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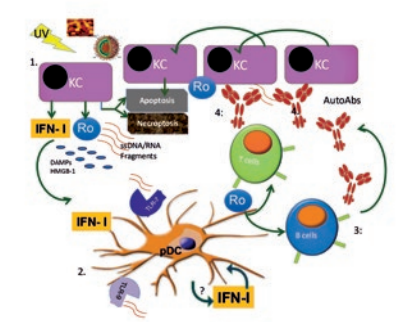

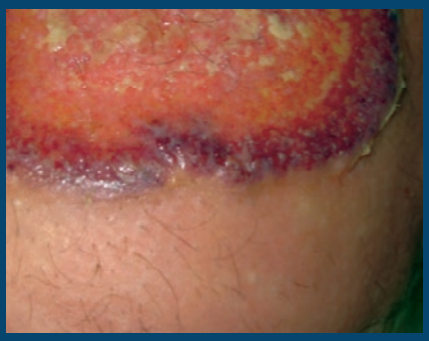

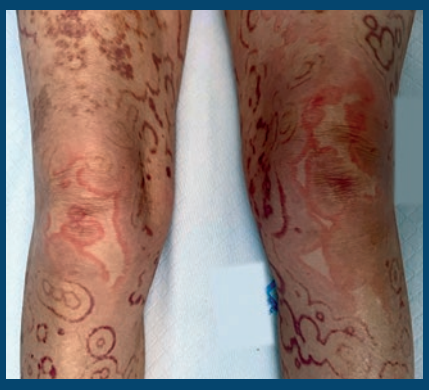

In this issue:

Portuguese Journal of Dermatology and Venereology

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1. Teste clínico com sérum + creme SPF50, resultado médio na superfície das manchas escuras calculado em 33% dos melhores resultados em painel, após 2 meses. O resultado médio em 35 mulheres é de -65%
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LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

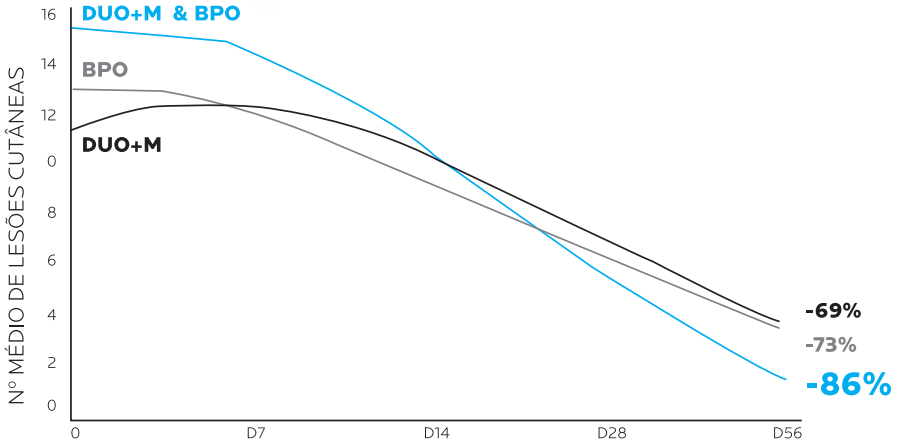
EFFACLAR DUO+M

COM **[PHYLOBIOMA]**
INGREDIENTE ATIVO VEGETAL RICO EM POLIFENÓIS. PARA ATUAR ESPECIFICAMENTE NO **FILOTIPO IA1** DA ***C. ACNES***
+
[AQUA POSAE FILIFORMIS, ÁCIDO SALICÍLICO, LHA, ZINCO, NIACINAMIDA, MANOSE, PROCERAD]

MODULAÇÃO DO **MICROBIOMA**
REDUZ A **SEVERIDA DA ACNE** E A **HIPERPIGMENTAÇÃO PÓS-INFLAMATÓRIA**
AÇÃO ANTIRRECIDIVA
INDICADO EM **TERAPÊUTICA ADJUVANTE**

TESTADO EM COMBINAÇÃO COM AS PRINCIPAIS TERAPÊUTICAS PARA A ACNE
BPO, ADAPALENO, EPIDUO®, RETINÓIDES, ERITROMICINA E/OU TRETINOÍNA, ANTIBIÓTICOS TÓPICOS

POTENCIA O TRATAMENTO EM TERAPÊUTICA ADJUVANTE



Estudo clínico, com 64 doentes em 3 grupos: EFFACLAR DUO+, BPO e EFFACLAR DUO+ em combinação com BPO, durante 56 dias.

COM **[PHYLOBIOMA]**
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TESTADO EM TODOS OS FOTOTIPOS. TESTADO A PARTIR DOS 10 ANOS.

LA ROCHE-POSAY. *LIFE-CHANGING SKINCARE*

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

A ROTINA LIPIKAR

MELHORA EM 93% A SEVERIDADE GLOBAL DA **DERMATITE ATÓPICA** EM TODOS OS FOTOTIPOS[1]

1
LIPIKAR
ÓLEO LAVANTE AP+

2
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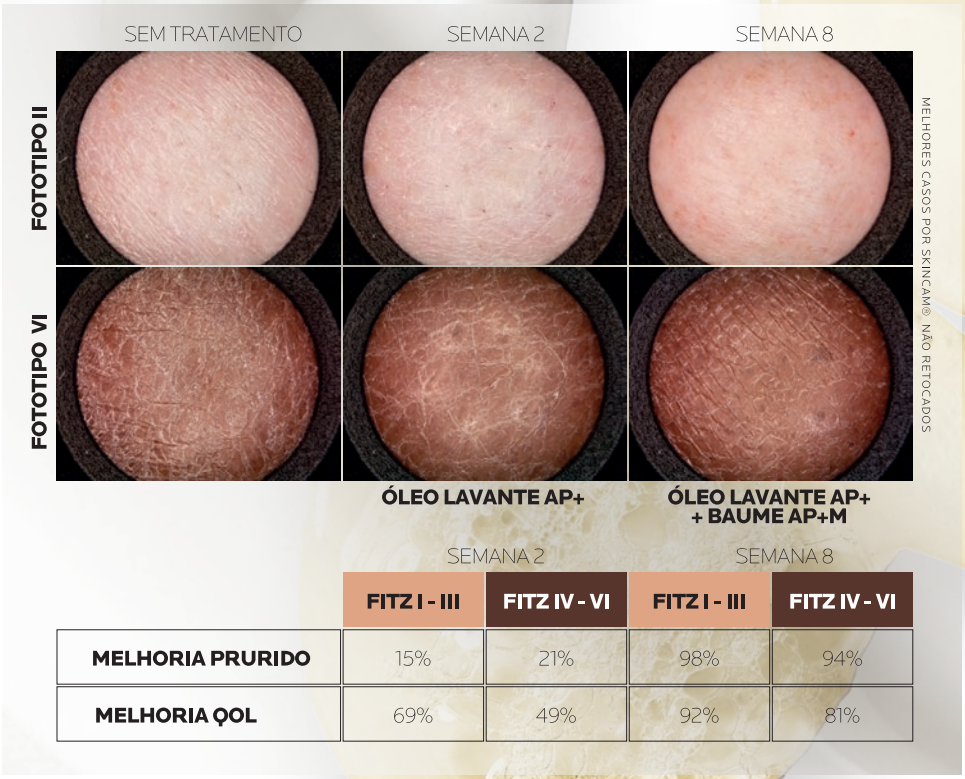

	SEMANA 2		SEMANA 8	
	FITZ I - III	**FITZ IV - VI**	**FITZ I - III**	**FITZ IV - VI**
MELHORIA PRURIDO	15%	21%	98%	94%
MELHORIA QOL	69%	49%	92%	81%

Estudo clínico em 69 indivíduos com dermatite atópica. Fototipos I - VI com diversas etnias. Utilização isolada de Lipikar Óleo Lavante AP+ durante 2 semanas (1x/dia), seguida de Lipikar Óleo Lavante AP+ e Lipikar Baume AP+M (2x/dia) durante 8 semanas. A severidade da dermatite atópica foi medida utilizando as escalas: Investigator Global Assessment (IGA) and Eczema Area and Severity Index (EASI). A melhoria do prurido foi avaliada pela escala Worst Itch Numeric Rating Scale (WI-RNS). A melhoria da qualidade de vida foi avaliada pela escala Quality of life assessed by Dermatology Life Quality Index (DLQI).

LA ROCHE-POSAY. *LIFE-CHANGING SKINCARE*

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Portuguese Journal of Dermatology and Venereology

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EDITORIAL

The Portuguese Journal of Dermatology and Venereology striving for 2025

Margarida Gonçalo[1,2] and *João Borges-da Costa[3]*

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The Portuguese Journal of Dermatology and Venereology (PJDV), the official publication of the Portuguese Society of Dermatology and Venereology, has been published regularly for 82 years, initially under the designation of Trabalhos ou Revista da Sociedade Portuguesa de Dermatologia e Venereologia. In 2022, we changed the editorial board, the publisher and adopted the English as the official language of the journal, just keeping the Portuguese language in the abstracts and keywords, to be in line with the main scientific language of dermatology and venereology. Since then, we have been receiving manuscripts from all over the world that have highly enriched the scientific content of the journal. This was, however, still insufficient for indexation of PJDV in PubMed Central, although it has already been accepted in several other important indexation platforms, such as Scopus, Scielo, RCAAP, Google Scholar, and DOAJ.

At this moment, we are again renewing the editorial team to engage younger dermatologists, to try to increase the number and quality of submitted manuscripts, especially from Portuguese dermatologists whose high quality of clinical and basic dermatological research is highly appreciated and dispersed through many publications in foreign journals. This effort to publish in "our national journal" and further enrich its scientific and educational content is mandatory if we really want to be successful in the next application for indexation in PubMed. It is our intention to involve more the new generation of dermatologists or of future dermatologists and the different working groups of our dermatological society and engage the new generation to further increase the visibility of our journal in social media.

With the publication of this last number of 2024, we want to thank all the authors who have trusted the Journal and contributed to enrich its content, all the reviewers who, with their suggestions and comments, have improved the quality of the manuscripts and all the editorial team who has made the success of this journal for the past 2 years.

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REVIEW ARTICLE

Pyoderma gangrenosum - An update and literature review

Pioderma gangrenoso - Uma atualização e revisão da literatura

Leandro Costa[1], André Aparício-Martins[2], and Margarida Gonçalo[1,2]*

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Abstract

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis, often associated with systemic diseases, including inflammatory bowel disease, rheumatoid arthritis, and hematological disorders. Its etiopathogenesis is complex, including neutrophil dysfunction, immunological dysregulation, and genetic alterations. PG lesions can be single or multiple, with varying sizes and morphologies, affecting different anatomical areas. The most common clinical variant is the ulcerative/classic, but bullous, pustular, vegetative, peristomal, and post-surgical variants are also described. Indeed, the diagnosis of PG is challenging due to the heterogeneous clinical presentation and the absence of specific analytical and histopathological findings. Moreover, its lesions can mimic cutaneous ulcers of other etiologies. A wide array of complementary tests may be required not only to rule out alternative diagnoses but also to investigate underlying systemic diseases and extracutaneous manifestations. PG has a significant impact on the quality of life. Its treatment relies on a multimodal approach aimed to reduce disease activity, optimize wound healing, manage pain, and treat associated comorbidities. Topical and systemic immunomodulatory drugs, analgesics, and appropriate wound care are the available therapeutic options. Therefore, this review provides a narrative synthesis of the published literature, contributing to a better understanding of the disease and an optimized approach to these patients.

Keywords: Pyoderma gangrenosum. Neutrophilic dermatosis. Autoinflammation. Autoimmunity. Immunosuppression.

Resumo

O pioderma gangrenoso é uma dermatose neutrofílica frequentemente associada a doenças sistémicas, nomeadamente doença inflamatória intestinal, artrite reumatóide e distúrbios hematológicos. A sua etiopatogenia é complexa, incluindo disfunção dos neutrófilos, desregulação imunológica e alterações genéticas. As lesões do pioderma gangrenoso podem ser únicas ou múltiplas, com tamanhos e morfologias variadas, afetando diferentes áreas anatómicas. A variante clínica mais comum é a ulcerativa/clássica, mas as variantes bolhosa, pustulosa, vegetativa, periestomal e pós-cirúrgica estão também descritas. De facto, o diagnóstico de pioderma gangrenoso é desafiante devido à apresentação clínica heterogénea e à ausência de alterações laboratoriais e histopatológicas específicas. Além disso, as suas lesões podem mimetizar úlceras cutâneas de inúmeras etiologias. Um vasto conjunto de exames complementares pode ser necessário não só para excluir diagnósticos alternativos, mas também para investigar doenças sistémicas subjacentes e manifestações extracutâneas. O pioderma gangrenoso tem um impacto significativo na qualidade de vida. O seu tratamento baseia-se numa abordagem

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multimodal com o objetivo de reduzir a atividade da doença, otimizar a cicatrização das feridas, controlar a dor e tratar comorbilidades associadas. Imunomoduladores tópicos e sistémicos, analgésicos e cuidados de penso adequados são as opções terapêuticas disponíveis. Assim, esta revisão oferece uma síntese narrativa da literatura publicada, contribuindo para uma melhor compreensão da doença e uma abordagem otimizada aos pacientes.

Palavras-chave: Pioderma gangrenoso. Dermatose neutrofílica. Autoinflamação. Autoimunidade. Imunossupressão.

Introduction

Pyoderma gangrenosum (PG) is included in the group of neutrophilic dermatoses[1-4], along with Sweet' syndrome and Behçet' disease[4-8], which share a histopathological substrate rich in neutrophils[4-9]. The diagnosis of PG is challenging due to its rarity, variable clinical presentation, and the absence of specific markers[2,9-15]. Although it has been recognized for over a century, its etiopathogenesis remains poorly understood, and there is no consensual treatment[2,8]. Thus, the approach to a patient with PG is complex, requiring a better understanding of the physiopathology and the development of new therapeutic targets.

Therefore, we performed a review of the published literature on PG to provide the medical community a better understanding and management for this disease. PubMed was the primary database consulted. The revised articles are predominantly < 10 years old, with a higher prevalence of articles from the last 5 years. There were no restrictions regarding language or study type; however, most of the chosen articles are narrative reviews, systematic reviews, and case reports.

Epidemiology

The global annual incidence of PG is estimated at 3-10 cases per million individuals[8,11,13,15-18]. The prevalence is approximately 5.8 patients per 100,000 individuals[14,16,19], with PG affecting predominantly those over 50 years of age[10]. Women are slightly more affected than men[15-17] and pediatric patients account for only 4%[8,15,16].

Etiopathogenesis

The etiopathogenesis of PG is complex and remains poorly understood, but genetics, neutrophil dysfunction, and immunological dysregulation are main contributing factors[2,8,9,20-23]. The pilosebaceous unit may be the initial target of the inflammatory process, due to the absence of lesions in body areas without follicular adnexal structures[24,25].

Defects in neutrophil chemotaxis, phagocytosis and metabolism[1,20,23,26], along with oligoclonal expansion of T cells observed in skin biopsies highlights the potential role of these cells[1,19,21,23], also supported by the overexpression of cytokines and chemokine, namely, interleukin (IL)-8, IL-17, Tumor necrosis factor-α (TNF-α) and CXCL-1/2/3/16, and matrix metalloproteinases 2 and 9[1,2,19,20,23,27,28]. Elevated levels of IL-1β suggests an autoinflammatory process induced by the activation of the inflammasome[21,23,27,29]. This may also explain the association with other diseases with mutations in the *PSTPIP-1* gene that regulates the inflammasome, namely, the PAPA, PASH, and PAPASH syndrome which includes apart from PG, acne, pyogenic arthritis and hidradenitis suppurativa[1,8,23,27,29]. Furthermore, pathergy can be explained by an inflammatory reaction to trauma.

Furthermore, specific genetic loci associated with a higher susceptibility to inflammatory bowel disease (IBD) are commonly found in PG patients, suggesting a common genetic background[1,23,26].

Various medications appear to induce PG lesions, including some used in the treatment of comorbidities and even in the treatment of PG, such as TNF-α antagonists, rituximab, and gefitinib[1,9,14,20].

Clinical presentation

The clinical presentation of PG is heterogeneous. Solitary or multiple lesions, differing in size, depth, and morphology may occur[9,26]. The pre-tibial area is the most common site[9,30], but any skin area can be affected[15,26,30,31]. Typically, cutaneous lesions are extremely painful[16] and are not associated with lymphangitis or lymphadenopathy[6].

The most recognized clinical variants include ulcerative/classic, bullous, pustular, vegetative, peristomal, and post-surgical PG[1,6,19,22]. Transformation from one variant to another can occur[27] and usually each subtype is related to different systemic diseases[1,6,19].

Extracutaneous manifestations can occur, such as scleritis, corneal ulcers, aseptic pulmonary nodules, pleural effusions, sterile hepatic and splenic abscesses,

neutrophilic myositis, sterile osteomyelitis, and aortitis[1,16,19,22,32]. Consequently, a patient with PG may experience multiple symptoms including fever, malaise, abdominal pain, myalgia, arthralgia, respiratory, and visual changes[6,9,16,31].

Ulcerative/classic PG

Ulcerative PG is the most common variant, representing about 85% of cases. It predominantly affects the legs, possibly due to greater exposure to trauma[10,12,19,26,27], and includes two stages: ulcerative and cicatricial[1].

The ulcerative phase presents with a painful papule, pustule, or nodule that evolves, within 1-2 days, into an expansive ulcer with well-defined borders. The edges are raised, with an erythematous, violaceous, or purpuric hue, sometimes with pustules and epidermal detachment (Figs. 1 and 2). The ulcer base is covered by a non-specific necrotic tissue[1,19], typically associated with a hematopurulent exudate[30]. It may be limited to the superficial dermis or extend through the subcutaneous tissue to the muscular fascia[26]. Pain is usually severe and disproportionate to the physical examination, especially if the progression is fast[1,10,12,26]. When multiple ulcers are present, they may gradually merge, sparing delicate strips of normal epidermis[11].

In the cicatricial phase, the wound margin develops epithelial extensions projecting into the ulcer, known as Gulliver's sign, creating a distinct cribriform or "cigarette paper" appearance (Fig. 3)[1,12,18,19].

Systemic diseases most frequently associated with the classic variant are IBD, hematological malignancies, rheumatoid arthritis (RA), seronegative arthritis, and monoclonal gammopathies[6,10,11].

Bullous PG

In bullous PG, the initial presentation is a painful vesicle in an erythematous base that evolves into blue-gray blisters. These blisters may coalesce and upon erosion, they form a shallow, superficial ulcer with a necrotic base[11,26,27,33]. Bullous PG typically appears in unusual locations such as the face, dorsum of the hands or extensor surfaces of the arms. This variant is significantly associated with myeloproliferative disorders, especially acute myeloid leukemia (AML)[1,4,10,11,34].

Pustular PG

Pustular PG is a rare clinical variant often observed in association with other types of PG[8]. This subtype features painful sterile pustules surrounded by an erythematous halo, symmetrically distributed on the trunk and extensor surfaces of the limbs[1]. There are reports of scalp and penis involvement, in association with other types of PG[8]. Pyostomatitis vegetans, a pustular intraoral eruption strongly associated with IBD, may represent a mucosal form of pustular PG[11,19]. This clinical variant is often described in IBD exacerbations, improving with treatment of the enteropathy, but can also occur in quiescent IBD[11,26].

Vegetative PG

Vegetative PG, also known as superficial granulomatous pyoderma, is considered the rarest and the mildest variant of PG. Its clinical presentation ranges from vegetative lesions to superficial ulcers, lacking the violaceous undermined edge and the hematopurulent exudate seen in the classic variant. It typically presents as a single, minimally symptomatic lesion on the trunk. These lesions are more likely to resolve spontaneously without scarring and show a fast response to topical therapies. The vegetative PG is not strongly associated with systemic diseases[1,8,10,11].

Peristomal PG

Peristomal PG can affect approximately 0.6% of patients with stomas annually. It is characterized by classic ulcers surrounding the stoma and it is believed to represent a pathergy response to trauma. It can develop shortly after surgery or later, possibly due to skin irritation caused by feces/urine, adhesives, or stoma devices[8,11,26,27,35].

Post-surgical PG

Post-surgical PG manifests as an erythematous patch followed by an ulcer, localized in the surgical wound and mimicking its dehiscence (Fig. 4)[6]. This variant mostly develops within the first 2 weeks after any surgical procedure[26]. Surgical interventions most frequently associated with post-surgical PG include mammoplasties, laparotomies, and skin grafts[30]. When the breast is involved, the nipple is generally spared. Only one in six patients with this variant has a personal history of PG[1].

Associated diseases

PG is the second most common cutaneous manifestation of IBD[36], particularly ulcerative colitis[1,36].

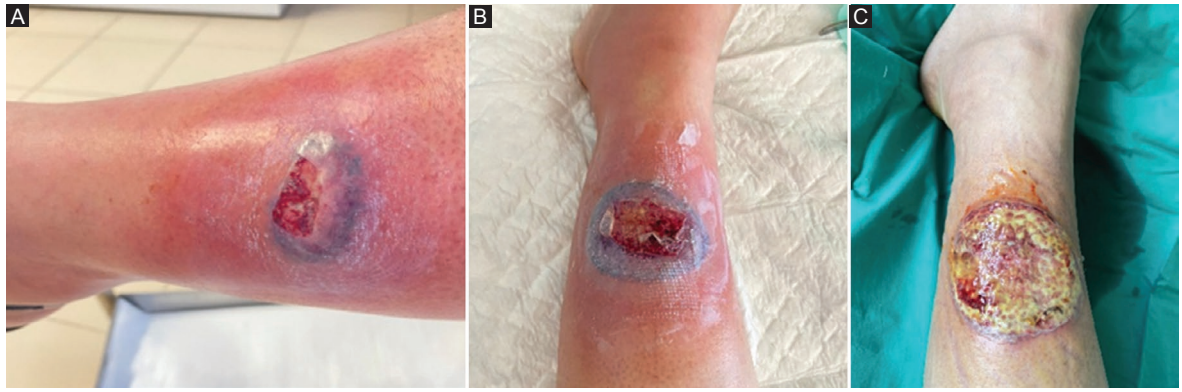

Figure 1. A-C: evolution of an ulcerative pyoderma gangrenosum lesion on the leg over 4 days.

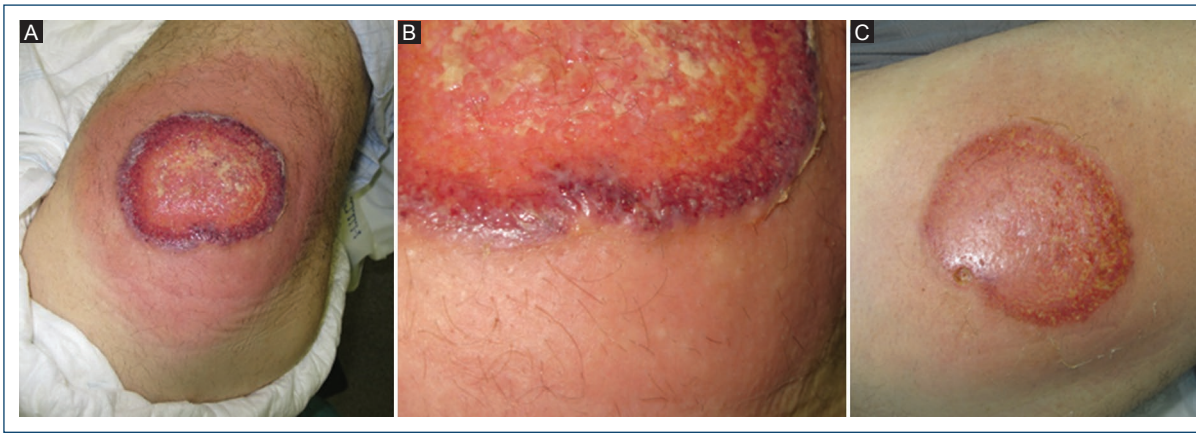

Figure 2. A: ulcerative pyoderma gangrenosum lesion surrounded by an erythematous halo, **B:** with raised violaceous edges, and pustules causing superficial detachment. **C:** the same lesion after 4 days of oral corticosteroid therapy.

The activity of IBD does not directly correlate with PG[14], as PG can precede the onset of IBD or even persist after surgical intervention[26]. However, PG usually appears after the diagnosis of IBD[19,37]. The classic, peristomal, and pustular variants are commonly observed, with the latter being more related with disease activity[11].

Inflammatory arthropathies, such as RA and some seronegative arthritis, are frequently associated with PG, especially its classic variant[6,19].

Hematological disorders are also associated with PG, especially myelodysplastic syndrome (MDS), AML, and monoclonal gammopathy of undetermined significance, predominantly of the immunoglobulin A type. In most cases, the diagnosis of a hematological malignancy precedes the development of PG that often presents with multifocal lesions[5] and in AML in atypical locations and mostly as the bullous. Legs are frequently involved, except in B-cell Non-Hodgkin lymphoma, where lesions predominantly affect the genital area[1,5,10,11].

Diagnosis

The diagnosis of PG is a challenge due to its variable clinical presentation and the absence of specific laboratory and histological findings[1,3,4,6,9-14]. It is considered a diagnosis of exclusion, but some well-defined diagnostic criteria have been developed (Table 1)[3,4,6].

The skin biopsy cannot provide a definitive diagnosis of PG, as histological features are nonspecific and vary depending on the biopsy location, stage, and clinical subtype, but histopathology is useful for excluding alternative diagnoses, particularly malignancies and infections[9-12,16,27].

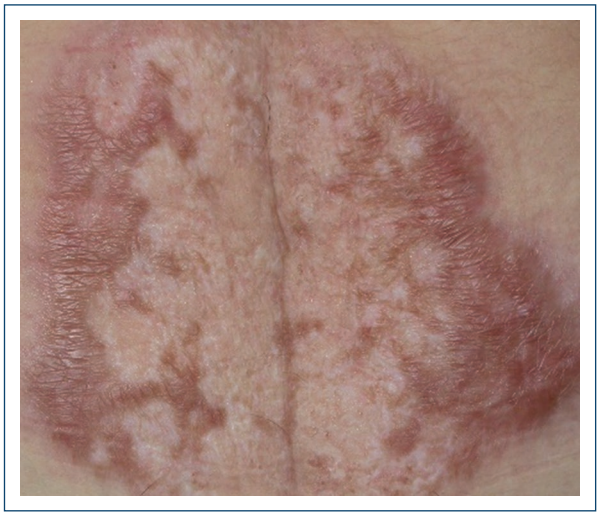

Figure 3. Cribiform or "cigarette paper" scar of the pyoderma gangrenosum lesion.

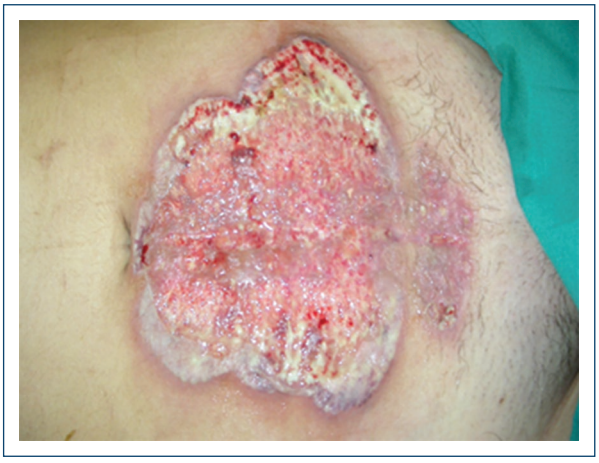

Figure 4. Ulcerative pyoderma gangrenosum with the typical undermined edge and pustules that emerged on a surgical wound of a cesarean section, with centrifugal growth.

The need for an accurate diagnosis before beginning appropriate treatment must overlap the risk of exacerbating PG due to biopsy-induced pathergy[12,26].

In classic PG, there is a significant infiltration of neutrophils in the dermis and subcutaneous tissue, which leads to necrosis of pilosebaceous units and epidermis[9,10,16,27]. The bullous variant of PG presents with subcorneal, subepidermal, and intraepidermal blisters, along with a dermal neutrophilic infiltrate and microabscesses. In the pustular form, there is an accumulation of neutrophils under the stratum corneum and in the dermis, associated with subepidermal edema. The infiltrate tends to be concentrated around the hair follicles, and the infundibulum often shows signs of rupture or perforation. Vegetative PG is characterized by a palisaded granulomatous reaction, neutrophilic abscesses with sinus tracts, and pseudoepitheliomatous hyperplasia[9-11,16,33].

