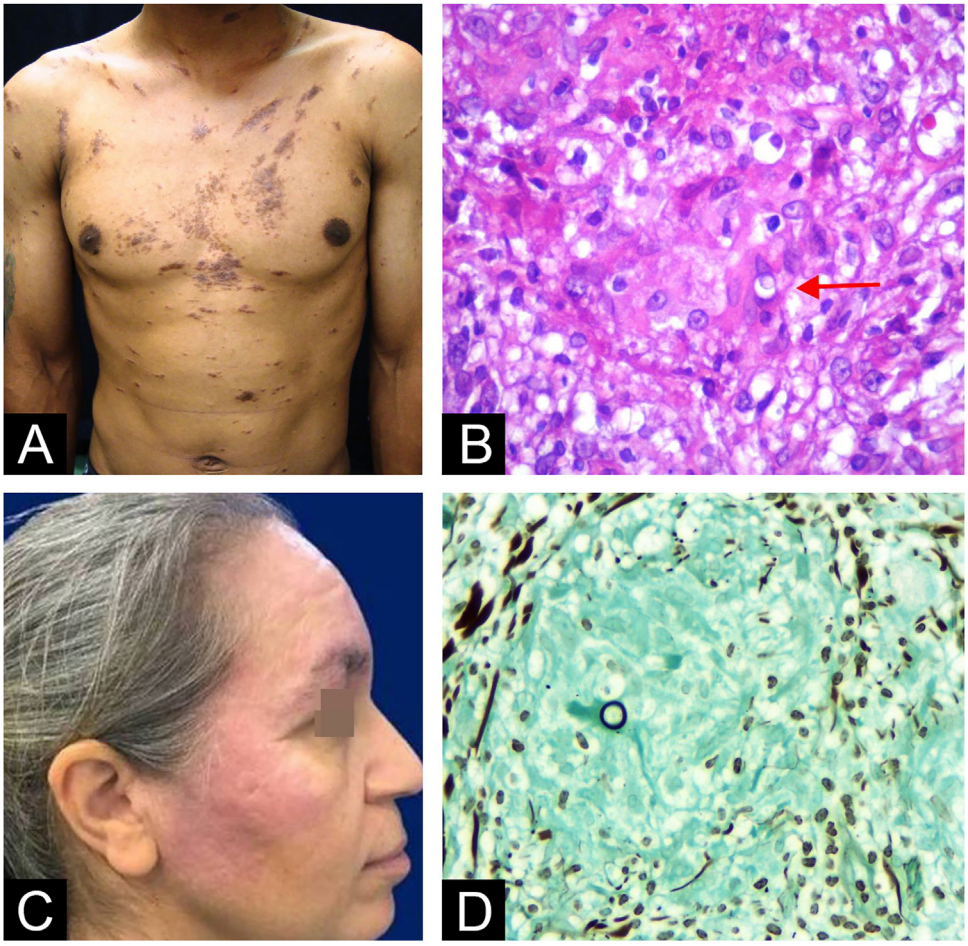

Fig. 1 Patient 1 (A) Brownish plaques on the trunk and (B) A rare non-sporulating yeast element with thick wall in the dermis (arrow) at hematoxylin and eosin stain. Patient 2 (C) Red plaques on face and (D) Unique birefringent fungal structure within a dermal granuloma at Grocott stain.

tant to the pathogen.[5,15] It seems that this immune response pattern is species independent.[10,11]

Marques et al. analyzed 152 PCM patients treated at a Brazilian tertiary hospital and found that ulcerative and vegetative/verrucous lesions accounted for 50.1% of cases, whereas infiltrative lesions (including sarcoidosis-like forms) comprised 26.6% of cases. Although classic PCM lesions predominantly affect the cephalic region due to their contiguity with mucosal involvement, sarcoidosis-like PCM lesions also primarily affect this area, as observed in all cases from our study.[2] The increased vascular perfusion in this region may further predispose to cephalic involvement.

Our review found that sarcoidosis-like PCM cases are more common in women, unlike the typical male predominance in other PCM forms. Estrogen receptors in *Paracoccidioides* spp. may inhibit the conversion of mycelium or conidia into the infectious yeast form, leading to fewer skin lesions and pulmonary involvement.[1,5] However, an extensive laboratory and imaging workup is recommended in all sarcoidosis-like PCM.[14]

Histologically, sarcoidosis-like PCM lesions are characterized by epithelioid granulomas with multinucleated giant cells, often containing few or no detectable fungal elements. This can lead to frequent misdiagnosis, as documented in 84% of the patients in our literature review. Sarcoidosis is the primary differential diagnosis, given its potential pulmonary and lymphatic involvement, as well as its cutaneous manifestations, which occur in 35% of cases.

Cutaneous sarcoidosis most commonly affects white women of working age, with papules and plaques frequently appearing on the face (61%) and often preceding systemic manifestations.

Leprosy, an endemic disease in Brazil, can histologically resemble PCM in its tuberculoid form. In ambiguous clinical presentations, histological findings may lead to misdiagnosis, resulting in inappropriate treatment and delayed correct diagnosis.[3,6,7] To improve diagnostic accuracy, culture and serological testing – preferably combining two modalities such as immunoblotting and immunodiffusion – are recommended to rule out infectious causes.

Sarcoidosis-like PCM responds well to standard antifungal therapy, with rapid improvement of skin lesions. Nevertheless, treatment should be maintained for at least nine months. In cases where serologic tests are initially positive, they can be useful for monitoring treatment response.

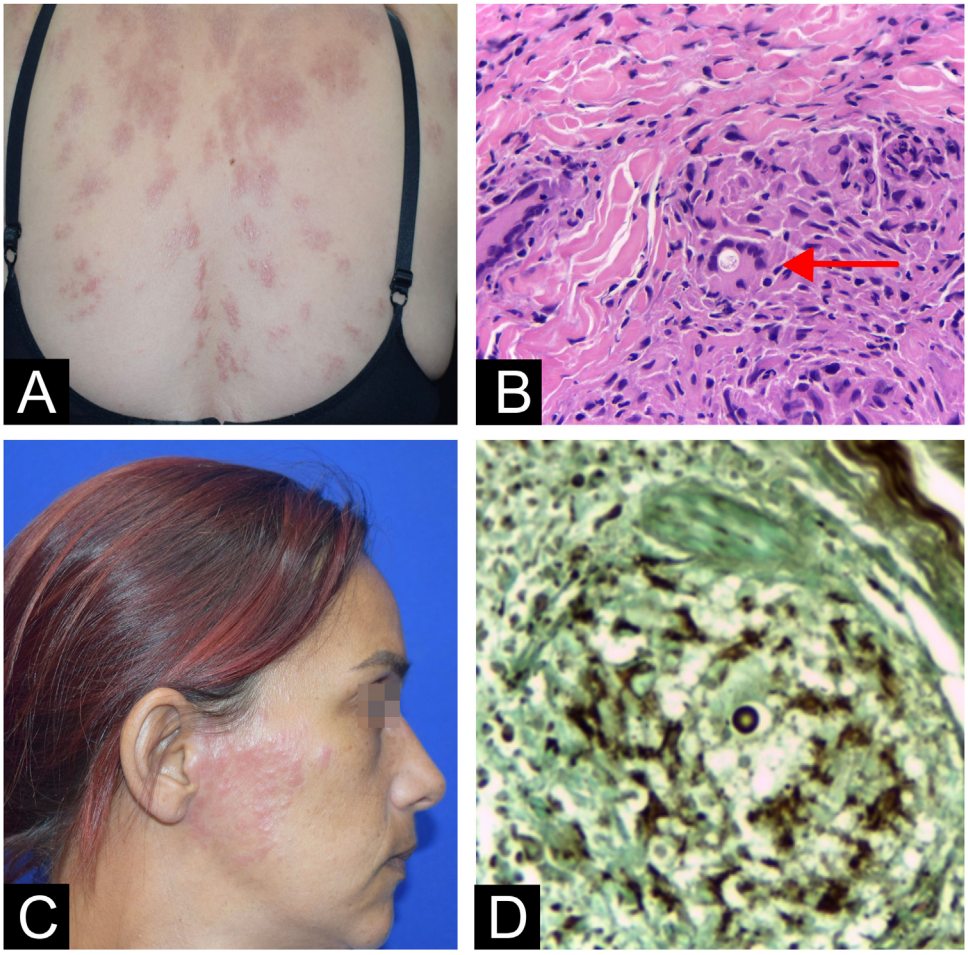

Fig. 2 Patient 3 (A) Red plaques disseminated on the trunk and (B) Yeast inside giant cell (arrow) at hematoxylin eosin stain. Patient 4 (A) Pre-auricular red plaque and (D) Dermal granulomas showing an isolated yeast element at Grocott stain.

