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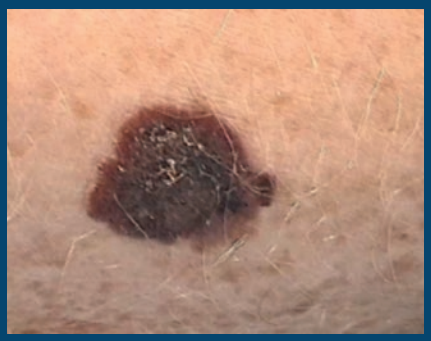

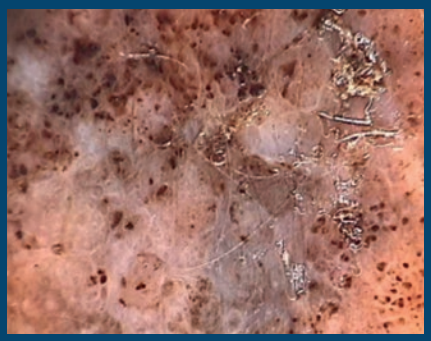

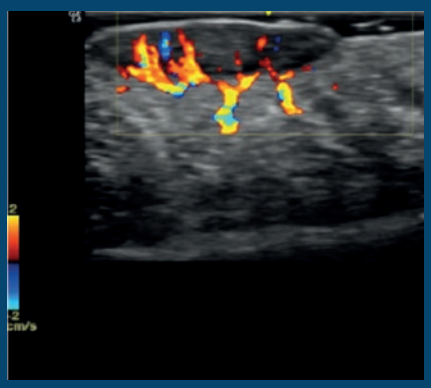

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REVIEW ARTICLE

Comprehensive analysis of amphotericin B: innovations and clinical applications in tropical dermatoses and beyond – a narrative review

Análise abrangente da anfotericina B: inovações e aplicações clínicas em dermatoses tropicais e além – uma revisão narrativa

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Abstract

Amphotericin B (AmB), a natural polyene macrolide derived from *Streptomyces nodosus*, has emerged as a versatile therapeutic agent with significant implications for tropical and systemic infections. Originally developed for treating life-threatening fungal infections, the therapeutic utility of AmB has expanded to include various tropical dermatoses, namely, leishmaniasis. The drug demonstrates remarkable mechanisms of action, including cholesterol sequestration, lipid peroxidation, and immune system modulation. Despite its broad spectrum of activity, challenges remain in establishing standardized treatment protocols. Ongoing research continues to explore combination therapies and optimize dosing strategies, positioning AmB as a critical tool in combating tropical infections with complex clinical presentations.

Keywords: Amphotericin B. Chromoblastomycosis. Cutaneous mucormycosis. Leishmaniasis. Post kala-azar dermal leishmaniasis.

Resumo

A anfotericina B (AmB), um macrolídeo poliênico natural derivado de *Streptomyces nodosus,* surgiu como um agente terapêutico versátil com implicações significativas para infeções tropicais e sistémicas. Originalmente desenvolvido para tratar infeções fúngicas fatais, a utilidade terapêutica da AmB inclui também várias dermatoses tropicais, nomeadamente as leishmanioses. O medicamento demonstra mecanismos de ação notáveis, incluindo sequestro de colesterol, peroxidação lipídica e modulação do sistema imunológico. Apesar de seu amplo espectro de ação, ainda há desafios no estabelecimento de protocolos de tratamento padronizados. Continuam a ser exploradas terapêuticas combinadas e otimizar estratégias de dosagem, posicionando a AmB como uma ferramenta crítica no combate a infeções tropicais com apresentações clínicas complexas.

Palavras-chave: Anfotericina B. Cromoblastomicose. Mucormicose cutânea. Leishmaniose. Leishmaniose dérmica pós-Kalazar.

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Introduction

Amphotericin B (AmB) is a natural polyene macrolide, extracted through fermentation from the soil actinomycete *Streptomyces nodosus*. Although developed primarily for the treatment of life-threatening systemic fungal infections, presently the utility of AmB has extended for the management of complicated cutaneous and visceral leishmaniasis (VL). Besides, there are reports describing the use of AmB in subcutaneous mycoses, onychomycosis, and superficial fungal infections with promising outcomes[1].

Mechanism of action

AmB causes fungal cell death mainly by binding to ergosterol of the cell membrane which leads to pore formation and ultimately fungal cell destruction, as represented in figure 1[2]. In addition, for leishmaniasis, other mechanisms postulated include cholesterol sequestration in the host membrane, thereby blocking interaction of the parasite with host macrophages (mandatory for initiation and perpetuation of infection)[3,4], lipid peroxidation, with subsequent protozoal destruction, antagonism of endosome-lysosome fusion[5,6], apoptosis of the parasite[7] and promotion of IFNγ production from natural killer cells, which helps macrophage activation[6].

Clinical uses

Invasive fungal infections (IFIs)

The incidence of IFIs has increased remarkably in recent years. Comorbidities such as neutropenia, human immunodeficiency virus infection (HIV)/acquired immunodeficiency syndrome (AIDS), and cancer are often encountered in patients presenting with IFIs, with an increased predisposition for resistance to antifungal agents[8-10].

AmB continues to be the reference drug in treating IFIs, essentially due to its broader mechanism of action. Due to the association of several adverse effects with the conventional formulation of AmB (d-AmB), various newer AmB preparations have now been developed with an effort to reduce the toxic effects of d-AmB. Newer lipid-based formulations with a favorable lipid solubility of AmB include liposomal AmB (L-AmB), AmB colloid dispersion (ABCD), and AmB lipid complex (ABLC) (Table 1)[8,11-18]. Main IFIs where AmB is utilized are cryptococcal meningitis, candidemia, and invasive candidiasis (namely, in neutropenic patients or chronic disseminated candidiasis), neonatal candidiasis, and invasive aspergillosis[19-22]. The dose of d-AmB for IFIs is 1 mg/kg/day, which is administered for a period of 5-7 days, followed by transition to other anti-fungal drugs[1,19]. In addition, a single 10 mg/kg dose of d-AmB was found to be equally effective[20]. Liposomal AmB is given at 3-5 mg/kg/day and holds efficacy similar to voriconazole for invasive aspergillosis[21,22].

Cutaneous mucormycosis (CM)

CM is an emerging mycotic infection commonly encountered in immunosuppressed individuals and patients with uncontrolled diabetes. It often occurs following direct inoculation through trauma with a non-specific presentation closely mimicking other dermatologic disorders[23]. Although d-AmB is the therapy of choice, lipid formulations are often used, due to their favorable toxicity profile[24]. In fact, studies reveal AmB as the most active drug against mucorales, with minimum inhibitory concentrations (MICs) of ≤ 1 mg/mL in majority of tested strains[25]. Apart from AmB therapy, which should be initiated within 5 days of diagnosis, surgical debridement and control of underlying immunosuppression are equally important.

Recommended dosing of d-AmB is 1-1.5 mg/kg/day or 0.5-1 mg/kg/day, respectively, for immunosuppressed or immunocompetent patients with CM. L-AmB is dosed at 5-10 mg/kg/day and ABLC is administered at 5-7.5 mg/kg/day in both immunosuppressed and immunocompetent individuals[26]. Treatment duration is still not determined, with some authors suggesting to continue therapy till clinical/radiological resolution, and others recommending a treatment period of 6-8 weeks[26,27].

Interestingly, successful use of L-AmB has been documented in an extremely pre-term infant (< 28 weeks) who developed primary CM along with polymicrobial sepsis, within the first 10 days of life. L-AmB given for a period of 4 weeks resulted in spontaneous sloughing of the fungal eschar and no long-term sequelae[28].

Furthermore, the use of topical AmB, both as combination and monotherapy for CM has been described[29,30]. In a 6-month-old infant with leukemia, severe necrotizing skin and soft-tissue mucormycosis of the chest wall was treated with systemic L-AmB, local wound control, surgical resection, and topical AmB, which was successfully added due to incomplete response to systemic L-AmB alone[29].

AmB 3% cream was found to be highly effective in treating vaginal mucormycosis in a 56-year-old woman,

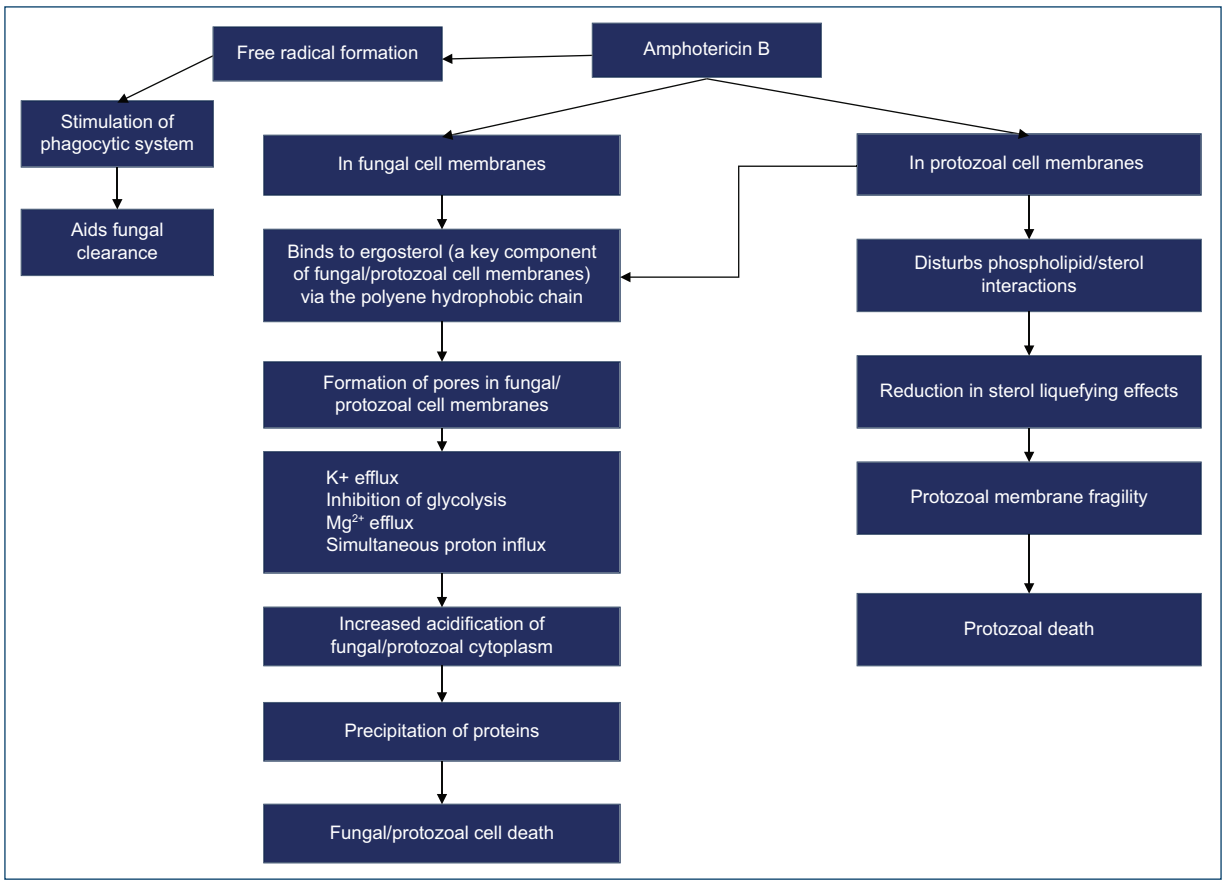

Figure 1. Mechanism of action of amphotericin B.

with a once-daily application schedule for 3 weeks, but due to relapse after therapy cessation, AmB cream was restarted for another month and gradually tapered as an alternate day schedule for 2 months with complete clinical and mycological cure (MC), even at 12 months of follow-up[30].

Chromoblastomycosis

Chromoblastomycosis represents a cutaneous/subcutaneous mycotic infection caused by a group of dematiaceous (black) fungi and occurs following traumatic skin inoculation, with the majority of lesions involving the lower extremities of outdoor workers[31].

At present, existing trials regarding its treatment are limited; with oral itraconazole and terbinafine constituting the primary therapeutic pillars for chromoblastomycosis. Unfortunately, cure rates are low and relapse rates are high[32].