A broad range of additional tests may be required, not only to rule out alternative diagnoses but also to investigate associated systemic diseases and extracutaneous manifestations of PG[6,9,12].

A complete blood count, along with erythrocyte sedimentation rate and C-reactive protein, as well as kidney and liver function, should be assessed along with urine analysis to search for Bence Jones protein, serum protein electrophoresis, and immunofixation to exclude monoclonal gammopathy, autoantibody tests to rule out connective tissue diseases, RA, antiphospholipid syndrome (APS), granulomatosis with polyangiitis (GPA), and other vasculitis, and coagulation studies to exclude thrombotic causes of ulceration. Lower limb echo Doppler should be performed to evaluate for venous insufficiency and peripheral arterial disease. Fecal calprotectin analysis and colonoscopy should be conducted if IBD is suspected. Serological tests for Hepatitis B virus, Hepatitis C virus, human immunodeficiency virus, and an interferon-gamma release assay for *Mycobacterium tuberculosis* should be performed to exclude underlying infections before starting immunosuppressive therapy. A chest X-ray and computed tomography scan should be considered if extracutaneous manifestations are suspected[4,10-12,27,38].

Differential diagnosis

The differential diagnosis of classic PG includes venous insufficiency ulcers, cutaneous infections, APS, GPA and other vasculitis, factitious ulcers, vascular occlusive disorders, and malignancies[12]. Bullous PG should be differentiated from autoimmune blistering dermatoses, erythema multiforme and the superficial bullous variant of Sweet' syndrome[5,6,8,11,13,27,34]. Pustular PG should be distinguished from bacterial pyodermas, pustular psoriasis, Sneddon-Wilkinson disease and drug reactions[6]. Peristomal PG must be differentiated from bacterial and fungal skin infections, chemical dermatitis and irritative or allergic eczema[35].

Treatment

Treatment can be challenging, with several factors to consider when choosing the best therapeutic

Table 1. Comparison of suggested diagnostic criteria for pyoderma gangrenosum[3,7,10,19,75]

Criteria	Daniel Su et al. (2004)*	Delphi Consensus (2018)†	ParaceIsus (2019)‡
Major criteria	Rapid progression of a painful, necrotic cutaneous ulcer with an irregular, violaceous, and undermined border	Biopsy with a neutrophilic infiltrate	Progressive disease (3 points)
	Exclusion of other causes of cutaneous ulceration		Absence of relevant differential diagnoses (3 points)
			Reddish-violaceous wound border (3 points)
Minor criteria	Clinical history suggestive of pathergy or clinical finding of cribriform scarring	Exclusion of infection on histopathology/ microbiological assessment	Improvement with immunosuppressive treatment (2 points)
	Systemic diseases associated with pyoderma gangrenosum	Pathergy	Typical irregular ulcer shape (2 points)
	Histopathologic findings (sterile dermal neutrophilic infiltrate ± mixed inflammatory infiltrate ± lymphocytic vasculitis)	Personal history of inflammatory bowel disease or inflammatory arthritis	Severe pain - > 4/10 on visual analogue scale (2 points)
	Treatment response (rapid response to systemic steroids)	Papule, pustule or vesicle that rapidly ulcerates	Lesion at site of previous trauma (2 points)
		Peripheral erythema, undermining border, and tenderness at the site of ulceration	Suppurative inflammation in histopathology (1 point)
		Multiple ulcers (at least one on the anterior surface of the leg)	Undermined wound border (1 point)
		Cribriform or wrinkled paper scars at healed ulcer sites	Associated systemic disease (1 point)
		Reduction in ulcer size after immunosuppressive treatment	

*Diagnosis requires both major criteria and at least two minor criteria.
†Diagnosis requires confirmation of the major criteria and at least 4 of the 8 minor criteria.
‡Score ≥ 10: pyoderma gangrenosum highly probable. Score < 10: pyoderma gangrenosum unlikely.

option. These include the site, depth, size, and number of the lesions, extracutaneous involvement, comorbidities, side effects, and costs[1,14]. Treatment goals are disease activity reduction, wound healing optimization, pain control, and prevention/treatment of secondary infections[1,12,26,34].

Although there are no guidelines, PG treatment is based on the use of topical and systemic immunomodulatory drugs, analgesia, and wound care[1,11,12,25,39,40]. Their use is based on expert opinions and data from case reports, small case studies, and a limited number of randomized clinical trials[1,25].

Topical treatment

Topical treatment is mostly used as an adjunct to systemic therapy[14]. However, a subset of patients with a reduced number of small ulcers without involvement of deep structures may be treated only with topical therapy, mostly high-potency corticosteroids and calcineurin inhibitors tacrolimus and pimecrolimus[11,31]. When used as monotherapy, both have the same level of evidence for mild or unilesional disease. The most common adverse effect of topical calcineurin inhibitors is a burning sensation, which can be reduced if refrigerated before use[14,25,26,41,42]. Regarding corticosteroids, they are generally used as creams or ointments or intralesional injections and, in peristomal PG, as lotions, foams, mixtures with adhesive agents, through inhalers or impregnated tapes. In addition, new ostomy bases are being developed to prevent skin complications around the stoma[14,42-44]. Topical corticosteroids can lead to cutaneous atrophy and delay in wound healing, but a low rate of significant side effects is reported[14].

Other topical therapies have also been described, including 0.5% nicotine cream, platelet-derived growth

factor, nitrogen mustard, coagulation factor XIII, gels with cyclosporine, dapsone, sodium cromoglycate, phenytoin solution, benzoyl peroxide, 5-aminosalicylic acid, and becaplermin[1,14,26,31,42,45]. Topical timolol appears to be effective in promoting reepithelialization in the scarring phase of wounds[46].

Systemic treatment

Systemic treatment is indicated in severe or multilesional PG and, in milder cases if there is no improvement after 2-4 weeks of topical therapy. A large multicenter retrospective cohort study and an expert survey showed that patients with PG receive, on average, two different systemic agents, emphasizing the importance of drug combination in clinical practice[14,25,38,47].

Systemic corticosteroids are the first-line therapy. Oral prednisolone (0.5-1 mg/kg/day) induces a clinical response in about 40-50% of cases, with heterogeneous rates of complete response depending on the severity of PG and associated systemic diseases. The therapeutic response can be observed in 2-3 days[1,14,25,47,48] with reduction of pain, exudate, edema, and erythema[11]. Once healing is achieved, the dose of oral corticosteroid can be gradually tapered. Adverse effects such as osteopenia, weight gain, glaucoma, cataracts, hyperglycemia, diabetes, Cushing's syndrome, immunosuppression, adrenal insufficiency, and psychosis should be monitored[1,14,25,42].

Cyclosporine has the same level of evidence as systemic corticosteroids. In fact, a randomized clinical trial involving 112 patients with PG compared cyclosporine (4 mg/kg/day) with prednisolone (0.75 mg/kg/day), found equivalent clinical outcomes in healing time, inflammation reduction, reported pain, and incidence of adverse reactions[2,14,25,26,41,49]. Thus, cyclosporine is a solid alternative, especially in patients with limitations to corticosteroid use but it is contraindicated in patients with renal insufficiency and high blood pressure. Combining systemic corticosteroids with cyclosporine is also a possible option, especially if ulcers are in sensitive areas such as the face, neck, and genitals, or associated with extracutaneous manifestations. In these situations, intravenous pulses of methylprednisolone 1000 mg for 3-5 consecutive days is also an effective alternative, with a faster outcome[1,14,25].

Other systemic therapies, including methotrexate, azathioprine, mycophenolate mofetil, dapsone, thalidomide, colchicine, intravenous immunoglobulin, sulfasalazine, and granulocyte and monocyte adsorption apheresis have been reported in controlling disease activity, however, controlled trials supporting the effectiveness of these therapies is scarce[1,11,14,15,25,26,50,51]. After cyclosporine, dapsone, and mycophenolate mofetil are the non-biological corticosteroid-sparing agents with more scientific evidence for PG treatment[14].

Biological agents are a promising therapeutic approach in PG, including TNF-α, IL-1β, IL-17, IL-23, and C5a inhibitors[1,11,14,25,52,53]. Among TNF-α inhibitors, adalimumab and infliximab have higher response rates[14,25]. However, infliximab remains the only anti-TNF-α agent with demonstrated efficacy in classical PG, based on a double-blind, randomized controlled trial[54]. Moreover, it is also treating synchronous diseases, such as IBD[1,11,14,38]. IL-1β inhibitors, namely, anakinra, canakinumab, and gevokizumab, are of particular interest in patients with autosomal dominant autoinflammatory syndromes, such as PAPA[14,25,53,55]. Spesolimab is an IL-36 receptor blocker recently approved for generalized pustular psoriasis that has also shown excellent results in the treatment of PG, particularly in refractory cases, with very rapid clinical responses according to some reports[56,57].

The appropriate time for discontinuation of systemic therapy remains a therapeutic challenge. The primary purpose of systemic therapy lies in modulating the inflammatory activity of the disease, with pain reduction and regression of the livid wound margin. In the absence of overt signs of persistent inflammation, tapering of systemic therapy is mandatory, until the complete healing of skin lesions[11,14].

Wound care

In addition to topical and systemic therapies, appropriate wound care is essential for wound healing[34,40]. Moreover, it reduces local pain and the risk of superinfection[40].

Wound cleansing should be performed with caution, namely, with sterile water especially when using silver-based dressings, as the chloride ions present in saline inhibit silver cations action[34]. Due to pathergy, surgical debridement is not recommended[11,14,34], especially during the inflammatory phase and in the absence of systemic immunosuppression[14], and more conservative debridement is more convenient, including autolytic and enzymatic methods[1,14,25].

The choice of dressings must be individualized, depending on the disease phase, wound nature, and pain level[25,34]. In the inflammatory phase with active

ulceration with erythematous edges, antimicrobial and hyper absorbent dressings are preferable, whereas in the healing phase, foam dressings such as polyurethane and silicone foam, are more suitable[25,40]. Dressings containing antimicrobials, such as polyhexanide or silver, decrease the microbiological load in the wound, are more useful in the active phase[14,58], but prophylactic topical antibiotic therapy is not advised due to the risk of bacterial resistance and contact dermatitis[34]. For exudative lesions, absorbent dressings, particularly alginate or hydrofiber dressings, are recommended[11,25,34,40] and for hemorrhagic ulcers, priority should be given to the use of alginates due to their hemostatic properties[25].

Surgical treatment of PG lesions in the active phase is not recommended. However, partial-thickness skin grafts have shown promising results, especially when applied with negative pressure therapy, and under systemic immunosuppression[25,34,39,59]. This approach appears to accelerate healing and promote early wound closure[39,59,60]. Considering that corticosteroids and other immunosuppressants delay wound healing, combining medical therapy with these surgical interventions may be advantageous once therapeutic success can be achieved with a lower burden of systemic therapy[39].

Hyperbaric oxygen therapy seems to be a promising alternative, given its influence on neovascularization, edema reduction, inflammation control, collagen synthesis by fibroblasts, and bacterial load attenuation[61]. As a rescue therapy, it has been successful in achieving partial improvement or even complete healing in cases of PG refractory to conventional treatments, with a satisfactory safety profile[62-65].

In addition, compression therapy is beneficial in most ulcers located on the lower extremities[34,66]. as it reduces edema associated with inflammation and appears to promote wound healing[1,14,34,40]. However, it is important to exclude peripheral arterial disease[1] and consider that excessive compression may induce pathergy, especially if disease inflammation is not controlled[11].

Analgesia

PG is a highly painful dermatological condition[26]. The depth of the ulcer and associated nerve damage may contribute to the higher pain intensity reported by patients. In addition, with nerve fiber regeneration, hypersensitivity may arise in the previous wound area, requiring an adequate approach to pain[67]. Thus, simple analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) may be insufficient, with opioids, antidepressants, and anticonvulsants being required for an adequate pain control[26,67]. Topical lidocaine can also be useful[25], and the topical application of cannabis is a promising alternative[68]. The use of NSAIDs is not recommended in the presence of an underlying IBD, as they are associated with gastrointestinal exacerbations[26].

Finally, the importance of analgesia transcends the imperative need to comfort by enabling an easier wound care and the proper application of compression therapy[1,34].

Other considerations

Various clinical conditions may coexist with PG and its treatment is important, as it can have a positive impact on disease activity. These treatments include drugs with anti-inflammatory and immunomodulatory properties that are effective in PG and underlying diseases, such as anakinra, in the context of PAPA syndrome[14,25,53,55], ustekinumab, infliximab, and other TNF-α inhibitors, in the context of IBD[1,11,14,26,38], and methotrexate, frequently used in RA[25,50]. In addition, interventions such as colectomy (in individuals with ulcerative colitis), cytapheresis (in patients with leukemia or potentially IBD), and administration of thalidomide (in cases of MDSs) may also be used[15,31,51,69-73].

In a malignant scenario, the administration of immunosuppressants must be carefully managed, limited to appropriate minimum doses, or less immunosuppressive drugs, such as methotrexate[25,31].

When there is superinfection, corroborated by positive blood cultures and increased levels of C-reactive protein in blood analysis, antibiotics have to be added and immunosuppression should be maintained, except in cases of sepsis[31].

Prognosis and impact on quality of life

PG is a chronic disease, with lesions tending to heal slowly, over several months. In addition, it can have an unpredictable clinical course[9,26,31], recurring in more than 25% of cases[37], even after a rapid and complete clinical response to initial treatment[31]. High disease severity, ulcerative and bullous variants, advanced age, associated diseases refractory to treatment, and secondary infection are associated with a poor prognosis[31], as well as the male sex, given the higher prevalence of neoplasia and hematological disorders[5,9]. The risk of

death in patients with PG is 3 times higher than in the general population[26].

PG is a debilitating condition with a very significant biopsicossocial impact that clearly compromises patients' quality of life. Painful ulcers may limit mobility and lead to difficulties in daily activities. The odor and visual impact of the lesions contribute to an overwhelming social stigma, leading to the construction of a negative body image and decreased self-esteem. States of anxiety and depression can emerge and cause changes in eating and sleeping patterns. Comorbidities amplify clinical complexity and furthers worsens quality of life. In addition, frequent medical consultations and treatments are both costly and time-consuming[1,14,26,31,74].

Conclusion

PG is a rare neutrophilic dermatosis with a challenging diagnosis and treatment. A detailed anamnesis and thorough physical examination are mandatory, including searching for signs of pathergy, extracutaneous involvement, or underlying comorbidities.

Pathergy should not exclude performing a biopsy as, despite the absence of specific histological markers, histopathology reveals a typical neutrophilic infiltrate and allows exclusion of neoplasms and infections. Other complementary tests should be considered for differential diagnosis and to search for extracutaneous involvement and systemic diseases, including IBD, RA, hematologic disorders, and neoplasms.

PG treatment is based on a multimodal approach whose main objectives are to reduce inflammation and disease activity, optimize wound healing, control pain, prevent or/treat secondary infections, and control associated comorbidities. In solitary, small, and shallow lesions, topical treatment with corticosteroids or calcineurin inhibitors, complemented by appropriate wound dressing, is usually sufficient. In multiple, larger, and deeper lesions, systemic therapy is mandatory. Corticosteroids and cyclosporine are first-line treatments, in combination in severe disease. Infliximab has the same level of evidence as the previous drugs but is usually reserved for refractory disease or in the presence of concomitant IBD. Other pharmacological agents have shown benefit but lack strong scientific evidence. Surgical treatment of PG lesions in the active phase is not advised. However, partial-thickness skin grafts have shown promising results, especially when applied after negative pressure therapy and under systemic immunosuppressants. In addition, a rehabilitation plan can optimize patients' mobility and improve their independence in activities of daily living. Patient education is also crucial, including physical activity, smoking cessation, and trauma avoidance. PG is not just a dermatological condition as it transcends the biological domain, permeating the emotional and social aspects of patients' health. Thus, psychological support could also be offered.

Finally, despite the recent advances in the therapeutic armamentarium, PG remains a potentially debilitating disease, with a threefold risk of death compared to the general population. Therefore, a more specific and effective therapeutic approach is mandatory, requiring a deeper understanding of the pathophysiological mechanisms.

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REVIEW ARTICLE

Cutaneous lupus erythematosus: a review of new and emerging therapies

Lúpus eritematoso cutâneo: revisão de novas terapêuticas emergentes

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Abstract

Cutaneous lupus erythematosus (CLE) is an autoimmune connective tissue disorder with heterogenous skin manifestations. According to the current therapeutic guidelines for the treatment of CLE, short courses of topical corticosteroids remain the first-line treatment for localized disease, while topical calcineurin inhibitors offer a safer alternative with lower side effects. Regardless of CLE subtype, antimalarials are the first-line systemic treatment for disfiguring and widespread skin lesions and prevent systemic involvement. In addition, the use of systemic corticosteroids should be restricted to patients with highly active and/or severe CLE. Second-line treatments include methotrexate, retinoids, and dapsone, while mycophenolate mofetil is considered third-line option. Moreover, thalidomide should be reserved for use in recalcitrant CLE patients, preferably in combination with antimalarials. Despite the considerable impact of CLE on quality of life, therapeutic options remain insufficient and, aside from hydroxychloroquine and corticosteroids, no other systemic treatments are approved. This review offers a brief overview of CLE pathogenesis and the current development landscape for new and emerging systemic therapies, highlighting promising targeted drugs such as anifrolumab (anti-type 1 interferon), deucravacitinib (allosteric tyrosine kinase 2 inhibitor), litifilimab (plasmacytoid dendritic cell-targeted therapy), iberdomide (cereblon-targeting ligand), and belimumab (B-cell targeted therapy), among others.

Keywords: Cutaneous lupus. Clinical trials. Anifrolumab. Iberdomide. Litifilimab. Belimumab.

Resumo

O lúpus eritematoso cutâneo (LEC) é uma doença autoimune do tecido conjuntivo que se apresenta com manifestações cutâneas muito heterogéneas. De acordo com as diretrizes terapêuticas atuais, ciclos curtos de corticosteróides tópicos mantém-se como tratamento de 1ª linha na doença localizada, enquanto os inibidores da calcineurina tópicos são uma alternativa mais segura, com menos efeitos secundários. Independentemente do subtipo de LEC, os antimaláricos são o tratamento sistémico de primeira linha nos casos de lesões cutâneas generalizadas e desfigurantes e na prevenção do envolvimento sistémico. Além disso, o uso de corticóides sistémicos deve ser restrito a doença com atividade severa. Os tratamentos de segunda linha incluem metotrexato (MTX), retinóides e dapsona, enquanto o micofenolato de mofetil (MFM) é considerado uma opção de terceira linha. Além disso, a talidomida deve ser reservada para casos de LEC refratários a outros tratamentos, preferencialmente em combinação com antimaláricos. Apesar do impacto considerável na qualidade de vida, as opções terapêuticas no LEC permanecem insuficientes e, além da hidroxicloroquina e dos corticóides, nenhum outro tratamento

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sistémico está aprovado. Esta revisão oferece uma breve visão geral da patogénese do LEC e do panorama atual do desenvolvimento de novos tratamentos sistémicos, destacando terapêuticas dirigidas promissoras como anifrolumab (anti-interferão tipo 1), deucravacitinib (inibidor alostérico da tirosina cinase 2), litifilimab (terapêutica dirigida às células dendríticas plasmocitóides), iberdomide (ligante modulador dirigido ao cereblon) e belimumab (terapêutica dirigida às células B), entre outros.

Palavras-chave: Lúpus cutâneo. Ensaios clínicos. Anifrolumab. Iberdomide. Litifilimab. Belimumab.

Introduction

Cutaneous lupus erythematosus (CLE) is an autoimmune connective tissue disorder with heterogenous manifestations, which may present with exclusively skin involvement or as part of systemic lupus erythematosus (SLE).

According to the 2004 classification system modified by Düsseldorf, CLE is divided into four distinct subtypes even though patients may exhibit overlapping features: acute CLE (ACLE), subacute CLE (SCLE), chronic CLE (CCLE), and intermittent CLE (ICLE) or lupus erythematosus tumidus (LET). These heterogeneous skin presentations are grouped under the umbrella of CLE based on the characteristic clinical and histologic features and their ability to present concomitantly with SLE despite significant interindividual variation[1].

CCLE can be further divided into chronic discoid lupus erythematosus (CDLE), lupus erythematosus profundus (LEP), and chilblain lupus erythematosus (ChLE), with CDLE being the most common subtype of CCLE[2]. ACLE and SCLE often present with widespread maculopapular to annular skin lesions, mainly on sun-exposed areas, whereas CDLE is characterized by scattered, disc-like scarring plaques[3]. Histopathologically, CLE is marked by the presence of lymphocytic infiltrates, deeper and denser in CDLE compared to SCLE, and necroptotic keratinocytes at the dermo-epidermal junction[4]. However, the classification of CLE subtypes should be considered flexible, as overlapping clinical and histological features are common.

Furthermore, the risk of developing systemic disease varies with different clinical subtypes of CLE. ACLE is associated with a higher risk of SLE, occurring in about 80% of cases, whereas localized CDLE is associated with SLE in only about 5% of cases[4,5]. The current evidence suggests that CLE and SLE are closely related yet distinct diseases with different courses[4].

CLE is a significant cause of morbidity, potentially affecting psychological well-being and quality of life to an extent similar to or greater than chronic hypertension, congestive heart failure, type 2 diabetes, and heart attacks[6].

The only US Food and Drug Administration (FDA)-approved drugs for CLE are hydroxychloroquine and glucocorticoids, which were approved under earlier regulations before the current clinical trial standards[7,8]. Off-label treatments include other antimalarials such as chloroquine and quinacrine, as well as immunosuppressants such as methotrexate and mycophenolate mofetil. Additional treatment options include dapsone, retinoids (such as acitretin, isotretinoin, and alitretinoin), thalidomide, and lenalidomide[7,8]. No systemic treatments for CLE have been approved by the FDA in over 60 years, but, recently, new targeted therapies for SLE, such as belimumab and anifrolumab, have recently received approval from the (FDA) and European Medicines Agency (EMA) and their specific effect on cutaneous lesions is also being evaluated.

Most information on the pathogenesis, clinical trials, and new drugs for CLE comes from studies based on SLE, with limited involvement of dermatologists and often without properly distinguishing CDLE from acute and subacute variants.

Patients included in SLE clinical trials must have a diagnosis of SLE, including a positive ANA, according to the most recent ACR/EULAR classification criteria. As a result, this requirement excludes the majority of CLE patients who have negative ANA and do not have concomitant SLE, despite the potential benefit from targeted treatments also for CLE[9]. Moreover, the outcome measures typically include only a few non-specific skin assessments, such as “rash” or “alopecia”, and many trials do not consider the use of the Cutaneous Lupus Erythematosus Disease Activity Index (CLASI) as a primary endpoint[9,10]. SLE patients with skin manifestations do not accurately represent CLE patients, and assessing cutaneous improvement in these trials with CLE-Investigator’s Global Assessment criteria is insufficient for evaluating skin disease activity[9].

Consequently, drugs that may be effective for CLE but do not demonstrate efficacy for SLE may not receive approval. Therefore, clinical trials dedicated to

CLE patients are needed to directly assess the efficacy of new tailored treatment options.

This review provides a brief overview of CLE pathogenesis and the current landscape of development for new and emerging systemic therapies for CLE.

Pathogenesis

Chronic inflammation, which creates a positive feedback loop involving both the innate and adaptive immune systems, is a characteristic feature across all CLE subtypes[1,7].

A complex interaction between genetic variants traits, epigenetic modifications, and environmental triggers underlies the pathogenesis. Environmental triggers such as ultraviolet light exposure, smoking, or certain drugs can lead to cellular damage in individuals with a susceptible genetic and epigenetic background[11,12]. Involved genes encode proteins that participate in cell signaling, cell death cascades (apoptosis and ubiquitination), DNA degradation (such as DNAse/TREX1 defects), clearance of cell debris (immune complexes), as well as cellular adhesion and the activation or regulation of the immune system, including innate immune system activation and B-cell/T-cell function[1,13].

Keratinocyte apoptosis and secondary necroptosis release cytosolic and nuclear debris into the extracellular space and instigate an inflammatory response with the release of damage-associated molecular pattern molecules, such as high mobility group box 1 protein, autoantigens such as Ro52 and Ro60, and cytokines such as CXCL chemokines, interleukins (ILs), and interferons (IFNs)[1,13,14]. It is also known that elevated expression of type I interferon (IFN-I) plays a central role in the pathogenesis of LE by creating an inflammatory loop[15]. This further amplifies the autoimmune response by recruiting plasmacytoid dendritic cells (pDCs) and enhancing antigen presentation. Upon activation, B cells produce autoantibodies against nuclear components, while cytotoxic T cells target basal keratinocytes, leading to interface dermatitis, particularly in CLE subtypes with superficial involvement[1,17]. Cytotoxic markers like granzyme B, expressed by CD8+ T cells, are found in CLE skin lesions and are likely induced by INF-I[18] (Fig. 1).

Until recently, it was believed that IFN-I was produced by recruited pDCs. However, recent data indicate that pDCs in the lesional skin and peripheral blood of CLE patients may not be the main producers of IFN-I, whereas in the skin keratinocytes might produce high amounts of INF-I[1,16]. Recent trials of drugs targeting pathways involving IFN-I have shown promising results in CLE, but the role of pDCs and INFs in the pathogenesis of CLE requires further investigation.

Targeted therapeutic agents

Based on CLE pathogenesis, potential therapeutic targets include different inflammatory cytokines and their receptors or intracellular targets and different cells involved in CLE pathogenesis, namely plasmacytoid DC, B, and T cells. Here, we review the new and emerging potential treatments in CLE focusing on each specific target (Table 1).

IFN-targeted therapies

INF RECEPTOR INHIBITION

Anifrolumab

Anifrolumab is a fully human, effector-null, IgG1κ monoclonal antibody directed against the INF-α/β/ω receptor subunit 1 (IFNAR1), providing a total inhibition of all IFN-I (IFNα, IFNβ, IFNε, IFNκ, and IFNω) and thereby interrupting the positive feedback loop of inflammation and keratinocyte damage[19,20]. Compared to skin tissue from other autoimmune diseases, the involved skin of patients with SLE exhibits one of the highest signatures for INF activity[20]. Similarly, Merola et al. demonstrated this finding using RNA tape sampling analyses in chronic lupus erythematosus[21].

Anifrolumab has been approved by the FDA since 2021 and by the EMA since 2022 for the treatment of SLE, based on data from one phase II (MUSE) and two phase III (TULIP-1, TULIP-2) clinical trials.