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Renata Ferreira Magalhães: Manuscript critical review; final approval of the final version of the manuscript.

Paulo Eduardo Neves Ferreira Velho: Manuscript critical review; effective participation in the propaedeutics/therapeutics; final approval of the final version of the manuscript.

Andrea Fernandes Eloy da Costa França: Writing of the manuscript; effective participation in the research guidance; final approval of the final version of the manuscript.

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Research data availability

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Conflicts of interest

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LETTER - THERAPY

Disseminated miliary lupus on the face: successful treatment with oral dapsone and topical metronidazole

Dear Editor,

Lupus miliaris disseminatus faciei (LMDF) is a rare granulomatous dermatosis of which the etiology is not yet fully elucidated, characterized by the appearance of erythematous papules on the central region of the face, although cases of extrafacial involvement have been reported.[1] Its pathogenesis remains uncertain, and its relationship with chronic inflammatory processes and hypersensitivity reactions is being discussed.[2,3]

LMDF predominantly affects young adults, with a slight predominance in males, and has a self-limiting course, and may leave residual atrophic scars. Histopathologically, it shows epithelioid cell granulomas with central necrosis and surrounding lymphocytic infiltrate, including multinucleated giant cells. However, the histological pattern may vary depending on the stage of the disease.[4] Due to clinical and histological similarities, LMDF can be confused with other facial granulomatous dermatoses, such as granulomatous rosacea and sarcoidosis. The presence of caseous necrosis in granulomas is a distinctive element that aids in diagnostic differentiation.[5,6]

The objective is to present a clinical case of LMDF in a male patient, highlighting its clinical manifestations, complementary examinations, and response to treatment, emphasizing the main diagnostic and therapeutic challenges of the condition.

A 49-year-old man came to the office presenting with multiple micropapules on the periocular, nasolabial, glabella, and malar regions, symmetrically distributed, sometimes with pustules (Figs. 1 and 2), without diffuse redness, desquamation, or associated telangiectasias. In addition, recent endoscopic examinations showed moderate antral enanthematous gastritis, erosive esophagitis, intra-

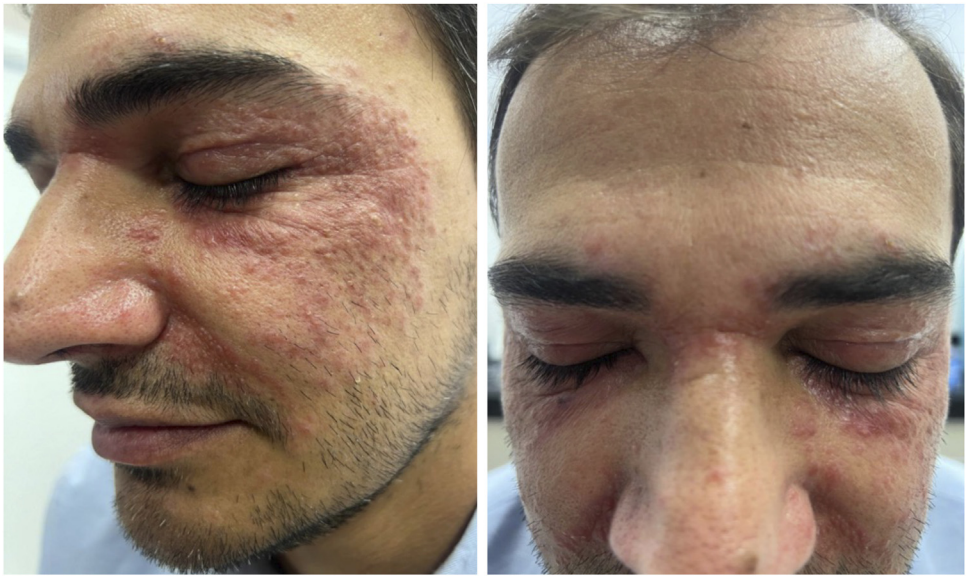

Figure 1 Multiple small erythematous papules, mostly grouped in plaques, on an erythematous base, on the periocular, nasolabial, and malar regions, symmetrically distributed. Photographs obtained with a smartphone.

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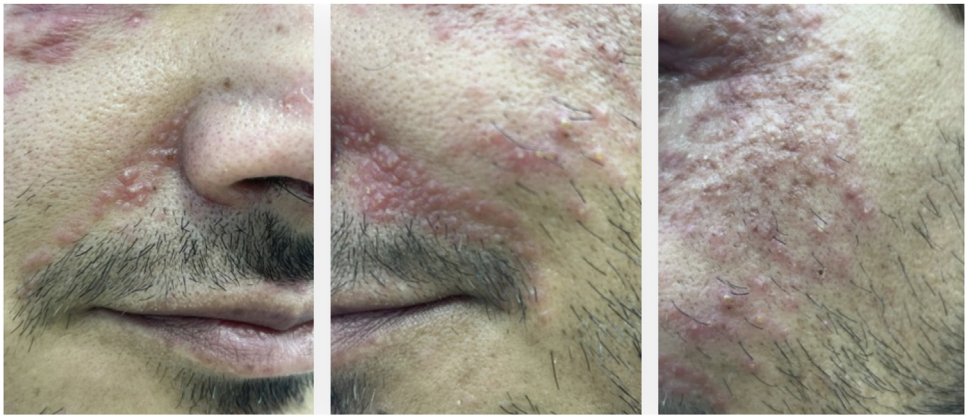

Figure 2 Close-up view of the skin lesions, showing hundreds of papules clustered on an erythematous background and some pustules. Photographs taken with a smartphone.

mucosal lymphoid follicles in the sigmoid colon and rectum, as well as active chronic ileitis - unrelated to the dermatological disease, according to the literature. The condition began approximately six months before, and there was a prior diagnosis of discoid lupus, according to the anatomopathological report.

Initial treatment included hydroxychloroquine on alternate days, topical pimecrolimus, moisturizers, and sunscreen. After six months, even with the addition of oral corticosteroids and topical tacrolimus, there was no significant improvement. A new biopsy was performed, with suspicion of periorificial dermatitis or LMDF. The anatomopathological examination revealed epithelioid cell granulomas, some with central caseous necrosis and lymphohistiocytic infiltrate with giant cells (Fig. 3). Tests for fungi and AFB (PAS and Fite-Faraco staining) were negative, confirming the hypothesis of LMDF.

Treatment was initiated with minocycline 100 mg/day and prednisone 20 mg/day, with gradual reduction of corticosteroid therapy over 15 days, in addition to top-

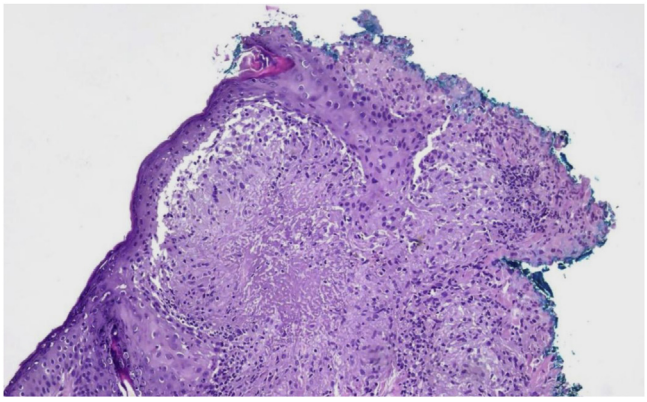

Figure 3 Skin sections show epidermis with hypergranulosis. The superficial dermis shows granulomas of epithelioid cells, some with central areas of necrosis in a caseous pattern and surrounding lymphohistiocytic infiltrate with multinucleated giant cells. (Hematoxylin & eosin, ×40).

Figure 4 Patient after 4 months of treatment.

ical metronidazole. After 30 days without a satisfactory response, it was decided, in agreement with the gastroenterologist (consulted at the patient's request), to introduce dapsone 100 mg/day orally, while maintaining topical metronidazole. By the twentieth day, a significant response was observed, with near resolution after four months (Fig. 4).