AmB has been used in two reports for chromoblastomycosis[33,34]. In the first report, intravenous L-AmB for 1 month was helpful in attaining MC in a 37-year-old woman with chromoblastomycosis of the right breast. Following this, the patient was maintained on itraconazole (200 mg/day) and 5-flucytosine (4 g/day) for 12 months with no relapse[33]. In the second report, intralesional AmB (obtained by dissolving 25 mg of AmB in 20 mL of sterilized water and 5 mL of 2% lidocaine solution to make 1 mg/mL of AmB) given once weekly for 19 weeks along with 500 mg/day of oral terbinafine was successful in attaining clinical cure of chromoblastomycosis in a 75-year-old farmer who had the disease for 12 years, and was unresponsive to oral itraconazole, cryotherapy, and complete surgical excision[34].

Despite these promising reports, more robust clinical data are needed in relation to the precise dosing schedule of AmB and its combination with other antifungals for treating chromoblastomycosis.

Blastomycosis

Blastomycosis is a chronic granulomatous and suppurative systemic mycosis primarily affecting the lungs;

Table 1. Salient points related to the lipid formulations of amphotericin B

Feature evaluated	Liposomal AmB	AmB colloid dispersion	AmB lipid complex
Components	Unilamellar lipid structure AmB complexed with 3 major components, soy phosphatidylcholine, distearoylphosphatidylglycerol and cholesterol (2:1:1:0.8)	Disc-like lipid structure AmB and cholesteryl sulfate (1:1)	Ribbon-like lipid structure AmB complexed with L-α-dimyristoyl-phosphatidyl glycerol (1:7:3)
Year of approval by the US-FDA	1977	1996	1995
Standard dose	3 mg/kg/day	3-4 mg/kg/day	5 mg/kg/day
Pharmacokinetics	Extraordinarily high serum concentrations $T_{1/2}$ of 152 h < 10% is excreted unchanged in the urine and feces Small particle size Substantial escape from the MPS Higher C_{max} and higher AUC	Lower serum levels Larger size/poor dissociation Rapidly engulfed by MPS Lower C_{max} and AUC	Low serum levels Higher organ distribution (lungs) Larger molecule Engulfed by MPS Lower C_{max}, low AUC, high volume distribution

MPS: macrophage phagocytic system; AUC: area under the curve; AmB: amphotericin B; US-FDA: United States Food and Drug Administration.

with involvement of the skin, bones, and central nervous system (CNS) in disseminated forms[35]. Although itraconazole is employed as the first-line drug for most cases, AmB proves to be valuable in widespread and disseminated forms of the disease. Furthermore, in cases unresponsive to itraconazole, AmB has demonstrated efficacy[36].

Histoplasmosis

Histoplasmosis is a highly infectious mycosis caused by *Histoplasma capsulatum* that primarily affects the lungs. Although most pulmonary lesions heal spontaneously in immunocompetent hosts, in immunosuppressed individuals this progresses to disseminated histoplasmosis, with mucocutaneous involvement serving as an important diagnostic clue[37]. Regimen of AmB in the management of histoplasmosis consists of 0.7 mg/kg/day for d-AmB, 3-5 mg/kg/day for liposomal AmB; that may need to be continued for a period of 2-4 months[38,39].

Recently, in a randomized controlled trial, a single high dose of L-AmB (10 mg/kg) in HIV/AIDS-related disseminated histoplasmosis was documented to be non-inferior to the standard therapy with AmB. Besides, a single induction dose would considerably reduce drug acquisition costs (almost 4-fold) and help in simplifying treatment[39]. However, more robust data are needed to confirm these findings.

Cutaneous fusariosis

Fusariosis is a complex infection caused by the pathogenic fungus *Fusarium* spp., which is commonly found in soil and water, and transmitted to humans following traumatic inoculation. Based on the host's immune status, the clinical presentation of fusariosis differs: localized and superficial symptoms confined to the skin in immunocompetent individuals, and invasive and disseminated lesions in immunosuppressed patients. Prolonged periods of neutropenia predispose to disseminated fusariosis, which is associated with high mortality[40]. d-AmB (1-1.5 mg/kg/day) in combination with terbinafine (250 mg TID) and subsequent intravenous L-AmB (5 mg/kg/day) has demonstrated efficacy in treating a case of disseminated infection with *Fusarium oxysporum* following chemotherapy for acute myelogenous leukemia[41]. Furthermore, in a granulocytopenic patient with myelodysplastic syndrome post-peripheral blood stem cell transplant, combination of L-AmB (3 mg/kg/day) and terbinafine (250 mg TID) showed efficacy in treating fusariosis, following failure with voriconazole[42].

Interestingly, successful combination of voriconazole and AmB in disseminated fusariosis in a patient with neutropenic fever has been reported[43]. Although voriconazole still remains the first-line choice of fusariosis, some *Fusarium* species like *Fusarium proliferatum* have shown low susceptibility to voriconazole[42]. In such

scenarios, AmB proves to be a valuable alternative, and if combined with other antifungals, superior outcomes can be expected.

Protothecosis

Human protothecosis is an algal infection due to the environmentally ubiquitous achlorophyllic algae, *Prototheca* spp. Clinically, it presents in three forms, namely, as cutaneous lesions, olecranon bursitis, and disseminated/systemic infections[44]. Most treatments in protothecosis are drawn from isolated case reports, limited case series, and *in vitro* studies.

Among the available treatments, AmB displays the best activity against *Prototheca* spp. For cutaneous lesions, systemic as well as topical use of AmB has been attempted[45]. For olecranon bursitis, intrabursal administration of AmB is suggested in patients ineligible for bursectomy[46]. In systemic disease, intravenous AmB (including liposomal preparations) is considered the drug of choice. The dosing is similar for invasive mycotic infections, but responses may be variable. Combination with doxycycline, fluconazole, voriconazole and itraconazole may be beneficial in recalcitrant cases[47-51].

Congenital and neonatal candidiasis

Congenital candidiasis is a rare entity, manifesting within the first 6 days of life. It usually occurs following intrauterine candidal infection and may be localized, involving the skin alone, or have a generalized presentation resulting in respiratory distress, meningitis, with ultimate sepsis and death[52].

Systemic treatment with AmB (0.5-1 mg/kg/day) is the preferred line of management in neonates with disseminated systemic candidiasis, respiratory distress, and/or sepsis. Lipid-associated preparations of AmB (3.5 mg/kg/day) are reserved for those cases with invasive candidiasis and severe pre-existing renal insufficiency. Further, for infections involving the CNS, 5-flucytosine (50-100 mg/kg/day) is used in combination with AmB. At present, no controlled studies have defined the exact duration of therapy; however, a minimum of 21-28 days is suggested[53,54].

Genital candidiasis

Vulvovaginal candidiasis (VVC) is one of the most common infections of the female genital tract[55]. Topical AmB has demonstrated efficacy in the treatment of refractory VVC due to *Candida glabrata* and *Candida krusei*. In the two reports on *C. glabrata* VVC, AmB 100 mg plus flucytosine 1 g in Aquagel (total 8 g) was given by a vaginal applicator for 14 nights. Following completion of treatment, all patients outlined significant symptomatic improvement as well as negative cultures[56,57].

In the publication on *C. krusei* VVC, 3% amphotericin gel (containing d-AmB with Aquagel lubricant gel and propylene glycol) was developed and administered intravaginally for 14 days. Although patient's symptoms resolved after 1 month, vaginal cultures remained positive[58].

Oral candidiasis

D-AmB oral suspension has been recommended by the IDSA to treat oral candidiasis refractory to fluconazole[20].

Pityriasis versicolor (PV)

PV, a mild yet chronic superficial cutaneous mycosis caused by *Malassezia* yeasts, is currently treated with several topical azole compounds; the cornerstone of PV therapy[59]. Although never used for this indication, lipophilic properties of AmB may suggest favorable effects, as observed in a study where topical AmB 0.4% was equally effective as clotrimazole 1% in obtaining clinical and mycologic cure for PV[60]. However, based on this anecdotal report, no significant conclusions can be drawn.

Onychomycosis

At present, oral itraconazole and terbinafine are the recommended first-line drugs for onychomycosis[61]. However, due to adverse effects and concomitant drug interactions, their utility in many individuals may not be suitable, making it mandatory to consider alternative approaches to tackle these issues. In such scenarios, topical therapy might offer advantages like better site selectivity, avoidance of systemic adverse effects, and easy application at the site of fungal infection. Besides, topical antifungal agents available at present (amorolfine, ciclopirox olamine, and azoles) have proven valuable, despite their lower potencies and limited on-site penetration[62].

Topical AmB in onychomycosis has recently been evaluated in two reports[63,64]. In the first, a topical formulation consisting of 0.3% AmB in 30% dimethyl sulfoxide (DMSO) cream (group A, n = 10) was compared

with 30% DMSO cream (group B, n = 9) in non-dermatophyte onychomycosis daily for 36 weeks, with clinical cure in 70% of patients in Group A and 22% patients in Group B, and MC rates in 80% and 44.4% of patients in Group A and Group B, respectively[63]. In the second report, topical nano liposomal AmB 0.4% gel was utilized in 12 onychomycosis patients for a period of 12-36 weeks twice daily over the entire surface of the affected nails, including a 6 mm margin around the cuticle. At 12 weeks, 50% showed complete clinical cure (CCC), 16.66% outlined an effective clinical response and 16.66% denoted a partial clinical response. MC was observed in 50% of patients at week 12. At week 24, CCC and MC were observed in 91.66% of patients, with 8.33% delineating no response. Apart from temporary nail detachment in one patient, no other adverse events were reported. Notably, in one patient, nano-liposomal AmB induced CCC at week 12 in fluconazole-resistant onychomycosis[64].

Furthermore, MICs of non-liposomal AmB are lower for *Candida albicans*, *C. glabrata*, *Trichophyton rubrum,* and *Fusarium solani,* making it a potential quasi-efficient alternative for onychomycosis, demanding lower doses and having the advantage of topical use, without any off-target systemic side effects[64]. Nevertheless, more studies become essential to strengthen these observations.

Dermatophytosis

At present, there are no clinical studies on the use of AmB *in vivo* for dermatophyte infections, although *in vitro* studies have demonstrated susceptibility of dermatophytes to AmB, even though with variable results. Terbinafine is considered the most effective drug against *T. rubrum* and *T. verrucosum* followed by AmB[65].

In another evaluation, AmB was inferior to caspofungin and itraconazole but superior to ketoconazole and fluconazole against all dermatophytes tested[66]. Interestingly, Coelho et al.[67], elucidated AmB to be the most superior drug against microconidia of *T. rubrum* and *Trichophyton tonsurans* in comparison to fluconazole, terbinafine, itraconazole and griseofulvin. Despite these positive findings, clinical application of this data warrants caution because *in vitro* susceptibility may not always translate to *in vivo* efficacy.

Nevertheless, topical AmB may at least in part provide a solution to the annoying issue of recalcitrant dermatophytes. However, it cannot be overlooked that AmB remains the primary drug for invasive life-threatening fungal infections, and it would be prudent to restrict its use only to very specific cases, where it is justified.

Cutaneous leishmaniasis (CL)

Leishmaniasis is a protozoal disease transmitted by sandfly vectors and is endemic in 88 countries, commonly in tropical and subtropical regions. Clinical manifestations of leishmaniasis range from aggressive cutaneous ulcers to systemic multi-organ disease (that constitute VL)[68].

At present, systemic therapy for CL is only recommended in old-world CL with mucosal involvement, or patients with complicated cutaneous lesions; defined as ≥ 3 lesions, lesions with diameters > 30 mm, lesions in anatomic locations unsuitable for local treatment, and lesions refractory to local therapy[69,70].

Common drugs currently employed for systemic therapy in leishmaniasis include pentavalent antimony, AmB, fluconazole, and miltefosine. No prospective clinical trials comparing the efficacy of any of these drugs for complicated CL have been conducted, with the choice of therapy relying solely on retrospective case descriptions and case series. d-AmB and lipid-bound AmB products are well-established treatments for VL[71]. However, in complicated CL, there is no clear consensus regarding its systemic use, as well as the optimal dosing schedule. Besides, in this scenario, L-AmB is preferable, due to reduced nephrotoxicity, and its ability to specifically target macrophages in which leishmania parasites develop[72]. Presently, the dosing schedule stated by the American Society of Tropical Medicine for VL is employed for this indication, and consists of intravenous L-AmB (3-4 mg/kg/day) on days 1-5, 10, 17 and then weekly until healing or a cumulative dose of 40 mg/kg is achieved[73].