In all published phase II and III clinical trials, CLASI was used to assess changes in skin manifestations. In TULIP-1 trial, no differences in CLASI scores were found between patients receiving anifrolumab and those on placebo. In contrast, TULIP-2 trial showed a statistically significant difference, with 49% of anifrolumab-treated patients achieving a ≥ 50% improvement in CLASI-A compared to 25% in the placebo group[22,23]. In addition, the *post hoc* analysis of the MUSE phase 2 trial indicated that anifrolumab was more effective in treating skin lesions that in addressing arthritis, particularly among patients with a strong IFN signature[20]. A 3-year extension of the TULIP-2 trial has demonstrated a favorable long-term safety profile for anifrolumab. The most common side effects were mild to moderate respiratory infections, with a slightly

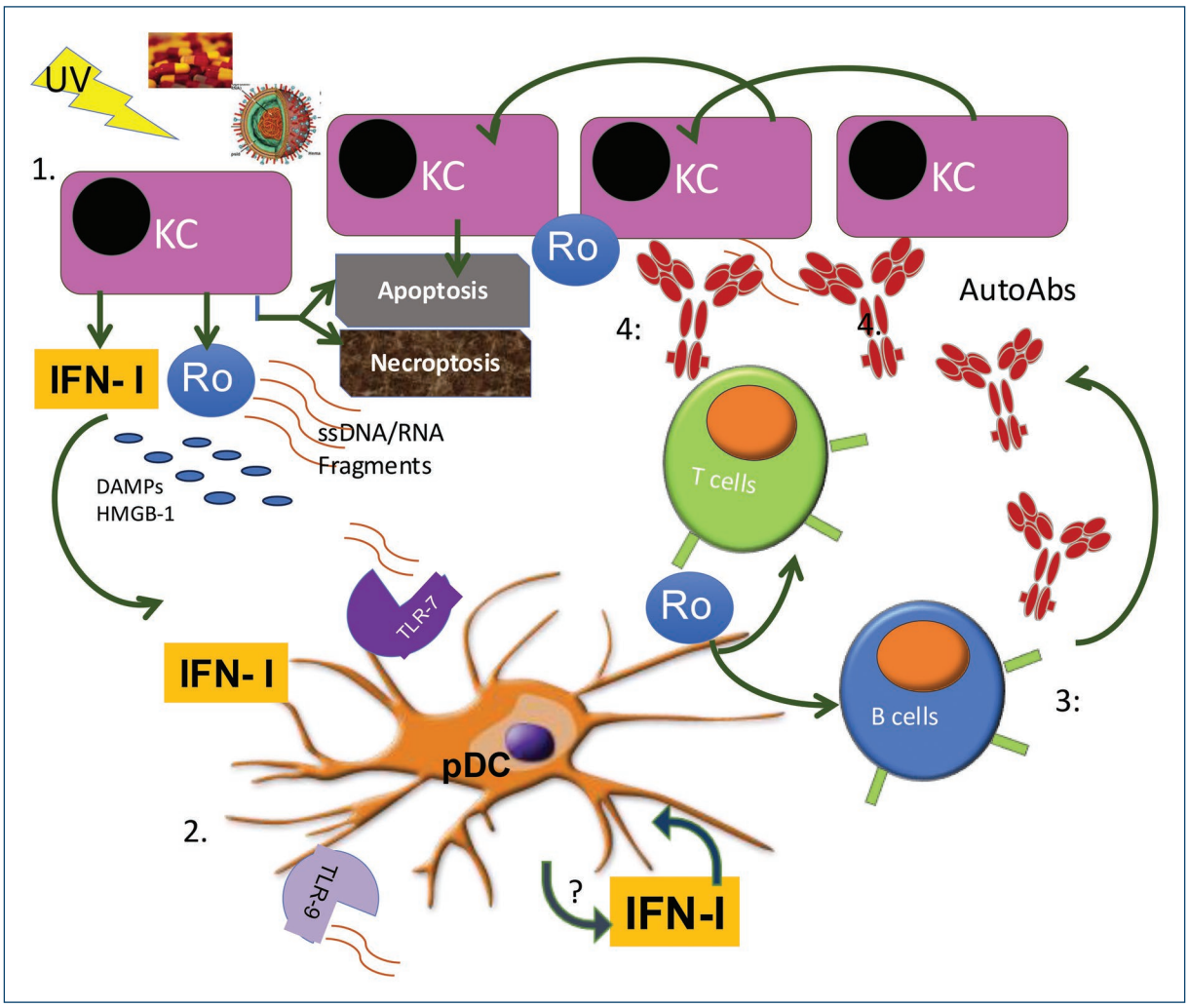

Fig. 1. Schematic presentation of the circular pathomechanisms involved in cutaneous lupus erythematosus (CLE), showing the contribution of both the innate and acquired immune response involving keratinocytes (KC), plasmocytoid dendritic cells (pDC), B and T cells, even though other cells are also involved, namely neutrophils. 1: in susceptible individuals, keratinocytes respond in an exaggerated way to the effect environmental factors such as ultraviolet light, smoke, drugs, or virus and enter a process of apoptosis or necroptosis, releasing cytosolic and nuclear debris into the extracellular space, namely RNA fragments and ribonucleoproteins (Ro52/60) that, upon deficiency of degradation, will be recognized as autoantigens. Keratinocytes also release damage-associated molecular patterns (DAMPs), such as high mobility group box 1 protein (HMBG-1), and pro-inflammatory mediators such as chemokines, interleukins, and especially type I interferons (IFN-I). 2: Toll-like receptors 7/9 (TLR-7/9) present on pDC can recognize RNA fragments and under the influence of INF-I will be activated to enhance antigen presentation to T and B cells. 3: B cells produce autoantibodies that will bind circulating or free autoantigens. 4: T cells, particularly cytotoxic T cells, target basal keratinocytes inducing their necroptosis/apoptosis with further contribution to the reinitiation the inflammatory cycle. The elevated expression of IFN-I plays a central role in the initiation and perpetuation of an inflammatory loop in CLE.

elevated risk of viral infections such as varicella-zoster and herpes zoster, and also influenza, nasopharyngitis, and bronchitis. Less common side effects included mucosal candidiasis and joint or muscle pain[46,47].

A multicenter, randomized, double-blind, placebo-controlled, phase III study (LAVENDER) is ongoing to evaluate the efficacy and safety of anifrolumab in adults with refractory CCLE and/or SCLE. The results of this study will further elucidate the potential benefits of anifrolumab in patients with isolated CLE.

Real-life observational studies support the efficacy of anifrolumab in treating refractory mucocutaneous

Table 1. Main therapeutic targets in development for cutaneous lupus erythematosus and respective drugs

Therapeutic target	Drug	Administration
Type I interferon		
Interferon-α/β/ω receptor subunit 1	Anifrolumab*†	i.v./s.c.
Interferons	Rontalizumab and sifalimumab	i.v./s.c.
TYK2	Deucravacitinib†	Oral
PanJAK1	Tofacitinib†	Oral
JAK1/2	Baricitinib†	Oral
JAK1	Upadacitinib†	Oral
PanJAK	Delgocitinib†	Topical
JAK1/2	Ruxolitinib†	Topical
Plasmacytoid dendritic cells		
Blood dendritic cell antigen 2	Litifilimab	s.c.
Immunoglobulin-like transcript 7	Daxdilimab	s.c.
Cereblon-targeting ligands	Iberdomide	Oral
B cells		
B-cell activity factor	Belimumab*	i.v.
CD20	Rituximab*	i.v.
BTK	Fenebrutinib and branebrutinib	Oral
T cells		
CD40 ligand	Dapirolizumab	i.v.
CD28	Lulizumab	s.c.
Interleukins 12/23	Ustekinumab†	s.c.
TNF-alfa	Etanercept	s.c.
Others		
Extracellular RNA	RSLV-132	i.v.
TLR-7	DS-7011a	i.v./s.c.

*Approved for SLE.
†Approved for other indications and available in the European and/or American market.
TYK: tyrosine kinase; JAK: janus kinase; BTK: Bruton tyrosine kinase; TNF: tumor necrosis factor; TLR: toll-like receptor; i.v: intravenous; s.c.: subcutaneous.

manifestations in patients with CLE[24-45]. A review on the real-world efficacy of anifrolumab in 137 SLE patients showed promising results across almost all CLE variants, including DLE, ACLE, SCLE, ChLE, LET, lupus panniculitis (*"lupus profundus"*), and lupus pernio. Rapid improvement was observed within 4 weeks, with fewer than 20% of patients being non-responders[46]. These results may suggest that patients with skin-limited lupus may also significantly benefit from anifrolumab treatment.

Rontalizumab and sifalimumab

Rontalizumab and sifalimumab, two others humanized IgG1 anti-IFN-α monoclonal antibodies targeting multiple IFN-α subtypes, showed mixed results in phase II trials and have not progressed to phase III trials[48].

The ROSE trial evaluated the efficacy of rontalizumab in 238 patients with moderate-to-severe SLE but failed to meet its primary and secondary endpoints in both overall patient group and on those with a high IFN signature. Nevertheless, an exploratory analysis found unexpectedly higher benefits for patients with low IFN scores, emphasizing the importance of stratifying lupus patients based on their IFN signature[48].

Sifalimumab, tested in a phase IIb trial in 431 patients with active SLE, showed a greater percentage of patients reaching the primary endpoint compared to placebo, with consistent improvements across various measures, including CLASI[49]. However, higher herpes zoster infection rates and a decision to prioritize the more promising anifrolumab led to the discontinuation of further sifalimumab studies[49].

Janus kinase/signal transducers and activators of transcription (JAK/STAT) inhibitors

Deucravacitinib

Deucravacitib is an oral selective allosteric tyrosine kinase-2 (TYK2) inhibitor approved for the treatment

of moderate-to-severe plaque psoriasis[50]. The mechanism of action involves suppressing the downstream effects of various cytokines, including IL-10, IL-12, IL-23, and IFN-I. This cytokine profile is involved in SLE and DLE pathogenesis[51].

Recently, there have been promising results for TYK-2 inhibitors in the management of LE. In the PAISLEY phase II trial for SLE, 69.6% of patients with a baseline CLASI-A score of ≥ 10 showed a CLASI-50 response at week 48 in the 3 mg BID group, compared to 16.7% in the placebo group[52]. This supports the potential benefit of deucravacitinib across various SLE skin manifestations. There are already some case reports indicating the efficacy of deucravacitinib in treating recalcitrant LET, SCLE, and DLE[49,53-55]. In addition, a reduction in IFN-I signaling was observed at all dosage levels[52].

Most of adverse events described were mild-to-moderate with upper respiratory tract infections, urinary tract infections, nasopharyngitis, and headaches being the most frequently reported[52].

At present, two phase III studies for deucravacitinib in SLE (NCT05617677 and NCT05620407) and a phase II trial focusing on patients with active DLE/SCLE are ongoing (NCT04857034).

Baricitinib

Baricitinib, an oral selective JAK1 and JAK2 inhibitor approved for rheumatoid arthritis, atopic dermatitis, and alopecia areata, showed promising results as a treatment for SLE in phase 2 trials and the SLE-BRAVE-I study[56]. In this latter study, the primary endpoint (SLE Responder Index 4 at week 52) was achieved in the 4 mg group[56]. However, these positive results were not confirmed in the SLE-BRAVE-II trial, where baricitinib failed to meet the primary efficacy endpoint and major secondary endpoints[57]. Nevertheless, there are a few reports showing efficacy in CLE, namely in lupus panniculitis and linear CLE[58,59].

Tofacitinib

The phase II pilot study was discontinued due to low recruitment. However, preliminary results showed that among the five DLE patients who received 5 mg of oral tofacitinib twice daily, two experienced a 75% improvement in their CLASI-A scores by week 24[7,60]. Results from the phase Ib/II trial in CLE are not yet available (NCT03288324).

In addition, case reports demonstrated that tofacitinib-induced rapid remission in seven out of ten patients with active skin and/or musculoskeletal disease, as well as significant improvement in three patients with recalcitrant cutaneous SLE[61,62].

Upadacitinib

Upadacitinib is a selective JAK1 inhibitor used in the treatment of rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, and ulcerative colitis. In a phase II double-blind trial including 341 SLE patients, both the combination therapy of elsubrutinib and upadacitinib, as well as upadacitinib monotherapy, significantly improved disease activity and reduced the risk of relapse[61].

There are few case reports indicating significant improvement in cutaneous lesions associated with SCLE, LET, and DLE[63-65].

Filgotinib and lanraplenib

Filgotinib, a JAK1 inhibitor, and lanraplenib, a spleen TYK inhibitor, were tested in a phase II trial in patients with moderate-to-severe CLE[7]. The trial failed to meet its primary endpoint of change in the CLASI-A score at week 12 and one serious adverse event occurred in the filgotinib group[61,66].

Delgocitinib

Delgocitinib, a TYK2 and pan-JAK inhibitor, was assessed in a phase II trial (NCT03958955) that was discontinued due to insufficient recruitment[1,7]. The trial did not achieve its primary endpoint at week 6[7]. However, a recent case report described the successful treatment of facial SCLE lesions using delgocitinib 0.5% ointment[67].

Ruxolitinib

Ruxolitinib, a JAK 1/2 inhibitor, is effective in the treatment of several immunologic skin diseases, including alopecia areata and atopic dermatitis, and has also been shown to control skin lesions in a case of ChLE[68]. Using *in vitro* models, including a 3D epidermal model stimulated by nucleic acid fragments, ruxolitinib was shown to decrease levels of CXCL10, a key chemokine induced by IFN-I[68,69].

Currently, an open-label phase II trial is underway to evaluate the efficacy of ruxolitinib 1.5% cream in adults with DLE.

pDC-targeted therapies

Litifilimab

The blood dendritic cell antigen 2 (BDCA2), a receptor specific to the surface of pDCs, acts as a negative regulator of INF-I production, a well-known key factor in the pathogenesis of SLE[70]. Litifilimab is a subcutaneous humanized IgG1 monoclonal antibody that binds to BDCA2, causing its rapid internalization from the surface of pDCs. This process results in the subsequent downregulation of signaling through toll-like receptor (TLR) 7/9 that recognizes nucleic acid fragments and subsequent reduction in the production of all type I and III IFNs, IL-6, and several chemokines[9,70].

In the phase I trial (NCT02106897), which involved 54 healthy controls and 12 SLE patients, single doses of litifilimab showed a favorable safety profile. Furthermore, serum concentrations of litifilimab were correlated with decreased expression of IFN, as well as reduction in CLASI-A scores and skin IFN-I –induced proteins in skin[7,70]. Of the eight patients who received a single dose, six showed a reduction of at least 4 points in their CLASI-A score at week 4 and/or week 12, which was corroborated by decreased IFN-I–induced proteins levels in lesional biopsies[7,70].

LILAC was a phase II, multicenter, placebo-controlled, two-part trial, which evaluated the efficacy of litifilimab in patients with SLE. The Part A of the study involved 110 patients with SLE and showed that litifilimab at a dose of 450 mg was superior to placebo in joint involvement, but secondary outcomes, as the CLASI-50 response at week 24 and changes in CLASI-A score at weeks 12, 16 and 24, did not show statistically significant differences between treatment and placebo groups[7,71]. In Part B that enrolled 132 participants with moderate-to-severe SCLE and/or DLE, the percentage change in CLASI-A from baseline at 16 weeks showed significant improvements in all litifilimab dosing groups (50, 150, and 450 mg arms) compared to placebo. Subsequent analysis confirmed a statistically significant dose-response effect for this primary endpoint, but, due to limited statistical power, the study could not effectively evaluate secondary endpoints[7,71,72].

Most adverse events in the litifilimab group were mild or moderate, with diarrhea, nasopharyngitis, urinary tract infections, falls, and headaches being the most frequently reported, occurring in ≥ 5% of the participants. In addition, viral infections, namely three cases of influenza, two cases of herpes zoster, one case of herpes keratitis, and one case of viral gastroenteritis, including four serious adverse events, occurred in the litifilimab groups[71,72].

A phase II Part A/phase III Part B multicenter, randomized, double-blind trial (AMETHYST, NCT05531565) evaluating litifilimab in SCLE and CCLE is currently underway.

Future studies should investigate whether treatment of CLE patients with litifilimab can prevent progression to SLE or development of lupus nephritis.

Daxdilimab

Daxdilimab is a monoclonal antibody that targets immunoglobulin-like transcript 7, leading to the depletion of pDCs. Following a favorable improvement in the CLASI-A response observed in its phase I trial, recruitment is underway for a phase II trial focusing on patients with moderate-to-severe DLE (NCT05591222)[73].

Cereblon-targeting ligands

Iberdomide

The protein cereblon (CRBN) is a substrate receptor of the cullin 4-really interesting new gene (RING)-E3 ubiquitin ligase complex $CRL4^{CRBN}$, which mediates selective protein ubiquitination and degradation through the proteasome[74,75]. Iberdomide, a high-affinity CRBN ligand, inhibits this complex, promoting polyubiquitination and proteasomal degradation of hematopoietic transcription factors Ikaros (IKZF1) and Aiolos (IKZF3). This results in the suppression of pDCs and IFN-I response, reduction in B cells and anti-dsDNA antibodies, and an increase in IL-2 production and regulatory T (Treg) cells[74,75].

A phase II randomized, double-blind, placebo-controlled, ascending-dose trial evaluated iberdomide safety and efficacy in active SLE patients. At week 24, the 0.45 mg iberdomide dose achieved a 54% SRI-4 response rate compared to 35% with placebo, with higher responses in patients with a high IFN-I or Aiolos gene signature. These responses were maintained or improved over 52 weeks among all dosing groups. Secondary outcomes showed that the 0.45 mg dose had significant CLASI-50 response differences from placebo in SCLE and CCLE, but not in ACLE[76].

Gastrointestinal events and infections, mostly mild or moderate and dose-dependent, were the most common adverse events[76].

Iberdomide has not undergone a skin-specific trial and no phase III trials are currently planned.

B-cell–targeted therapies

Belimumab

Belimumab is a fully humanized IgG1γ monoclonal antibody that inhibits selectively the B-cell activity factor (BAFF), a crucial cytokine that regulates B-cell survival and activation. BAFF is a member of the tumor necrosis factor ligand superfamily primarily found on hematopoietic cells, but also expressed in epithelial cells, adipocytes, and keratinocytes[77]. Studies showed that BAFF overexpression and elevated serum levels were linked to increased SLE disease activity and, for this reason, belimumab became the first biological treatment to be tested and subsequently approved for SLE treatment[77].

A *post hoc* analysis of pooled data from five phase III randomized, placebo-controlled trials (BLISS-76, BLISS-52, North East Asia, BLISS-SC, and EMBRACE) assessed the effects of belimumab on SLE disease activity focusing on specific mucocutaneous manifestations and vasculitis in 3086 patients. At week 52, belimumab group showed significant improvements over placebo in four SELENA-SLEDAI items (vasculitis, rash, alopecia, and mucosal ulcers) and in nine BILAG items (mild maculopapular eruption, localized active discoid lesions, mild alopecia, small mucosal ulceration, malar erythema, subcutaneous nodules, swollen fingers and cutaneous vasculitis), with the largest treatment difference in vasculitis[78]. Improvement in skin disease activity was also confirmed in the Belimumab in Real-Life Setting Study (BeRLiSS-JS)[79]. Current evidence shows that belimumab takes about 20 weeks to achieve a significant clinical response, with its maximum effect seen at 1 year[7,77]. In addition, belimumab has been associated with increased risk of depression, self-injury, and suicide, so it should be used with caution in psychiatric patients[77].

A phase III, multicenter 24-week trial (BELI-SKIN, EUDRA-CT: 2017-003051-35) is now underway to assess efficacy of belimumab in refractory cutaneous manifestations.

Rituximab

Rituximab is a monoclonal antibody directed against the CD20 antigen, leading to B cell depletion. At present, it is recommended in SLE guidelines for cases resistant to standard immunosuppressors. However, rituximab failed to achieve efficacy in improving skin activity in two large randomized controlled trials in SLE patients (EXPLORER and LUNAR trials)[80].

Subsequent studies have demonstrated mixed results, with a retrospective study suggesting that rituximab may be effective in the treatment of severe CLE in some patients with systemic disease, especially those with acute and non-specific types[81]. Moreover, a prospective study in SLE patients described new-onset CCLE or SCLE flares with rituximab treatment in patients with no baseline skin activity[82].

Fenebrutinib and branebrutinib

Fenebrutinib and branebrutinib are selective Bruton's tyrosine kinase inhibitors that target B cells and myeloid cells involved in the pathogenesis of SLE. In a phase II trial, fenebrutinib failed to demonstrate efficacy in patients with moderate to severe active SLE. The trial results revealed no significant difference in the SRI-4 between fenebrutinib-treated group and placebo group[83]. A phase II trial showed that branebrutinib was not superior to placebo in the percentage of patients achieving a ≥ 50% decrease from baseline mCLASI activity score at week 24, which measured skin erythema and scale/hypertrophy and inflammation of the scalp[7].

T-cell–targeted therapies

Dapirolizumab

Dapirolizumab is an antibody fragment that targets the CD40 ligand (CD40L), mainly expressed on activated T cells and platelets. CD40L has long been an attractive therapeutic target due to its crucial role in adaptive immune activation and driving pathological processes in SLE. However, previous studies with a prior anti-CD40L prototype showed increased thrombo-embolic events, possibly due to platelet aggregation resulting from fragment crystallizable (Fc)-mediated cross-linking[84,85]. Therefore, dairolizumab was developed without a functional Fc domain to mitigate this effect.

In a phase II randomized, placebo-controlled study of dapirolizumab for SLE, secondary outcomes showed that dapirolizumab group had greater improvements in CLASI activity scores at week 24 compared to the placebo, with continued superiority at week 48. Although

infection rates were higher in these patients, there was no increased risk of thromboembolism[85].

A phase III trial (NCT04294667) in SLE is ongoing but does not include any skin-specific primary or secondary outcome measures.

Lulizumab

Lulizumab is a monoclonal antibody that targets CD28, a crucial T cell costimulatory molecule, thereby preventing the activation of pathogenic T cells involved in autoimmune diseases[86].

In a 24-week randomized, multicenter, double-blind study of 349 patients with SLE, lulizumab did not meet its primary endpoint of BICLA response rates. Additional efficacy outcome measures, which included CLASI-20 and CLASI-50, also did not reveal significant differences between groups[86].

Other targets

Ustekinumab

Ustekinumab is a monoclonal antibody inhibiting the p40 subunit of IL-12 and IL-23, approved for the treatment of psoriasis, psoriatic arthritis, and inflammatory bowel disease. Increased levels of these ILs in serum and tissue samples from patients with SLE, have sparked interest in ustekinumab for treating SLE and potentially CLE[87].

A *post hoc* analysis of the CLASI-50 response at week 24 demonstrated that ustekinumab was superior to placebo. Although these results seemed robust, in the phase III LOTUS study, there were no significant differences between treatment groups in the response rates for SRI-4 at week or CLASI activity improvement at week 52. The primary and secondary endpoints were not achieved, and the study was discontinued[88].

Etanercept

Etanercept is a TNF-α inhibitor that potentially treats active lesions with a reduced risk of systemic TNF effects, such as disease flares and drug-induced SCLE. In a phase II trial (NCT02656082) evaluating the efficacy and safety of intra-dermal injection of etanercept in discoid lupus erythematosus, 52% achieve a 20% decrease in the modified limited Score of Activity and Damage in DLE (ML-SADDLE) at week 12[7].

RSLV-132

Circulating extracellular RNA is the primary trigger of IFN-I in SLE, which plays a central role in the SLE pathogenesis. RSLV-132 is a novel catalytically active human RNase molecule fused to human IgG1 Fc that digests extracellular RNA, thereby inhibiting immune activation through Toll-like receptors and IFN pathways[89].

A phase II trial involving SLE patients with moderate-severe cutaneous disease activity showed no significant improvement in CLASI score after 6 months of RSLV-132 therapy. However, a trend toward clinical improvement was observed in participants with higher SLEDAI and CLASI scores, potentially suggesting that patients with more active systemic disease are most likely to benefit from RNase therapy[89].

DS-7011a

DS-7011a is a monoclonal antibody against TLR7 which is thought to contribute to the lupus pathogenesis[77]. Currently a phase 1b/2 randomized, double-blind, placebo-controlled, randomized trial is ongoing to assess the efficacy of DS-7011a in SLE and active CLE.

Other cytokines

Other considered therapies included BT063 (monoclonal antibody targeting IL-10), vobarilizumab (nanobody against IL-6), PF-04236921 (IL-6 monoclonal antibody), and avizakimab (anti-IL-21 monoclonal antibody). However, results from phase II studies were disappointing[7].

Conclusion

CLE is a significant cause of morbidity with a high risk for permanent scarring and depigmentation, which could negatively impact psychological well-being and quality of life of the patients. Treatment of CLE remains challenging due to the insufficient current available therapeutic options and recalcitrant disease, often requiring several immunosuppressive drugs with significant risk of systemic side effects. Therefore, this shortfall in effectively managing the disease highlights the need to develop new and improved treatment options.

While there have been exciting advances in new drugs for SLE, it remains crucial to develop tailored clinical trials focused on CLE patients with validated measures specific to skin disease, at to its different

subtypes. SLE patients with skin involvement do not accurately represent CLE patients, and the outcome measures of SLE trials are insufficient for capturing meaningful changes in skin activity. The identification of selective biomarkers, such IFN signature pointed out in some studies, is fundamental for individualized therapy by classifying potential responders and should be a focus of future research.

New emerging treatments targeting specific pathways involved in CLE pathogenesis, with recent phase II and III trials for anifrolumab, litifilimab, and deucravacitinib, have shown the most promising results, but there is still a long way to find highly efficacious and safe drugs for CLE.

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Conflicts of interest

J. Xará: none; M. Gonçalo has participated in lectures, advisory boards and/or clinical trials from Abbvie, Almirall, Amgen, Astra-Zeneca, Biogen, Leo Pharma, Lilly, Novartis, Pfizer, Sanofi, Takeda.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Pattern of skin disorder among patients attending skin outpatient department in tertiary care teaching hospital of district Almora: a retrospective study

Padrão de distúrbios de pele entre pacientes atendidos no ambulatório de dermatologia em hospital escola de cuidados terciários do distrito de Almora: um estudo retrospectivo

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Abstract

Objectives: The aim of this study was to assess the morbidity profile of patients attending dermatology outpatient department in a tertiary care center of Kumaun region, North India. **Methods:** The present study was a retrospective, record-based cross-sectional study in which OP registers of the Department of Dermatology from July 2023 to July 2024 were analyzed. Skin diseases were grouped into different groups and the frequency of cases in each group was studied. Data analysis was performed using Microsoft Excel and Statistical Package for the Social Sciences software version 16. **Results:** A total of 5118 patients were recorded in this study. About 44.7% were male while 55.2 % were females. All disorders were broadly classified into non-infectious and infectious dermatoses, out of them acne was most common in non-infectious group while tinea was most common in infectious group. **Conclusion:** Infections and eczemas which could be managed in primary healthcare set-up contributed to the majority of the OP attendance of our tertiary care center. The peripheral institutions should be strengthened in manpower and the level of knowledge and skills.

Keywords: Acne. Eczema. Fungal infection. Drug reaction. Almora.

Resumo

Objetivos: O objetivo deste estudo foi avaliar o perfil de morbilidade dos doentes seguidos no ambulatório de dermatologia de um centro terciário da região de Kumaun, norte da Índia. **Métodos:** O presente estudo foi retrospectivo, baseado em registros e com delineamento transversal, no qual os registros ambulatoriais do Departamento de Dermatologia, de julho de 2023 a julho de 2024, foram analisados. As doenças de pele foram agrupadas em diferentes categorias, e a frequência dos casos em cada grupo foi estudada. A análise dos dados foi realizada usando o Microsoft Excel e o software SPSS versão 16. **Resultados:** Um total de 5118 pacientes foi registrado neste estudo. 44,7% eram homens, enquanto 55,2% eram mulheres. Todos os distúrbios foram amplamente classificados em dermatoses infecciosas e não infecciosas; entre eles, a acne foi a mais comum no grupo não infeccioso, enquanto a tinea foi a mais comum no grupo infeccioso. **Conclusão:** As infecções e eczemas, que poderiam ser gerenciados em unidades de atenção primária, contribuíram para a maioria dos atendimentos

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no ambulatório do nosso centro de cuidados terciários. As instituições periféricas devem ser fortalecidas em termos de recursos humanos, conhecimento e habilidades.

Palavras-chave: Acne. Eczema. Infecção fúngica. Reação a medicamentos. Almora.

Introduction

Skin is the largest organ of the body and acts as the first barrier to exogenous insults such as injury and microbes thereby reflecting the health status of an individual[1,2]. Diseases of the skin are becoming an important concern at all levels of society and affect all age groups: infants, teenagers, adults, and the elderly[3]. They show variable patterns in different countries as well as different parts of the country. These variations across the country are observed especially in developing countries such as India[3].

It is more so in India, where the climate, socioeconomic status, religions, and customs are widely varied in different parts of the country[4]. Apart from environmental factors, the skin disease pattern varies depending on the occupation, socioeconomic status, age, and sex of the patients. Patterns of skin diseases from tertiary care centers in Kerala have been studied earlier[5,6].

Although the burden of skin diseases is significant, the majority of people affected with skin problems do not report to health centers and hospitals to seek medical advice. The prevalence of skin diseases in the general population has varied from 7.86 to 11.16% in India as reported in various studies[7,8].