Dapsone is a dihydropteroate synthetase inhibitor drug with anti-inflammatory action. It has been used since the 1940s in the treatment of leprosy and various dermatoses, including granuloma annulare and dermatitis herpetiformis. Its potential adverse effects include methemoglobinemia, agranulocytosis, hepatitis, peripheral neuropathy, and hemolytic anemia, none of which were observed in the patient.[7]

Several systemic treatments are described as effective in LMDF: isotretinoin, dapsone, corticosteroids, clofazimine, metronidazole, topical tacrolimus, diode laser (1450 nm), and non-ablative fractional laser (1565 nm). Early use of low doses of corticosteroids can prevent scarring.[8] The present case had results similar to those described by Patel et al.,[6] in a 51-year-old woman, and Zawar et al., in a 23-year-old man treated with dapsone 100 mg/day for four weeks.[5]

In view of the above, it is concluded that the accurate diagnosis and adjusted therapeutic approach were fundamental for the management of LMDF. Considering the rarity of the condition and the slow response to conventional treatments, the combination of oral dapsone (100 mg/day) with topical metronidazole demonstrated efficacy and safety, highlighting the importance of a personalized strategy and continuous follow-up to optimize clinical results and minimize aesthetic and functional impacts.

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Research data availability

Not applicable.

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Authors' contributions

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Luciana Lócio Rosado: Design and planning of the study; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript; article reviewer.

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Conflicts of interest

None declared.

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LETTER – THERAPY

Long follow-up treating CHILD nevi with topical cholesterol and statins☆

Dear Editor,

CHILD nevi comprise the cutaneous manifestations typical of CHILD syndrome, an acronym for Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defect, a rare, X-linked dominant genetic disease, lethal to males, resulting from mutations in the NSDHL gene, which belongs to the cholesterol biosynthesis pathway.[1]

Altered cholesterol biosynthesis affects myelin formation and organogenesis, resulting in neurological, skeletal, and visceral malformations.[2,3] CHILD nevi arise as a physiological compensation for the lipid-poor and inflamed skin barrier due to the accumulation of its precursors, resulting in erythematous-squamous plaques that follow Blaschko's lines, with a predilection for fold areas, associated with pruritus and recurrent skin infections, which affects quality of life and represents a potential life-threatening risk.[1,4]

Laboratory tests are usually normal, and histopathological examination of CHILD nevi reveals nonspecific psoriasiform changes, which are useful for ruling out differential diagnoses. Clinical evaluation and, when available, genetic testing confirm the diagnosis.[1]

The first treatments used for CHILD nevi were topical keratolytic agents, emollients, corticosteroids, and calcineurin inhibitors, oral retinoids or methotrexate, showing unsatisfactory results, in addition to representing risks inherent to prolonged use and in potentially fertile patients.[5] Therapeutic proposals based on the disease pathogenesis provide more satisfactory results and include the topical association of cholesterol with statins, aiming to replace the deficient lipid while inhibiting an initial phase of cholesterol biosynthesis, preventing the accumulation of potentially toxic sterols and other mediators.[6–9]

The present case describes the long-term follow-up (1 to 23 years) of five female patients with CHILD Syndrome in the Pediatric Dermatology outpatient clinic of Hospital das Clínicas, Faculty of Medicine, Universidade de São Paulo, Brazil.

All five cases had CHILD nevi, with pruritus and recurrent infections, which improved when the lesions became thinner and less inflamed. Ipsilateral limbs' hypoplasia with CHILD nevi was the rule; in Case 5, there was aplasia of the right upper limb. Three of the five patients have the left side affected (1, 3, and 4), with cases 1 and 3 having more associated malformations (Table 1). Studies suggest that the right side is more affected (7/3 ratio), but patients with left-sided involvement tend to have a worse prognosis, as visceral abnormalities are more common.[1,2,4]

The two longest-standing patients in the follow-up (Cases 1 and 2) used topical keratolytic agents (10% urea, occlusive salicylic acid), emollients, and calcipotriol at the beginning of treatment, with an unsatisfactory therapeutic response. Cutaneous therapy with lovastatin and cholesterol showed a satisfactory response in four of the five patients.

The average time required to obtain a satisfactory response with therapy based on the disease pathogenesis was two months, with daily use at the beginning of treatment (Fig. 1), which could be reduced to two or three times a week when the skin became thin and less inflamed. A satisfactory response was considered to be the thinning of the CHILD nevi, the reduction of pruritus and abrasions that predispose to infections, also facilitating adaptation for the use of prostheses in hypoplastic limbs, in addition to a reported improvement in quality of life.

Loss of efficacy was observed over the years, a fact not yet described, without improvement with the association of keratolytic agents or calcipotriol. Observing the principle of potency of pharmacological action of statins,[10] lovastatin was replaced with other drugs with more potent action, such as 2% simvastatin and then 2% atorvastatin, when loss of efficacy was identified during follow-up and therapeutic response was re-established. Case 1 was treated with Lovastatin and then switched to Simvastatin, temporarily stabilized, but continues with irregular treatment and recrudescence of lesions. Case 2 required a third formulation, atorvastatin (Fig. 2). Case 3 has remained stable with lovastatin alone for eight years. Cases 4 and 5 were started with simvastatin, are stable, and also satisfied with the obtained results.

☆ Study conducted at the Department of Dermatology, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

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Table 1 Comparative analysis of the clinical characteristics and therapeutic response of 5 cases of CHILD Syndrome.

	Case 1	Case 2	Case 3	Case 4	Case 5
Patient's age	24 years	12 years	8 years	2 years	1 year and 9 months
Time of follow-up	23 years	12 years	8 years	2 years	9 months
Affected side of the body	Left	Right	Left	Left	Right
Predilection for skin lesions in fold areas	Yes	Yes	Yes	Yes	Yes
Discomfort with pruritus and infections in CHILD nevi	Yes	Yes	Yes	Yes	Yes
Limb hypoplasia or agenesis	UL + LL	UL + LL	LL	UL + LL	UL + LL
Other malformations	Scoliosis Hearing loss	Hearing loss	Ovoid vertebral bodies Craniosynostosis Left pyelic ectasia Patent foramen ovale	No	Scoliosis
Treatment with 2% Lovastatin + 2% topical Cholesterol	6 years	9 years	8 years	No	No
Treatment with 2% Simvastatin + 2% topical Cholesterol	4 years	8 months	No	2 years	9 meses
Treatment with 2% Atorvastatin + 2% topical Cholesterol	No	1 year and 6 months	No	No	No
Skin clinical stability	No	Yes	Yes	Yes	Yes
Improvement in quality of life and pruritus with treatment.	Yes	Yes	Yes	Yes	Yes

UL, Upper Limb; LL, Lower Limb.

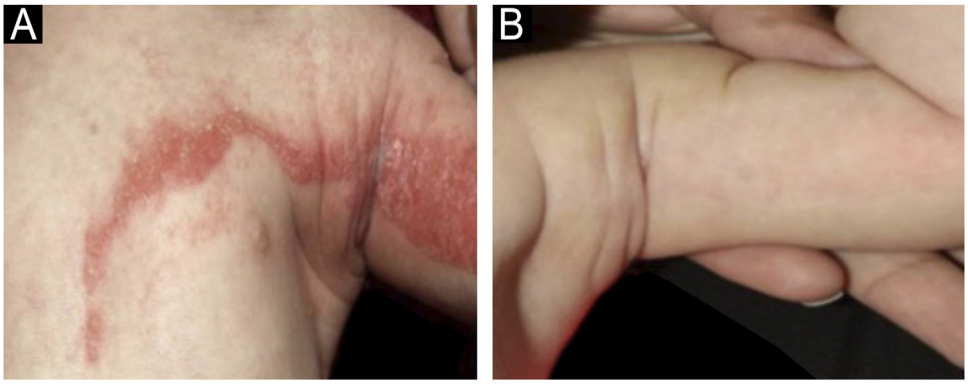

Fig. 1 CHILD nevus, showing Blaschkoid lesion in fold area of a newborn patient (a) without treatment (b) after two months of use of topical 2% Simvastatin + 2% Cholesterol.

Studies with larger sample sizes and long-term follow-up are needed to understand clinical evolution and establish effective therapeutic guidelines. This is the first publication with long-term follow-up of CHILD nevus treatment with statins, focusing on the long-term loss of response to the less potent lovastatin, and subsequent re-establishment of response with the use of topical simvastatin and atorvastatin, with satisfactory results for the patients.