Besides, in uncomplicated CL, the use of intralesional and topical AmB has demonstrated propitious outcomes (Table 2)[74-77]. Moreover, as it is administered locally, systemic adverse effects with AmB are expected to be minimal. Although spontaneous healing of lesions may occur in uncomplicated CL, treatment is recommended to accelerate cure and reduce scar formation, especially in cosmetically important sites[78].

Post-Kalazar dermal leishmaniasis (PKDL)

PKDL is a complication of VL characterized by macular, maculopapular, and nodular rash in a patient

Table 2. Studies outlining the utility of topical and intralesional amphotericin B for uncomplicated cutaneous leishmaniasis

No.	Authors	Study type	Details	Remarks
1	Goyonlo et al.[74]	Prospective study	93 patients 79 unresponsive to intralesional meglumine antimoniate AmB deoxycholate intralesional once a week until lesion resolution 10.31 ± 5.41 injections	Complete remission at 12 weeks 63.5% (urban leishmaniasis) 66.7% (rural leishmaniasis) 54.6% (lupoid leishmaniasis) Partial remission at 12 weeks 20.6% (urban leishmaniasis) 33.3% (rural leishmaniasis) 22.7% (lupoid leishmaniasis) No response at 12 weeks 15.9% (urban leishmaniasis) 22.7% (lupoid leishmaniasis) No recurrence (rural leishmaniasis) Recurrence < 6 months 4 patients (urban leishmaniasis) 2 patients (lupoid leishmaniasis) Recurrence at 6-12 months 2 patients (lupoid leishmaniasis) Recurrence at > 12 months 2 patients (lupoid leishmaniasis) Negligible side effects No premature discontinuation
2	Goswami et al.[75]	Prospective study comparing 2 doses of intralesional AmB (2.5 mg/mL vs. 5 mg/mL)	Group A (n = 25) 2.5 mg/mL/week 8 weeks Group B (n = 25) 5 mg/mL/week 8 weeks	At 8 weeks, Group A Complete response (72%) Partial response (20%) No response (8%) At 8 weeks, Group B Complete response (56%) Partial response (28%) No response (16%) At 12 weeks, Group A Complete response (88%) Partial response (8%) No response (4%) At 12 weeks, Group B Complete response (64%) partial response (24%) no response (12%) Side effects - pain (< 30 min) at injection site - no treatment discontinuation
3	Layegh et al.[76]	Comparative clinical trial topical liposomal AmB versus intralesional meglumine antimonate	n = 39 patients: topical liposomal AmB (3-7 drops twice daily-8 weeks) + 11 not adherent n = 37 intralesional meglumine antimoniate weekly (max. 2 mL-8 weeks) + 23 not adherent	At 8 weeks, clinical cure AmB group (56.4%), Meglumine antimoniate (67.6%). Besides, at 6 months of follow–up, no recurrence of lesions was reported Limited side effects in both groups
4	López et al.[77]	Open-label, randomized non-comparative phase Ib/II clinical trial Topical 3% AmB cream	80 patients uncomplicated cutaneous leishmaniasis Group A (n = 40) 3% AmB cream TID – 4 weeks Group B (n = 40) 3% AmB cream BID – 4 weeks	Definite cure at 90 days Group A (39.4%) Group B 35.3% No adverse events

AmB: amphotericin B.

apparently cured, inadequately treated, or untreated for VL[79]. L-AmB is the second-line treatment for PKDL in patients where miltefosine is contraindicated[80].

Miltefosine (2.5 mg/kg/day in children and 100 mg/day in adults) is preferred over AmB due to its oral route of administration, but it has a high cost. d-AmB (1 mg/kg for 60-80 infusions) is often associated with nausea, vomiting, fever, rigor, and other toxicities accounting for patient non-compliance[81]. To tackle this issue, low dose d-AmB (0.5 mg/kg/day) for 20 infusions, for 3 courses,

at an interval of 15 days between each course has been attempted with promising results, including shortening the duration of hospitalization and improving tolerability[82]. Furthermore, L-AmB is being used for treating PKDL with lesser toxicity compared to d-AmB.

In a randomized open-label study comparing L-AmB versus miltefosine for PKDL, the final cure rate as per protocol analysis was 74.5% and 86.9% for L-AmB and miltefosine, respectively. Further, relapse of PKDL was observed in 25.5% of patients in the L-AmB group and 13% of patients belonging to the miltefosine group. Besides, no patient in both groups developed any serious adverse effect[83].

Interestingly, combination therapy with L-AmB and miltefosine has been assessed for PKDL by Ramesh et al.[80]. Association of L-AmB (3 injections 5 mg/kg on days 1, 8, and 15) with miltefosine (100 mg/day capsules for 45 days) was compared with miltefosine monotherapy (90 days) and demonstrated rapid decline in parasite load, along with 100% clinical cure and no reports of relapse. However, in the miltefosine monotherapy group, although gradual reduction in parasite load and ultimate clinical cure was attained, 25% of patients relapsed at 18 months of follow-up[80]. Given the promising report of this association, more clinical trials are warranted to substantiate the above finding. Moreover, the briefer duration of therapy along with minimal side effects encourage further application of this therapy for the treatment of PKDL.

Amphotericin adverse effects

In ~80% of patients, infusion-related adverse effects and nephrotoxicity is documented. As AmB interacts also with cholesterol in human cell membranes, toxicity is expected. Common adverse effects include:

- Hypokalemia, hypomagnesemia, and anaphylaxis[84].
- Nephrotoxicity correlates with conventional AmB, but it is reversible post-AmB cessation. Besides, avoiding concomitant nephrotoxic drugs and appropriate hydration can reduce the incidence of nephrotoxicity, and liposomal formulations have considerably lower chances of renal toxicity. Vasoconstriction of afferent renal arterioles results in decreased renal blood flow and GFR accounting for nephrotoxicity[85].
- Long-term AmB is associated with normochromic, normocytic anemia secondary to low erythropoietin concentrations[86].
- Initial doses of AmB often cause fever, headache, cheilitis, hypotension, tachypnea, and vomiting within 2-6 h of perfusion. Transient substernal chest pain and flank pain are observed predominantly with d-AmB and ABCD (rarely with L-AmB and AMLC), but resolve on discontinuation and administration of intravenous diphenhydramine. This is explained by the release of proinflammatory cytokines such as interleukin (IL-1β), tumor necrosis factor-α, IL-6, and IL-8, after recognition via toll-like receptors and transmembrane signaling protein CD14[8].
- Cutaneous reactions mainly comprise of urticarial reactions and thrombophlebitis at the injection site. Drug rash with eosinophilia and systemic symptoms and cutaneous vasculitis have also been described with L-AmB[8,87,88]. The suggested etiology of urticarial eruptions is liposomal activation of the complement cascade and subsequent release of C3a and C5a[89].
- Rare side effects include new onset dilated cardiomyopathy with associated heart failure that subsides within 6 months of treatment discontinuation. Other unusual toxicities include hyperbilirubinemia, elevated hepatic transaminases, pancreatitis, and pseudohypophosphatemia (observed even with L-AmB)[89].

Amphotericin in special populations

Pregnancy

During pregnancy, AmB should be used only when indicated. According to IDSA guidelines, for invasive candidiasis in pregnancy, AmB is the drug of choice. Further, potential adverse effects on the fetus can be reduced by using the ideal body weight of the mother rather than the total body weight. Furthermore, it would be preferable to use the liposomal formulation due to the minimal risk of teratogenicity[90].

Lactation

AmB can be used during lactation. As it is highly protein-bound, has a large molecular weight, and is poorly absorbed, the probability of its secretion in breast milk is minimal[91].

Pediatric patients

All preparations of AmB have been used in children with documented safety and efficacy. However, its usage in neonates still needs more data[92].

Geriatric patients

ABLC given to elderly patients at a dose of 5 mg/kg/day is not associated with significant adverse events[21].

Table 3. Storage and administration guidelines for Amphotericin B

Feature evaluated	AmB deoxycholate	Liposomal AmB
Storage requirements	Store in dry form at 2-8°C away from light	Store in dry form at 2-8°C away from light
Reconstitution	50 mg vial + 10 mL sterile water (5 mg/mL solution)	50 mg vial + 12 mL sterile water (4 mg/mL solution)
Further dilution	500 mL of 5% dextrose (0.1 mg/mL)	5% dextrose to have 1-2 mg/mL (adults) 0.2-0.5 mg/mL (infants and children)
Test dose	0.1 mg/kg (not exceeding 1mg) infusion over 20-60 min	0.1 mg/kg (not exceeding 1mg) infusion over 20-60 min
Administration	Over 2-6 h via a distal vein Immediately after preparation	Over 2-6 h via a distal vein Immediately after preparation
Premedication	For infusion-related reactions Paracetamol Diphenhydramine Corticosteroids (30 min before infusion)	For infusion-related reactions Paracetamol Diphenhydramine Corticosteroids (30 min before infusion)
Monitoring requirements	Daily serum creatinine Regular K^+, Mg^{2+}, Ca^{2+}, PO_4^- Proper hydration For infusion-related reactions (15 min-3 h) Signs of hypokalemia	Regular K^+, Mg^{2+}, Ca^{2+}, PO_4^- Proper hydration For infusion-related reactions (15 min-3 h) Signs of hypokalemia
Dose adjustment	If serum creatinine > 2.5 mg/dL Reduce dose by 50%, or Switch to L-AmB	Based on clinical response
Special consideration	Higher risk of nephrotoxicity Careful monitoring of renal function	Better renal tolerance Preferred in patients with/at risk of renal dysfunction
Emergency monitoring	For suspected hypokalemia (muscle cramps, drowsiness) Immediate ECG Serum K^+ measurement Prompt correction of electrolytes Adequate hydration	For suspected hypokalemia (muscle cramps, drowsiness) Immediate ECG Serum K^+ measurement Prompt correction of electrolytes Adequate hydration

Patients with renal and hepatic impairment

No dose adjustment is needed in patients with renal impairment based on creatinine clearance estimate. L-AmB has been successfully dispensed in patients with pre-existing renal impairment. The effect of L-AmB in patients with hepatic impairment is not known[21].

Storage and administration

This is elaborated in table 3.

Drug interactions

As AmB is not metabolized by the cytochrome P_{450} pathway, documented drug-drug interactions are few. Cyclosporine and tacrolimus used in kidney transplant can increase the toxicity of AmB, and there is an increased risk of hypokalemia with concomitant use of digoxin and corticosteroids[93].

Amphotericin resistance

Fortunately, AmB resistance is rare compared to other antifungal agents. However, resistance has been encountered for *Aspergillus terreus* due to a reduction in polyene-induced oxidative stress[94], for *Aspergillus flavus* and *Candida tropicalis* due to an increase in 1,3α-glucan and 1,3β-glucan fraction that leads to an alteration of the fungal cell wall with subsequent AmB resistance[95,96], and for various *Candida* spp. a mutation in the *ERG* genes that alters the sterol composition of the fungal cell membrane, thereby preventing AmB antifungal effects[97].

Novel oral amphotericin formulations

To date, oral AmB formulations are at various stages of preclinical development with some making it to human clinical investigations. Oral AmB lipid-based formulation has been specifically designed to reduce

limitations existing with intravenous formulations as per the treatment of systemic mycoses and VL[98].

This formulation consists of a self-emulsifying mixture of monoglycerol oleate, lauroyl polyoxyl-32 glyceride, and D-α-tocopherol polyethylene glycol succinate (a penetration enhancer). Besides, this formulation further stabilizes the less toxic monomeric form of AmB[98].

Recently 2 human phase-I clinical studies have been completed with the oral AmB formulation (capsule). Further, in both phase-Ia and Ib human clinical studies, the primary endpoint of safety and tolerability following administration of single ascending doses and repeated doses were met, including no signs of kidney, liver, and gastrointestinal adverse effects[99].

Besides, the self-nanoemulsifying drug delivery system was utilized for AmB encapsulation to enhance its oral bioavailability[100]. With the above promising findings, oral AmB could revolutionize the management of many tropical dermatoses due to easier administration, reduced toxicity, cost efficacy, and the ability to be stored at room temperature.

Conclusion

AmB is a valuable drug for the treatment of many tropical dermatoses. With research going on regarding oral preparations of the drug, its utility could become more widespread due to the ease of administration. Further, although the use of topical AmB has been employed for PV and genital candidiasis, the use of AmB *per se* cannot be widely employed for these indications, due to very low quality of evidence (confined to case reports or trials with groups of 10 patients).