Uttarakhand is primarily a hilly state situated in northwest region of India. It is divided into two regions, namely, Kumaun and Garhwal. Uttarakhand comprises 13 districts (7 in Garhwal region and 6 in Kumaon). The districts in Kumaon region are, namely, Alomra, Bageshwar, Champawat, Nainital, Pithoragarh, and Udham Singh Nagar. They constitute over 40% of the geographical area of the state, with over 80% covered by mountains. Soban Singh Jeena Government Institute of Medical Science and Research, Almora is one of the referral centers for Kumaun division.

Although there are a significant number of studies at a national level to understand the dermatological pattern, there is a paucity of studies in Kumaun region of Uttarakhand in this regard. The aim of this study was to assess the morbidity profile of patients attending dermatology outpatient department in a tertiary care center of Kumaun region, North India.

Materials and methods

A retrospective, record-based cross-sectional study was conducted from July 2023 to July 2024. The OP registers of the department during this period were analyzed. The registers were taken after getting permission from the Superintendent, Head of the Department, and the Institutional Ethics Committee.

The study included all new patients entered on the OP register on Monday, Wednesday, and Friday. Due to the selection of week and weekend days, this OP population included patients of all ages and sexes. Diagnosis was primarily clinical, supported by relevant investigations, and as per entry in the OP register. Data collected from the register were documented and analyzed. Patients diagnosed with skin cancer, subungual, ocular, and visceral lesions, and metastases were excluded from the study. For analysis, different skin diseases were broadly grouped into different groups, and the frequency of cases in each group was studied. The groups were eczemas, psoriasis, lichen planus, pityriasis rosea, other papulosquamous diseases, pigmentation disorders, vitiligo, fungal, bacterial and viral infections, parasitic infestation, sexually transmitted infections, leprosy, connective tissue diseases, and drug reactions. Data analysis was performed using Microsoft Excel and Statistical Package for the Social Sciences software version 16.

Result and observations

A total of 5118 (only new patients) patients were included in the study conducted over a period of 1 Year. 44.7% were male while 55.2% were females. The mean age of patients was 31.7 ± 17.1 years and approximately half of them were residents of Almora district (Table 1 and Fig. 1). All disorders were broadly classified into non-infectious and infectious dermatoses, out of them acne was the most common in non-infectious group while tinea was the most common in infectious group (Tables 2 and 3). Acne vulgaris was the most common dermatoses followed by tinea among all the patients. Furthermore, acne vulgaris was the most common dermatoses among female patients (Table 4).

Table 1. Sociodemographic profile of patients (n = 5118)

Variables	Frequency (no. %)
Age	
< 18 years	808 (15.8)
18-60 years	3916 (76.4)
> 60 years	394 (7.7)
Gender	
Male	2290 (44.7)
Female	2828 (55.2)
Locality	
Almora	2069 (40.4)
Pithoragarh	1770 (34.6)
Bageshwar	750 (14.6)
Champawat	529 (10.3)

Table 2. Pattern of non-infectious dermatosis (n = 5118)

Disease	Frequency (no. %)
Acne	1091 (21.3)
Drug reaction	457 (8.9)
Psoriasis	320 (6.2)
Miliaria	350 (6.8)
Urticaria	239 (4.7)
Alopecia	190 (3.7)
Eczema	186 (3.6)
Seborrheic dermatitis	186 (3.6)
Vitiligo	167 (3.3)
Lichen planus	80 (1.6)
Milia	78 (1.5)
P. Alba	49 (1)
SLE/DLE	47 (0.9)
Keloid	40 (0.8)
Tropical steroid-damaged face	40 (0.8)
Skin tag	31 (0.6)
PMLE	22 (0.4)
Epidermal cyst	06 (0.1)
Plaque psoriasis	06 (0.1)

SLE/DLE: systemic lupus erythematosus/discoid lupus erythematosus, PMLE: polymorphous light eruption.

Table 3. Pattern of infectious dermatoses (n = 5118)

Disease	Frequency (no. %)
Tinea	577 (11.3)
Scabies	305 (6)
Warts	144 (2.8)
Herpes zoster	132 (2.6)
Pityriasis versicolor	93 (1.8)
Furuncle/carbuncle	77 (1.5)
Herpes simplex	58 (1.1)
Impetigo	47 (0.9)
Folliculitis	43 (0.8)
Hyperhidrosis	15 (0.3)
Gonorrhea	11 (0.2)
Dengue rash	07 (0.1)
Pityriasis rosea	07 (0.1)
Chicken pox	06 (0.1)
Candida	05 (0.1)
Bullous pemphigus	03 (0.1)
Hansen's disease	03 (0.1)

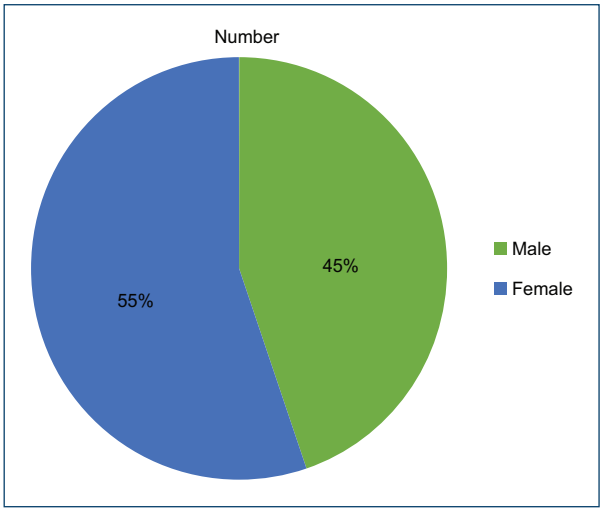

Figure 1. Gender distribution of patients (n = 5118).

Discussion

A rising trend of skin-related problems is noted in developing countries, including India. This can be correlated to multiple factors such as lower socioeconomic strata, climatic conditions, lack of access to health care, lower educational levels, and so on[9-11]. The impact of dermatological problems in resource-poor areas of the world is important in forming a concerted and sustainable global response toward bringing down

Table 4. Distribution of patients according to age and gender (n = 5118)

Disease	Female			Male		
	< 18 years	18-60 years	> 60 years	< 18 years	18-60 years	> 60 years
Eczema	07 (7)	70 (70)	23 (23)	13 (15.1)	55 (64)	18 (20.9)
Alopecia	05 (5.1)	93 (94.9)	0	03 (3.3)	88 (95.7)	01 (1.1)
Seborrheic dermatitis	20 (25.3)	54 (68.4)	05 (6.3)	26 (24.3)	75 (70.1)	06 (5.6)
Acne	105 (15.6)	566 (84)	03 (0.4)	104 (24.9)	313 (75.1)	0
Urticaria	25 (18.4)	101 (74.3)	10 (7.4)	28 (27.2)	66 (64.1)	09 (8.7)
Drug reaction	42 (15.7)	201 (75)	25 (9.3)	35 (18.5)	125 (66.1)	29 (15.3)
Psoriasis	05 (3)	118 (71.1)	43 (25.9)	03 (1.9)	121 (78.6)	30 (19.5)
Lichen planus	03 (8.1)	25 (67.6)	09 (24.3)	01 (2.3)	34 (79.1)	08 (18.6)
PMLE	0	08 (80)	02 (20)	01 (8.3)	09 (75)	02 (16.7)
SLE/DLE	01 (3.1)	23 (71.9)	08 (25)	01 (6.7)	12 (80)	02 (13.3)
Vitiligo	19 (22.9)	48 (57.8)	16 (19.3)	30 (35.7)	46 (54.8)	08 (9.5)
Skin tag	01 (5)	19 (95)	0	0	11 (100)	0
Keloid	02 (10)	16 (80)	02 (10)	0	19 (95)	01 (5)
Pityriasis alba	12 (46.2)	12 (46.2)	02 (7.7)	21 (91.3)	02 (8.7)	0
Miliaria	17 (31.5)	37 (68.5)	0	12 (50)	12 (50)	0
Tropical steroid damaged face	0	28 (87.5)	04 (12.5)	0	08 (100)	0
Tinea	26 (12.2)	169 (79.3)	18 (8.5)	38 (10.4)	308 (84.6)	18 (4.9)
Pityriasis versicolor	11 (26.2)	29 (69)	02 (4.8)	11 (21.6)	39 (76.5)	01 (02)
Furuncle/carbuncle	04 (7.3)	49 (89.1)	02 (3.6)	02 (9.1)	19 (86.4)	01 (4.5)
Folliculitis	02 (8)	22 (88)	01 (4)	03 (16.7)	15 (83.3)	0
Herpes simplex	03 (8.6)	31 (88.6)	01 (2.9)	01 (4.3)	19 (82.6)	03 (13)
Herpes zoster	04 (5.6)	51 (71.8)	16 (22.5)	02 (3.3)	41 (67.2)	18 (20.9)
Warts	14 (19.4)	55 (76.4)	03 (4.2)	06 (8.3)	64 (88.9)	02 (2.8)
Impetigo	21 (84)	04 (16)	0	12 (81.8)	03 (13.6)	01 (4.5)
Miliaria	03 (1)	285 (98.3)	02 (0.7)	03 (5)	57 (95)	0
Scabies	36 (26.9)	86 (64.2)	12 (9)	46 (26.9)	107 (62.6)	18 (10.5)
Miscellaneous (others)*	05 (16.1)	25 (80.6)	01 (3.2)	05 (16.1)	25 (80.6)	01 (3.2)

*Epidermal cyst, hyperhidrosis, dengue rash, gonorrhea, pityriasis rosea, chicken pox, plaque psoriasis, candida, bullous pemphigus, leprosy included in miscellaneous (others).
PMLE: polymorphous light eruption; SLE: systemic lupus erythematosus; DLE: discoid lupus erythematosus.

the burden[12,13]. In our study, the maximum number of patients were in the age group of 18-60 years of age group (76.4%), followed by the < 18 years of age group (15.8%). The least number of patients were found in the elderly age group, that is, > 60 years age group (7.7%). In a study conducted by Jain et al.[7]. The most common age group was different to our study, that is, 21-30 years (54.8%). However, the elderly age group (> 60 years) formed a significant proportion of 20.4% of patients and the least number of patients were in the 11-20 years age group (3.7%). In our study, the highest number of patients were in the 18-60 years age group could be because they are the most mobile group of the population, and > 60 years being the least prevalent group

because of least mobility and ignorance toward these non-life threatening skin problems.

The prevalence of infective skin disorders noted in a few studies varied from 42.68 to 63.65%[6,14,15]. On detailed analysis, it was found that infectious skin disorders (51.2%) outnumbered the non-infectious skin disorders (48.7%) in our study. Grover et al.[3] recorded a similar pattern of diseases where infectious cases (59.1%) were more common than non-infectious cases (40.9%). In contrast to our study, many studies noted that non-infectious diseases were more common than infectious ones. Bommakanti and Pendyala[16] recorded 60.15% cases of non-infectious diseases. This spectrum of dermatoses with predominant infectious diseases can be attributed to the fact that the community setting had overcrowding, ignorance toward healthcare, and poor hygiene. The differences in the distribution of infectious and non-infectious dermatoses in various studies can be attributed to different climatic and geographical diversities as well as different susceptibilities of different population groups.

Among the infectious group of disorders, fungal infections dominated the spectrum with 11.3% of all study subjects, followed by scabies (6%). A similar pattern was noted by Das and Chatterjee[15] with the most common infections being tinea (12.3%).

Scabies was found in < 10% of all new cases in the present study. Likely among all cases scabies was present in 8.9% in study from Imphal[17]. In a study from Mangalore, Karnataka, among the infective disorders, 9.4% of scabies cases were reported[6].

In the non-infectious group of diseases, we noted that the most common disease was acne (21.3%), followed by drug reaction (8.9%), miliaria (6.8%) closely followed by psoriasis (6.2%). Such a high percentage of acne can be attributed to the fact that we had a significant number of study subjects in the adolescent age group and early adulthood. These results were much higher than the study conducted in Kerela where the prevalence of drug reaction reported was only 0.2%[18].

Among children, both males and females skin and subcutaneous infections (eg. Pityriasis alba, Vitiligo) were the most common diagnosis. Two other similar studies which were carried out among children in India and Pakistan and showed that skin infection comprised 83.3% and 60% of skin diseases, respectively[19,20]. Higher proportion of the skin and subcutaneous infections among children is also comparable to a study conducted in Wardha district in Maharashtra on 666 children aged 0-14 which found that infective dermatoses contributed 63.5% of all dermatoses[21].

Proportion of cases of vitiligo and urticaria was 3.3 and 4.7% which was comparable to the study done in Kerala, 4.7% and 3.5%, respectively[22]. The results of studies from Mali and Ethiopia are similar[5,23].

Significant differences between males and females were seen in some diseases. Male: female ratio in these diseases was as follows – drug reaction (189:268), acne vulgaris (417:674), leprosy (13:2), connective tissue diseases (15:32), and tinea (364:213). These results were comparable to the study conducted in northern Kerela India[11,18,24].

Limitations

The main limitation was that the study was only conducted for one year and patients coming on only three days in a week were selected. However, authors believe that this is worth reporting because of the rarity of such studies. These findings have to be reassessed in more long-term studies.

Conclusion

Although the present study was conducted in a tertiary center, most of the cases were common dermatological conditions such as infections and eczemas which should be ideally managed in the primary healthcare set-up. To achieve this, the peripheral institutions should be strengthened with manpower and the required level of knowledge in dermatology. More focused and effective training of medical students about the management of common skin conditions at the undergraduate level, at least two week's compulsory posting in dermatology during an internship, and continuing medical education for practitioners, are important in this regard.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Evaluation of the impact of the COVID-19 pandemic on patients with psoriasis using immunobiologicals

Avaliação do impacto da pandemia de COVID-19 em pacientes com psoríase em uso de imunobiológicos

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Abstract

Objective: Psoriasis is a systemic inflammatory and immune-mediated disease. The treatment of this condition with immunobiologicals has shown excellent responses, however, one of the known adverse effects is susceptibility to infections due to interference with the immune system. The objective of the present study is to evaluate the evolution of a population of patients with psoriasis using immunobiologicals during the coronavirus pandemic. **Methods:** A cross-sectional observational study that included patients with psoriasis taking immunobiologicals for at least 6 months between March 2020 and August 2022. **Results:** A total of 86 patients with psoriasis using immunobiologicals with a mean age of 54.9 years were included, and 27.8% also had psoriatic arthritis. Of the 86 patients, 42 had at least one episode of COVID-19, of whom 90.4% reported mild symptoms. Of those affected by the infection, 38.1% needed to seek medical attention and < 5% needed hospitalization; no patient needed hospitalization in the intensive care unit. **Conclusion:** Across the data collected, it was possible to conclude that it is safe to use immunobiologicals in patients with psoriasis in the setting of SARS-CoV-2 infection.

Keywords: Psoriasis. COVID-19. Immunobiological treatments.

Resumo

Objetivo: A psoríase é uma doença inflamatória sistêmica e imunomediada. O tratamento desta condição com imunobiológicos tem apresentado excelentes respostas, entretanto, um dos efeitos adversos conhecidos é a suscetibilidade a infecções devido à interferência no sistema imunológico. O objetivo do presente estudo é avaliar a evolução de uma população de pacientes com psoríase em uso de imunobiológicos durante a pandemia do coronavírus. **Métodos:** Estudo observacional transversal que incluiu pacientes com psoríase em uso de imunobiológicos por pelo menos 6 meses entre março de 2020 e agosto de 2022. **Resultados:** Foram incluídos 86 pacientes com psoríase em uso de imunobiológicos com média de idade de 54,9 anos, sendo que 27,8% também apresentavam artrite psoriásica. Dos 86 pacientes, 42 apresentaram pelo menos um episódio de COVID-19, dos quais 90,4% relataram sintomas leves. Dos acometidos pela infecção, 38,1% precisaram procurar atendimento médico e menos de 5% necessitaram de internação hospitalar; nenhum paciente necessitou de internação em unidade de terapia intensiva. **Conclusão:** Por meio dos dados coletados, foi possível concluir que há alguma segurança no uso de imunobiológicos para psoríase no contexto de infeção por SARS-CoV-2.

Palavras-chave: Psoríase. COVID-19. Tratamentos imunobiológicos.

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Introduction

Psoriasis is an immune-mediated inflammatory systemic disease associated with genetic and environmental factors, with a predominance of skin lesions. Worldwide prevalence ranges from 0.91 to 8.5%, with an estimated 1.31% in Brazil[1,2]. Treatment should be chosen according to the severity and extent of the clinical manifestation and psycho-emotional impairment. Priority should be given to general measures and topical therapy, followed by phototherapy and systemic therapy. If the patient does not improve, has contraindications or the condition is more severe, new systemic treatments should be considered.

Treatment with immunobiologicals for psoriasis that is severe or refractory to conventional treatments has proved to be innovative and has excellent lesion clearance rates in most patients. Despite their relatively recent use, many of their adverse side effects are already known, such as susceptibility to infections due to interference with the immune system. The pathogenesis of psoriasis includes immune pathways mediated mainly by T cells and cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-12 (IL-12), IL-23, and IL-17[3]. Biological therapies that target these cytokines make them a major innovation in the treatment of psoriasis over the past 20 years, significantly changing the response to the treatment of psoriasis and psoriatic arthritis. Some studies, however, have found that the overall infection rate is higher in these patients, making these drugs risk factors for serious infections[4,5]. Nonetheless, it should be noted that the specific susceptibility to SARS-CoV-2 is not contemplated in these studies, and the most recent literature mentions that it could have a different immune response compared to other respiratory viruses[6].

During the COVID-19 pandemic, many questions were raised about whether or not to continue using immunobiologicals, due to concerns about the possibility of them enhancing more severe cases of acute respiratory syndrome. Some studies have tackled the subject, but there are still many questions as to a consensual approach or how patients have been clinically maintained during the pandemic. Data collected and presented in this study was based on "PsoProtect Me", a questionnaire created by a group of doctors and scientists from St John's Institute of Dermatology, Guy's and St Thomas' Hospital London; a Dermatology Center at the University of Manchester; and patient representatives from the UK Psoriasis Association, who assessed the impact of COVID-19 on psoriasis[1]. Therefore, assessing the impact of COVID-19 on patients undergoing immunobiological treatment would help to clarify the response to SARS-CoV2 infection under these drugs.

Materials and methods

The present study is a cross-sectional observational study to evaluate the clinical evolution of a population of patients with psoriasis taking immunobiologicals during the coronavirus pandemic, since the use of immunobiologicals might increase the risk of higher infections' severity.

Patients from the Dermatology service diagnosed with psoriasis who had been prescribed immunobiologicals for at least 6 months were evaluated from March 2020 to August 2022.

The research was approved by the local Research Ethics Committee (CAAE: 64655122.8.0000.0020) according to resolution no. 466/2012 of the National Health Council and the Helsinki Conventions. Patients considered eligible for the study and interested in participating were informed of the content of the study and signed an Informed Consent Form. A questionnaire designed specifically for this research was then applied, based on "PsoProtect Me". The information collected was entered into an electronic spreadsheet for further statistical evaluation.

Data were initially described by setting up frequency tables for categorical variables and calculating descriptive measures (mean, median, standard deviation, minimum, and maximum) for quantitative variables. Pearson's Chi-squared test was applied to verify bivariate statistical correlations, using a 5% significance rate.

Results

In this study, 86 patients were investigated, 59.3% male and 40.7% female. The average age at the time of analysis was 54.9 years (between 27 and 81 years), with an average weight of 85 kg (45-25 kg). Of the analyzed patients, 76.7% declared themselves as white, 15.1% as brown, 5.8% as black and 2.3% as yellow. The average age at diagnosis of psoriasis was 30.9 years (ranging from 2 to 71 years), and 93.0% had plaque-type psoriasis, followed by inverted and pustular psoriasis. Around 27.8% also had psoriatic arthritis. Regarding comorbidities, the most prevalent were hypertension (39.5%), dyslipidemia (33.7%), diabetes mellitus (24.4%), and depression (10.4%), with 23.2% of cases reporting no other health problem apart from psoriasis.

Regarding COVID-19 vaccination, only 1 patient was not vaccinated (1.1%). The remaining 98.8% were vaccinated, and 81% received 4 or more doses. The vaccination schedules evaluated were, in order of prevalence, AstraZeneca (35.5%), CoronaVac (27.6%), Pfizer (27.6%), and Janssen (7.8%).

As for treatment, the most frequently used immunobiologicals were ustekinumab (33.7%) and adalimumab (29.0%), followed by secukinumab (18.6%), etanercept (5.8%), infliximab (5.8%), risankizumab (5.8%), and ixekizumab (1.1%).

Concerning stress assessment during the pandemic, almost 42.0% of patients reported a worsening of their stress level (classified as mild, moderate, or intense, respectively in 27.6%, 52.3%, and 19.2%), 40.6% reported maintaining the same level of stress as before the pandemic and 17.4% reported no stress. Approximately 21.4% of the patients reported a worsening of their psoriasis due to the stress of the pandemic, while 78.5% did not observe any worsening of the lesions.

Of the 86 patients evaluated, 51.1% reported never having been diagnosed with COVID-19, while 48.8% had a COVID-19 diagnosis at some point, although only 88.1% had a laboratory confirmation, but they had typical symptoms and in 73.1% there was a family member with confirmed COVID-19. Among psoriasis patients who had COVID-19, 90.4% had only 1 episode, while 9.5% had two episodes, and 69.4% of the episodes of SARS-CoV-2 infection occurred between 2021 and 2022. Approximately 41.0% had the disease before the first dose of the vaccine and just over 23.0% after the booster dose. The most frequent symptoms reported were fever (54.7%), body aches (52.3%), and cough (42.8%). Regarding the degree of symptoms, over 90.4% reported mild symptoms, 4.7% had moderate symptoms, and 4.7% had severe symptoms. Of those affected by COVID-19, 38.1% of patients needed to seek medical attention, < 5% needed hospitalization, and no patient required admission to an intensive care unit. COVID-19 symptoms, such as asthenia and anosmia, persisted in 7.1% of cases.

Evaluating psoriasis severity in patients who had COVID-19, < 5% reported that their psoriasis became worse during the infectious episode, with 95.2% maintaining a stable skin condition. After the episode, 4.7% showed worsening, with new diffuse plaques, 85.7% kept stable and 9.5% demonstrated an improvement in psoriasis, as shown in table 1.

Among patients who had COVID-19 infection, the most frequent immunobiological treatments were ustekinumab (40.4%) and adalimumab (30.9%) (Table 2). Just 17.0% interrupted their psoriasis treatment during the infection, returning soon after their respiratory symptoms had completely recovered. Patients taking immunobiologicals when they had an infection were instructed, according to institutional protocol, to contact their assisting physician for instructions on how to pause treatment until their symptoms had completely improved.

There was no significant association between patients with psoriatic arthritis and severe COVID-19 symptoms (p = 0.66), and there was no significant correlation for higher risk of infection or severe symptoms in patients with psoriasis related to age at diagnosis of COVID-19, gender, or weight. A significant association was found between the average age at diagnosis of psoriasis and the risk of COVID-19 infection (p = 0.02), with patients with an earlier onset of psoriasis symptoms having a higher risk of SARS-CoV-2 infection (Table 3).

Table 1. Psoriasis evolution during COVID-19

Clinic	Before* (%)	Total (n)
No new skin lesions	14 (33.3)	42
Few new skin lesions	23 (54.7)	
Multiple new skin lesions	5 (11.9)	
Clinic	**During† (%)**	**After‡ (%)**
No change	40 (95.2)	36 (85.7)
Worsened	2 (4.7)	2 (4.7)
Improved	0	4 (9.5)

*Before COVID-19.
†During the period of COVID-19.
‡After COVID-19. n: total number of patients.

Table 2. Immunobiological therapy in use during COVID-19

Drug	Patients (n)	%
Ustekinumab	17	40.4
Adalimumab	13	30.9
Secukinumab	7	16.6
Infliximab	3	7.1
Risankizumab	1	2.3
Etanercept	1	2.3
Total	42	100

n: total number.

Table 3. Comparison of COVID-19 incidence between groups

Groups	COVID-19		p
	Yes	No	
Age (mean, years)	53.5 year	56.3 year	0.19
Female (n)	17	18	0.97
Male (n)	25	26	0.97
Weight (mean, kg)	86.5 kg	83.5 kg	0.38
Age at psoriasis diagnosis (mean, years)	27.7 year	33.9 year	0.02
Psoriatic arthritis (n)	10	12	0.66

n: number of patients.

Patients with hypertension or dyslipidemia had a higher incidence of symptomatic COVID-19 compared to the other comorbidities; however, this result was not statistically significant (p = 0.82), as shown in table 4.

Patients who took ustekinumab had a higher incidence of SARS-CoV-2 infection compared to the other drugs; however, this result was not statistically significant (p = 0.48), nor was it related to more severe cases of the infection.

Discussion

The first cases of SARS-CoV-2 were identified in December 2019 in Wuhan, Hubei Province, China, and after the spread of the virus, the COVID-19 pandemic was declared by the World Health Organization in March 2020. Since then, there has been concern and caution about changes related to healthcare. In this context, special attention has been directed at patients taking immunobiological drugs for psoriatic disease[1], considering that immunomodulatory therapies have a theoretically increased risk of serious infections compared to the general population. However, some studies indicate that SARS-CoV-2 infection could have a different immune response to other respiratory viruses[6,7].

As psoriasis can be exacerbated by various factors, including infections, vaccines, stress, and others, there has been some concern about the clinical course of the disease and the susceptibility to infections of those undergoing immunobiological therapies during the coronavirus pandemic[8].

The first molecule used to treat psoriasis was anti-TNF. TNF-α, is an inflammatory cytokine produced by macrophages during acute inflammation. It has a significant role in the defense of the host against intracellular bacterial infections, such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*, and is crucial to the formation of epithelial granuloma[9,10]. At present, four anti-TNF-α agents are in use for the treatment of psoriasis: adalimumab, certolizumab pegol, etanercept, and infliximab[11]. An increased risk of opportunistic infections has been reported in patients with inflammatory intestinal disease who were taking anti-TNF-α therapies[12]. However, there are no relevant research results on SARS-CoV-2 infection for patients with psoriasis undergoing anti-TNF-α treatment. Some case reports show that these patients may have an infection with no clinical symptoms[13]. In this trial, adalimumab was the second most used specific treatment during the pandemic and, together with infliximab and etanercept, was the class most patients were taking (40.6%). Even in these circumstances, there was no risk of more severe symptoms of COVID-19 infection or increased risk of infection in psoriasis patients taking anti-TNF drugs. Some recent studies have indicated that anti-TNF-α or anti-IL drugs were associated with a lower risk of serious infection compared to conventional psoriasis therapies[7].

In addition to anti-TNF-α drugs, there are anti-IL-17 agents approved for the treatment of psoriasis, such as secukinumab, ixekizumab, and brodalumab. IL-17 plays a vital role in protecting the host against infections, especially on the skin and in the mucous membranes, such as the lungs, intestines, and oral cavity. Similar to TNF-α, the average serum levels of IL-17 in COVID-19 patients were considerably higher than in the control group, and it was also observed that the systemic level of IL-17 has a positive and significant correlation to Transforming growth factor-beta, which is viewed as a predictive factor of the severity of the disease in COVID-19 patients[14,15]. Around 18.6% of the patients in this evaluation were receiving secukinumab, and there was no apparent increase in the risk of infection, nor any increase in the severity of COVID-19 with the use of this medication. This is in line with the current literature, which found that treatment with anti-IL-17 did not confer an increased risk of COVID-19 or its complications in patients with psoriasis[16].

Other agents target IL-23, such as Ustekinumab which blocks the common p40 subunit of IL-12 and IL-23, guselkumab and risankizumab, which focuses on the p19 subunit of IL-23. Unlike TNF-α and IL-17, IL-23 does not appear to be involved in the response to coronavirus and viral pneumonia or have a major impact on

Table 4. Correlation of comorbidities with the incidence of COVID-19

COVID-19	Hypertension (n)	Dyslipidemia (n)	Diabetes (n)	No comorbidities (n)
Yes	17	13	8	8
No	17	16	13	12
p	0.82	0.82	-	-

n: number of patients.

antiviral immunity[13]. The safety of IL-23 inhibitors during the COVID-19 pandemic was reported in a multicenter study performed during the first 4 months of the pandemic in Italy. In this study, only 1 patient (1.8%) had an upper respiratory tract infection, 3 patients (5.3%) had contact with individuals infected with SARS-CoV-2 and no one had a SARS-CoV-2 infection among the 57 patients evaluated[17]. These results indicated that the use of IL-23 inhibitors did not increase the rate of SARS-CoV-2 infection, similar to our analysis. Furthermore, ustekinumab was the most used therapy (33.7% of patients), without an increase of COVID-19 severity[17].