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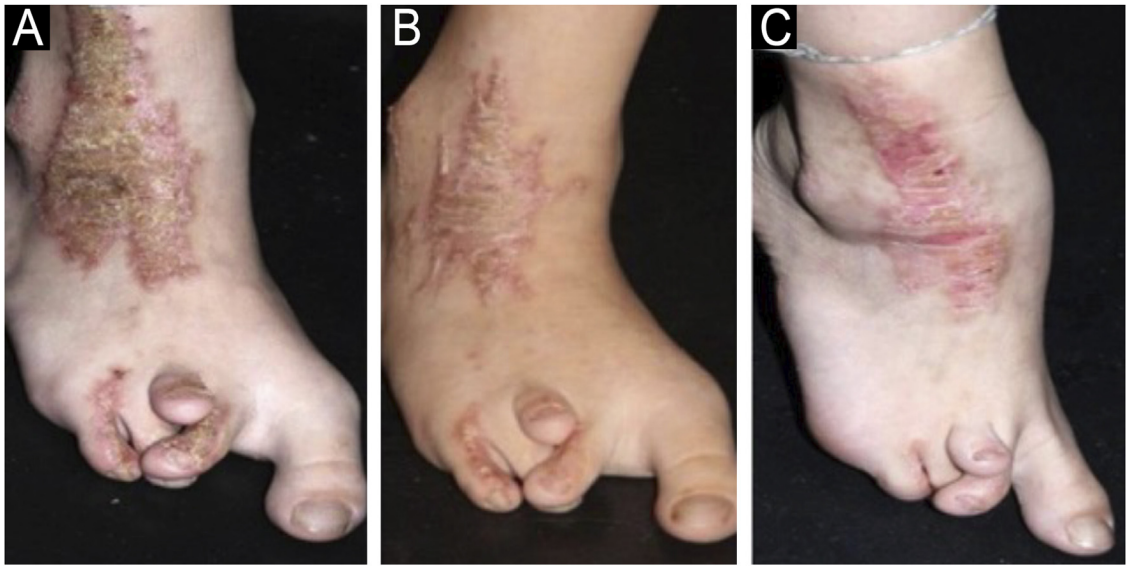

Fig. 2 CHILD nevus on the right lower limb associated with dysplasia. (a) Recurring lesion after nine years of use of 2% Lovastatin + 2% cholesterol. (b) Partial improvement with replacement with 2% simvastatin + 2% cholesterol. (c) Significant improvement after replacement with topical 2% atorvastatin + 2% cholesterol.

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Authors' contributions

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Conflicts of interest

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LETTER – THERAPY

Rapid clinical response in refractory discoid lupus erythematosus treated with anifrolumab☆

Dear Editor,

Cutaneous Lupus Erythematosus (CLE) is an autoimmune disease with variable clinical expression. It may present as an exclusively cutaneous condition or as one of the multiple manifestations of Systemic Lupus Erythematosus (SLE). Discoid Lupus Erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus. Lesions typically affect photoexposed areas and appear as indurated erythematous plaques that evolve with follicular hyperkeratosis, atrophy, and central hypopigmentation with peripheral hyperpigmentation. These lesions can lead to severe and disfiguring scarring, particularly when located on the nose, ear pinnae, and eyelids.[1]

Anifrolumab is a fully human monoclonal antibody targeting the type I interferon receptor subunit.[1] It was recently approved for the treatment of moderate-to-severe SLE and is administered as a 300 mg intravenous infusion every four weeks. Although it is not currently approved for the treatment of CLE, data from phase III clinical trials (TULIP-1 and TULIP-2) have shown significant improvement in CLE manifestations in patients with SLE.[2] Additionally, several case reports have demonstrated its rapid and marked efficacy in DLE.[3–5]

We report a case of severe, treatment-resistant discoid lupus erythematosus with facial involvement that showed a dramatic and rapid response to anifrolumab.

A 56-year-old woman with Fitzpatrick skin phototype IV and history of smoking presented with longstanding DLE involving the face, auricular region, and forearms. She had been followed in Dermatology for over 10 years and had previously been evaluated for systemic involvement, which was excluded on multiple occasions. Her past treatments included high-potency topical corticosteroids, calcineurin inhibitors, oral prednisolone, and hydroxychloroquine, with inadequate disease control.

After a two-year loss to follow-up, she was re-evaluated. She had continued hydroxychloroquine 400 mg/day and topical corticosteroids but reported no improvement. Clinical examination revealed erythematous-crusted plaques with central hypopigmentation and peripheral hyperpigmentation, atrophy, and signs of chronic inflammation, predominantly affecting the malar region, nasal pyramid, and upper lip. Additional lesions were present on the auricular conchae and forearms. Systemic lupus erythematosus was again excluded. Methotrexate was initiated at 10 mg/week and increased to 20 mg/week, along with strict photoprotection. After one year of methotrexate therapy, the patient showed no meaningful clinical improvement (Fig. 1A–B). Given the severity and resistance to standard therapies, anifrolumab was introduced.

A remarkable clinical response was observed after only eight weeks of treatment. There was near-complete resolution of facial inflammation and scaling, with noticeable reduction in lesion size and repigmentation at the periphery of previously hypopigmented areas (Fig. 2A–B). No adverse events were reported.

This case highlights a severe, scarring form of DLE that was unresponsive to multiple standard therapies, including hydroxychloroquine, topical and systemic corticosteroids, and methotrexate. Treatment with anifrolumab led to a rapid and substantial clinical improvement, suggesting that type I interferon blockade may be a promising therapeutic option for refractory CLE, particularly in patients with chronic and atrophic lesions and poor quality of life. This case underscores the potential role of anifrolumab in managing difficult-to-treat CLE and supports the need for further studies to establish its efficacy and safety in cutaneous forms of lupus beyond systemic lupus erythematosus.

☆ Study conducted at the Unidade Local de Saúde Almada-Seixal, Almada, Portugal.

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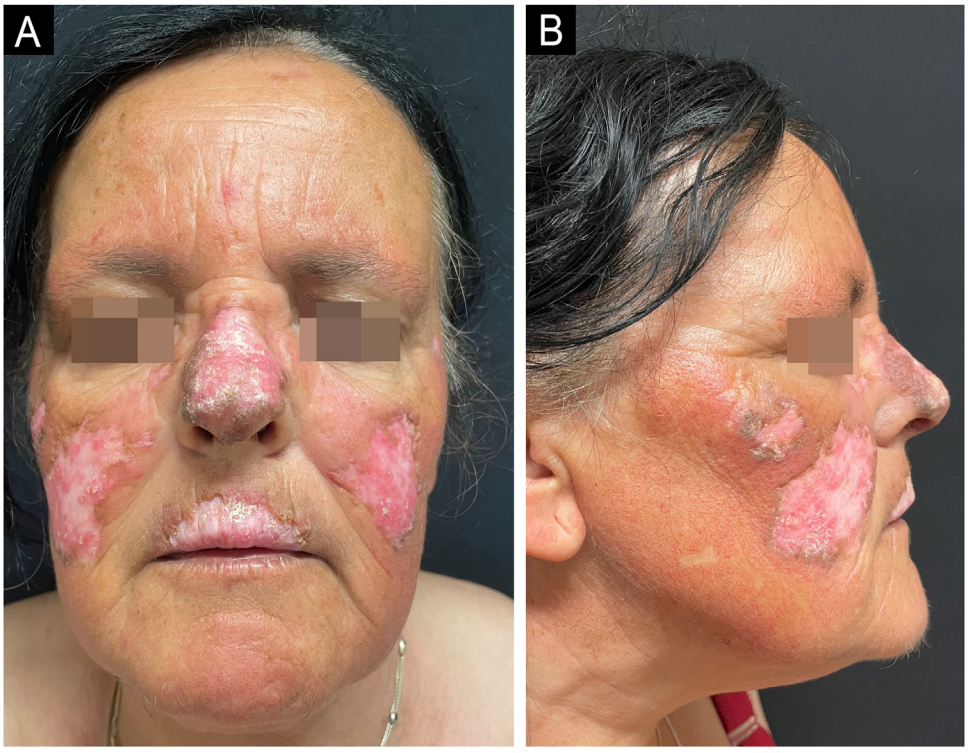

Fig. 1 (A–B) Chronic cutaneous lupus erythematosus of the face before treatment with Anifrolumab.