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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REVIEW ARTICLE

Crisaborole: a dermatologic perspective

Crisaborole: uma perspectiva dermatológica

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Abstract

Crisaborole is a non-steroidal boron-containing topical phosphodiesterase-4 inhibitor that has been approved by the US-FDA for the treatment of atopic dermatitis in children (> 3 months of age) and adults. More recently, its efficacy has been outlined in the treatment of many other dermatoses, including vitiligo, psoriasis, morphea, seborrheic dermatitis, stasis dermatitis, and vulvar leukoplakia, to name a few. While crisaborole represents a valuable non-steroidal alternative in dermatological therapy, the primary limitation is its high cost compared to other topical agents. Nevertheless, despite this limitation, its use in recalcitrant cases can be worth considering.

Keywords: Crisaborole. Atopic dermatitis. Psoriasis. Vitiligo. Morphea.

Resumo

O crisaborole, é um inibidor tópico não esteroide da fosfodiesterase-4 contendo boro, aprovado pelo US-FDA para o tratamento de dermatite atópica em crianças depois dos 3 meses de idade e adultos. Ultimamente, a sua eficácia foi reportada no tratamento de muitas outras dermatoses, incluindo vitiligo, psoríase, morfeia, dermatite seborreica, dermatite de estase e leucoplasia vulvar, para citar algumas. Embora o crisaborole represente uma alternativa não esteroidal valiosa na terapia dermatológica, a principal limitação é seu alto custo em comparação a outros agentes tópicos. No entanto, apesar dessa limitação, seu uso em casos recalcitrantes pode valer a pena ser considerado.

Palavras-chave: Crisaborole. Dermatite atópica. Psoríase. Vitiligo. Morfeia.

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Introduction

Crisaborole is a boron containing topical phosphodiesterase-4(PDE4) inhibitor approved by the FDA for topical treatment of mild to moderate atopic dermatitis (AD) in patients aged 3 months or older[1,2]. The presence of the boron atom in crisaborole facilitates drug penetration through human skin, thus enhancing its dermal concentrations[1]. Although, initially used as a non-steroidal topical drug for AD, crisaborole has demonstrated benefit in the management of various other dermatological disorders. This review will comprehensively elucidate the utility of crisaborole in AD, as well as other dermatoses.

Pharmacokinetics

Following twice daily crisaborole application, maximum plasma concentrations are achieved within 3-24 h, with steady state systemic concentrations available by 8 days, along with a mean accumulation factor of 1.9[3]. The drug is 97% bound to plasma proteins, and metabolized into two inactive metabolites. The major metabolite is 5-(4-cyanophenoxy)-2-hydroxyl benzyl alcohol, which is further oxidized to produce the other metabolite, 5-(4-cyanophexy)-2-hydroxylbenzoic acid. Both metabolites attain steady-state systemic concentrations by day 8 of crisaborole initiation. Major route of drug elimination is through the kidneys[3].

Mechanism of action

Crisaborole inhibits the enzyme PDE4 in a competitive and reversible way; a schematic representation of which is outlined in figure 1[4]. Crisaborole inhibits PDE4, an enzyme that breaks down cyclic adenosine monophosphate (cAMP). By inhibiting PDE4, crisaborole increases intracellular cAMP levels, which subsequently activates protein kinase A (PKA). This activation leads to phosphorylation of the transcription factor CREB (cAMP response element-binding protein) and inhibition of nuclear factor-κB. These molecular changes ultimately result in decreased production of pro-inflammatory cytokines (including tumor necrosis factor [TNF]-α, Interleukin [IL]-2, IL-4, IL-5, IL-23, and Interferon-gamma [IFN-γ]) and increased production of anti-inflammatory cytokines (such as IL-10). The presence of boron in crisaborole's structure enhances skin penetration by forming a reversible bond with the hydroxyl groups in the stratum corneum, allowing more efficient dermal delivery of the active compound.

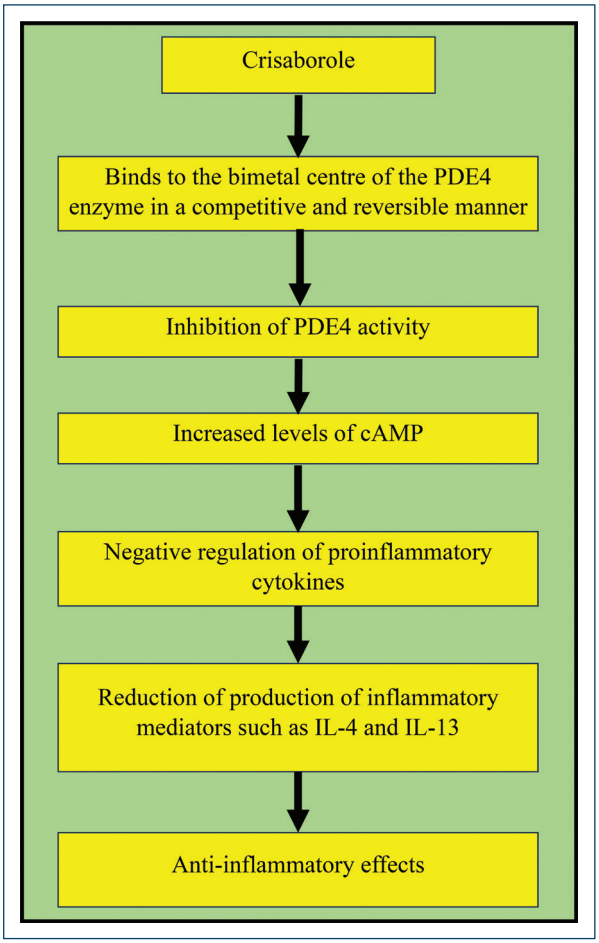

Figure 1. Mechanism of action of crisaborole.

Clinical uses

Atopic dermatitis

AD is a chronic endogenous eczema, typically known for its relapsing and remitting course. Although topical corticosteroids (TCSs) are still considered the mainstay of AD treatment, their long-term usage is not recommended due to adverse effects, namely, skin atrophy, telangiectasia, striae, as well as suppression of the hypothalamo-pituitary adrenal axis, which is often a concern in pediatric patients[2]. To counter these adversities, it becomes essential to use an alternative drug that is effective, as well as safe for long-term treatment. Although, topical calcineurin inhibitors (TCIs) such as tacrolimus and pimecrolimus hold value in the treatment of AD, newer agents in the therapeutic arsenal of AD are always welcome. Crisaborole offers yet another option in this category, with a different mechanism of action, demonstrating efficacy, without the side effects of TCS.

Table 1. Studies outlining the benefits of crisaborole in atopic dermatitis

No.	Authors	Study type	Details	Remarks
1	Paller et al.[1]	Two double-blind, vehicle-controlled phase 3 trials (AD-301; AD-302) in 1527 patients aged 2-79 years.	Randomization to crisaborole (n = 763) or vehicle (n = 764) twice daily for 28 days.	Better treatment response for crisaborole (Trial 1: 32.8% vs. 25.4%; p = 0.038, Trial 2: 31.4% vs. 18%; p < 0.001). IGA Score 0/1 more frequent with crisaborole (Trial 1: 51.7% vs. 40.6%; p = 0.005; Trial 2: 48.5% vs. 29.7%; p < 0.001). Statistically significant improvement in pruritus, and AD lesions.
2	Zane et al.[7]	Phase Ia open-label to assess efficacy of 2% crisaborole ointment in 34 AD patients aged 2-17 years.	Crisaborole ointment twice daily for 28 days.	IGA score of 0 (clear) or 1 (almost clear) in 64.7%. Improvements in erythema (–64.9%), excoriation (–58.2%), exudation (–64.3%), pruritus (–63.3%) lichenification (–61.3%).
3	Murrell et al.[8]	Double-blind phase II trial in 25 adults aged 18-75 years with mild to moderate AD.	All patients treated with crisaborole Q12H or vehicle for 28 days, each to one of the two target lesions. All patients had two target lesions, with one treated with crisaborole ointment twice daily and the other with vehicle for 28 days in a split-body design.	68% of patients with greater reduction in AD severity index scores for the lesion treated with crisaborole versus vehicle.
4	Eichenfield et al.[9]	Randomized, double-blind, vehicle controlled, phase III study 270 patients aged 3 months-18 year.	Group 1 (n = 135) - crisaborole Q12H for 52 weeks Group 2 (n = 135) vehicle Q12H for 52 weeks.	At 52 weeks the mean number of flares and mean number of flare free days significantly lower in Group 1 (34.6 days difference).
5	De et al.[10]	4-week open label study on 19 mild-to-moderate AD (aged 2-16 years).	2% crisaborole ointment Q12H for 30 days.	IGA reduction from 2.58 ± 0.61 to 0.095 ± 0.78 (p < 0.001). Pruritus score reduced from 2.32 ± 0.478 to 0.84 ± 0.60 (p < 0.001). Statistically significant improvement in AD lesions.
6	Schlessinger et al.[11]	Phase IV open label study (CrisADe CARE 1).	137 infants with mild-to-moderate AD 3-24 months' old Crisaborole Q12H for 28 days.	Adverse events in 22 patients (16.1%): site discomfort (2.9%), erythema (2.9%); and site pain (3.6%).

Although, the exact mechanism of crisaborole in AD is incompletely understood, following topical treatment, studies have shown decreasing levels of AD biomarkers on lesional biopsy specimens from day 0 to 8 and 15 and significant downregulation of genes involved in Th2, Th17 and Th22 pathways, with consequent reduction in the production of inflammatory mediators[5]. Moreover, higher levels of PDE4 have been identified in AD patients, and inhibition of PDE4 by crisaborole in monocytes reduces pro-inflammatory cytokines[6]. This manifests clinically as a rapid and persistent improvement in pruritus and a reduction of AD associated signs and symptoms, as early as the 1st week of treatment. Besides, as pruritus is reduced, the itch-scratch cycle is broken, which is associated with improvement in the quality of life (QoL) in these patients.

However, despite treatment success in approximately 31-47% of AD patients with ~49-65% investigator static global assessment scores of clear or almost clear in clinical trials, crisaborole still remains a second-line topical agent for AD behind TCS and needs to be reserved for patients unresponsive or unable to use TCS. Various studies on the utility of crisaborole in AD are outlined in table 1[1-7,11].

Vitiligo

Nagui et al.[12], in their study, outlined significantly higher levels of PDE4 in the skin and serum of vitiligo patients compared to controls ($p < 0.001$), suggesting PDE4 to play a role in disease pathogenesis. Inhibition of PDE4 is associated with elevated levels of cAMP that suppresses expression of TNFα, IL-23, and IFNγ, along with an increase in IL-10 and IL-12 (anti-inflammatory mediators), and in this way halts perpetuation of the inflammatory process in vitiligo[13]. Furthermore, the cAMP pathway has shown to promote melanogenesis by inducing melanocyte differentiation and proliferation[14]. Based on these findings, crisaborole (2%) ointment has been used for vitiligo.

Tam et al. outlined the beneficial role of crisaborole in a 71-year-old man with vitiligo involving his forearm and dorsal aspect of hands unresponsive to clobetasol propionate (0.05%) and tacrolimus (0.1%). Notable re-pigmentation of the vitiliginous patches was evident within 10 months of crisaborole use, and by 22 months, repigmentation further increased, along with control of disease progression[15].

In another report, crisaborole was beneficial in promoting repigmentation of persistent vitiligo over the ears in a Hispanic male in his 40's, who had failed to respond to TCS and TCIs. Within 1-month of treatment, scattered areas of perifollicular pigmentation was witnessed over both ears[16]. Both patients tolerated treatment well, with no adverse effects.

Based on these reports, crisaborole may serve as a potential option in vitiligo with minimal body surface area involvement. Further, combination of crisaborole with phototherapy and microneedling are other avenues for future research[15,16].

Psoriasis

The role of PDE4 in the pathogenesis of psoriasis is clearly demonstrated and, apremilast, an oral PDE4 antagonist has been well established in psoriasis therapeutics, with its approval in moderate-to-severe plaque psoriasis and psoriatic arthropathy. Once PDE4 is blocked, release of multiple inflammatory mediators including TNFα, IFNγ, IL-1β, IL-2, IL-5, and IL-6 and various chemokines are decreased, thus contributing to disease regression[17].