Concerning the evaluation of psoriasis' worsening and stress during the pandemic, it was observed that 42% of patients reported more stress levels, however, < 25% observed a worsening of skin lesions, maintaining optimum control of the disease with the use of biological therapies in the stressful scenario of the pandemic. A significant association was observed with an increased risk of COVID-19 infection in patients who had an earlier onset of psoriasis symptoms ($p = 0.027$), which could be explained by the fact that these individuals have often been exposed to the inflammation of psoriatic disease for longer since immunobiological treatments are still fairly recent in the context of dermatology.

Despite the small sample size of this study, there was no increased risk of infection or severity of COVID-19 in psoriasis patients taking immunobiological therapies, corroborating what has been described in the literature in the post-pandemic period[18]. Most current studies show that immunobiological therapies used in psoriasis do not present a higher risk of SARS-CoV-2 infection or even an increased hospitalization rate; in some cases, the risk was even lower than the overall population, conferring some protection for these patients[7,19,20]. Based on this, it can be considered that immunobiological therapies remain safe treatment options in the context of COVID-19 and can be continued even in the context of a pandemic.

Conclusions

As psoriasis is considered to be a chronic, immune-mediated inflammatory disease, it is associated with various comorbidities such as metabolic syndrome and psoriatic arthritis, among others, making it a multisystem disease. The treatment chosen to control psoriasis must take into account the severity and extent of the clinical picture. In this context, immunobiological therapies have revolutionized the treatment of psoriatic disease. Despite their relatively recent use, many of the adverse effects of immunobiological therapies are already known, such as increased susceptibility to infections. However, the specific relationship with the infection caused by SARS-CoV-2 was hardly contemplated in the studies, and more recently it has been observed that it could have a different immune response compared to other respiratory viruses.

After analyzing the impact of immunobiological therapies during the COVID-19 pandemic, it is possible to conclude that the results suggest the relative safety of these treatments concerning SARS-CoV-2 infection. The absence of a significant increase in the risk of infection or severe COVID-19 in psoriasis patients undergoing these therapies is an encouraging finding. Considering the data obtained in this study, as well as the evidence presented in the literature, it is possible to affirm that immunobiological therapies to control psoriasis are safe and effective, even amid a global pandemic. Nonetheless, it is essential to emphasize the need for further research to improve understanding of the safety of these medications in the context of public health emergencies similar to the COVID-19 pandemic. Expanding knowledge in this area will not only strengthen existing evidence but will also help guide more precise and safer clinical conduct in the face of future pandemics.

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Conflicts of interest

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Protection of people and animals. The authors declare that no experiments were performed on humans and/or animals for this research.

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Use of artificial intelligence to generate texts. The authors declare that they did not use any type of generative artificial intelligence in the writing of this manuscript nor for the creation of figures, graphs, tables, and/or their respective captions.

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CASE REPORT

Hydroxychloroquine-induced hyperpigmentation in a patient with anti-synthetase syndrome

Hiperpigmentação induzida pela hidroxicloroquina numa doente com síndrome anti-sintetase

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Abstract

Hydroxychloroquine is a widely prescribed antimalarial drug to treat immune-mediated diseases, with a good safety profile. We present the case of a 37-year-old woman, Fitzpatrick's phototype IV, who presented to our outpatient Dermatology Department with a 1-year history of symmetrical blue-gray discoloration on the anterior aspect of the legs. The patient had a diagnosis of anti-synthetase syndrome, treated with prednisolone, hydroxychloroquine, rituximab, cyclosporine, and acetylsalicylic acid. The blood work was unremarkable. The skin biopsy revealed hemosiderin and melanin (Perl's and Fontana-Masson staining) deposits inside dermal histocytes. The diagnosis of antimalarial-induced hyperpigmentation was established. Cutaneous blue-gray discoloration is a common antimalarial skin toxicity, mainly in women with darker skin. Its pathophysiology is unclear, but local trauma, ultraviolet radiation, and the concomitant use of corticosteroids, anticoagulants, and antiplatelet drugs seem to contribute as triggers. This case illustrates that a high level of suspicion and adequate clinicopathologic correlation is necessary to establish a correct diagnosis.

Keywords: Antimalarials. Drug-induced abnormalities. Hydroxychloroquine. Hyperpigmentation. Idiopathic inflammatory myopathies.

Resumo

A hidroxicloroquina é um fármaco antimalárico frequentemente utilizado no tratamento de doenças imunomediadas, com bom perfil de segurança. Apresentamos o caso de uma mulher de 37 anos, fototipo IV de Fitzpatrick, encaminhada à consulta de Dermatologia por manchas cinzento-azuladas simétricas na face anterior das pernas com 1 ano de evolução. A doente tinha diagnóstico de síndrome anti-sintetase, medicada com prednisolona, hidroxicloroquina, rituximab, ciclosporina e ácido acetilsalicílico. A avaliação analítica não revelou alterações. A biópsia cutânea demonstrou depósitos de hemossiderina e melanina (colorações Fontana-Masson e Perls) em histiócitos na derme, compatível com hiperpigmentação induzida por antimaláricos. As discromias cinzento-azuladas são um efeito adverso cutâneo comum dos antimaláricos, sobretudo em mulheres de fototipo alto. A fisiopatologia não está completamente esclarecida, mas o trauma local, a radiação ultravioleta e a toma concomitante de

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corticosteroides, anticoagulantes e antiagregantes parecem contribuir como desencadeantes. Este caso ilustra que o diagnóstico da hiperpigmentação induzida pela hidroxicloroquina implica um elevado nível de suspeição e correlação clínico-patológica.

Palavras-chave: Antimaláricos. Alterações induzidas por fármacos. Hidroxicloroquina. Hiperpigmentação. Miopatias idiopáticas inflamatórias.

Introduction

Hydroxychloroquine is an antimalarial drug that is widely prescribed in dermatology and rheumatology, due to its immunomodulatory and photoprotective properties, namely in systemic and cutaneous lupus erythematosus and idiopathic inflammatory myopathies[1,2]. Although antimalarial drugs have a good overall safety profile, skin adverse events are not rare and are frequently overlooked[2,3]. Skin, nail, and mucous membrane blue-gray discoloration is one of the most common skin toxicities of antimalarial drugs and may occur in 10-25% of patients[2-4]. Herein, we report a case of hydroxychloroquine-induced hyperpigmentation in a patient with anti-synthetase syndrome that illustrates that a high level of suspicion and adequate clinicopathologic correlation is necessary to establish a correct diagnosis and to determine optimal patient management.

Case report

A 37-year-old woman, Fitzpatrick's phototype IV, presented to our outpatient dermatology department with a 1-year history of asymptomatic, bilateral dark patches on her lower limbs. Her past medical history was relevant for anti-synthetase syndrome, which was diagnosed when she was 32 years old due to proximal muscle weakness, polyarthritis, and fingers' hyperkeratosis and fissuring (mechanic's hands). The patient's autoimmune serology was positive for anti-Jo-1 antibodies and anti-Ro/SSA and negative for the remaining antibodies. She was under treatment with prednisolone 10 mg/day, hydroxychloroquine 400 mg/day, and rituximab pulses every 6 months, which were initiated 4 years before the cutaneous discoloration began. One year before, the patient was also prescribed cyclosporine 200 mg/day and acetylsalicylic acid 150 mg/day, given her wish for childbearing. The patient denied taking any other drugs than the ones mentioned before or applying any specific topical products. She also denied pain or pruritis, previous local trauma, preceding skin eruption, chronic venous insufficiency complaints, and any other local or systemic symptoms.

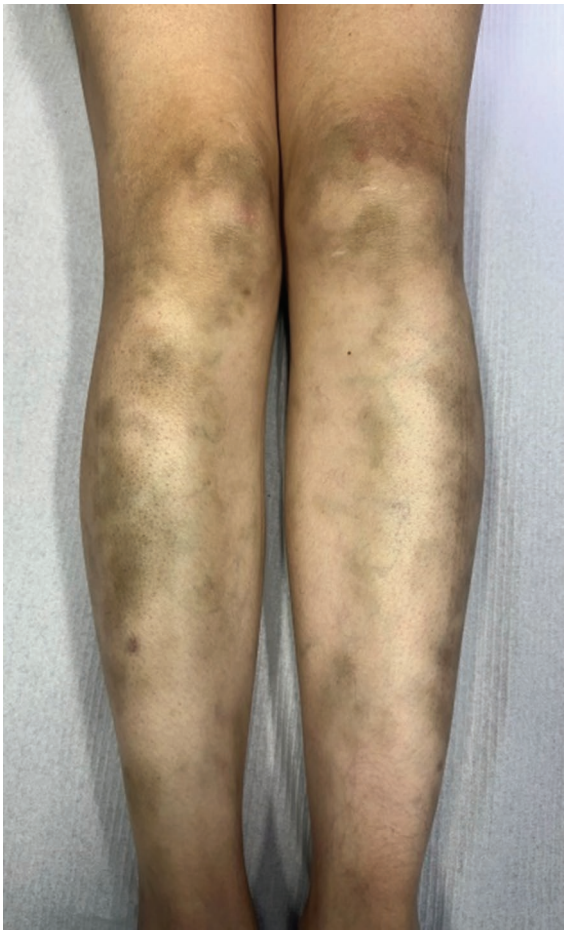

Figure 1. Clinical image. Symmetrical, ill-defined, mottled blue-grey patches on the anterior aspect of both legs and knees.

On physical examination (Fig. 1), there were non-tender, symmetrical, ill-defined, mottled blue-grey patches on the anterior aspect of both legs and knees. There was no pigmentation at other body sites including the oral mucosa and the nails. The diagnostic hypothesis of antimalarial drug-induced skin discoloration was considered. Laboratory examination revealed a normal complete blood count, normal coagulation studies and platelet function tests, normal iron and ferritin levels, and was otherwise unremarkable. Histopathologic examination of a punch skin biopsy (Fig. 2) showed hemosiderin (Perls staining) and melanin (Fontana-Masson staining)

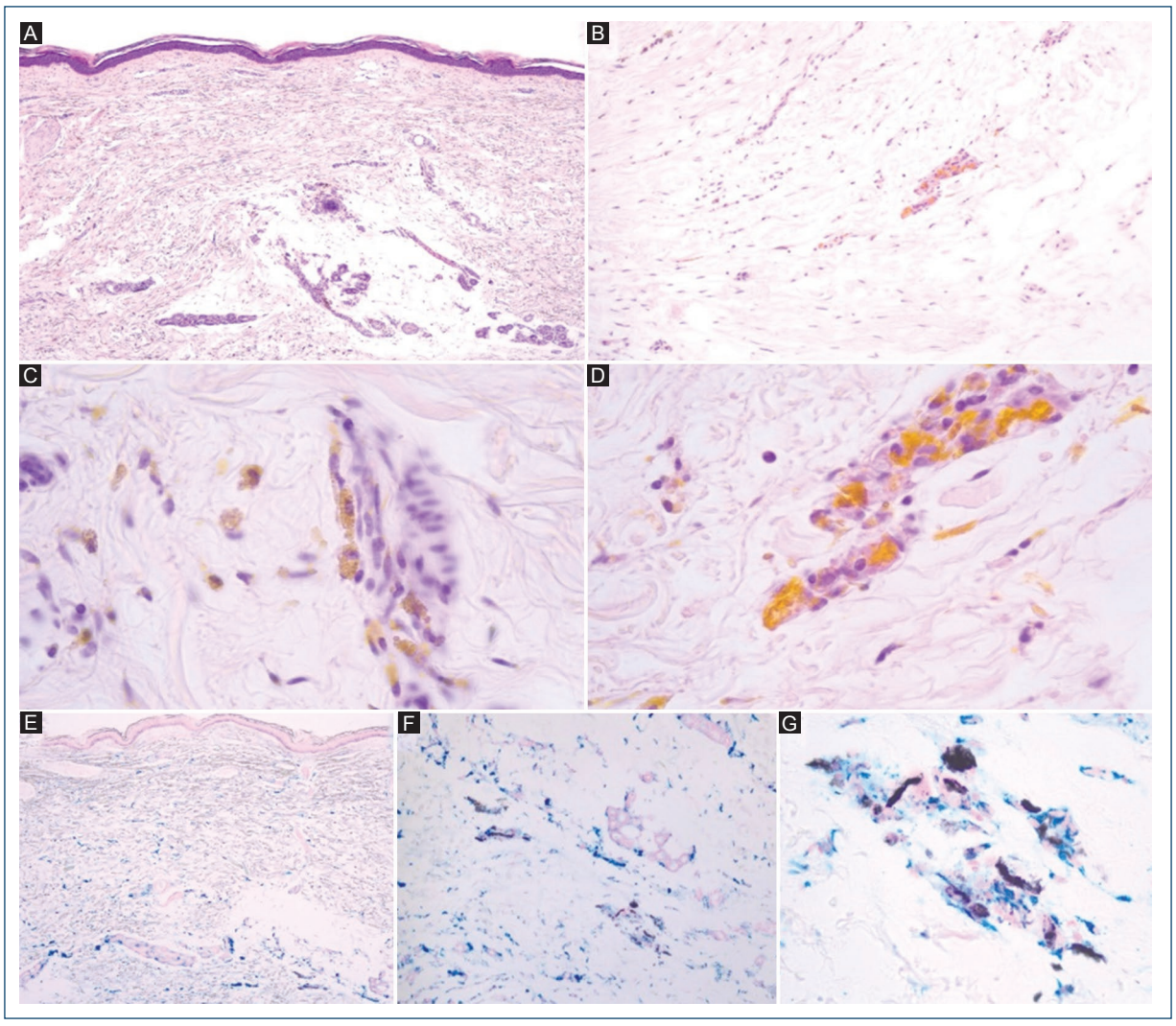

Figure 2. Histopathological examination. **A:** hematoxylin-eosin, original magnification ×40) yellowish-to-brown interstitial and perivascular pigmented granules throughout the dermis, of different qualities. **B:** hematoxylin-eosin, original magnification ×100): darker (superior left corner of the image) and lighter (center of the image) pigment deposits. In higher magnification, there are fine dark-brown intrahistiocytic pigment granules. **C:** hematoxylin-eosin, original magnification ×400), and thick yellow-brown intrahistiocytic and interstitial pigment granules. **D:** hematoxylin-eosin, original magnification ×400). Simultaneous Perls/Fontana-Masson staining demonstrated that these pigment granules corresponded to intrahistiocytic melanin, and intrahistiocytic, and interstitial hemosiderin. **E-G:** Perls/Fontana-Masson staining, original magnification ×40, ×100, and ×400, respectively).

deposits inside dermal histocytes. The diagnosis of hydroxychloroquine-induced cutaneous hyperpigmentation was established. The patient had an ophthalmology appointment that excluded retinopathy and other ocular toxicities.

A multidisciplinary discussion of the different management approaches for this case was conducted, including Dermatology, Rheumatology, Obstetrics, and Ophthalmology. The treatment options were also discussed with the patient. We took into consideration that the patient had an anti-synthetase syndrome with present signs of disease activity, that she had a previous late fetal loss, and had positive anti-Ro/SSA antibodies with increased pregnancy and neonatal risk (namely for neonatal lupus), and also that interrupting the treatment did not guarantee clinical resolution of the discoloration. Therefore, we decided to maintain treatment with hydroxychloroquine. The patient was treated with azelaic acid cream 200 mg/g twice a day and photoprotective measures, with moderate improvement.

Discussion

Cutaneous blue-gray discoloration is a common antimalarial drug skin and mucous membrane toxicity, affecting up to 10-25% of patients, and it seems to be more frequent with chloroquine than hydroxychloroquine[2-4]. It mainly affects women with darker skin types[1,3,4], such as our patients.

Clinically, hydroxychloroquine-induced hyperpigmentation presents as bluish or blue-grey macules and patches that most commonly occur bilaterally on the anterior aspects of the legs, but can also less frequently be seen on the arms, forearms, face, oral mucosa, trunk, nails, and axilla[1,2,4]. The latency of this skin adverse event is variable. In most series, the majority of cases occur within the first 5 years of treatment, with a median duration of 3 years[1,3,5].

The pathophysiology of this skin discoloration is not completely understood, and there is no significant association with the cumulative dose of hydroxychloroquine[1,3,4]. Some reports have demonstrated that local trauma, ultraviolet radiation, and the concomitant use of corticosteroids, anticoagulants, and antiplatelet drugs may contribute to triggers[1-3]. It is believed that local trauma and the use of antithrombotic drugs, alongside hydroxychloroquine-induced damage of dermal vessels, may lead to erythrocyte extravasation, with hemoglobin release into the extracellular space. The subsequent heme breakdown induces iron deposits in the form of interstitial and intra-histiocytic hemosiderin complexes in the dermis. The hemosiderin deposition then causes melanocyte activation, with increased production of melanin[1-3]. Cutaneous histopathologic studies of patients with hydroxychloroquine-induced hyperpigmentation demonstrate the presence of both hemosiderin and melanin dermal deposits (as in our patient) and also show significantly higher iron concentrations in biopsy specimens of pigmented lesions compared with normal skin, corroborating this theory[1-3,5]. However, several other mechanisms may be implied, such as direct melanocyte stimulation by hydroxychloroquine and accumulation of drug metabolites[3].

The association between skin discoloration and ocular adverse events (retinopathy, corneal, and lens opacities) in patients taking hydroxychloroquine is still controversial[1,2,5]. Although some authors believe that antimalarial drug-induced pigmentation may be a marker for patients at risk of ocular complications[2,6], these data mostly refer to patients taking chloroquine and this correlation has not yet been significantly established in the literature[1,5]. Further studies are still needed to better understand this potential association, and in view of this, patients receiving antimalarial therapy who develop pigment abnormalities should have frequent ophthalmological examinations[6,7].

Nevertheless, most reports in the literature to this date state that other than possible esthetic or psychosocial impact (which was not relevant in our patient), skin pigmentation has no other systemic consequences for patients. Furthermore, the hyperpigmentation may not resolve after drug discontinuation[3,5], and in patients who keep taking the drug, the pigmentation seems to remain stable[1]. Therefore, drug discontinuation is not always necessary[1], especially if ocular complications have been excluded and the benefits outweigh the potential risks, as in our patient.

Conclusion

This case of hydroxychloroquine-induced hyperpigmentation in a patient with anti-synthetase syndrome illustrates that skin discoloration is a common cutaneous adverse event of this drug, but that it is not necessarily associated with other serious side effects such as retinopathy, and therefore does not always imply drug discontinuation. This case also highlights that a high level of suspicion and adequate clinicopathologic correlation are necessary to establish a correct diagnosis and that a multidisciplinary approach is crucial in these complex cases to determine the optimal management for each specific patient.

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CASE REPORT

The role of narrowband ultraviolet B phototherapy in the treatment of refractory osteomalacia

O papel da fototerapia com radiação ultravioleta B de banda estreita no tratamento de osteomalacia refratária

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Abstract

Osteomalacia is a disorder of mineralization of newly formed osteoid that can be precipitated through mechanisms that result in hypocalcemia, such as prolonged vitamin D deficiency. Treatment is mainly focused on **v**itamin D supplementation; however, it can be largely ineffective in malabsorption syndromes. Targeted phototherapy is the localized delivery of ultraviolet light largely used in Dermatology to treat several skin diseases. It is also known that ultraviolet B radiation increases serum 25-hydroxyvitamin D levels. Although its role in the treatment of vitamin D deficiency is largely based on clinical experience, it should be considered, particularly in refractory cases. We report a 60-year-old female with osteomalacia secondary to vitamin D deficiency due to malabsorption after gastric bypass surgery. High dose supplementation of **v**itamin D and calcium was largely ineffective. Narrowband ultraviolet B was initiated resulting in marked clinical response and normalization of 25-hydroxyvitamin D serum levels.

Keywords: Phototherapy. Narrowband ultraviolet B phototherapy. Osteomalacia. Vitamin D deficiency.

Resumo

A osteomalácia caracteriza-se por um distúrbio da mineralização do osteoide recém-formado que pode ser precipitado através de mecanismos que induzem hipocalcemia, nomeadamente, deficiência prolongada de vitamina D. O tratamento consiste na suplementação que, contudo, pode ser ineficaz nas síndromes de má absorção. A fototerapia consiste na aplicação terapêutica de luz ultravioleta amplamente utilizada na Dermatologia. Sabe-se também que a radiação ultravioleta B aumenta os níveis séricos de 25-hidroxivitamina D. Embora o seu papel na deficiência de vitamina D seja essencialmente baseado na experiência clínica, deve ser considerada, particularmente, em casos refratários. Relatamos uma mulher de 60 anos com osteomalácia secundária a deficiência de vitamina D por síndrome de má absorção após bypass gástrico. A suplementação com doses elevadas de vitamina D e cálcio foi ineficaz. O tratamento com UVB banda estreita resultou numa resposta clínica significativa e normalização dos níveis séricos de 25-hidroxivitamina D.

Palavras-chave: Fototerapia. Fototerapia UVB banda estreita. Osteomalacia. Deficiência de vitamina D.

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Introduction

Osteomalacia is a disorder of decreased or defective mineralization of newly formed osteoids at sites of bone turnover that can occur both in children and adults. Several disorders can cause osteomalacia through mechanisms that result in hypocalcemia, hypophosphatemia, or direct inhibition of the mineralization process. Severe and prolonged vitamin D deficiency (25-hydroxyvitamin D [25(OH)D3] < 10 ng/mL) can result in hypocalcemia, secondary hyperparathyroidism, secondary hypophosphatemia, and osteomalacia[1]. The most common risk factors include limited sun exposure, insufficient dietary intake of calcium and vitamin D, and malabsorption syndrome (e.g. related to gastrointestinal bypass surgery)[2,3]. Targeted phototherapy is the localized delivery of ultraviolet light largely used in dermatology to treat several inflammatory and/or lymphoproliferative skin diseases. It is also known that ultraviolet B (UVB) radiation increases serum 25(OH)D3 levels and that artificial UVB radiation exposure from tanning beds (sunbeds and sunlamps) is effective in increasing and maintaining serum 25(OH)D3 levels[4]. However, because there are no defined safe limits for UVB exposure[5], it is not usually recommended as first-line therapy for vitamin D deficiency. One possible exception refers to patients with malabsorption who remain vitamin D deficient, even with high-dose oral supplementation.

Clinical case

We report a case of a 60-year-old Caucasian female, Fitzpatrick skin type II, with a past medical history relevant for bariatric surgery (gastric bypass) 6 years earlier. Initially evaluated by Rheumatology due to generalized myalgias and muscle weakness, it was later diagnosed with osteomalacia secondary to severe vitamin D deficiency related to malabsorption. A blood work-up revealed normocytic and normochromic anemia with normal renal function, calcium, phosphorus, and albumin levels. Serum electrophoresis and erythrocyte sedimentation rates were normal. Importantly, low levels of 25(OH)D3 - 10 ng/mL (sufficiency 30-100 ng/mL) - and high levels of parathyroid hormone (PTH) - 489 pg/mL (normal range 9-72 pg/mL) - were detected. Supplementation with fixed daily combination of calcium carbonate 1250 mg with cholecalciferol 400 IU plus weekly cholecalciferol 22400 IU for 3 months resulted in no improvement in 25(OH)D3 - < 4 ng/mL - and persistently high PTH-733 pg/mL (Fig. 1). Bone mineral density measured by dual-energy X-ray absorptiometry at this time revealed –3.5/–2.1 (T score/Z score) of lumbar spine and –3.8/–2.5 (T score/Z score) of total hip. Supplementation was optimized to daily calcium carbonate 2500 mg and cholecalciferol 25000 IU for an additional 6 weeks and, at this point, symptomatic improvement was noted but with persistently low 25(OH)D3 of 13 ng/mL and high PTH of 190 pg/mL. Considering the incomplete response despite optimized treatment and the high treatment cost of supplementation, targeted phototherapy was considered, and the patient was referred to the Dermatology department. After excluding contraindications to targeted phototherapy, narrowband ultraviolet B phototherapy (NB-UVB) – 311 nm - 3 times weekly was initiated at 200 mJ/cm^2 with 100 mJ/cm^2 increment at each treatment session until reaching 2.500 mJ/cm^2. Baseline 25(OH)D3 level was drawn – 6.3 ng/mL. No changes in supplementation or sun exposure habits during NB-UVB therapy were made. After 28 sessions of NB-UVB, treatment frequency was reduced to once weekly completing a total of 32 sessions. No adverse events were reported. At this time, 25(OH)D3 was remeasured revealing a significant increase in serum levels - 52 ng/mL - accompanied by significant symptomatic improvement. The decision to hold phototherapy was made. Three months later the patient was asymptomatic, however, 25(OH)D3 serum levels fell to 5.9 ng/mL. Phototherapy was reintroduced maintaining the above treatment protocol with NB-UVB 3 times weekly. After a total of 24 sessions, 25(OH)D3 was remeasured, achieving 34 ng/mL. At this time, phototherapy was suspended, and the patient is currently at 2-month follow-up after the last treatment session.

Discussion

Targeted phototherapy is a common therapeutic option for several dermatologic conditions with a long history in the field. To date, several treatment protocols are available for diseases such as psoriasis, vitiligo, atopic dermatitis, and mycosis fungoides, among others[6]. However, the role of phototherapy in the management of patients with osteomalacia due to low 25(OH)D3 levels is not widely known, even among dermatologists. Vitamin D can be generated in the upper layers of the skin during exposure to natural or artificial light by generating provitamin D from 7-dehydrocholesterol (7-DHC, provitamin D)[7]. Optimal synthesis occurs in narrow UVB spectra between 295 and 300 nm, with a peak at 297 nm. It is known that exposure to NB-UVB significantly increases 25(OH)D3 levels, particularly in patients

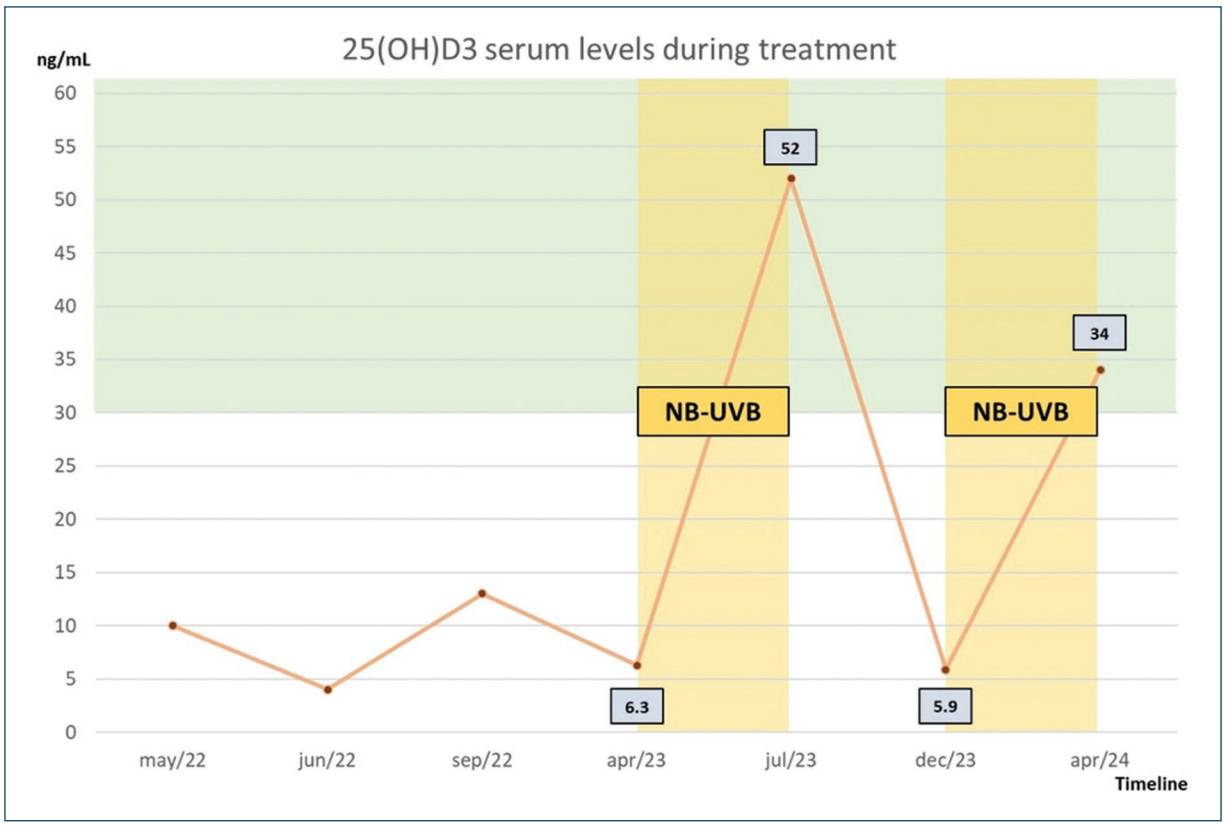

Figure 1. Serial measurements of 25(OH)D3 serum levels since initial follow-up. The green area represents vitamin D sufficiency levels (≥ 30 ng/mL) and the yellow area is the duration of narrowband ultraviolet B phototherapy (NB-UVB) treatment sessions. Note the absent response despite optimized oral supplementation from May/22 to Apr/23 and marked improvement during NB-UVB phototherapy reaching sufficiency values.

with low vitamin D status[8]. Although, the ideal treatment length is included in the broadband UVB spectrum at 297 nm, we have decided on NB-UVB, which targets a specific wavelength of 311 nm close to the optimal synthesis of 25(OH)D3, due to its better safety profile and tolerance, allowing higher treatment doses while maintaining efficacy. Optimal treatment protocols, however, have not yet been established and both dose and treatment frequency should be guided by 25(OH)D3 levels and patient tolerance[8]. Multiple treatment sessions and possibly maintenance treatment can be needed to achieve sustained optimal levels of 25(OH)D3.