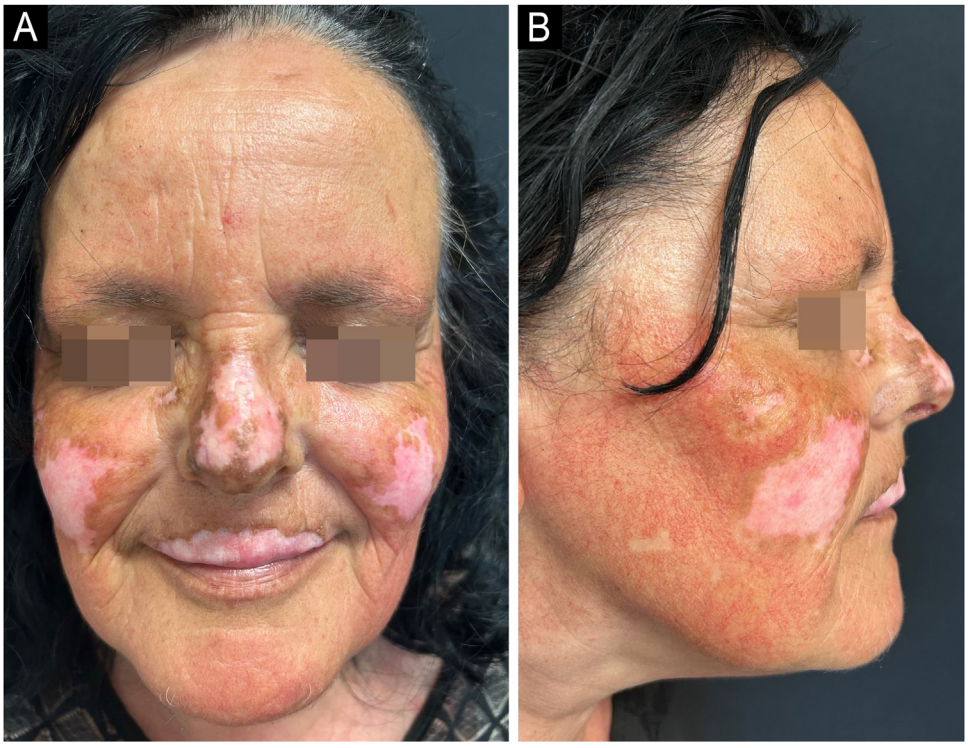

Fig. 2 (A–B) Chronic cutaneous lupus erythematosus of the face after only 8 weeks of treatment with Anifrolumab.

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Research data availability

Does not apply.

Conflicts of interest

None declared.

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LETTER – THERAPY

Treatment of extensive oral leukoplakia with diode laser – Successful case report☆

Dear Editor,

Oral leukoplakia (OL) is the most common potentially malignant disorder, defined as a non-removable white patch or plaque that cannot be clinically or microscopically characterized as another lesion; therefore, its diagnosis is made by exclusion.[1] OL has a variable malignant transformation rate, between 3.5% and 9.5%.[2,3] After confirmation of its diagnosis through incisional biopsy, recommendations for discontinuing risk factors such as smoking and alcohol consumption, and the application of surgical or non-surgical therapeutic methods are given to achieve its resolution.[1]

Non-surgical approaches include the topical application of retinoids, bleomycin, cyclooxygenase inhibitors, and photodynamic therapy. However, these have been associated with a high recurrence rate, adverse effects, and a lack of scientific evidence.[1] Surgical intervention should be performed, whenever possible, using conventional excision procedures with a cold scalpel or other technologies such as high-power laser, which has been extensively explored in the last decade.

In more extensive leukoplakia, the cold scalpel procedure becomes challenging due to the risk of bleeding and the infeasibility of joining the tissues by suturing. Given the aforementioned limitations, the diode laser emerges as a viable option, as it allows a precise incision, ensures hemostasis, and eliminates the need for suturing.[4] Long-term studies on the prognosis of OL after surgical removal with a diode laser are scarce.[5–7] This article describes a case of extensive OL, with high-grade epithelial dysplasia, in the buccal mucosa, successfully treated by surgical laser.

A 57-year-old male patient, a smoker (15 cigarettes a day for 43 years), showed, four years before, a painless white plaque with a slightly verrucous surface, approximately 3 cm in size, located on the left buccal mucosa

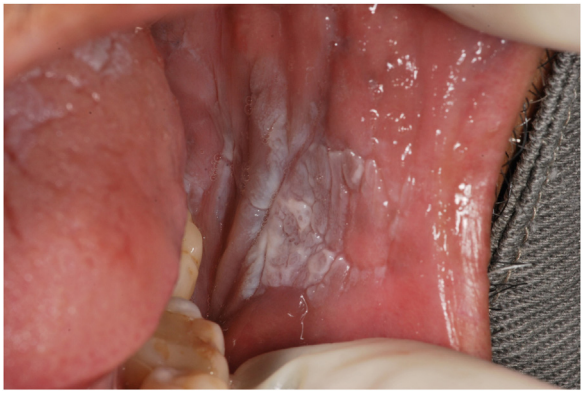

Fig. 1 Initial image of the lesion in the buccal mucosa on the left side.

(Fig. 1). Given the appearance of the lesion, the diagnostic hypothesis was leukoplakia. An incisional biopsy was performed, and smoking cessation instructions were given. Microscopic examination revealed high-grade epithelial dysplasia, corroborating the clinical diagnosis of leukoplakia (Fig. 2). Considering the lesion location and extent, the treatment of choice was complete excision using High-Power Diode Laser (TW Surgical Laser, MMOptics, São Carlos-SP, Brazil), delivering the beam with a 400 μm optical fiber, 808 nm wavelength (infrared) in continuous mode and 1.5 W power. The procedure was performed under local infiltrative anesthesia with 2% mepivacaine with vasoconstrictor (1.8 mL). For postoperative care, oral analgesics (1 g dipyrone every 12 hours in case of pain) and 0.12% chlorhexidine digluconate mouthwash, three times a day, for 14 days were prescribed. After seven days, the area appeared raw and painless (Fig. 3). After 30 days, no recurrence was observed, and complete healing of the area was noted. After 18 and 30 months (Fig. 4), clinical examination revealed no recurrence of the lesion. Despite instructions regarding smoking cessation, the patient still reports smoking, although less frequently. Therefore, continuous follow-up is essential.

The literature is unanimous on the positive effects of lasers in oral surgeries, such as absence of mechanical trauma, adequate hemostatic capacity, visualization of the surgical field, antisepsis of the surgical wound, elimination of the need for sutures, and pain and edema reduction in

☆ Study conducted at the Stomatology Refresher Course, Instituto Diagnosis, Maringá, PR, Brazil.

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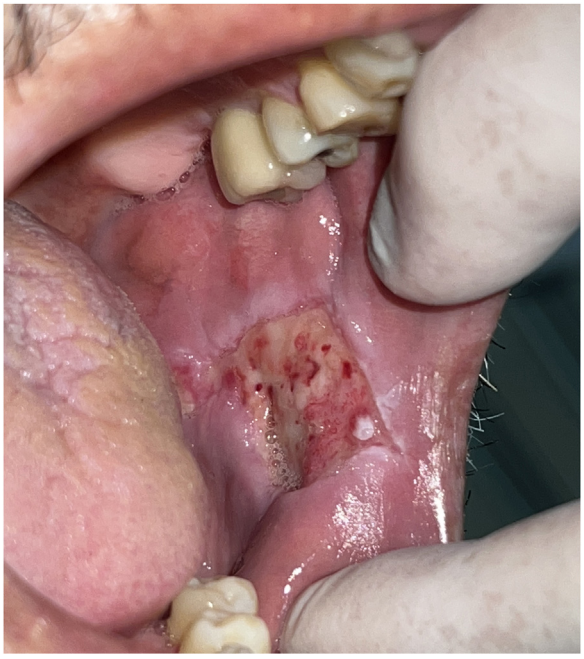

Fig. 2 Representative image of healing seven days after surgery with a diode laser.

the postoperative period.[4,8–10] The thermal impact of the surgical laser can cause the closure of blood and lymphatic vessels, minimizing the possibility of neoplastic cells being disseminated to other organs through circulation.[9]

In the present case report, the choice of the diode laser was mainly due to the extent and anatomical site of the lesion, aiming to provide the patient with the benefits this surgical technique offers. The scar evolution was carefully monitored, corroborating the postoperative advantages that the technique provides. In this case report, after 30 months, the clinical aspect did not reveal recurrences, suggesting the effectiveness of the surgical procedure and excellent prognosis.

Based on this case report, it can be suggested that the use of diode laser in selected cases of OL offers the possibility of removing extensive lesions in a single surgical procedure, with decontamination of the surgical field, residual photobiomodulation effect (modulation of inflammation, analgesia, and acceleration of healing), with excellent hemostasis and visualization of the surgical field, as well as reduced postoperative medication and greater patient comfort. However, the use of this technology is still limited due to the small number of qualified professionals and high cost.