Topical therapy in psoriasis demonstrates greater clinical efficacy in anatomical sites with thin non-scaly plaques, given the thickness of stratum corneum being inversely proportional to drug absorption[18]. Thus facial, anogenital and intertriginous sites serve as favorable targets for the trial of newer agents.

Hashim and col. in a double-blind, randomized, and vehicle-controlled study evaluated the utility of crisaborole (2% ointment applied twice daily [Q12H]) as monotherapy for intertriginous, facial and anogenital psoriasis. Following 8 weeks of treatment, there was an 81% change of the target lesion severity scale in patients receiving crisaborole; with 71% of participants achieving lesional clearance. In addition, there were no reports of adverse skin reactions at the application sites[18].

Despite the favorable profile of crisaborole in psoriasis in this report, more studies are ongoing to confirm the benefit of crisaborole. Further, its use in combination with TCS both as continuous and pulse therapy needs evaluation.

Morphea

Morphea, also referred to as localized scleroderma, is a clinical condition characterized by skin and soft-tissue inflammation and sclerosis.

In a single-arm, open-label, pilot study of seven adult patients with active morphea involving < 20% total body surface area, unresponsive to TCS, crisaborole 2% ointment applied twice daily for 12 weeks induced histologic reduction of dermal fibrosis in five of seven patients, and clinical reduction in size of treated plaques among six of seven patients, at the end of treatment[19].

Reduction of dermal fibrosis by crisaborole in morphea may be linked to its ability in interfere with the release of IL-6 from M2 macrophages[20]. Though promising, more studies are required to assess the utility of crisaborole in morphea.

Seborrheic dermatitis

In seborrheic dermatitis (SD) PDE4 inhibitors have been studied as a potential new approach. These drugs outline their effects in SD by increasing levels of cAMP and suppressing pro-inflammatory molecules[21]. The utility of crisaborole 2% ointment, following twice weekly applications for 4 weeks in treating chronic SD of the nasolabial folds, was first emphasized by Lui et al. in an individual case report. Following completion of treatment, notable reduction in scaling and erythema was witnessed[22].

This was followed by the communication of Peña et al.[23], who highlighted the efficacy of crisaborole (2% ointment Q12H application) in treating mild/moderate

facial SD in 30 patients aged 18–80 years. Following 1 month of treatment, in 83.3% patients, significant reduction of the Investigator Global Assessment Scale to clear or almost clear was reported, along with improvement in erythema, scaling, dryness, and pruritus. All patients tolerated the treatment well, except for one, who discontinued therapy due to headache and facial pain at week 2 of treatment. Randomized controlled trails are therefore warranted to confirm the use of crisaborole in SD, and whether its combination with other topical/systemic drugs would be more beneficial.

Stasis dermatitis

Stasis dermatitis (SDe) is a chronic inflammatory dermatosis associated with venous insufficiency. Since inflammation plays a central role in the pathogenesis of SDe, targeting inflammation represents a logical therapeutic strategy[24]. By blocking PDE4, crisaborole helps reducing production of inflammatory cytokines which may prove beneficial in treating SDe[25].

In a randomized, proof-of-concept phase 2a study, crisaborole 2% ointment applied Q12H (n = 33) versus vehicle (n = 32) was assessed in patients with SDe unresponsive to TCS, TCIs or compression garment. Following 6-weeks of treatment, the total sign score had significantly reduced from baseline in subjects treated with crisaborole versus vehicle (–52.5% vs. –10.3%; p = 0.0004). Treatment was tolerated well in most patients, with none of them discontinuing treatment due to adverse effects secondary to crisaborole. Treatment-emergent adverse events (TEAEs) were observed in 43.8% of participants receiving vehicle treatment and 39.4% of those receiving crisaborole. Most common TEAEs with crisaborole were dermatologic that included pruritus (n = 3; 9.1%), erythema (n = 2; 6.1%), and contact dermatitis (n = 2; 6.1%). Other notable TEAEs experienced with crisaborole were urinary tract infection (n = 2; 6.1%) and headache (n = 2; 6.1%). Serious/severe adverse events occurred in 3% (n = 1) of crisaborole-treated participants, compared to 12.5% (n = 4) of vehicle-treated subjects[25]. Although promising, more research is warranted with crisaborole for SDe.

Vulvar leukoplakia

Vulvar leukoplakia (VL) is a vulvar skin disease characterized with pruritus, vulvar skin hypopigmentation, and epidermal hyperkeratosis; and dermal inflammatory infiltrates characterizing the hallmark histological profile[26].

In a prospective, randomized controlled clinical trial with 2 groups of VL patients (50 each) receiving either crisaborole 2% ointment Q12H or topical vitamin E Q12H, an effective response rate of 92% for crisaborole versus 52% for vitamin E was observed at 2 weeks of treatment. Two patients receiving crisaborole complained of local pain and ulceration that subsided after crisaborole withdrawal. No such adverse effects were reported with vitamin E[26].

Suggested mechanism of crisaborole in VL is associated with its anti-inflammatory effects following PDE4 blockade with resultant cAMP elevation, and subsequent blockade of TNFα, IFNγ, and IL-2[26].

Inflammatory linear verrucous epidermal nevus (ILVEN)

Crisaborole may be of value in the treatment of ILVEN due to the possible involvement of cellular immunologic processes in its pathogenesis.

Barney et al.[27], successfully treated a 5-year-old boy with crisaborole (2% ointment Q12H application), with no side effects.

In another report, a 9-year-old girl who had failed prior treatment with TCS, pimecrolimus and calcipotriene, responded favorably with crisaborole 2% ointment[28].

Besides, as crisaborole exhibits good safety, it can be used for a longer duration, which can be a promising new therapeutic option in ILVEN.

Knuckle pads

Knuckle pads (KPs) represent zones of fibrotic skin thickening over the knuckles and are mainly a clinical diagnosis. Crisaborole (2% ointment Q12H application) demonstrated efficacy in a 45-year-old man with a 6-year history of KPs involving the knuckles and ankles, unresponsive to intralesional triamcinolone and topical clobetasol. Within 2 weeks of crisaborole use, combined with triamcinolone acetonide and neomycin plaster, remarkable improvement was witnessed[29]. This was attributed to the ability of crisaborole to inhibit hyperkeratosis and fibroblast chemotaxis as a result of its PDE4 antagonizing property, with its boron containing structure, enhancing penetrability[29]. Nonetheless, the contributory anti-inflammatory role of triamcinolone acetonide and the occlusive environment provided by

the patch in promoting skin softening by improving medication permeability cannot be undermined.

Chronic hand dermatitis

In a retrospective review involving 251 patients with chronic hand dermatitis (CHD), crisaborole induced improvement of symptoms in 72.2% of patients after 4 weeks of treatment, with an average reduction of 43% in symptom severity as measured by the hand eczema severity index. As TNFα and IFNγ are involved in the pathophysiology of CHD, by blocking PDE4, crisaborole subsequently inhibits these proinflammatory mediators, and elevates IL-10 (an anti-inflammatory cytokine), contributing to improvement in CHD[30].

Further in a patient with hand dermatitis following frequent use of a hand sanitizer, 2% crisaborole ointment helped lesion resolution within 8 weeks of treatment, with no adverse effect[31].

Necrobiotic xanthogranuloma

In an anecdotal report, crisaborole 2% ointment was reported to bring about complete resolution of necrobiotic xanthogranuloma in a patient with associated multiple myeloma. The exact mechanism though remains elusive[32].

Lichen simplex chronicus

The beneficial role of crisaborole was shown in a 15-year-old girl with *lichen simplex chronicus* of the right posterolateral ankle refractory to topical steroids. Significant resolution was observed at 2-week, 2-month, and 5-month of follow up and was considered to be due to anti-inflammatory properties of crisaborole[33].

The level of evidence for the use of crisaborole for various dermatologic indications is represented in table 2.

Table 2. Level for evidence for the use of crisaborole in various dermatoses

Serial no.	Indications in dermatology	Level of evidence for crisaborole use
1	Atopic dermatitis	A
2	Vitiligo	E
3	Psoriasis	C
4	Morphea	D
5	Seborrheic dermatitis	B
6	Stasis dermatitis	B
7	Vulvar leukoplakia	B
8	Inflammatory linear verrucous epidermal nevus	E
9	Knuckle pads	E
10	Chronic hand dermatitis	B
11	Necrobiotic xanthogranuloma	E
12	Lichen simplex chronicus	E

A: double blind study: at least one prospective randomized double blind controlled trial without major design flaws; **B:** clinical trial with 20 or more subjects: prospective clinical trials with 20 or more subjects, trials lacking adequate controls or another key facet design, which would normally be considered desirable; **C:** clinical trial with < 20 subjects: small trials with < 20 subjects with significant design limitations, very large number of case reports (at least 20 such in literature); **D:** series of 5 or less subjects: series of patients reported to respond with at least five reports of the same in literature; **E:** anecdotal case reports.

Adverse effects

The most common adverse effects seen with crisaborole are mild-to-moderate stinging and burning that generally resolve within 24 h in most patients[2].

Dosage and administration

Crisaborole 2% ointment is given as a Q12H application schedule, with no dose adjustment in patients with hepatic/renal impairment[3]. If concomitant use of an emollient is needed, the patient should apply crisaborole at least 15 min before emollient use, to obtain maximal efficacy[34]. Emollients also help reducing stinging and burning following crisaborole use[34].

Use in special populations

Regarding the use of crisaborole in pregnancy and lactation, data are scant. However, animal studies have not indicated a cause for concern. Similarly, for patients aged ≥ 65 years, there are insufficient data determining whether geriatric patients respond differently from younger patients[3].

Drug interactions

Riociguat, a soluble guanylate cyclase stimulator is contraindicated with both non-selective PDE4 and PDE5 inhibitors due to the potential of these

medications to enhance the hypotensive effect of riociguat[35]. While this interaction is documented for systemic PDE inhibitors, the risk with topical crisaborole is minimal due to limited systemic absorption. Nevertheless, caution is advised in patients receiving riociguat.

Cost-effectiveness

The cost-effectiveness of crisaborole is a major consideration in clinical practice. With an average wholesale price of approximately $580-650 (for a 60g tube), crisaborole is considerably more expensive than generic topical corticosteroids (ranging from $10 to 50/tube) and slightly more expensive than TCIs ($200-300/tube). Due to the higher cost of crisaborole, it's use as an alternative steroid sparing drug may be a limiting factor in developing countries[36].

Future direction

The role of crisaborole in mono- or combination therapy, as well as pulse therapy with TCS (using crisaborole on weekdays, and TCS on weekends, to minimize TCS-induced side effects) is a newer avenue to consider in inflammatory dermatoses. The utility of nanoparticles incorporated with crisaborole to enhance drug penetration is another prospect that can be considered. Furthermore, the application of crisaborole in treating various inflammatory dermatoses in the pediatric population needs scrupulous evaluation. Last but not the least, head-to-head comparative trials of crisaborole with TCIs and TCS are warranted to substantiate the exact position of crisaborole in the treatment algorithm of AD.

Conclusion

Crisaborole has shown to be a valuable topical agent for many dermatoses apart from AD. Due to its non-steroidal nature, it serves as a safe therapeutic option that can be continued for a longer duration. The only drawback is the high cost compared to other topical agents.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Assessment of metabolic syndrome in patients diagnosed with melasma in a dermatology service

Avaliação de síndrome metabólica em pacientes diagnosticados com melasma em um serviço de dermatologia

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Abstract

Objectives: The aim of this study was to evaluate the prevalence of metabolic syndrome (MetS) criteria in patients diagnosed with melasma. Few studies have evaluated metabolic parameters in patients with melasma, a chronic inflammatory skin condition. MetS is a complex disease represented by a set of factors related to central fat deposition and insulin resistance. There is an increased cardiovascular risk in individuals with this syndrome, and several studies seek to establish correlations between MetS and other inflammatory diseases such as psoriasis, hidradenitis suppurativa, lichen planus, vitiligo, and atopic dermatitis. **Methods:** Cross-sectional prevalence study assessing MetS in participants diagnosed with melasma between July and October 2024. **Results**: Fifty-eight women were included in the study, with a mean age of 46.7 years and a mean melasma duration of 10.5 years. 29.3% of the participants met three or more criteria for MetS. **Conclusion:** There was a considerable prevalence of MetS among the study participants. Although this association does not prove causality, it suggests the importance of considering metabolic factors in the clinical management of melasma and in the prevention of complications related to MetS.

Keywords: Melasma. Metabolic syndrome. Obesity.