Conclusion

This case report intends to increase awareness among physicians, in particular dermatologists and rheumatologists, on the role of targeted phototherapy, particularly, NB-UVB, in the treatment of diseases associated with low 25(OH)D3 levels, such as osteomalacia.

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Conflicts of interest

None.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

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CASE REPORT

Congenital triangular alopecia: case report

Alopecia triangular congênita: relato de caso

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Abstract

The authors present a case of congenital triangular alopecia (CTA), also known as temporal triangular alopecia, and debate its clinical presentation and diagnostic considerations. The patient, a 15-year-old male without comorbidities, exhibited left temporal alopecia since birth, seeking medical attention due to esthetic concerns. Dermatological examination revealed a well-defined area of alopecia, and trichoscopy exhibited vellus hairs of varying lengths, surrounded by terminal follicles and white hairs which are characteristic findings of the disease. The discussion explores the possible congenital nature of CTA, its clinical and trichoscopic features, histopathological characteristics, and the necessity for accurate differential diagnosis.

Keywords: Congenital alopecia. Non-cicatricial alopecia. Congenital triangular alopecia. Alopecia areata.

Resumo

Os autores apresentam um caso de alopecia triangular congênita (ATC), também conhecida como alopecia triangular temporal (ATT), debatem sua apresentação clínica e considerações diagnósticas. O paciente, um adolescente do sexo masculino de 15 anos sem comorbidades, referia alopecia temporal esquerda desde o nascimento e procurou ajuda médica devido ao impacto estético. O exame dermatológico revelou área de alopecia temporal bem definida e a tricoscopia exibiu pelos velus de comprimentos variados, cercados por folículos terminais e pelos brancos, que são achados característicos da doença. A discussão explora a possível natureza congênita da ATC, suas características clínicas e tricoscópicas, características histopatológicas e a necessidade de um diagnóstico diferencial preciso.

Palavras-chave: Alopecia congênita. Alopecia não-cicatricial. Alopecia triangular congênita. Alopecia areata.

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Introduction

Congenital triangular alopecia (CTA), also known as temporal triangular alopecia (TTA), is a rare form of scalp alopecia. It typically manifests at birth or in early childhood, with no gender predilection. Sabouraud called attention to this condition in 1905 and in 1926 considered it as part of the Brauer syndrome[1,2]. Also referred to as Brauer's nevus, CTA can occur as an isolated condition or have an autosomal dominant inheritance[2].

CTA often presents as a triangular-, oval-, or spear-shaped zone, measuring up to 4 cm in diameter, with fine hairs within the area of alopecia[3,4]. The most common presentation is unilateral, however, bilateral cases have been described[4]. Although its etiology remains unknown, associations with congenital anomalies such as pigmentovascular phakomatosis and Down syndrome have been reported[5]. CTA is a form of non-scarring alopecia and typically remains stable throughout life. Although not harmful or symptomatic, esthetic concerns may arise due to its distinctive shape and location.

Understanding the characteristics of CTA and exploring potential treatment options are crucial for providing appropriate support to patients.

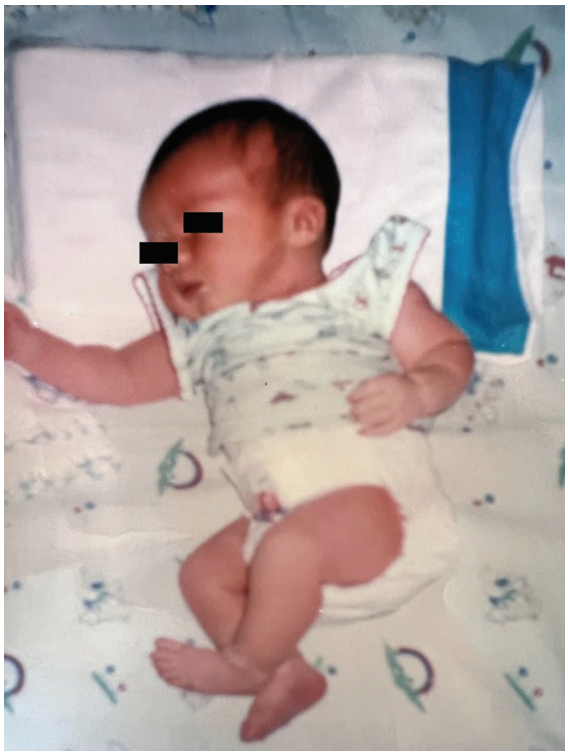

Figure 1. The alopecic area was observed in the patient as a newborn.

Case report

A 15-year-old Caucasian male student, born in Rio de Janeiro, without comorbidities or use of chronic medications, was observed in the dermatology department due to 'an area without hair'. He reported alopecia in this area since birth and denied any periods of worsening or improvement (Fig. 1). He previously received a diagnosis of alopecia areata and underwent topical corticosteroid therapy for a brief period but discontinued treatment due to a lack of clinical response.

Upon dermatological examination, the patient exhibited alopecia in the left temporal region, measuring approximately 3 cm by 2 cm, with a negative hair pull test (Fig. 2). Simultaneously, scalp trichoscopy revealed vellus hairs of varying lengths, surrounded by terminal follicles, white hairs, normal follicular openings, and an absence of erythema, yellow dots, or black dots (Fig. 3).

With the diagnosis of CTA, the patient received guidance about the natural course of the disease, which is characterized by stability. Furthermore, details were provided concerning potential poor responses when compared to treatment modalities utilized in different types of alopecia, such as minoxidil and topical corticosteroid therapy. Therefore, the patient opted not to undergo further therapeutic proposals.

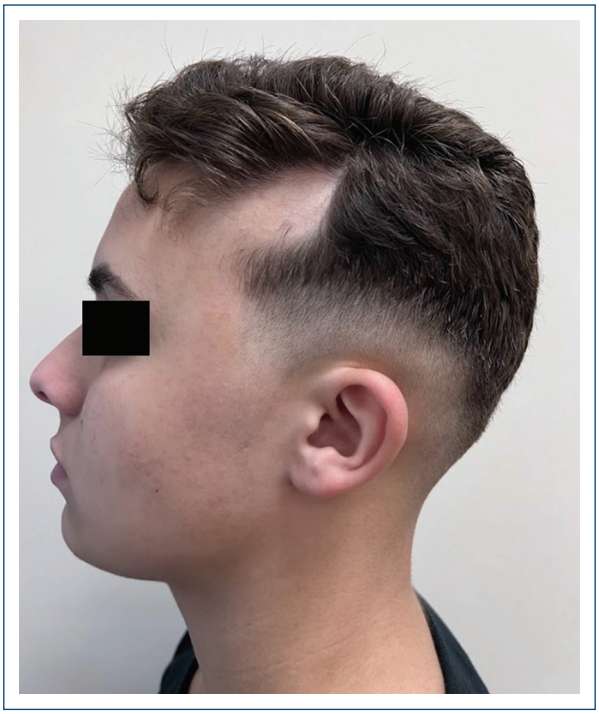

Figure 2. A triangular-shaped alopecic area with 3 cm in its largest diameter in the left temporal region. The hair pull test was negative.

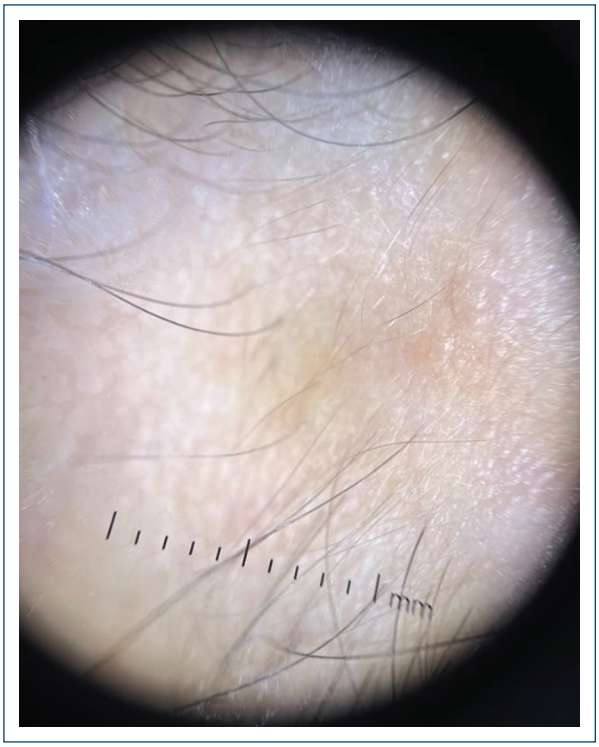

Figure 3. Scalp trichoscopy shows vellus hairs of varying lengths, surrounded by terminal follicles, white hairs, and normal follicular openings.

Discussion

CTA is considered congenital by most authors, although there is disagreement as its manifestation typically occurs between 3 and 6 years of age, and in some cases, it may present in adulthood. This discrepancy has led some authors to prefer the term 'TTA[2,6].' CTA manifests equally in both sexes, with most cases observed in Caucasians or Asians[7].

Pathogenesis remains unknown, and the genetic basis is not clearly understood. It is believed that the gradual transition from vellus to terminal hairs does not occur in the alopecic area.

Diagnosis is predominantly clinical[3,4] and certain trichoscopic findings contribute to confirmation in suspected cases. These findings include short vellus hairs of varying lengths, white hairs, typical location, the absence of change in size and typical shape of the alopecic area, and numerous vellus hairs in trichoscopy. Lack of response to intralesional/topical corticosteroids is a difference regarding confusion with alopecia areata[2,8].

Characteristic histopathological features include the absence of inflammatory cells in the dermis, unaltered collagen, and normal sweat glands. The epidermis appears normal with follicular keratosis. Hair follicles are reduced in size with preserved density, and there is a replacement of terminal hairs by vellus hairs, resembling androgenetic alopecia. The absence of fibrous scarring tissue adjacent to the outer root sheath distinguishes CTA from androgenetic alopecia[5,9].

The primary differential diagnosis is alopecia areata. Although both manifest as a patch of alopecia, these entities differ in terms of symptoms, clinical signs, trichoscopic features, causes, and progression[10]. Both conditions (CTA and alopecia areata) can have a significant emotional impact due to hair loss, affecting the self-esteem and body image of affected individuals. However, it is crucial to differentiate between these conditions for accurate diagnosis and appropriate treatment. CTA is a stable and non-progressive condition, whereas alopecia areata may have a more variable and unpredictable course[7,10].

Furthermore, other differential diagnoses to consider in the clinical presentation of patchy alopecia include aplasia cutis, chemical or physical trauma, end-stage lichen planopilaris, traction alopecia, trichotillomania, and tinea capitis[6].

In the treatment of CTA, options include esthetic camouflage, hair transplantation, and surgical excision of the affected area, particularly in those patients with esthetic/emotional concerns[6,7].

Knowledge of the disease and its associations enables precise diagnosis, avoiding unnecessary and traumatic treatments.

Conclusion

Congenital triangular alopecia (CTA) is a rare, benign condition of non-scarring alopecia that usually presents at birth or in early childhood. Accurate identification of this condition is essential to avoid erroneous diagnoses and unnecessary treatments. Understanding CTA and its specific clinical manifestations allows dermatologists to provide appropriate guidance and emotional support to patients, helping them manage their expectations regarding treatment and the prognosis of the disease. Patient education about the benign nature and stability of CTA can reduce anxiety and improve satisfaction with clinical management.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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CASE REPORT

Serious generalized pustular psoriasis with evolution to plaque psoriasis: approach with spesolimab

Psoríase pustulosa generalizada grave com evolução para psoríase em placas: abordagem com spesolimab

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Abstract

Generalized pustular psoriasis (GPP) is characterized by an acute and severe variant of psoriasis, often accompanied by systemic symptoms, with the eruption of multiple sterile pustules over an area of erythema, associated or not with the form of plaque psoriasis. Epidemiological data on disease are limited, but a global prevalence is estimated at around 1-7 cases per million people, affecting mainly females, with a higher incidence in the fourth and fifth decades of life. Exacerbations are marked by varying degrees of inflammation and systemic symptoms and have an unpredictable evolution. Hyperactivity of the interleukin-36 (IL-36) inflammatory pathway was discovered as the main pathway responsible for causing the disease. Recently, the active substance spesolimab has shown excellent results in the treatment of GPP, with a mechanism of blocking IL-36 receptor activation, leading to the suppression of pro-inflammatory and profibrotic pathways in inflammatory skin and intestinal diseases.

Keywords: Psoriasis. Pustular psoriasis. Generalized pustular psoriasis. Plaque psoriasis. Spesolimab. Anti interleukin-36.

Resumo

A psoríase pustulosa generalizada (PPG) caracteriza-se por uma variante aguda e grave da psoríase, muitas vezes acompanhada de sintomas sistêmicos, com erupção de múltiplas pústulas estéreis sobre área de eritema, associada ou não à forma de psoríase placas. Os dados epidemiológicos sobre a doença são limitados, mas estima-se uma prevalência global em torno de 1-7 casos por milhão de pessoas, acometendo principalmente o sexo feminino, com maior incidência na quarta e quinta décadas de vida. As exacerbações são marcadas por graus variáveis de inflamação e sintomas sistêmicos e apresentam evolução imprevisível. A hiperatividade da via inflamatória da interleucina 36 (IL-36) foi descoberta como a principal via responsável por causar a doença. Recentemente, a substância ativa spesolimab tem mostrado ótimos resultados ao tratamento de psoríase pustulosa generalizada (PPG), com mecanismo de bloqueio da ativação de IL-36R, levando à supressão das vias pró-inflamatórias e pró-fibróticas em doenças inflamatórias cutâneas e intestinais.

Palavras-chave: Psoríase. Psoríase pustulosa. Psoríase pustulosa generalizada. Psoríase em placas. Spesolimab. Anti interleucina 36.

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Introduction

Generalized pustular psoriasis (GPP) is characterized by an acute and severe variant of psoriasis, often accompanied by systemic symptoms, with the eruption of multiple sterile pustules over an area of erythema, associated or not with the form of plaque psoriasis[1,2].

Epidemiological data on GPP are limited; it is estimated that the global prevalence is around 1-7 cases/million people, with a predominance of female patients[3]. The peak incidence appears to occur around the fourth and fifth decades of life, but cases have been described in all age groups[4].

The evolution of PPG exacerbations is unpredictable. In addition to the cutaneous symptoms described, exacerbations are marked by varying degrees of inflammation and systemic symptoms such as fever, fatigue, and myalgia, in addition to changes in laboratory tests – high C-reactive protein (CRP), neutrophilia, hypocalcemia, and hypoalbuminemia. Other organs are often affected and cholestasis, renal failure, or even circulatory shock can be part of the clinical picture of the disease, with a consequent increase in the risk of death[1-6].

GPP is considered a distinct entity from plaque psoriasis, with different clinical, genetic, and pathological characteristics[1,2,5].

Case report

A 42-year-old female Caucasian patient with a previous diagnosis of subcorneal pustulosis for 10 years under satisfactory control with dapsone 100 mg/day, developed in the previous 40 days clustered pustules in the inguinal region and lower limbs bilaterally. The medication was changed by a private dermatologist for methotrexate, with no clinical response within 2 weeks. She progressed with daily fever, severe arthralgia, loss of appetite, and headache, with progression of the lesions on the abdomen, back, and upper limbs, with no response to the introduction of amoxicillin with potassium clavulanate and prednisone 60 mg/day.

On admission to the dermatology ward, she presented with pustules disseminated throughout the integument over areas of erythema and confluence of pustular lesions forming lakes of pus, geographic tongue (Fig. 1), fever (maximum temperature of 38.9°C), and severe arthralgia, predominantly in the knees. There were no reports in the history of recent infections, use of other medications, or vaccinations. Histopathological examination demonstrated psoriasiform dermatitis with intraspinous, subcorneal, and intracorneal pustules (Fig. 2), supporting the diagnosis of

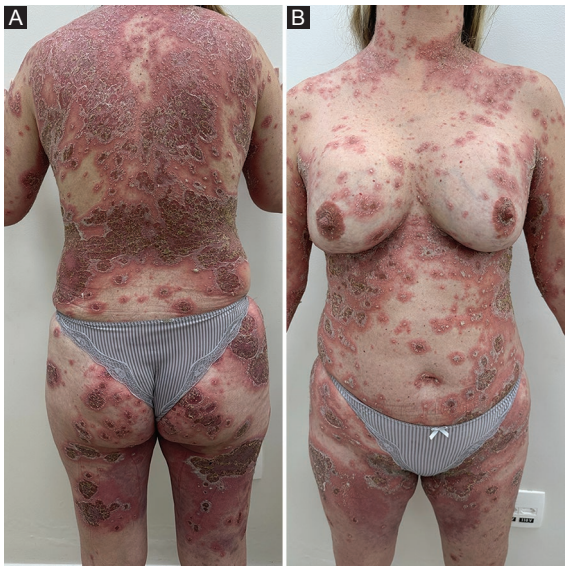

Figure 1. A and B: generalized pustular psoriasis in the acute phase: multiple pustules on an erythematous area.

GPP. Laboratory tests showed hemoglobin of 12.4 g/dL, leukocytosis (20,910 cells/μL, with 87.5% of neutrophils), CRP (34 mg/dL), erythrocyte sedimentation rate (105 mm), hypoalbuminemia (3.2 g/dL), in addition to urinary nitrite. In this case, cyclosporine 300 mg/day (5 mg/kg/day) was started as rescue therapy, corticosteroid therapy was suspended, and antimicrobial therapy was escalated to ceftriaxone with clindamycin to cover a possible cutaneous and urinary septic focus. During the hospital stay, there was a drop in hemoglobin to 7.8 g/dL and albumin to 1.8 g/dL, without the need for targeted treatment. The patient presented an excellent response to cyclosporine, with fever, arthralgia, and pustular pain resolving within 6 days (Fig. 3). After 1 month, she developed acute renal failure, with cyclosporine being reduced and secukinumab introduced (induction dose, 5 doses of 300 mg each with a 1-week interval between them). The gradual reduction of cyclosporine led to the return of the pustular condition, even after the 5 doses of secukinumab. At that time, ANVISA approved the drug spesolimab for the treatment of GPP. Anti-IL-17 therapy was then suspended, and a 900mg dose of the new biologic was administered, resulting in complete resolution of the pustules within 4 days. However, after 12 days, there was a recurrence of pustules in small quantities, along with erythematous plaques. Another dose of Spesolimab 900 mg was administered, with an interval of 16 days from the first dose. Two days after the second dose, there was complete remission of the pustules, with only erythematous and scaly plaques

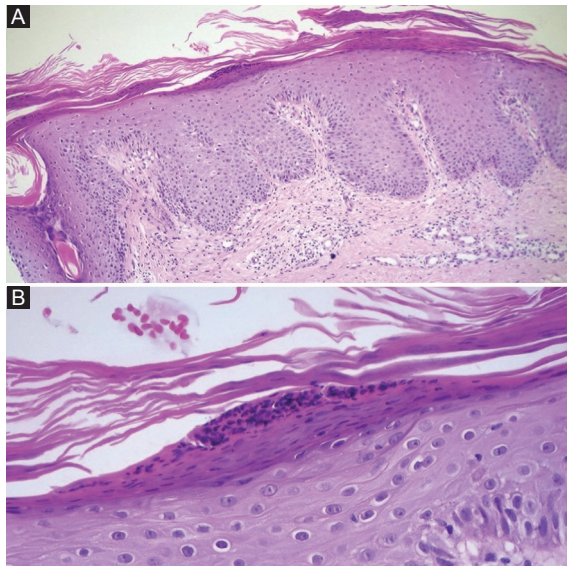

Figure 2. A: skin fragment showing psoriasiform dermatitis (H&E, ×100). **B:** fragment of skin showing intracorneal pustule, parakeratosis, and agranulosis (H&E, ×400).

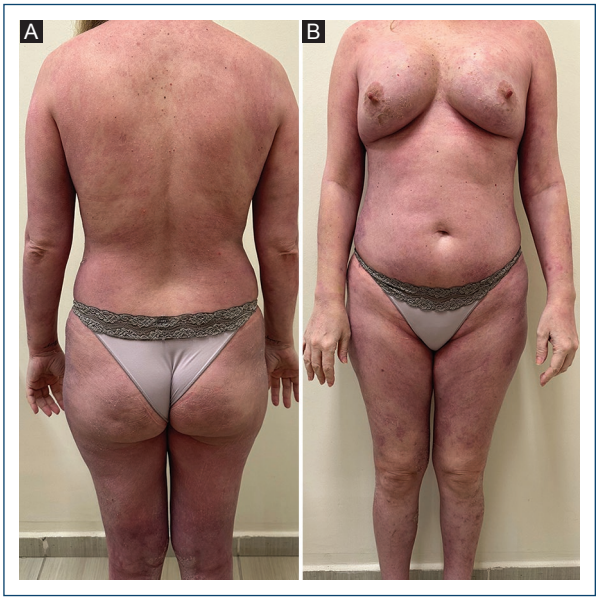

Figure 3. A and **B:** resolution of skin lesions 6 days after introduction of 5 mg/kg/day of cyclosporine.

scattered across the body (Fig. 4), confirmed by a new histopathological examination that diagnosed plaque psoriasis. Secukinumab was reintroduced at a maintenance dose of 300 mg/month, achieving complete control of the psoriatic plaques 1 week after resuming the medication. The patient used secukinumab for 7 months without

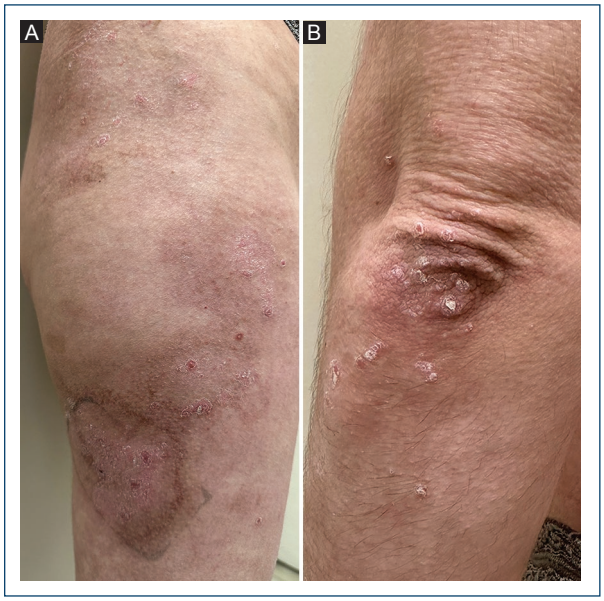

Figure 4. A and **B:** papules and small erythematous – scaly plaques 12 days after the use of spesolimab.

presenting any lesions. Currently, the patient remains under monthly follow-up with the assisting team, but at the patient's request, secukinumab was discontinued, and she has been without any medication and lesions for 5 months.

Discussion

Recently, hyperactivity of the interleukin-36 (IL-36) inflammatory pathway was discovered as the main pathway responsible for causing the GPP[2]. Different mutations in the IL36RN gene, which encodes the IL-36 receptor antagonist (IL-36Ra), have been described and confirm this pathway as the main one involved in the pathogenesis of GPP[5]. Spesolimab is a humanized IgG1 monoclonal antibody that binds to the human IL-36 receptor (IL-36R) and blocks (IL36R) signaling, inhibiting its binding to IL-36α, IL-36β, and IL-36γ. Thus, Spesolimab blocks the activation of IL-36R, leading to the suppression of pro-inflammatory and profibrotic pathways in inflammatory skin and intestinal diseases. In patients with GPP, blocking IL-36R signaling is a novel targeted therapeutic approach with excellent results[7,8], as in the present case.

Conclusion

Since generalized pustular psoriasis (GPP) has an inflammatory cascade distinct from plaque psoriasis,

marked by hyperactivity of the interleukin 36 (IL-36) inflammatory pathway, it is crucial to use targeted and effective therapies that block the IL-36 pathway. In this context, spesolimab has shown excellent results in controlling GPP flare-ups, through the mechanism of blocking IL-36R activation, leading to the suppression of pro-inflammatory and pro-fibrotic pathways in inflammatory skin and intestinal diseases. Given this and the case presented, this substance brings a new targeted therapeutic approach with satisfactory results, providing rapid relief of symptoms and a significant improvement in the quality of life of patients, representing another promising advance in immunology in dermatology.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

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CASE REPORT

Hand, foot, and mouth disease with exuberant presentation in an adult: case report

Doença mão-pé-boca com manifestação exuberante no adulto: relato de caso

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Abstract

The following report describes a case of hand, foot, and mouth disease (HFMD) in an adult patient, presenting atypical manifestations due to its clinical exuberance. The patient, a 26-year-old physician, reported the onset of fever and odynophagia followed on the 2nd day by vesicles and enanthema on the soft palate, associated with erythematous papules in the perioral and nasal dorsum regions, extending to the hands and feet. The lesions progressed in severity and number over the days, exhibiting unusual characteristics. Onychomadesis also manifested in the nails after the 6th week. The diagnostic investigation included a series of serologies, highlighting reactivity to Coxsackievirus. A biopsy of a papulovesicular lesion revealed the presence of keratinocyte necrosis and inflammatory reaction in the dermis. The discussion encompasses the pathogenesis of HFMD, its atypical manifestations in adults, and the importance of diagnostic elucidation. This case report contributes to understanding the clinical variations of HFMD in adults, emphasizing the need to consider this entity even outside the predominant age group.

Keywords: Hand, foot, and mouth disease. Coxsackievirus. Adult.

Resumo

O relato a seguir descreve um caso singular de Doença Mão-Pé-Boca (DMPB) em um paciente adulto, apresentando manifestações atípicas por sua exuberância clínica. O paciente, um médico de 26 anos, relatou o surgimento de manchas pelo corpo acompanhadas de febre e odinofagia. No segundo dia, observou-se o surgimento de vesículas e enantema no palato mole, associados a pápulas eritematosas na região perioral e dorso nasal, estendendo-se para mãos e pés. As lesões evoluíram em gravidade e quantidade ao longo dos dias, apresentando características incomuns. Onicomadese também se apresentou nas unhas após a sexta semana. A investigação diagnóstica incluiu uma série de sorologias, destacando a reatividade para o Coxsackievirus. A biópsia de uma lesão pápulo-vesiculosa evidenciou a presença de necrose de queratinócitos e reação inflamatória na derme. A discussão abrange a patogenia da DMPB, suas manifestações atípicas em adultos e a importância da elucidação diagnóstica. Este relato de caso contribui para a compreensão das variações clínicas da DMPB em adultos, destacando a necessidade de considerar esta entidade mesmo fora da faixa etária predominante.