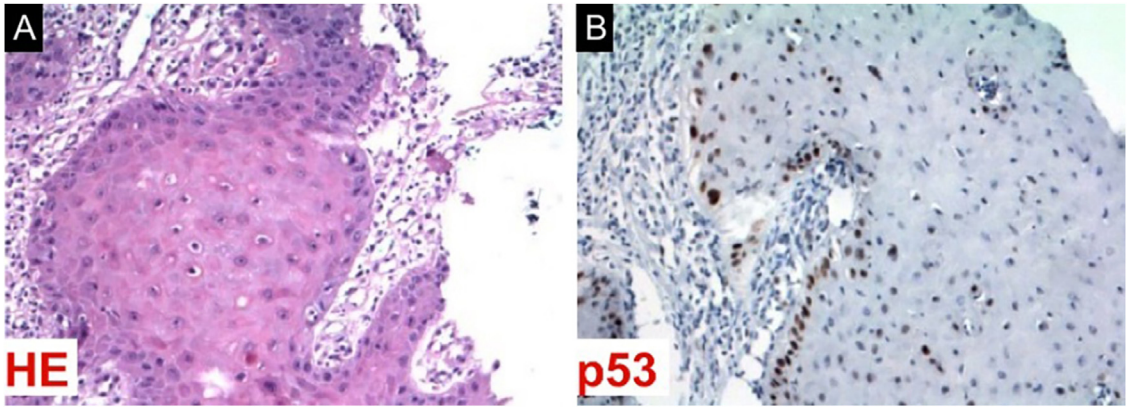

Fig. 3 (A) Photomicrograph showing epithelium with high-grade dysplasia. (B) Immunohistochemical study revealing expression for the tumor suppressor gene TP53.

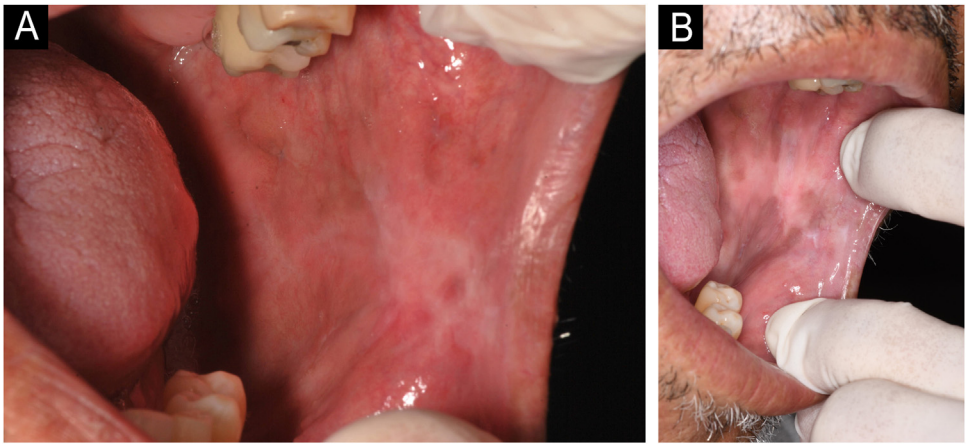

Fig. 4 Appearance of the left buccal mucosa after 30 months. The pigmented areas are suggestive of melanosis due to smoking.

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Research data availability

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Conflicts of interest

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LETTER - THERAPY

Type IV pityriasis rubra pilaris treated with ixekizumab

Dear Editor,

Juvenile Pityriasis Rubra Pilaris (PRP) is a rare inflammatory dermatosis of unknown etiology, presenting diagnostic and therapeutic challenges.[1] Despite a recognized peak incidence in early childhood, reports on the clinical management of pediatric PRP, particularly with newer biologic therapies, remain scarce. Recent studies have implicated immunologic pathways, particularly Interleukins (IL) 17 and 23, in the pathogenesis of PRP, suggesting potential targets for therapeutic intervention.[1]

An 8-year-old girl presented with a two-week history of progressive lesions, initially localized to the soles and subsequently extending to the palms, face, scalp, knees, elbows, and occipital and anogenital region. Symptoms included pruritus without diurnal variation. She had neither history of febrile episodes, recent medication use or vaccination, nor family history of dermatological disorders. Clinical examination revealed diffuse, symmetrical, orange, waxy palmoplantar keratoderma with fissures, accompanied by erythematous, scaly plaques with follicular accentuation on the elbows, knees, anogenital, face, scalp, and auricular areas (Fig. 1A–D). Histopathological findings confirmed PRP, showing characteristic focal and confluent hypergranulosis with alternating orthokeratosis and parakeratosis. Based on the clinical presentation and the histopathological findings, the patient was diagnosed with juvenile PRP type IV (circumscribed juvenile form). Initial treatment with high-potency topical corticosteroids yielded no improvement. Methotrexate 15 mg/week alongside a short course of prednisolone (10 mg/day) also proved ineffective. Due to the disease's severity and impact on quality of life, off-label ixekizumab (with an 80 mg loading dose) was introduced, in addition to methotrexate. Within four weeks of initiating therapy, the patient showed significant improvement. By the five-month follow-up, only post-inflammatory hypopigmentation remained on the knees and elbows, with complete resolution of lesions in the anogenital, face and scalp regions and a marked reduction in palmoplantar keratoderma infiltration (Fig. 2A–D). She successfully discontinued topical corticosteroids, began tapering methotrexate, and continues on ixekizumab (40 mg every four weeks) without any reported adverse effects, leading to a substantial improvement in both her quality of life and that of her family.

Given the heterogeneity of PRP, there is no universal treatment approach.[1] In our case, systemic retinoids were avoided due to the risk of premature epiphyseal closure. Instead, methotrexate was initiated as a second-line therapy; however, no response was observed after two months. Biologic therapies approved for psoriasis have been increasingly used in treatment-refractory PRP cases.[1]

Among anti-TNF-alpha agents, etanercept and adalimumab have been used to treat pediatric PRP, along with ustekinumab.[1] Responses have been variable; for instance, although many patients treated with ustekinumab showed impressive improvement, not all experienced sustained or durable responses.[1] To our knowledge, no cases of pediatric PRP treated with anti-IL-23 agents have been reported to date.

Regarding anti-IL-17 therapies, their mechanism of action in PRP likely involves the inhibition of IL-17-mediated keratinocyte proliferation and inflammatory pathways.[1,2] Ixekizumab, an anti-IL-17A antibody, is FDA-approved for the treatment of moderate to severe plaque psoriasis in children aged six years and older. While it has demonstrated efficacy in adult PRP, its safety and effectiveness in pediatric PRP remain to be fully established.[1] Similarly, secukinumab, another anti-IL-17A antibody, has shown efficacy in both adult PRP and in a reported case of type V PRP (atypical juvenile form).[1] Our case demonstrated remarkable subjective and objective improvement with ixekizumab, further supporting the only other reported case in the literature.[3] Ixekizumab was preferred over secukinumab because its single loading dose is more convenient than secukinumab's four weekly injections, making it a more practical choice for children. Regarding drug discontinuation, data on relapse rates in PRP remain limited. Based on the natural history of juvenile type IV PRP, the prognosis is uncertain; however, a proportion of cases resolves within 1–3 years of onset, with some achieving complete