Resumo

Objetivos: O objetivo deste estudo foi avaliar a prevalência dos critérios da síndrome metabólica (SM) em pacientes diagnosticados com melasma. Poucos estudos avaliaram parâmetros metabólicos em pacientes com melasma, uma condição inflamatória e crônica da pele. A SM é uma doença complexa representada por um conjunto de fatores relacionados à deposição central de gordura e resistência à insulina. Há um risco cardiovascular aumentado em indivíduos com essa síndrome, e vários estudos buscam estabelecer correlações entre a SM e outras doenças inflamatórias como psoríase, hidradenite supurativa, líquen plano, vitiligo e dermatite atópica. **Métodos:** Estudo transversal de prevalência avaliando síndrome metabólica em participantes diagnosticados com melasma entre julho e outubro de 2024. **Resultados:** 58 mulheres foram incluídas no estudo com idade média de 46,7 anos e tempo de evolução do melasma de 10,5 anos. 29,3% dos participantes apresentaram três ou mais critérios para síndrome metabólica. **Conclusão:** Houve considerável prevalência de SM entre as participantes do estudo, embora esta associação não comprove causalidade, sugere a importância de considerar os fatores metabólicos no manejo clínico do melasma e para a prevenção de complicações relacionadas à síndrome metabólica.

Palavras-chave: Melasma. Síndrome metabólica. Obesidade.

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Introduction

Melasma is a chronic, acquired pigmentation condition that predominantly affects women, accounting for 90% of cases. All ethnicities are affected, especially those with skin Types IV and V[1]. Although various factors are implicated in its pathogenesis, melasma has recently been considered a chronic inflammatory disease. The skin affected by the lesions, when compared to unaffected skin, shows significant inflammatory infiltration, epidermal atrophy, degeneration of the basal layer, solar elastosis, and disorganization of collagen fibers[1-3].

Metabolic syndrome (MetS) is a complex disorder represented by a combination of factors related to central fat deposition and insulin resistance. Individuals with this syndrome have an increased cardiovascular risk compared to the general population. Due to its growing prevalence, several studies have sought to establish correlations between MetS and other inflammatory diseases or immune-related conditions. In dermatological disorders, the presence of acanthosis nigricans, as well as diseases such as psoriasis, hidradenitis suppurativa, lichen planus, vitiligo, and atopic dermatitis, have been shown to be associated with MetS[4].

Despite the lack of an obvious correlation so far, MetS shares common pathological pathways with melasma, which is why this study aimed to assess the presence of MetS in patients with melasma.

Methods

Study design and patient selection

A cross-sectional prevalence study was conducted at the dermatology department of the University of Mogi das Cruzes between July 2024 and October 2024. A total of 58 female participants, aged over 18 years with a clinical diagnosis of melasma, were included in the study. The exclusion criteria were: (1) pregnant or postpartum women; (2) participants with edema of any nature, due to interference with body evaluation; (3) individuals with severe dermatological conditions (autoimmune, hereditary, or acquired) that could interfere with the clinical assessment of melasma. The study was approved by the Ethics Committee of the University of Mogi das Cruzes, and all patients signed the informed consent form.

Participants were assessed for age, skin phototype, duration of melasma, comorbidities, and laboratory test results, including fasting blood glucose levels, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), triglycerides (TG), glycated hemoglobin (HbA1C), and insulin levels. In addition, blood pressure, abdominal waist circumference, weight, height, and body mass index (BMI) were measured. MetS was defined according to the criteria established by the National Cholesterol Education Program = Adult Treatment Panel III[5], which includes the presence of three or more of the following components: elevated abdominal circumference (≥ 102 cm in men and ≥ 88 cm in women), elevated blood pressure (≥ 130/85 mmHg or on antihypertensive treatment), elevated TG (≥ 150 mg/dL or on treatment for hypertriglyceridemia), low HDL cholesterol levels (< 40 mg/dL in men and < 50 mg/dL in women), and elevated fasting glucose levels (≥ 100 mg/dL or on treatment for diabetes). The presence of three or more of these criteria was considered as fulfilling the criteria for MetS[5].

Statistical analysis

The exploratory data analysis included descriptive statistics, such as mean, standard deviation, median, minimum value, and maximum value for numerical variables, and frequency and proportion for categorical variables. For the analysis of continuous variables, descriptive statistics were considered, along with the Shapiro-Wilk test to assess the assumption of normality. The prevalence of MetS was analyzed using the Clopper-Pearson method (Altman, 2000), with the epiR package (Stevenson and Sergeant, 2024). Statistical analysis was performed using the R programming language (R Core Team, 2024).

Results

Clinical characteristics

The clinical characteristics of the participants are shown in table 1. The sample consisted of 58 women, with a mean age of 46.7 years and a mean melasma duration of 10.5 years. The mean levels of HDL, TG, fasting glucose, and TC were 54.9 mg/dL, 121 mg/dL, 91.8 mg/dL, and 193.2 mg/dL, respectively. The mean HbA1C was 5.4%, while the insulin levels and homeostasis model assessment of insulin resistance (HOMA-IR) were 10.9 μU/mL and 1.2, respectively. Regarding body composition, the mean BMI was 26.7, waist circumference was 87.6 cm, and the mean systolic blood pressure and diastolic blood pressure were 120.5 mmHg and 79.07 mmHg, respectively.

Table 1. Descriptive statistics of variables according to the presence or absence of metabolic syndrome

Variables	MetS negative (< 3 criteria for MetS) n = 41	MetS positive (≥ 3 criteria for MetS) n = 17
Age	45.4 ± 9.3	49.9 ± 10.0
WC	83.6 ± 10.0	97.1 ± 8.1
SBP	117.0 (95.0-130.0)	130.0 (120.0-160.0)
DPB	75.0 (63.0-100.0)	85.0 (80.0-104.0)
HDL	54.0 (44.0-109.0)	43.0 (31.0-91.0)
TG	93.0 (43.0-183.0)	196.0 (95.0-303.0)
Fasting glucose	89.0 (72.0-142.0)	100.0 (87.0-130.0)
LDL	106.0 (70.0-197.0)	118.0 (72.0-219.0)
TC	183.0 (136.0-288.0)	200.0 (142.0-307.0)
Weight	70.8 ± 10.7	78.9 ± 11.1
Height	1.63 ± 0.06	1.61 ± 0.08
BMI	26.1 ± 3.1	29.7 ± 2.7
HBA1C	5.4 (4.7-6.7)	5.7 (5.1-5.8)
Insulin	8.88 ± 4.85	18.87 ± 9.97
HOMA-IR	1.5 (0.6-4.8)	2.6 (2.3-9.3)
Evolution time of melasma	6.0 (1.0-28)	5.0 (2.0-30.0)
Skin phototype II	11 (27)	2 (12)
Skin phototype III	17 (41)	8 (47)
Skin phototype IV	12 (29)	7 (41)
Skin phototype V	1 (2)	0 (0)

WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; TG: triglycerides; LDL: low-density lipoprotein; TC: total cholesterol; BMI: body mass index; HbA1c: glycated hemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance. Continuous variables are described as mean ± standard deviation or median (minimum-maximum); categorical variables are described as number (percentage).

Components of metabolic syndrome

The estimated prevalence of MetS was 29.3%, with a standard error of 0.0598. The 95% confidence interval, ranged from 19.2% (lower limit) to 42.0% (upper limit).

Discussion

Few studies have assessed metabolic parameters in patients with melasma. In the study by Karaali[6], which compared 51 patients with melasma to 44 patients without the condition, MetS was more frequent in patients with melasma compared to the control group, although the author did not find statistical significance in his study. In our prevalence assessment, 29.3% of the participants had three or more criteria for MetS, however, 74% of the evaluated participants were overweight or obese, 53.4% had a waist circumference ≥ 88 cm, 18.9% presented altered fasting glucose and 25.8% alterations in HbA1c levels.

Ghassemi et al.[7] in a case-control study evaluating the lipid profile and fatty liver in patients with melasma, found significantly higher LDL levels (104.23 ± 25.00 mg/dL) in patients with melasma compared to the control group (89.85 ± 23.00 mg/dL, p = 0.020). In our assessment, the median fLDL was 106 mg/dL among patients without MetS and 118 mg/dL among patients with MetS. Regarding other lipid parameters, 39.6% of women had HDL levels < 50 mg/dL and 24.3% had TG > 150 mg/dL. A common pathway between MetS and melasma is the WNT signaling pathway, which plays a crucial role in various biological processes in the body. In MetS, studies have explored its relationship with body mass regulation, glucose metabolism, lipogenesis, and LDL clearance[8-10]. In melasma, the activation of the WNT receptor leads to the stabilization of β-catenin, which is translocated to the cell nucleus where it binds to transcription factors such as microphthalmia-associated transcription factor (MITF), stimulating the expression of genes involved in melanogenesis. Studies have also shown that the inhibitory factor of this pathway, known as Wnt-1 (WIF-1), is reduced in the skin affected by melasma. The negative regulation of WIF-1 promotes melanosome transfer, along with the expression of MITF and tyrosinase through the positive regulation of the WNT signaling pathway[10,11].

In obese patients, studies have observed higher rates of melanogenesis[12] and elevated levels of α-melanocyte-stimulating hormone, which binds to the melanocortin 1 receptor on human adipocytes and stimulates melanogenesis[13]. Moreover, adipose tissue is a key site for the peripheral production and metabolism of estrogens in women[14], and this hormone plays a role in the pathogenesis of melasma due to its effects on the skin through receptors, especially the ER2 receptor, which directly stimulates melanogenesis[3].

Regarding MetS, the most widely accepted theory of its pathophysiology is insulin resistance, in which an increase in adipose tissue plays an important role[4,15]. The accumulation of fat in MetS, along with the progressive development of insulin resistance, induces a cascade of hormonal changes. As such, when it comes to skin diseases, it is known that

conditions influenced by these changes, such as acne and androgenetic alopecia, may experience clinical worsening[4]. Although we did not find a significant difference, the group of participants with MetS had higher levels of insulin (18.87 ± 9.97) and HOMA-IR: 2.6 (2.3-9.3) compared to those who did not meet all the criteria for MetS. Regarding the evolution time of melasma in participants with MetS versus without MetS, the median melasma evolution time was 5 years (ranging from 2 to 30 years) and 6 years (ranging from 1 to 28 years), respectively, and there was no statistically significant difference between the two groups (p = 0.738). Similarly, the median age was 44 years (27-68 years) and 47 years (34-68 years) among patients without and with MetS (p = 0.139).

Thus, although there is no clear correlation between the two diseases, several common mechanisms are present in both conditions. Understanding these mechanisms and the potential associations of melasma with other conditions opens new perspectives for the development of more effective therapies for its treatment.

Conclusion

Despite the methodological limitations in a cross-sectional study with a limited sample size, the results demonstrate a considerable prevalence of MetS among the participants. This prevalence justifies the need for prospective studies with control groups to investigate causality and the mechanisms involved in this association. Although this association does not prove causality, it suggests the importance of considering metabolic factors in the clinical management of melasma and in the prevention of complications related to MetS.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Wound management and dressing selection in Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review

Manejo de feridas e seleção de curativos na síndrome de Stevens-Johnson e necrólise epidérmica tóxica: uma revisão sistemática

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Abstract

Objectives: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions, which lead to epidermal detachment and may be life-threatening. Apart from supportive and systemic treatment of the disease, appropriate dressing and wound management are essential for the care of patients with SJS/TEN. This study aims to assess which are the most used dressings for SJS/TEN, and how wound management can contribute to skin healing. **Methods:** Searches were performed in Cochrane Library, Embase, MEDLINE, and PubMed databases, using the following search terms: (SJS OR TEN) AND (Wounds OR Dressings). Information extracted on dressings was used as well as local care (including materials for cleansing, debridement, topical therapy, fixation, and time for dressing changing) and time for re-epithelialization. **Results:** A total of 17 articles published in the last 11 years were selected. Six (35.3%) mentioned silver-based topical therapies as treatment of choice. Allografts and porcine xenografts were cited by a further 6 (35.3%) studies, biosynthetic dressings with a combination of collagen mesh and silicone by 4 (23.5%), petrolatum-based products by 4 (23.5%), and patient's own detached skin as a biological dressing by 2 (11.8%) studies. **Conclusion:** Upon analysis of collected data, it was noted that little information is available on topical treatment in SJS and TEN, with no consensus on an ideal protocol for such cases. Therefore, dressing management for these disorders remains a challenge in care, and further research on this subject should be encouraged.