Palavras-chave: Doença mão-pé-boca. Coxsackvirus. Adulto.

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Introduction

This case describes the clinical presentation and diagnostic approach of a 26-year-old male patient residing in Rio de Janeiro, Brazil, who presented with complaints related to cutaneous lesions. The complexity of the case involves the identification of systemic symptoms and atypical dermatological manifestations, which, on evaluation, were associated with hand, foot, and mouth disease (HFMD). HFMD is a predominantly pediatric viral infection, primarily caused by enteroviruses, such as Coxsackie A16 and Enterovirus 71, but, in this case, manifested atypically in an adult[1].

Clinical case

The patient presented, on the 1st day of symptoms, with fever (38.3°C) and odynophagia, followed on the 2nd day by vesicles and enanthema on the soft palate. The condition progressed to erythematous papules capped with honey-colored crusts in the perioral and nasal dorsum regions, along with lesions on the palms and dorsum of the hands and dorsum and plantar region of the feet (Figs. 1 and 2). On the 3rd and 4th days, there was accentuation of the papulovesicles on the extremities, some ulcerating and forming erythematous papules with honey-colored crusts (Figs. 3 and 4). On the 5th day, dissemination occurred to the elbows, cubital fossae, and knees. The patient received only symptomatic treatment for symptom control, such as headache and myalgia and despite being a physician, denied known contact with others presenting similar symptoms.

Facial lesions resolved on the 13th day, followed by palmoplantar desquamation. Significant clinical improvement of the other lesions was observed on the 21st day, followed by onychomadesis in all twenty nails by the 6th week, with residual erythema and persistent post-inflammatory hyperpigmentation in the affected areas.

The results of serological tests revealed non-reactivity for rubella, measles, herpes virus, HIV1/2, HTLV1/2, and syphilis. However, Epstein–Barr immunoglobulin M (IgM) and IgG serology were reactive, despite a reported episode of odynophagia 30 days earlier. The chemiluminescent microparticle immunoassay technique assessed that the detectability of the IgM marker exhibited prolonged duration, thus constraining its clinical utility in characterizing acute infection. The assessment of neutralizing antibodies against Coxsackie B virus through serum examination using human epithelial cells revealed positive outcomes for infection. The test indicated that titers > 1/32 would suggest a recent infection. Given the common occurrence of cross-reactivity in enterovirus titration, higher titers typically correlate with the infecting serotype. Emphasis was given to serologies for Coxsackie virus B3 (B2: 1/64; B3: 1/512; B4: 1/16; and B5: 1/64), with elevated titers, confirming the infection.

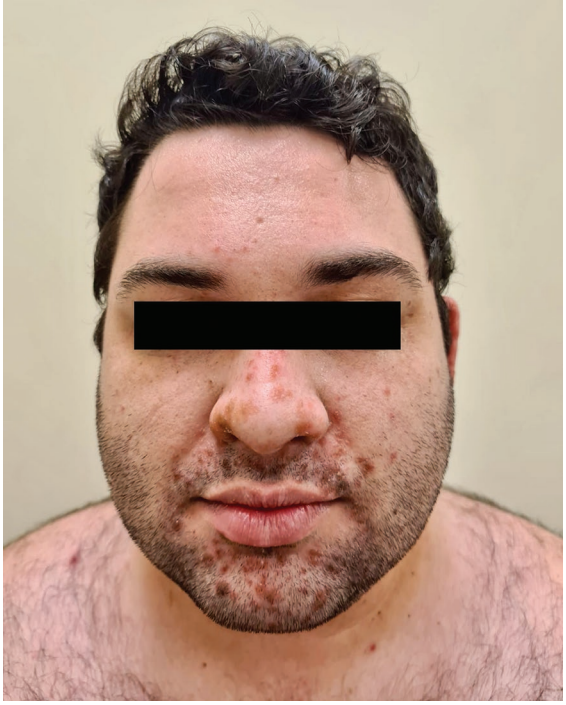

Figure 1. Presence of erythematous papules and macules with honey-colored crusts in the perioral region and on the nasal dorsum (day 2).

The patient was referred to the cardiology service for assessment of potential cardiac complications but failed to attend the subsequent appointment, claiming no symptoms in that regard.

Histopathology of a papulovesicular lesion on the right forearm revealed necrosis of keratinocytes in the upper portion of the epidermis, spongiosis, and exocytosis of lymphocytes. The upper dermis showed intense edema with an inflammatory reaction composed of lymphocytes, neutrophils, and erythrocytes (Figs. 5 and 6).

Discussion

HFMD, typically associated with pediatric cases, manifests clinically with fever, odynophagia, mucosal vesicles, and a papulovesicular rash on the extremities[1]. The atypical presentation in an adult, as observed in this case, poses a more challenging diagnostic scenario[1,2].

The viral classification of HFMD primarily involves the enterovirus genus, with a focus on Coxsackie A16 and

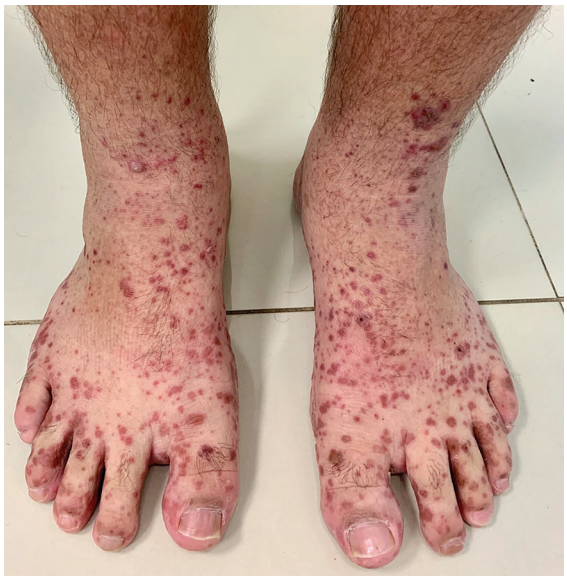

Figure 2. Vesicles, erythematous macules, erythematous papules, and crusts on the dorsum of the feet (day 2).

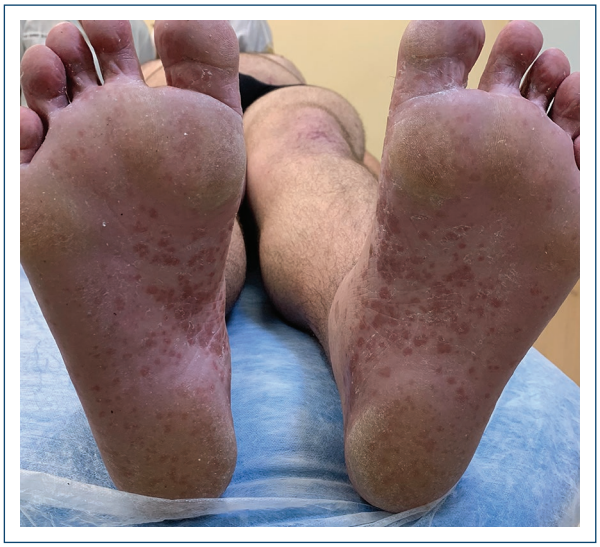

Figure 3. Erythematous papules and papulovesicles, some exulcerated, on the dorsum of the hands (day 3).

Figure 4. Erythematous papules and plaques, with honey-colored crusts, on the dorsum of the hands and wrists (day 4).

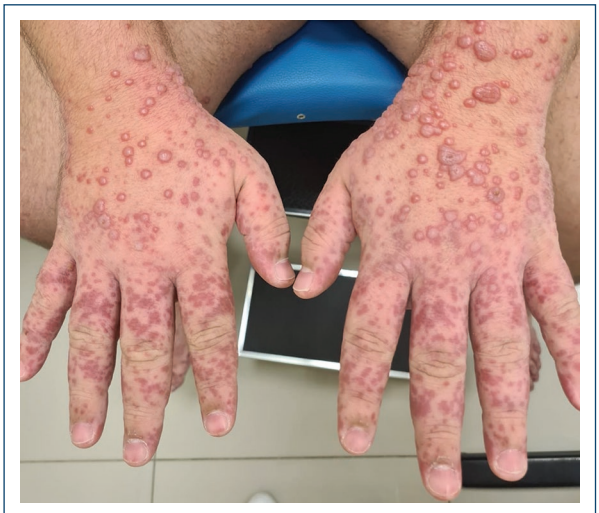

Figure 5. Necrosis of keratinocytes in the upper portion of the epidermis also shows spongiosis and lymphocytic exocytosis (H&E – ×100).

Enterovirus 71[3-5]. Transmission occurs through direct contact, commonly through oral and nasal secretions, feces, and contaminated objects, exhibiting a seasonal pattern with predominant outbreaks in spring and summer[6-8].

The patient's clinical presentation, with extensive involvement of the extremities progressing to onychomadesis, aligns with recent reports of HFMD in adults[9]. While most cases in the adult population are asymptomatic, more severe outbreaks have been documented, notably associated with serotype CA A6[9-11].

Diagnostic confirmation in this case relied on specific serologies, excluding other viral etiologies. Skin biopsy played a significant role, revealing histopathological features consistent with HFMD[6,8,11].

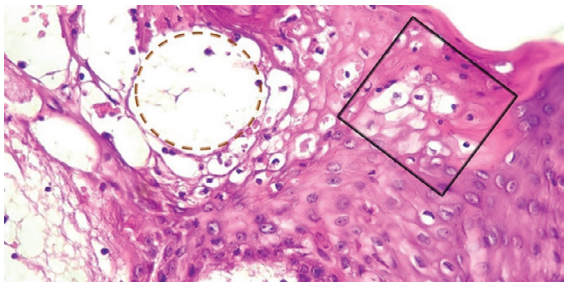

Figure 6. Presence of spongiosis (circle) and necrosis of keratinocytes (square) (H&E - ×400).

Treatment for HFMD is primarily symptomatic, emphasizing the need for infection control measures, as the patient is highly contagious during the presence of cutaneous lesions and fever. Recommendations include distancing from group and school activities, meticulous handwashing, and refraining from sharing personal items[12].

Understanding the clinical variability of HFMD across different age groups is crucial for accurate diagnosis and appropriate clinical intervention. This case underscores the importance of an integrated approach, combining clinical assessment and comprehensive laboratory examinations, such as serologies and histopathology, for diagnostic elucidation.

Although more prevalent in children, HFMD can manifest more severely in adults, as observed in this case. This report contributes to expanding knowledge about HFMD, particularly in the context of atypical clinical presentations, highlighting the significance of clinical and laboratory surveillance to address diagnostic challenges in adult patients.

Conclusion

This case report highlights the possibility of an atypical presentation of Hand, Foot, and Mouth Disease (HFMD) in adults, a condition typically associated with the pediatric age group. The exuberant clinical presentation, with extensive involvement of the extremities and subsequent onychomadesis, underscores the need to consider HFMD, even with atypical presentation, when suggestive areas are affected.

The diagnosis was confirmed through specific serologies and skin biopsy, which revealed histopathological features consistent with HFMD. Treatment was symptomatic, with ongoing monitoring of the condition.

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Conflicts of interest

The authors have no conflicts of interest in the subject matter or materials discussed in this manuscript.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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CASE REPORT

Borderline lepromatous leprosy mimicking lupus vasculitis: a rare case report from the Brazilian Amazon

Hanseníase borderline virchowiana simulando vasculite lúpica: um relato de caso raro no Amazonas

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Abstract

Leprosy is a neglected chronic infectious disease that is endemic in Brazil. It has a heterogeneous clinical presentation and often mimics other diseases, such as collagenosis, leading to underdiagnosis, incorrect treatment, and high morbidity. This report presents the case of a 40-year-old patient with erythematous-violaceous patches and papules on the lower limbs, simulating lupus vasculitis, associated with criteria for systemic lupus erythematosus, with no clinical improvement despite treatment. High suspicion and knowledge of the disease are necessary for early diagnosis, leprosy screening, and prevention of sequelae.

Keywords: Leprosy. Hansen disease. Systemic lupus erythematosus.

Resumen

A hanseníase é uma enfermidade crônica infectocontagiosa negligenciada e endêmica no Brasil. Apresenta clínica heterogênea e muitas vezes imitadora de outras doenças, como as colagenoses, ocasionando o subdiagnóstico, tratamento incorreto e alta morbidade. Apresenta-se neste relato o caso de uma paciente de 40 anos, com manchas e pápulas eritematovioláceas no terço distal dos membros inferiores, simulando vasculite lupica, associado a critérios para lúpus eritematoso sistêmico, mas sem melhora clínica a despeito do tratamento. É necessário ter alta suspeição e conhecimento da hanseníase objetivando diagnóstico precoce, rastreio e prevenção de incapacidades.

Palavras-chave: Lepra. Hanseníase. Lúpus eritematoso sistêmico.

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Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, an obligate intracellular bacillus with an affinity for skin tissue cells and peripheral nerves, as well as tropism for the reticuloendothelial system[1,2].

The disease can present a wide range of clinical manifestations, including different symptoms resulting from systemic involvement in multibacillary forms. This clinical polymorphism means that leprosy is considered a "great imitator," as it makes differential diagnoses with many diseases[2-4].

Multibacillary leprosy is associated with the presence of autoantibodies, and its clinical and laboratory characteristics can be similar to those of connective tissue diseases, especially systemic lupus erythematosus (SLE)[3-6]. Unfortunately, because of the similarities, health professionals do not recognize that leprosy can occur with rheumatic manifestations, and the correct diagnosis is often delayed[7].

In this case, we report a patient with borderline lepromatous leprosy who was diagnosed and treated as SLE for 5 years due to multisystem involvement. Due to the appearance of skin lesions that simulated lupus vasculitis, a histopathological biopsy was carried out which confirmed the diagnosis of leprosy. After treatment with multidrug therapy, the patient achieved complete remission of the disease.

Case report

Female, 40 years, presenting erythematous violaceous macules and papules, some with crusts and mild desquamation in the lower limbs (Figs. 1 and 2) for 3 months, associated with burning pain and pruritus. She was diagnosed back in 2017 with SLE with 4 out of 11 criteria from the American College of Rheumatology (ANA 1:320, speckled pattern; photosensitivity; pleural effusion and arthritis). The patient also presented livedo reticularis and 24-h proteinuria of 339 mg. She has been using hydroxychloroquine 400 mg and prednisone 20 mg, daily since the diagnosis.

With a clinical diagnosis of vasculitis related to SLE, a cutaneous biopsy was performed on the lower limbs and the prednisone dose was increased to 40 mg/day. On a follow-up consultation, cutaneous lesions worsened, and the patient developed polyarthralgia, peripheral edema 3+/4+, lower limb paresthesia, and walking difficulty.

Histopathology showed an inflammatory infiltrate constituted by lymphocytes, histiocytes, and neutrophil granulocytes, mainly around the perivascular, perineural, and blood vessel walls, along with red blood cell extravasation. The Wade-Fite special staining revealed Acid–Fast Bacilli, both isolated and grouped in globi, thus

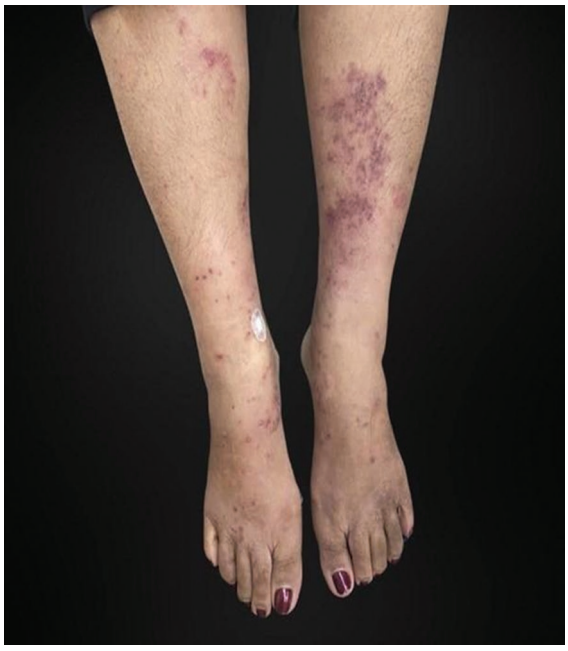

Figure 1. Lesions on the distal third of the lower limbs before the treatment.

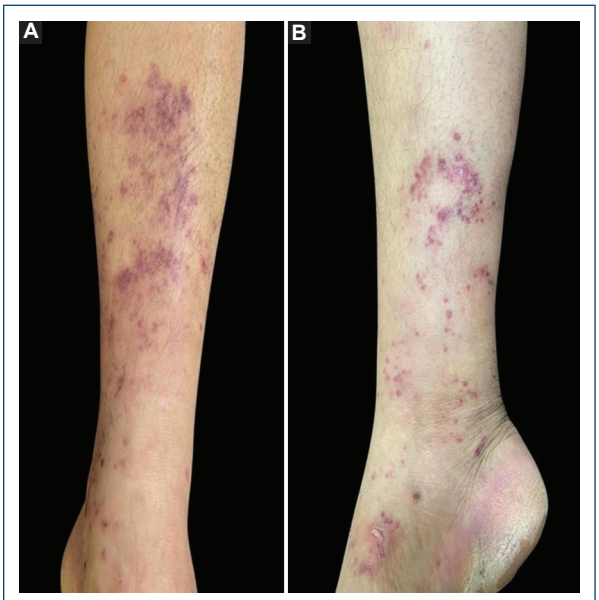

Figure 2. A: on a closer view, red-purple patches and papules, some with crusts. **B:** lesions with mild desquamation.

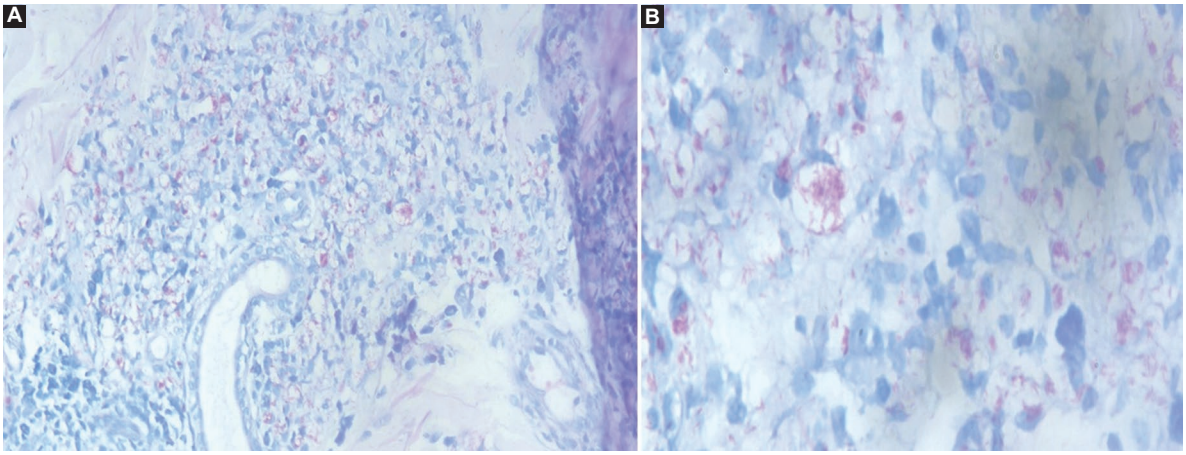

Figure 3. Histopathology of leprosy: isolated and clusters leprosy bacilli. **A:** WADE stain, 200× magnification. **B:** WADE stain, 1000× magnification.

confirming the diagnosis of borderline lepromatous leprosy (Fig. 3). The patient was prescribed with polychemotherapy (rifampicin, clofazimine, and dapsone) and prednisone 40 mg/day. After 20 days of treatment, there was a significant improvement in her condition and the ANA test was negative, corroborating the diagnosis of borderline Virchowian leprosy.

Discussion

Leprosy is a contagious disease neglected and endemic in Brazil[7]. Within the wide range of manifestations, its multibacillary form presents both systemic and cutaneous involvement, affecting mainly the skin, peripheral nerves, musculoskeletal system, mucous membranes, and lymphadenopathy[8]. These presentations depend on the individual immune response against the *Mycobacterium leprae*, with multibacillary forms, related to a poor T-cell response, prevalence of humoral response, and production of antibodies against the bacilli, but not sufficiently effective. Furthermore, there was a predominance of CD8+ T cells, with higher expression of Th2 cytokines (such as IL-4, 5, 6, 10, 25 and transforming growth factor beta) and activation of regulatory T cells[1,9].

Clinically, multibacillary leprosy presents as diffuse skin infiltration, bilateral or generalized papules, and nodules, leonine face, and madarosis, in addition to malar erythema, ulcers, and ischemic necrosis. Systemic manifestations such as Raynaud's phenomenon, polyneuropathy, multiple mononeuritis, muscle weakness, generalized lymphadenopathy, hepatosplenomegaly, and glomerulonephritis are due to the direct spread and proliferation of bacilli in the affected organ through the bloodstream[8].

Treatment generally involves therapy with multiple drugs, tailored to the individual's clinical presentation and the severity of the disease. Early recognition and intervention are essential to avoid long-term complications and impairments.

The heterogeneity of leprosy means that it can be misinterpreted with other rheumatological diseases. Some criteria for SLE were more prevalent in patients with multibacillary leprosy, mainly malar mash (44%), photosensitivity (29%), arthritis (21%), ANA (10%), antiphospholipid antibodies, and lymphopenia[10-12]. In the context of leprosy-endemic regions, the specificity of these criteria may be lower.

Although both lupus and leprosy vasculitis can have cutaneous manifestations and affect the peripheral nerves, they have distinct underlying mechanisms and require different approaches to diagnosis and treatment[13]. Nonetheless, in some cases, borderline lepromatous leprosy can present characteristics that mimic lupus vasculitis, highlighting the importance of a thorough differential diagnosis by health professionals. On the other hand, leprosy can be diagnosed in patients having really SLE[14,15].

As a result, due to its diverse and sometimes imitative clinic, leprosy is often underdiagnosed. Health professionals must be aware of its possible manifestations and know when to suspect it as a differential diagnosis for early diagnosis, treatment, and monitoring. As this is an infectious-contagious disease with high morbidity and socio-economic impact, interrupting the disease

cycle depends on easy access to the public health system, early diagnosis and treatment of the patient (especially multibacillary).

Conclusion

Leprosy can mimic collagenoses such as lupus, especially in countries endemic for this infectious disease. The disease should be suspected with the aim of early diagnosis. Be aware of the possibility of leprosy, especially in cases of collagenosis that are refractory to treatment.

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Conflicts of interest

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Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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CASE REPORT

Dermatoscopic features of blastic plasmacytoid dendritic cell neoplasm: a case report and review of the literature

Características dermatoscópicas de neoplasia blástica de células dendríticas plasmocitoides: relato de caso e revisão da literatura

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Abstract

Blastic plasmacytoid dendritic cell neoplasm is a malignant, aggressive, and rare tumor arising from plasmacytoid dendritic cell precursors. Because of its infrequency, information on clinical features and best treatment options is still lacking. Dermatoscopic features on this entity have only been reported in a few cases so far. Therefore, we describe a new case and review published data on this topic.

Keywords: Blastic. Plasmacytoid. Dendritic. Neoplasm. Dermatoscopy. Tumor.

Resumo

Neoplasia de células dendríticas plasmocitoides blásticas (BPDCN) é um tumor maligno, agressivo e raro que surge de precursores de células dendríticas plasmocitoides. Devido à sua infrequência, ainda faltam informações sobre características clínicas e melhores opções de tratamento. Características dermatoscópicas nesta entidade foram relatadas apenas em alguns casos até agora. Portanto, descrevemos um novo caso e revisamos dados publicados sobre este tópico.

Palavras-chave: Blastico. Plasmocitóide. Dendrítico. Neoplasia. Dermatoscopia. Tumor.

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Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an uncommon hematologic neoplasm, arising from plasmacytoid dendritic cell precursors. It tends to have an aggressive course and a poor prognosis. Presentation most commonly includes cutaneous lesions, with or without bone marrow involvement and leukemic spread[1]. Skin involvement may manifest as a solitary plaque/nodule with a brown to violaceous bruise-like tonality or as multiple nodules[2]. Dermatoscopic characteristics in this entity have seldom been published.

We present a case report of this infrequent neoplasm, describing dermatoscopic findings in our patient.

Clinical case

A 78-year-old male patient presented with a 4-month history of a painful indurated nodule on his scalp. Physical examination was notable for an erythematous-violaceous nodule of 3 × 3 cm on the vertex of the scalp (parieto-occipital region) (Fig. 1). Cervical lymphadenopaties were present.

Dermatoscopy revealed rosettes, perifollicular erythema, and nonblanchable red-violaceous structures. Some orange structureless areas were also evidenced (Fig. 2).

Histopathology showed infiltration of the dermis and hypodermis by cells with a blastic appearance, with positive TDT, focal CD43, Bcl-2, CD123, TCL-1, CD4, CD56, and Ki67 index of 30%. The diagnosis was compatible with BPDCN (Fig. 3).

Flow cytometry of the skin biopsy documented a cell population with an immunophenotype compatible with the same diagnosis.

Bone marrow aspirates evidenced a monomorphic hypercellular bone marrow. Flow cytometry reported 90% of cells with the same pathological immunophenotype. The leukemia spread was also noted, with a total of 59.120 leukocytes/μL, 77% of which were described as large cells of a lymphocytic appearance.

Treatment was started with chemotherapy, including 1 cycle of cyclophosphamide, doxorubicin, vincristine, prednisone followed by 5 cycles of cyclophosphamide, vincristine, dacarbazine. The patient presented full remission which lasted for roughly 2 months, subsequently undergoing relapse and death.

Discussion

BPDCN is a rare hematologic malignancy with variable forms of presentation. Cutaneous involvement is found in most cases[1].

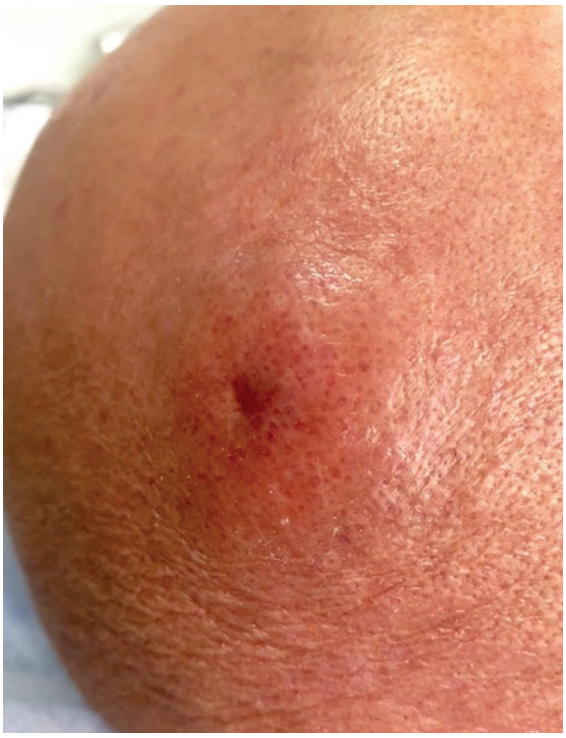

Figure 1. Erythemato-violaceous indurated nodule on the vertex of the scalp.