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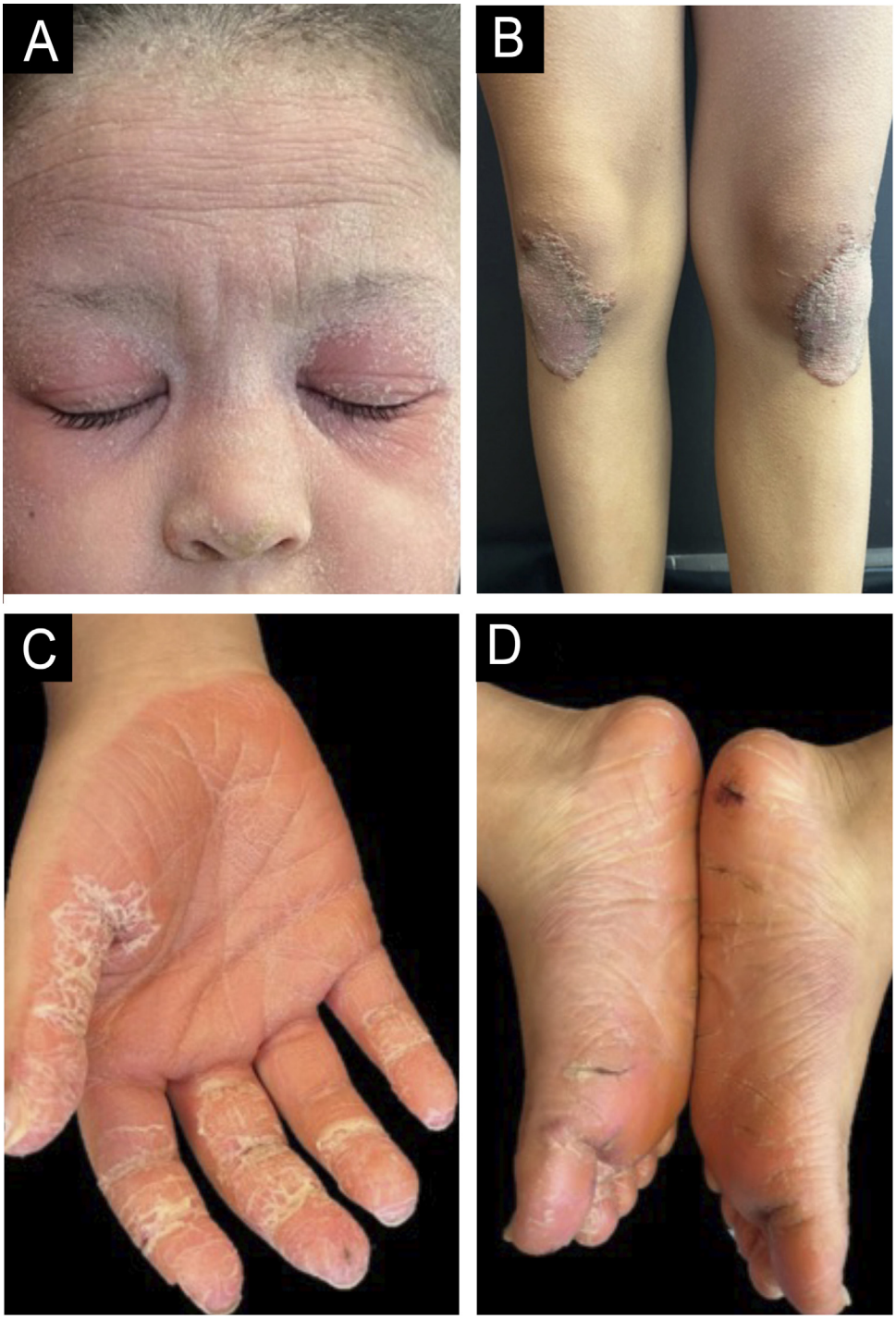

Figure 1 (A–B) Erythematous, scaly plaques with follicular accentuation on the face and knees. (C–D) Diffuse, symmetrical, orange, waxy palmoplantar keratoderma with fissures.

remission by late adolescence.[2] Considering the clinical context, ixekizumab therapy will be maintained with a planned gradual tapering regimen, individualized according to the patient's tolerability and disease control, with close surveillance for therapeutic response, adverse events, and risk of recurrence.

This case highlights the successful off-label use of ixekizumab in pediatric PRP, demonstrating its potential as a safe and effective treatment option. It offers a promising alternative to conventional therapies such as methotrexate and acitretin, which are frequently associated with significant toxicity and limited tolerability in children.

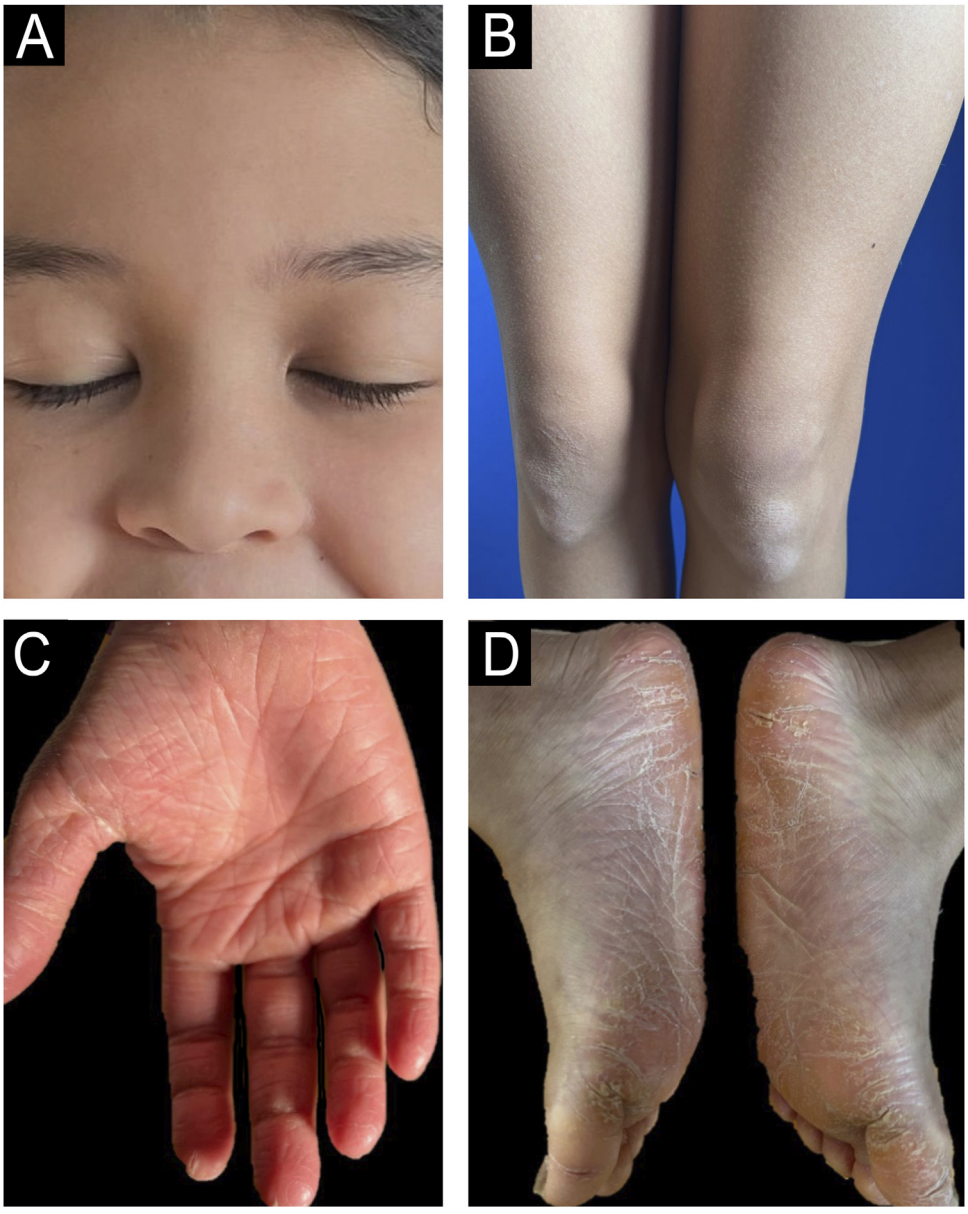

Figure 2 (A–B) By the five-month follow-up, only post-inflammatory hypopigmentation remained on the knees, with complete resolution in the face and scalp. (C–D) Marked reduction in palmoplantar keratoderma.

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Conflicts of interest

None declared.

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CORRESPONDENCE

Comment on ''The relationship of FricTest® responses with an urticaria activity score, urticaria control test and quality of life scales in patients with symptomatic dermographism''☆

Dear Editor,

We read with great interest the study by Kıraç et al. examining the associations between FricTest® response levels and clinical assessment tools in symptomatic dermographism.[1] Their work contributes to a practical effort to quantify disease activity and patient-reported burden using a tool with potential for broad clinical utility. The authors' findings demonstrated a moderate correlation between changes in the 4.5 mm and 4 mm FricTest® responses and validated scales, such as the urticaria control test (UCT), urticaria activity score (UAS), and dermatology life quality index (DLQI), suggesting that higher-intensity wheal reactivity may be more clinically informative.

However, key aspects of the statistical approach may limit the confidence in the strength and applicability of these associations. The analysis relied on Spearman correlation coefficients but did not report confidence intervals, which restricts the interpretability of the observed effect sizes. More importantly, correlation does not imply predictive capacity. Without regression modeling to adjust for baseline disease severity or demographic covariates, it remains unclear whether changes in FricTest® values are independently associated with treatment response or simply reflect regression to the mean. This limitation is not merely a technical issue. In a clinical setting, dermatologists must decide whether repeating the FricTest® meaningfully informs therapeutic adjustments or patient counseling. Without understanding its added predictive value over conventional scales (e.g., UCT), the test's standalone contribution remains unclear.