Keywords: Wounds. Stevens-Johnson syndrome. Toxic epidermal necrolysis. Dressings.

Resumo

Objetivos: A síndrome de Stevens-Johnson (SSJ) e a necrólise epidérmica tóxica (NET) são reações adversas cutâneas graves a medicamentos, que levam ao descolamento epidérmico e podem ser fatais. Além do tratamento de base, os cuidados locais e a seleção dos tratamentos tópicos/pensos são essenciais para o cuidado de pacientes com SSJ/NET. E objetivo e avaliar os diferentes cuidados locais e tipos de pensos mais utilizados na SSJ/NET e o seu contributo para a reepitelização nessas doenças. **Métodos:** Foram realizadas pesquisas nas bases de dados Cochrane Library, Embase, MEDLINE e PubMed, usando os seguintes termos de busca: (SJS OR TEN) AND (Wounds OR Dressings). Foram extraídas informações sobre os

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pensos utilizados bem como os cuidados locais (materiais usados para limpeza, desbridamento, terapia tópica, fixação e tempo para troca de curativo) e sua relação com a reepitelização. **Resultados:** Foram selecionados 17 artigos publicados nos últimos 11 anos. Seis (35.3%) estudos mencionaram terapias tópicas à base de pensos impregnados de prata como tratamento de escolha. Aloenxertos e xenoenxertos porcinos foram citados em 6 (35.3%) estudos, curativos biossintéticos com combinação de malha de colágeno e silicone foram citados por 4 (23.5%), produtos à base de vaselina por 4 (23.5%), e a própria pele destacada como curativo biológico por 2 (11.8%) estudos. **Conclusão:** Após a análise dos dados coletados, verificou-se que há pouca informação disponível sobre o tratamento tópico em SSJ e NET, não havendo consenso sobre um protocolo ideal para tais casos. Portanto, os cuidados locais continuam um desafio, devendo ser encorajadas mais pesquisas sobre esse assunto.

Palavras-chave: Feridas. Síndrome de Stevens-Johnson. Necrólise epidérmica tóxica. Curativos.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (NET) belong to the same disease spectrum of a severe and acute drug reaction, with epidermal necrolysis and detachment, skin blistering, cutaneous and mucosal erosions, and, commonly, systemic involvement[1-3]. The distinction between SJS and TEN depends on the percentage of detached skin surface (up to 10% in SJS, more than 30% in TEN, and between 10 and 30% in SJS/TN overlap)[1,2]. Annual incidence varies between 1.2 and 9.2 cases/million people for SJS, and 0.4-1.9/million for TEN[4,5], with a mean mortality of 30%[1,3].

Epidermal loss may affect response to infections, termo-regulation, and hydroelectrolytic balance. Despite different pathophysiologies and the need for timely suspension of the possible culprit and use of systemic immunomodulatory or immunosuppressant drugs, skin involvement may be viewed as a severe superficial but extensive burn[4,5]. A cornerstone of treatment lies in the proper care of denuded skin, to improve its protective activity, reduce pain, accelerate re-epithelialization, and, therefore, reduce time to complete healing and decrease the main complications, namely the risk of infection and sepsis, the predominant cause of death. An appropriate choice of the dressing and its correct use are essential, although this aspect is often overlooked[1,3].

The main objective of the current systematic review is to assess the most frequently used local skin cleansing measures for SJS/TEN and, especially, wound dressings, the way they were used, and their advantages.

Methods

For this systematic review, searches were performed in Cochrane Library, Embase, MEDLINE, and PubMed databases, with the following search terms: (SJS OR NET) AND (Wounds OR Dressings). Articles published in the last 11 years were selected (from 01 January 2013 to 31 December 2024). Inclusion criteria were: articles on the subject of SJS/TEN and dressings; articles that described dressings used; and articles published in English, Spanish, or Portuguese (Fig. 1). Meta-analysis, systematic review, cohort, and case-control articles were included in the current review. Exclusion criteria adopted were: articles focusing on treatment of SJS/TEN solely on mucosal membranes (as opposed to skin), and articles that did not directly address SJS/TEN.

Three independent researchers carried out searches and all articles filtered in the four databases were then initially selected based on their titles identifying whether they meet the inclusion criteria. No automation tools were used in this review. After the exclusion of duplicate studies, abstracts were critically appraised by three independent reviewers, to choose which articles would be fully read. Reference lists of selected articles were also evaluated, looking for other eligible works. Selected articles were then assessed regarding the risk of bias, using Joanna Briggs Institute (JBI) Critical Appraisal Tools[6], by two independent researchers. When these two researchers assigned different gradings for the same article, a third researcher proceeded to evaluate that article, and the two most similar evaluations were considered. A different version of the JBI Critical Appraisal Tool was used according to the category of each study: cross-sectional, case-control, cohort, review, or systematic review. This tool is constituted by 6-11 questions (which vary for each type of study) assessing the risk of bias. For each single article, the obtained score was divided by the maximum possible score to establish its grade (for instance, if six out of eight questions were answered positively for a study, its final score was 0.75). The study was then

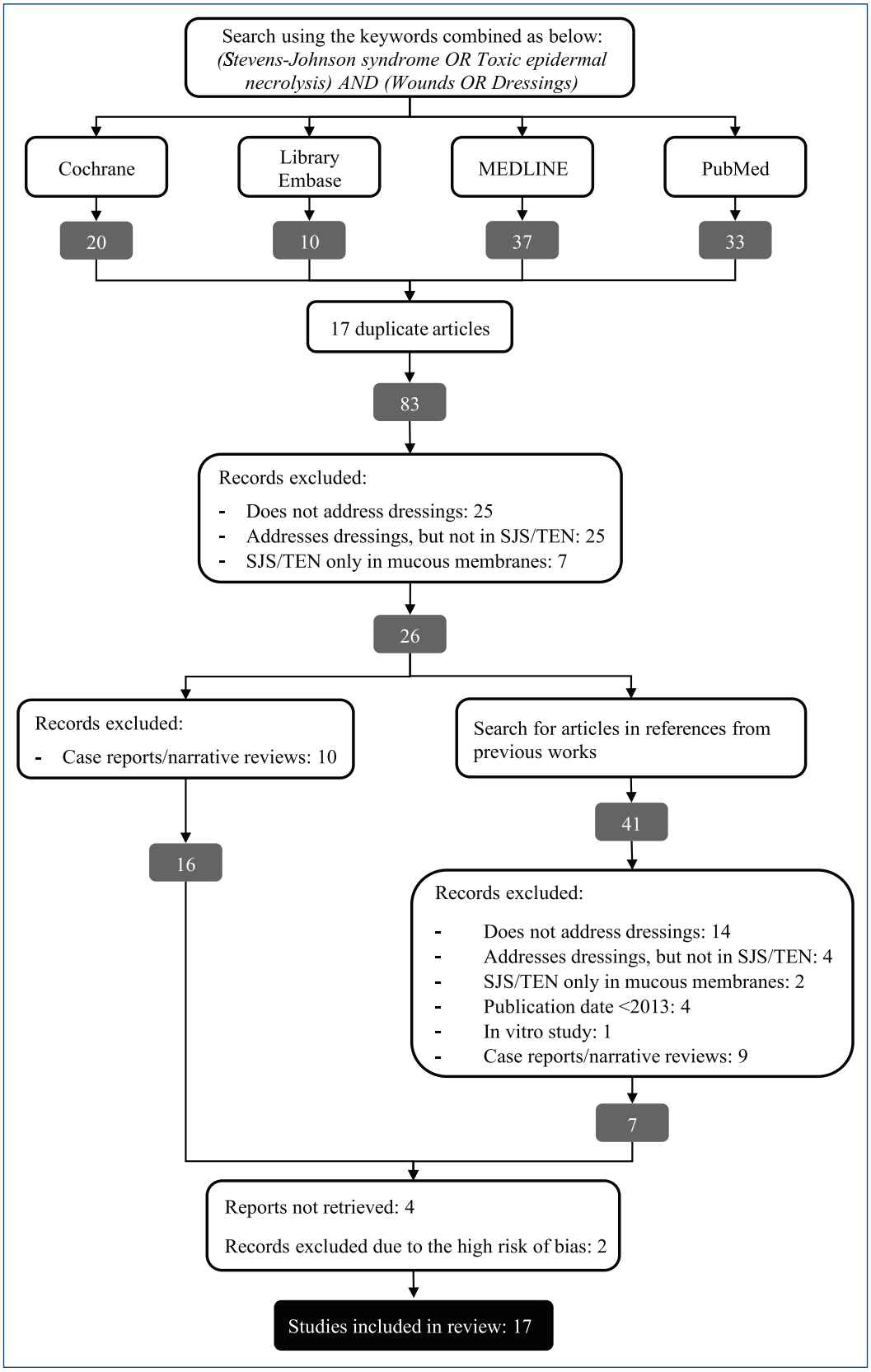

Figure 1. Flowchart for selection of studies for systematic review.

classified as high (score < 0.50), moderate (score 0.51-0.70), or low (score > 0.71) risk of bias. Articles deemed as with a high risk of bias were then excluded from this review.

Three independent authors extracted general data for each study (title, publication year, study type, name of first authors, name of journal), as well as data on study participants (mean age of patients, gender, comorbidities, nutritional status, mortality, affected body surface area, systemic treatments used, and pain assessment) and on dressings (what was used for cleansing, debridement, topical therapy/dressings and their fixation; frequency of dressing changes and time until re-epithelialization). When some of the data was not identified, it was considered "not applicable" or "not available." All data were collected in a descriptive way, given the high frequency of incomplete information.

Extracted data were aggregated into different topics, in the structure of a narrative synthesis, focusing mainly on dressings. Results obtained from studies were also aggregated and shown as tables.

The current review has passed through PROSPERO system[7] and is registered under number CRD42023483491. Moreover, it followed PRISMA guidelines[8] for its construction.

Results

Upon preparation of this systematic review, 100 articles were initially identified, out of which 17 were duplicates, and 67 did not meet the inclusion criteria. The remaining 16 articles had their reference lists searched through to find other eligible studies (41 additional articles). However, 34 out of the additional articles did not meet the inclusion criteria, and only the remaining seven were added to the 16 originals, totaling 23 articles. Out of these, four were excluded because they were not available in full, even after trying to contact authors and editors through email. Two further manuscripts were excluded because of assigned grades lower than 0.50 in JBI Critical Appraisal Tools. Ultimately, there were 17 remaining articles to be included in this systematic review (Fig. 2).

The 17 articles included five case-control studies, three systematic reviews, six expert consensus, two literature reviews, and one meta-analysis. General data for each study, including demographic/epidemiological data and systemic treatments used or recommended are displayed in table 1 and henceforth described.

General data

Out of the 17 articles included in this review, seven described the age and sex of participants (54.6% women and a mean age of 53.03 years)[9-13]. Only six articles reported the average percentage of body surface affected (BSA) in the participants, with an overall average of 52.51% BSA across these articles.

Most often mentioned comorbidities in studies were systemic arterial hypertension, epilepsy, and diabetes mellitus corroborating anticonvulsant drugs as common culprits in the pathogenesis of SJS/TEN[11].

In agreement with the lack of consensus on the best systemic treatment for SJS/TEN the majority of patients in these studies received either IVIG[4,11-15] or systemic corticosteroids[9,11,14], followed by ciclosporin[4,12,14,15]. Nutritional status, which is of utmost importance in this disease, was not commonly addressed. Nutritional therapy after hospital admission with oral or enteral feeding was frequently used, with one study reporting a daily caloric goal of 20-25 kcal/kg during the early catabolic phase and 25-30 kcal/kg during the recovery anabolic phase[16].

The next topics encompass each of the steps involved in wound management and dressing: cleansing, debridement, topical therapy, dressings, and their fixation, frequency of changes, time for re-epithelialization, pain assessment, and mortality. Data regarding employed or recommended dressings are displayed in table 2.

Cleansing

Cleansing consists of the removal of debris, foreign bodies, and sources of infection through applying solutions such as water, saline, and antibacterial solutions, among others[2]. Out of the 17 articles included in this review, 12 (70.6%) did not mention wound cleansing[4,10,11,13,15,17,18-22]. Among the others, all five reported or recommended cleansing with chlorhexidine[9,12,14,16,23], whereas two also recommended distilled water[14,16], and three saline solution[14,16,23].