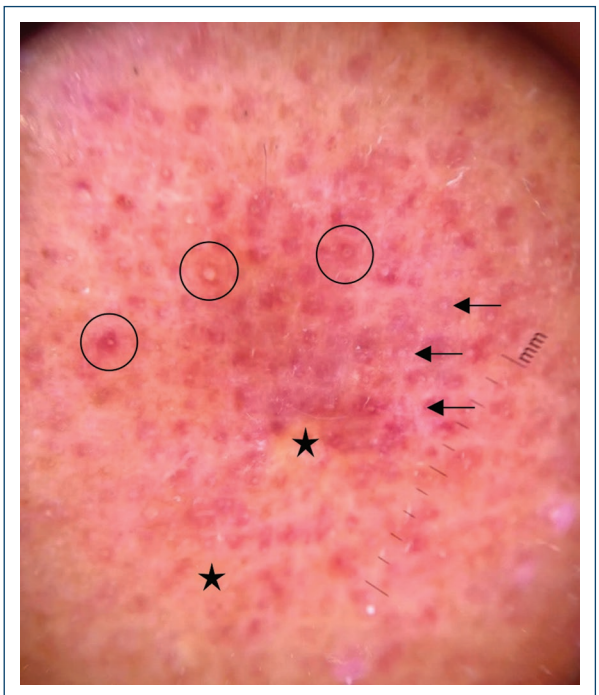

Figure 2. Dermatoscopy evidenced rosettes (arrows), perifollicular erythema (circles), nonblanchable red-violaceous structures, and orange structureless areas (stars).

Table 1. Clinical and dermoscopic characteristics documented in blastic plasmacytoid dendritic cell neoplasm

Age, sex	Location	Clinical morphology	Dermatoscopic features	Author, year of publication
75, male	Scalp (frontal and parietal region)	Large purplish, bruise-like lesion with nodular formation	Areas varying from red to purple with yellowish perifollicular structures	Martín-Carrasco et al., 2019[3]
14, male	Cheeks and left gluteus	Cheeks: gray-cyanotic dark spots resembling bruises. Left gluteus: bluish-purple nodule	Polymorphic large bluish-purple spots with a tendency to merge	Valiev et al., 2019[4]
65, male	Upper trunk	Asymptomatic nodules and plaques	Reddish and purplish nonblanchable structureless areas, surrounded by white halos. Homogeneous bluish-white areas	Nicklas et al.[5]
61, female	Upper trunk	Violaceous nodules and plaques	Pink-to-purple structureless areas with a white halo	Nicklas et al.[5]
78, male	Scalp (parieto-occipital region)	Erythemato-violaceous nodule	Rosettes, perifollicular erythema, and nonblanchable red-violaceous structures. Orange structureless areas	Case report in the present article

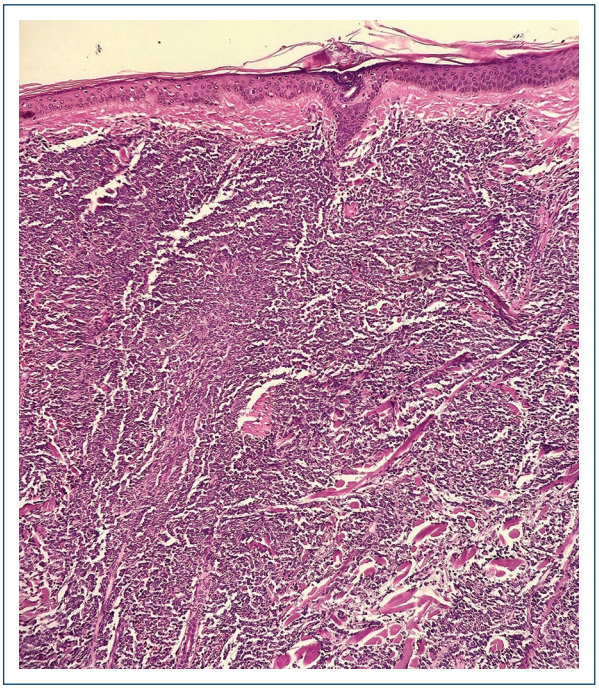

Figure 3. Histopathology evidenced a dense lymphocytic infiltrate forming cellular sheets, dissecting between collagen fibers, enveloping adnexal structures, and projecting deeply to the subcutaneous tissue. Red blood cell extravasation was also present.

Dermatoscopic features in this entity have been described only in a few cases, with pink/red to violaceous homogeneous areas, bluish areas or spots, and white halos as the most frequently described findings[3-5]. Nicklas et al. have hypothesized that the violaceous structureless areas may be related to the dermal infiltration of neoplastic cells and the presence of hemorrhage within the tumor and the white and the homogeneous bluish areas may be associated with fibrosis[5].

Our patient presented with some of these previously described features, such as nonblanchable red-violaceous structures that could correspond with the lymphocytic infiltrate and red blood cell extravasation. We also describe characteristics not previously documented, such as rosettes and perifollicular erythema that we believe correspond to perifollicular infiltration of neoplastic cells, and rosettes may represent the follicular occlusion due to this perifollicular infiltration and the presence of fibrosis.

Dermatoscopic features described in distinct types of lymphomas are very polymorphic. In our case, findings were different from those described in other lymphoproliferative tumors presenting as nodules or plaques. Nodular/plaque-type primary cutaneous T- and B-cell lymphomas more often present unfocused vessels (linear, dotted, and linear-curved), focal white and orange structureless areas and white lines[6,7]. Orange structureless areas appear to be the most strongly associated feature with these lymphomas, believed to be correlated with nodular lymphocytic infiltrates in the dermis[7]. Interestingly, although not evidenced in previous cases,

our patient presented this feature. Rosettes have also been reported in T-cell pseudolymphoma, classic mycosis fungoides, and recently in a case of primary cutaneous marginal zone lymphoma[8-10].

BPDCN is an uncommon tumor that prompts early diagnosis due to its aggressive behavior. Because of its infrequency, there are still no well-defined dermatoscopic criteria that may aid in its diagnosis. Furthermore, different clinical and histopathological presentations will also lead to variable features, as described in the different reported cases. Dermatoscopic features such as red/pink to violaceous structureless and white halos may be a clue to this diagnosis, but we observed new characteristics such as rosettes, perifollicular erythema, and orange structureless areas. These findings in association with a compatible clinical presentation must lead to early biopsy and additional studies.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

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DERMATOLOGY IMAGES

Truncal acne: the burden of a hidden disease

Acne do tronco: o impacto de uma doença escondida

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Acne, a chronic inflammatory disease affecting up to 85% of adolescents, significantly impacts mental health, self-esteem, and social interactions due to its visibility on the face[1]. This condition also extends to truncal acne, which is often overlooked by both patients and clinicians despite affecting about half of those with facial acne[2]. A case of a 23-year-old with severe truncal acne highlights the issue's neglect, leading to keloids and atrophic scars, underscoring acne's potential for lasting physical and psychological effects (Fig. 1). Acne scarring, a major consequence, results from an imbalance in collagen synthesis[1]. Treatments for scars, such as corticosteroid injections and laser therapy, show limited success[3]. The reluctance to discuss truncal acne, often due to misconceptions about hygiene, contrasts with a desire for treatment. Without specific guidelines for truncal acne, this case emphasizes the need for comprehensive care in dermatology, addressing all acne forms to prevent untreated consequences and improve patient outcomes.

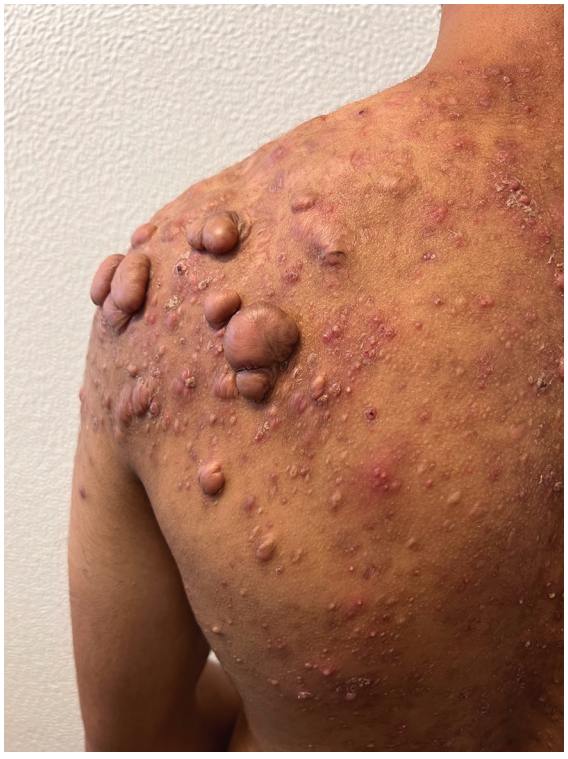

Figure 1. Keloid scars caused by severe truncal acne.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

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DERMATOLOGY IMAGES

Erythema gyratum repens as the first sign of colon adenocarcinoma

Eritema gyratum repens como manifestação inaugural de adenocarcinoma do cólon

Diana Bernardo, José M. Alvarenga, Martim Luz, and Glória da Cunha-Velho*

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An otherwise healthy 80-year-old woman presented to the emergency department with a 1-week history of erythematous annular, serpiginous, and circinate plaques and macules with centrifugal growth (Fig. 1A and B), evolving into concentric purpuric rings, predominantly distributed over the lower limbs (Fig. 2A and B) but also upper limbs and trunk (Fig. 2C). Lesions were accompanied by intense sensations of burning, heat, and pruritus. In addition, there was a history of anorexia and weight loss over 4 months, without any focal complaints, which had been attributed to an adjustment reaction to the death of her husband. Physical examination showed an emaciated appearance but was otherwise unremarkable. Skin biopsy showed non-specific perivascular pattern dermatitis, compatible with the proposed clinical diagnosis of erythema gyratum repens (EGR). Laboratory analysis revealed iron deficiency anaemia, with no other significant abnormalities. Breast ultrasound and mammography showed no abnormal findings. A whole body (thorax, abdomen, and pelvis) computed tomography scan demonstrated heterogeneous thickening of the cecum over a 5-cm extension, without other remarkable findings. Colonoscopy revealed a neoplasia in the proximal ascending colon involving 75% of the luminal circumference, with biopsy confirming adenocarcinoma. The skin condition was controlled symptomatically with topical corticosteroids and anti-histamines, and a right hemicolectomy was performed, obtaining a stage pT3 pN0 cM0 adenocarcinoma. The rash completely resolved and there has been no recurrence following the surgery.

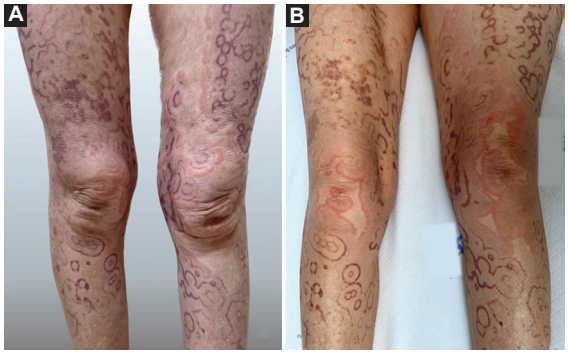

Figure 1. A and **B**: centrifugal growth evolving into concentric purpuric rings over 24 hours.

EGR is a distinctive but rare paraneoplastic dermatosis strongly associated with malignant neoplasms, particularly

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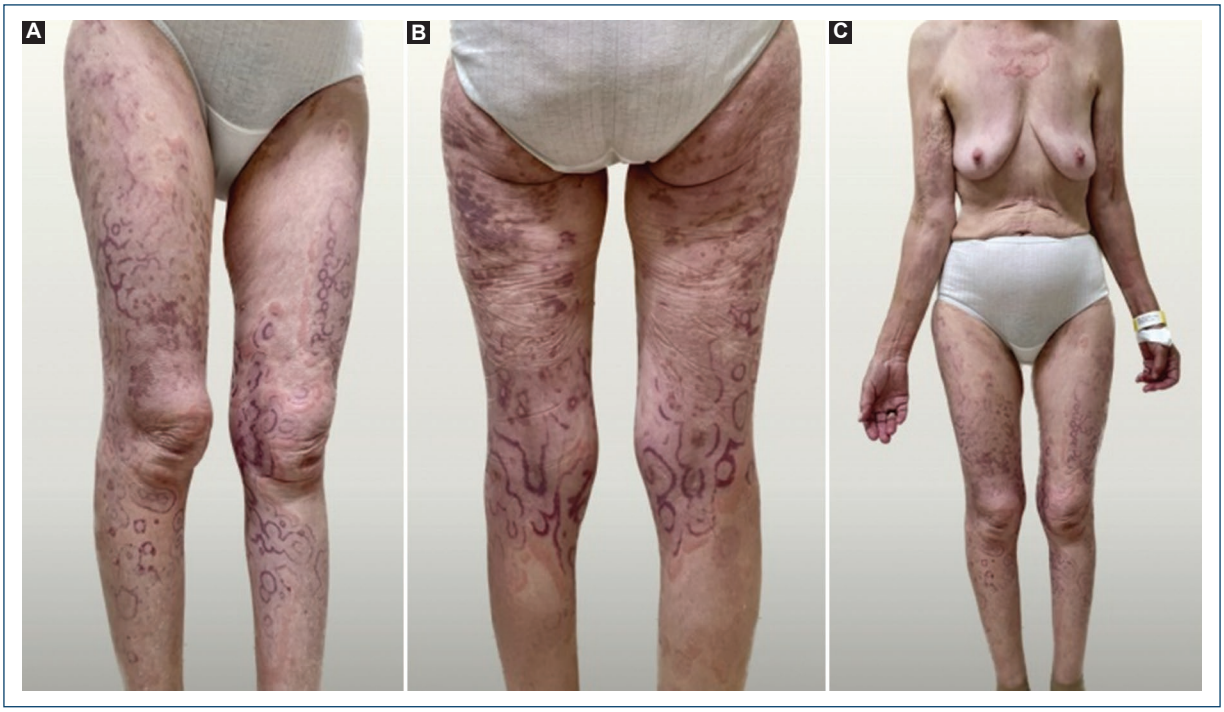

Figure 2. Erythematous annular, serpiginous, and circinate plaques and macules evolving into concentric purpuric rings, predominantly distributed over the lower limbs (**A** and **B**), but also upper limbs and trunk (**C**). Erythema gyratum repens has a characteristic "wood-grain" appearance.

of the lung, esophagus, and breast[1]. This rare case of EGR prompted the inaugural diagnosis of colon adenocarcinoma, enabling early detection and timely treatment.

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Conflicts of interest

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Ethical disclosures

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Confidentiality of data. The authors declare that they have followed the protocols of their workplace regarding the publication of patient data.

Right to privacy and written consent. The authors declare that they have obtained written consent from the patients and/or subjects mentioned in the article. The corresponding author must have possession of this document.

Use of artificial intelligence to generate texts. The authors declare that they did not use any type of generative artificial intelligence in the writing of this manuscript nor for the creation of figures, graphs, tables, and/or their respective captions.

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DERMATOLOGY IMAGES

A case of pemphigus erythematosus with classical facial butterfly configuration and trunk involvement

Um caso de pênfigo eritematoso com afeção facial clássica em borboleta e envolvimento do tronco

Margarida Brito-Caldeira, Miguel Santos-Coelho, Alexandre João, and Cândida Fernandes*

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A 50-year-old male presented with erythematous and scaly plaques on his face, scalp, chest, and dorsum with 1-year duration. Facial lesions affected particularly the malar region, bilaterally, strikingly sparing the nasolabial fold (Fig. 1). Histopathology of lesional skin (Fig. 2) revealed a subcorneal blister with discrete acantholysis in the granular layer. Direct immunofluorescence (Fig. 3) revealed intercellular deposits of Immunoglobulin G (IgG) and granular deposition of IgG in the basement membrane. These findings supported the diagnosis of pemphigus erythematosus (PE). Blood analysis revealed positive antibodies against desmoglein-1 (407 RU/mL, reference value < 20) and negative ANA and desmoglein-3 antibodies. Blood cell count and renal function were unremarkable. The patient was treated initially with oral prednisolone and rituximab with little control and is now under azathioprine and hydroxychloroquine with an excellent response.

PE, also known as Senear-Usher syndrome, is a localized variant of pemphigus foliaceus with clinical overlap with lupus erythematosus[1], hence the name of the disease. This is a rare autoimmune blistering

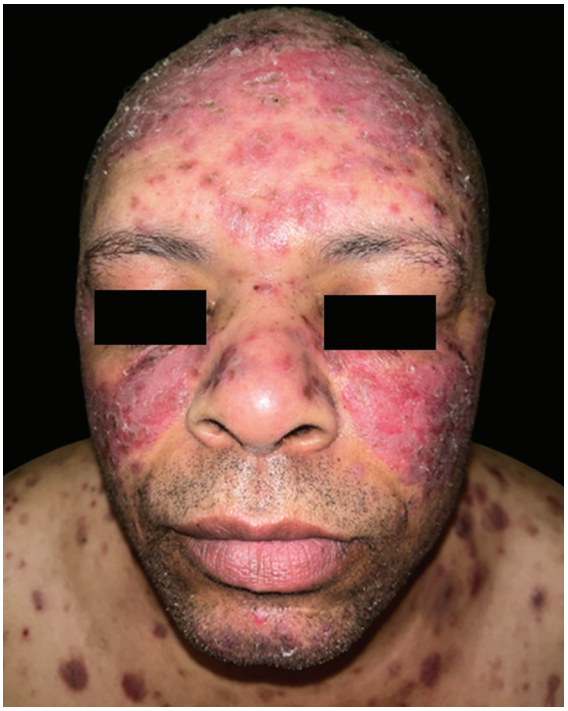

Figure 1. Erythematous and scaly dermatosis afecting the face, scalp and upper trunk.

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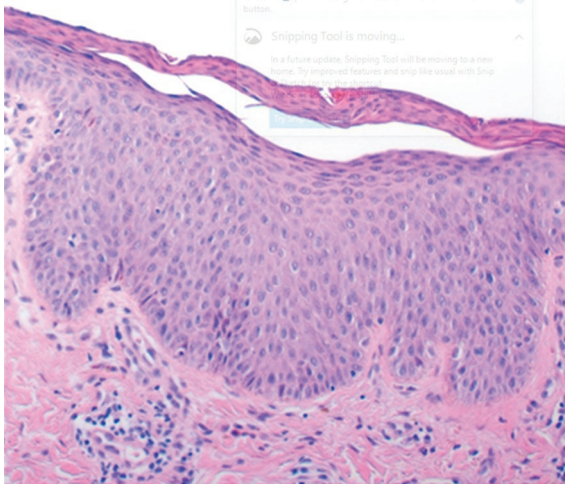

Figure 2. Routine histology of lesional skin, revealing subcorneal blister with discrete acantholysis in the granular layer. HE, x 200.

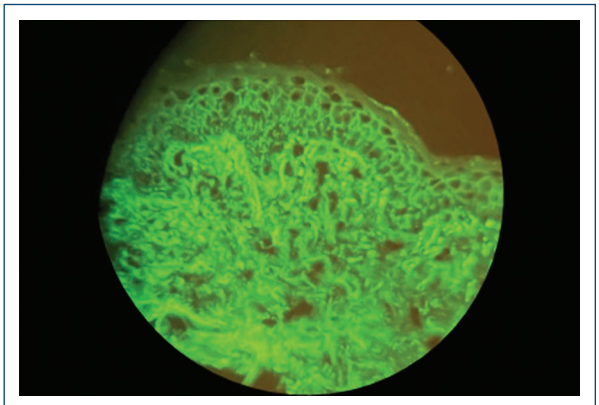

Figure 3. Direct immunofluorescence revealed intercellular deposits of IgG and granular deposition of IgG in the basement layer.

disorder, with little over 200 cases described in literature[2]. Clinically, erythematous scaly patches are found in typical locations of pemphigus foliaceus, with addition of the malar region in a butterfly distribution, simulating cutaneous lupus erythematosus. However, it is rare for patients to have systemic lupus erythematosus[3]. Histologically, PE is similar to pemphigus foliaceus, with superficial blisters below the stratum corneum or within the granular layer[3]. Direct immunofluorescence, however, differs from pemphigus foliaceus due to the granular deposition of IgG along the basement membrane, as in cutaneous lupus erythematosus.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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LETTER TO THE EDITOR

Schamberg's disease with an inverse pattern: an unique presentation

Doença de Schamberg com um padrão inverso: uma apresentação única

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The authors present a case of Schamberg's Purpura with an unusual distribution in a 46-year-old man who presented to the dermatology department with an asymptomatic eruption predominantly located on the genitalia and gluteal and axillary creases, with a progressive appearance over 1 month. There was no history of local trauma, infection, sexual contact or medication use apart from his usual anti-dyslipidemic, nor family history of similar disorders. Physical examination revealed symmetric, grouped pinhead-sized coalescent red-brown macules and papules, mainly scattered across the penis (glans and foreskin), gluteal and inguinal creases and axillae, and to a lesser extent in the lower limbs (Figs. 1A-E). Dermoscopy showed red-brown dots and globules in a coppery-red background (cayenne-pepper spots), as well as linear vessels. (Fig. 2A) No peripheral edema, varicose veins, or lymphadenopathy were noted, and the patient was otherwise well. Laboratory workup was unremarkable (including normal blood cell count, basic serum biochemistry and coagulation profile, and a negative venereal disease research laboratory test). Histopathological examination revealed a superficial perivascular and interstitial lymphohistiocytic inflammatory infiltrate, with extravasation of red blood cells and hemosiderophages (Pearls +), with no epidermal alterations, consistent with a pigmented purpuric dermatosis. (Figs. 2B and C) Inverse Schamberg's disease (SD) was assumed and the patient was treated with hydrocortisone butyrate 1mg/g cream and general measures, with marked improvement after 1 month. At the 6-month follow-up, the lesions continued to clear.

SD belongs to the spectrum of pigmented purpuric dermatoses (PPD), a group of chronic and recurring microvascular disorders accounting for 0.18% of reported skin conditions[1,2]. SD is the most common type, featuring the clinical characteristics herein described except for the location, with only one similar case documented in the literature[3]. Dermoscopy can prove useful, correlating with histopathological findings[4]. The precise mechanisms causing red blood cells extravasation from capillaries into the skin remains elusive, but potential factors such as venous hypertension, exercise-induced gravitational dependency, capillary fragility, and focal infections[1,2], were not found in this patient, neither are prototypical of such locations. Other factors occasionally associated with SD such as drugs (aspirin, glipizide, and hydralazine) and alcohol ingestion[1,2] were absent, but contact allergies to dyes or clothing[1,2] could not be completely ruled out, although not suggested by the patient history. Furthermore, some cardiovascular risk factors

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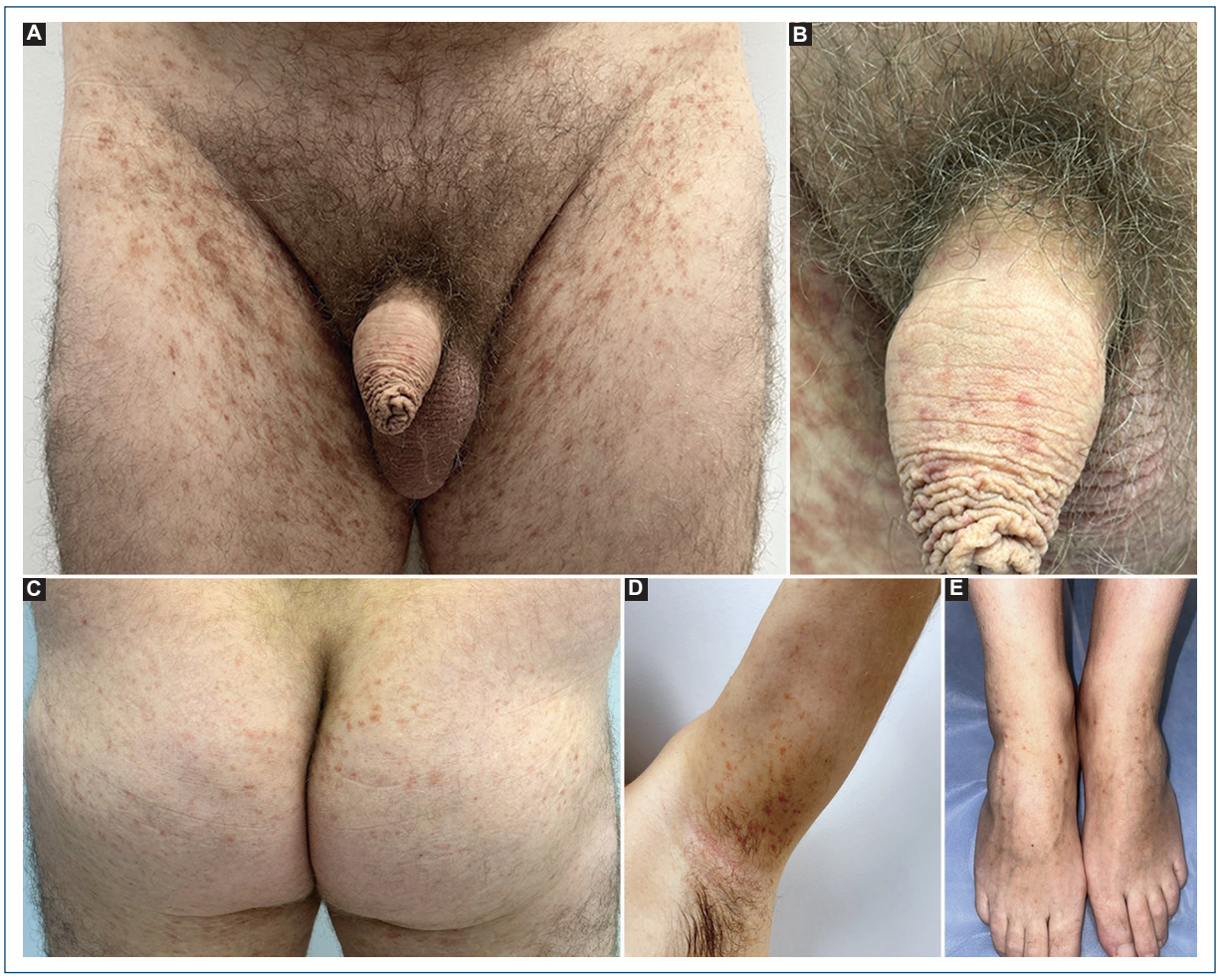

Figure 1. A-E: symmetric, grouped pinhead-sized coalescent red-brown macules and papules, mainly scattered across the **A-C:** penis glans and foreskin, gluteal and inguinal creases and **D:** axillae, and **E:** to a lesser extent in the lower limbs.

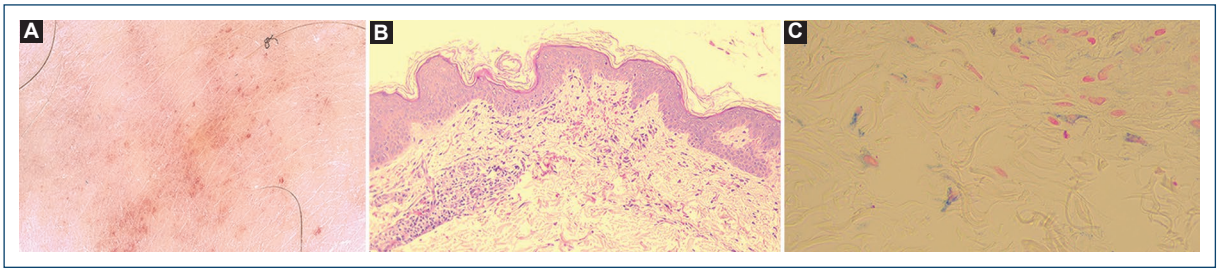

Figure 2. A: dermoscopy showing red-brown dots and globules in a coppery-red background (cayenne-pepper spots), as well as linear vessels. **B:** histopathology of the lesion revealed a superficial perivascular and interstitial lymphohistiocytic infiltrate, accompanied by extravasation of red blood cells, with no epidermal changes (hematoxylin and eosin stain). **C:** histopathology using Pearls stain demonstrated hemosiderophages, confirming Pearls positivity.

including dyslipidemia (as in our patient) have been associated with PPD[2,5]. Careful differentiation from other dermatological conditions (namely, purpuric clothing dermatitis, hyperglobulinemic purpura, early mycosis fungoides, and stasis pigmentation) is essential[1,2], given its benign nature. Treatment lacks standardized evidence and is often based on reported cases[1,2]. While symptom-directed measures are feasible (trigger

elimination, emollients, topical corticosteroids, topical calcineurin inhibitors, and oral antihistamines), compression therapy and phototherapy are not feasible for application in the locations reported herein.

In conclusion, our case raises awareness for a unique location of a rare condition, underlining the importance of considering such a diagnosis which may require histopathological confirmation for exclusion of alternative conditions.

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Ethical disclosures

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