Furthermore, the lack of correlation between FricTest® changes and visual analog scale (VAS) scores for itch and burning raises questions about the pathophysiological specificity of this measurement. If the test reflects mechanical wheel responsiveness but not subjective symptom severity, its role may be limited to diagnostic rather than longitudinal monitoring contexts.[2,3] This disconnect merits closer evaluation, particularly as symptomatic dermographism is fundamentally a patient-experienced condition.

Despite these concerns, this study adds value by suggesting that lower-pressure stimuli (3.5 and 3 mm) do not correlate well with validated scales. This narrows the clinically useful thresholds and may help streamline test administration protocols. This also reinforces the fact that excessive granularity in provocation testing may introduce statistical noise without clinical gain.

We commend the authors for integrating disease-specific and quality-of-life instruments in a unified analysis and for contributing data on a relatively under-investigated diagnostic tool. Future research should focus on validating these findings through multivariable models and exploring whether FricTest® changes the forecast of relapse or remission when used alongside standard scales.

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Conflicts of interest

None declared.

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CORRESPONDENCE

Comment on ''The relantionship of FricTest responses with an urticaria activity score, urticaria control test and quality of life scales in patients with symptomatic dermographism'' - Reply☆

Dear Editor,

We sincerely thank Dr. Prajnasini Satapathy and colleagues for their interest in our article and for their constructive observations. We appreciate the opportunity to clarify certain methodological aspects and the clinical interpretation of our findings.

Regarding the statistical approach, our study used the Spearman correlation test, as the Kolmogorov-Smirnov analysis indicated a non-parametric data distribution. Although confidence intervals for correlation coefficients were not provided, both the p-values and correlation magnitudes were transparently reported to indicate the direction and strength of the associations. In future studies with larger and more diverse populations, we intend to include 95% Confidence Intervals to improve precision and reproducibility.

The purpose of our study was exploratory in nature – to examine whether FricTest® responses correlate with validated disease activity and quality-of-life instruments such as UAS, UCT, and DLQI. We fully agree that regression modeling would offer additional insight into predictive value; however, given the limited sample size (n = 71) and single-center design, such analyses would have risked model overfitting. Future multicenter studies with larger cohorts are planned to evaluate whether FricTest® thresholds independently predict treatment response after controlling for clinical confounders.

The lack of correlation between FricTest® changes and VAS scores can be explained by the different domains these measures assess. FricTest® quantifies objective mechanical wheal reactivity, whereas VAS reflects patients' subjective symptom perception, such as itch or burning. Similar discrepancies between objective and subjective parameters have been reported in other studies of chronic inducible urticaria.[1,2] This divergence highlights that FricTest® primarily captures a physical threshold of dermographism rather than subjective disease burden.

We also emphasize that our study did not aim to demonstrate the superiority of FricTest® over established tools, but rather to explore its complementary role. The finding that 4 mm and 4.5 mm tips correlated best with changes in UCT and DLQI supports the clinical utility of FricTest® as an adjunctive monitoring instrument, potentially refining objective assessment in symptomatic dermographism.

As acknowledged in the article, the limited sample size and single-center setting constrain generalizability. Nevertheless, this pilot study was conducted within a certified UCARE center to generate preliminary data for larger validation projects.

In conclusion, we are grateful for the readers' valuable comments. We share the view that objective and standardized measures such as FricTest® may enhance disease activity monitoring when interpreted alongside patient-reported outcomes. We hope our response clarifies the study's intent and methodological framework and contributes to an informed discussion on quantitative tools in chronic inducible urticaria.

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Rukiye Yasak Güner: Writing, methodology.

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Research data availability

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CORRESPONDENCE

Letter to the Editor regarding: ''Pre-and post-analytical guidelines for the microscopic diagnosis of melanoma: recommendations from the Brazilian Society of Pathology''☆

Dear Editor,

We would like to express some concerns regarding the conclusions of Xavier-Junior et al.[1] The authors stated that ''the use of Mohs Micrographic Surgery (MMS) is not validated for the management of melanocytic lesions and may compromise diagnostic accuracy'', referencing a study that evaluated bias in trials involving both MMS and Staged Excision (SE).[2]

In that study, the authors concluded that randomized, bias-controlled trials comparing Wide Local Excision (WLE), SE, and MMS are needed, without asserting that MMS or SE are invalid. Furthermore, the study made no reference to WLE research, including those addressing lesions on the head and neck, which might have contributed to a more technically informed comparison among techniques.

The authors also observed that freezing a tumor suspected of melanoma may compromise diagnostic accuracy. One referenced study mentioned two investigations. The first discouraged the use of frozen sections for prognostic parameters – a point with which we agree. The diagnosis and microstaging of melanoma should be performed on permanent paraffin-embedded sections. It is important to note, however, that the same study highlighted that, in specific situations, MMS may offer advantages in the surgical management of melanoma.

The second referenced study[3] compared margin assessment in frozen en face sections of 13 melanomas with subsequent paraffin sections. However, the small and heterogeneous sample, lack of technical standardization, and the flawed assumption that deeper paraffin sections represent the gold standard severely limit its conclusions. The study measures sampling variability rather than true diagnostic accuracy or recurrence risk. It is known that 4 μm sections and rapid-freezing techniques are required for optimal histologic quality.

The National Comprehensive Cancer Network recommends MMS as an option for minimally invasive melanomas located in anatomically constrained areas. A recent systematic review and meta-analysis demonstrated higher cure rates than those achieved with WLE, with significantly lower local recurrence.[4] In addition, MMS has been associated with improved overall survival in head and neck melanomas.[5]

In special situations – such as large, ill-defined lesions located in anatomically constrained areas – techniques that allow complete margin assessment are crucial. In such cases, traditional histologic processing methods that assess only a portion of the true surgical margin raise concerns about incomplete excision and recurrence.

Despite ongoing criticism regarding the challenges of frozen-section analysis in melanocytic lesions, margin evaluation during MMS has proven effective, is widely validated in the literature, and is endorsed by leading international oncology panels.

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Roberto Gomes Tarlé: Critical literature review; manuscript critical review; preparation and writing of the manuscript; study conception and planning.

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Conflicts of interest

None declared.

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CORRESPONDENCE

Letter to the Editor regarding: ''Pre- and post-analytical guidelines for the microscopic diagnosis of melanoma: recommendations from the Brazilian Society of Pathology'' – Reply☆

Dear Editor,

We read with great interest the letter from Dr. Cunha regarding our recently published guideline.[1] Both the College of American Pathologists[2] and the NCCN[3] strongly discourage the use of frozen sections for most melanocytic lesions when standard clinical margins can be achieved without significant limitations. They emphasize that accurate melanoma diagnosis continues to rely on Hematoxylin and Eosin (H&E) sections from formalin-fixed, paraffin-embedded tissue, supplemented, when appropriate, by immunohistochemistry,[2–4] since melanoma represents a heterogeneous group of tumors with multiple histologic subtypes and distinct biological behaviors.[4]

The recommended peripheral surgical margins and methods for their assessment in head and neck melanoma and lentigo maligna remain subjects of considerable debate. This uncertainty largely reflects the lack of consistent, well-designed prospective studies addressing the management of these challenging lesions. A recent critical review identified a very high risk of bias (97.9%) among studies evaluating Mohs Micrographic Surgery (MMS) for melanoma.[5]

Although robust validation for the use of MMS in melanocytic lesions is still lacking, recent advances in this field deserve recognition. According to the latest NCCN guidelines for cutaneous melanoma, MMS – or other techniques that enable comprehensive margin assessment – may provide equivalent or even superior local control for certain pT1a melanomas in selected sites, particularly on the face, ears, and acral areas.[3] It is essential, however, that potential candidates be carefully selected and thoroughly counseled. The successful use of these techniques, which apply only to a small subset of melanoma patients, requires a well-trained and experienced multidisciplinary team. It is important to highlight that, considering melanomas arising in skin with extensive cumulative sun damage, histopathologic interpretation can be especially challenging. This difficulty arises from actinic melanocytic alterations and ill-defined tumor margins with ''skip'' areas[4] – factors that may be further compounded by technically suboptimal slides.

Finally, as also acknowledged by the NCCN,[3] no prospective comparative studies have yet evaluated the different excision methods for melanoma. This gap leaves the topic open for continued scientific discussion. Future prospective, independent, and well-designed studies are needed to clarify the potential role of MMS and other surgical techniques in the management of melanocytic lesions.

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Authors' contributions

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