Debridement

Debridement, comprising strategies intended for the removal of devitalized necrotic tissues that could impair healing and cause secondary infections, is not a consensual therapy, as shown in a systematic review concluded in 2020[23]. Out of the 17 selected articles for the current review, 10 (58.8%) did not detail if debridement was performed[4,10,13,14,16-19,21,22]. In total, 6 (35.3%)

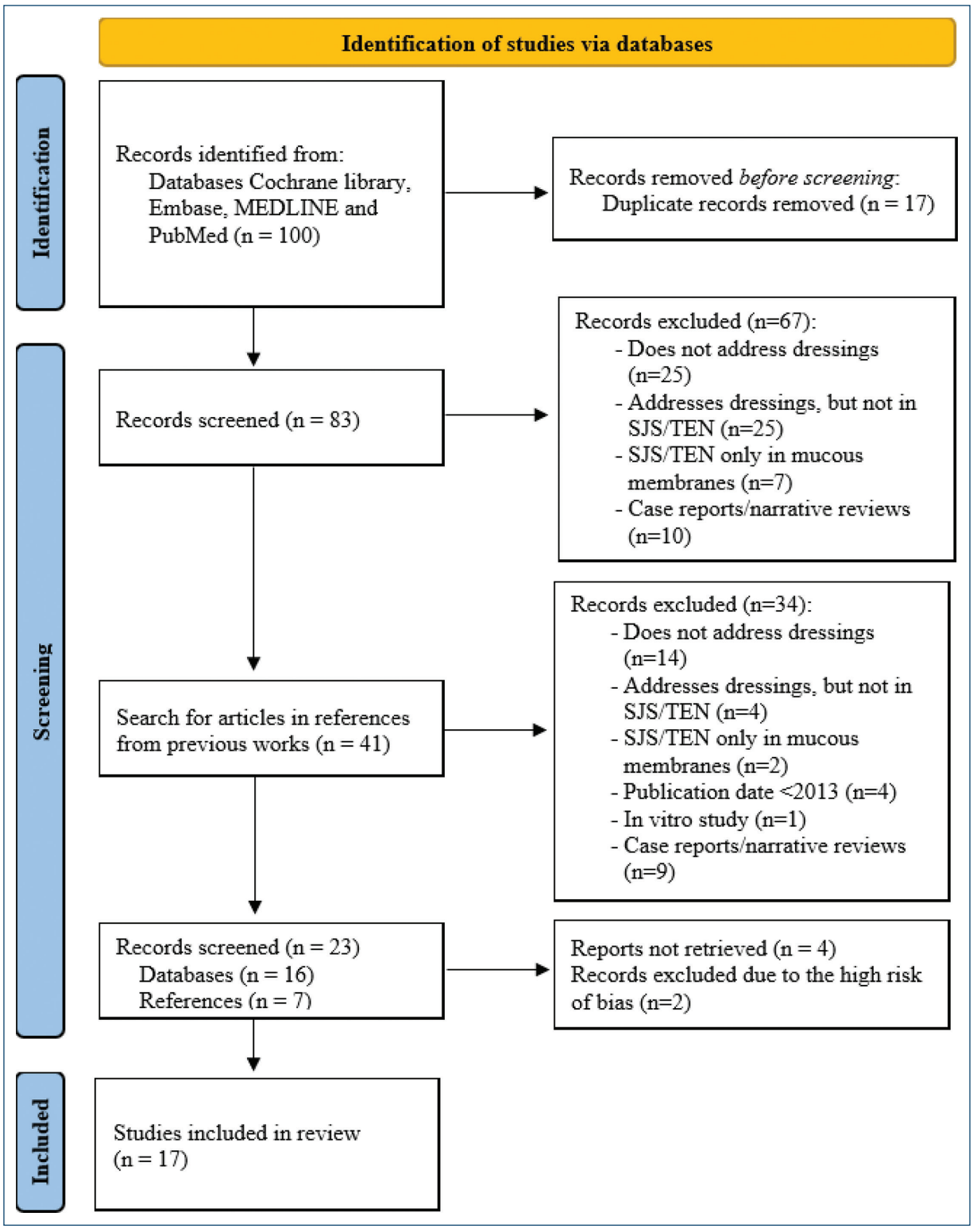

Figure 2. The systematic review on dressings in SJS/TEN.

studies opted for mechanical or surgical debridement, mostly in an operating room or under sedation upon arrival in the reference center, manually or with surgical gauzes and brushes[12,20,22]. Other types of debridement have been cited such as in hydrotherapy rooms (with or without sedation) or hydrosurgery[16]. An expert consensus published in 2016 in the Journal of the American Academy of Dermatology[24], found that 67.7% of experts

Table 1. General data of studies included in a systematic review on dressings in SJS/TEN

Reference	Study design	Mean age (years)	Participants, by gender	Comorbidities (n)	Nutritional status	Mean BSA (%)	Systemic treatment (% of individuals/ studies)	Mortality (%)
Schwartz et al.[17]	Expert consensus	NA	NA	NA	NA	NA	No level of evidence for any systemic treatment	NA
Mahar et al.[9]	Systematic review	46.8	291F/218M	Nd	Nd	All > 30%	IVIG (40%); SCS (30%); fluid replacement with albumin (35%)	30
Huang et al.[10]	Case-control	59.5	10F/10M	Nd	Nd	55.2% (30-85%)	Nd	5
Dodiuk-Gad et al.[18]	Multicentric – Expert consensus	NA	NA	NA	NA	NA	Most used IVIG, SCS, ciclosporin, anti-TNF.	NA
Young et al.[11]	Case-control	52	19 F / 5 M	SAH (18), smoking (7), hyperlipidemia (6), CAD (3), CHF (4), DM (6), seizures (4)	Nd	63%	IVIG (79.17%), SCS (29.17%)	12.5
Creamer et al.[16]	Guidelines	NA	NA	NA	Daily intake of 20-25 kcal/kg (early catabolic phase); 25-30 kcal/kg (recovery anabolic phase)	NA	Mainly supportive care + causative drug withdrawal	NA
Curtis et al.[24]	Expert consensus	NA	NA	NA	NA	NA	IVIG, ciclosporin	NA
Wolkenstein and Wilson[19]	Expert consensus	NA	NA	NA	NA	NA	No consensus. Most used IVIG, ciclosporin	NA
Cartotto[20]	Literature review	NA	NA	NA	NA	NA	No consensus. Most evidence support IVIG, ciclosporin	NA
Rogers et al.[12]	Case-control	59.5	26F/16 M	Nd	Nd	30% (10%-40%)	IVIG, ciclosporin, etanercept	Nd
Paggiaro et al.[13]	Systematic review	37.3	14 F/6 M	Nd	Nd	73.9% (45%-90%)	IVIG (75%)	10
Castillo et al.[4]	Literature review	NA	NA	NA	NA	NA	SCS, IVIG	10.8

(*Continues*)

Table 1. General data of studies included in a systematic review on dressings in SJS/TEN *(continued)*

Reference	Study design	Mean age (years)	Participants, by gender	Comorbidities (n)	Nutritional status	Mean BSA (%)	Systemic treatment (% of individuals/ studies)	Mortality (%)
Richard et al.[14]	Multicentric – Expert consensus	NA	NA	NA	NA	NA	IVIG (41.9%), SCS (9.7%), ciclosporin (6.5%), plasmapheresis (3.2%)	NA
Jaller et al.[23]	Systematic review	NA	NA	NA	NA	NA	Nd	NA
Lee et al.[15]	Meta analysis	51.8	100 F/127 M	NA	NA	NA	IVIG, ciclosporin	29.1
Dastagir et al.[21]	Case-control	66.3	NA	Nd	Nd	NA	Nd	19

n: number of individuals; NA: not applicable; Nd: not described; BSA: body surface area; F: female; M: male; IVIG: intravenous immunoglobulin; SCS: systemic corticosteroids; TNF: tumor necrosis factor; G-CSF: granulocyte colony-stimulating factor; CRP: C-reactive protein; DM: diabetes mellitus; SAH: systemic arterial hypertension; CAD: coronary arterial disease; CHF: congestive heart failure; SLE: systemic lupus erythematosus; CKD: chronic kidney disease; AF: atrial fibrillation atrial; MM: multiple myeloma; HCV: hepatitis C virus; COPD: chronic obstructive pulmonary disease.

did not perform debridement, and another systematic review concerning burn centers published in 2014[9], found that only 13 out of 20 selected studies mentioned debridement, with 9 (69.3%) in favor of routine active debridement and 4 (30.7%) indicating not do debride detached epidermis. A 2024 meta-analysis evaluating surgical debridement compared to the use of a bandage alone found no difference in mortality, but there was a significantly shorter re-epithelialization time in the group without debridement[15].

Topical therapies

Topical therapy represents the dressing itself or topical pharmacologic agents applied directly on the wound surface. Dressings described for SJS/TEN varied from petrolatum-impregnated gauzes to silver-containing dressings, silicone foams, collagen dressings (not specifying the subtype of collagen), porcine xenografts, among others[23]. Most studies report silver-based dressings (mostly silver-impregnated meshes), followed by biosynthetic membranes, and by xenografts or allografts.

Topical therapies were variable among studies, with no consensus on which is the best. In a systematic review made in 2020[23], high-potency topical corticosteroids were recommended in areas of erythematous skin not yet detached, and topical antimicrobials (not designating which one) or silver-impregnated dressings (also not designating which one) in areas of detached skin. Other mentioned dressings were biosynthetic skin substitutes with porcine collagen and cryopreserved cadaveric allografts or porcine xenografts for areas with epidermal detachment. For detached areas, British guidelines[16] recommend a first layer of dressing with a non-adhering material, such as PHMB-impregnated non-adhering gauze or silicone mesh, and a foam or other absorbing dressing as a second layer. Another systematic review, published in 2014[9], indicates silver nitrate-impregnated dressings as the most used, followed by synthetic skin substitutes, porcine xenograft, absorbing gauze, cadaveric allograft, emollient ointments and aqueous creams (not specified).

In 6 (35.3%) selected studies, silver-based topical therapies are mentioned as the treatment of choice, varying from silver ointments/creams to silver-impregnated foams, gauzes, or meshes[4,10,11,16,18,24]. In 5 (29.4%) there are no further details on the chosen silver-based dressing[11,16,18,24], and in 2 (11.8%) studies silver-impregnated hydrofiber foam was chosen[4,10]. A 2016 expert consensus[19] advised caution when using silver-impregnated dressings over large areas, due to the risk of increased

Table 2. Specific data on most used dressings for SJS/TEN in included studies

Reference	Study design	Materials/techniques used for dressings				Frequency of dressing changes	Time until re-epitheliazation	Pain scale
		Cleansing	Debridement	Topical therapy (% of use/ citations)	Fixation			
Schwartz et al.[17]	Expert consensus	Nd	Nd	Paraffin gauzes, porcine xenografts, human allografts, biosynthetic skin substitutes with porcine collagen	Nd	Nd	Nd	Nd
Mahar et al.[9]	Systematic review	Chlorhexidine (1)	Routine active debridement (9/20 studies)	Aseptic dressings (5%), silver nitrate-impregnated (10%), synthetic skin substitutes (20%), porcine xenograft (10%), absorbent gauze (5%), cadaveric/porcine graft (5%), emulsifying ointment/ aqueous cream (5%), and silver sulfadiazine (10%)	Nd	Cadaveric or porcine graft changed daily (1)	Nd	Nd
Huang et al.[10]	Case–control	Nd	Nd	Silver-containing hydrofiber and petrolatum gauze versus silver sulfadiazine	Nd	Case versus control twice weekly versus daily	Case versus control group: 16.75 versus 17.50 days (not significant)	Hydrofiber group; lower pain scores
Dodiuk-Gad et al.[18]	Multicentre – Expert consensus	Nd	Nd	Silver-impregnated dressings, synthetic dressings, topical antimicrobials, bioactive skin substitutes	Nd	Nd	Nd	Nd
Young et al.[11]	Case–control	Nd	Hydrotherapy + sedation	Porcine xenograft versus silver-impregnated dressing	Nd	Nd	Nd	Pain score 2.8 versus 6
Creamer et al.[16]	Guidelines	Warmed sterile water, saline, or chlorhexidine	if infected or necrotic areas hydrosurgery or antimicrobials (iodopovidone or chlorhexidine)	Greasy emollient (50:50 white soft paraffin/liquid paraffin) + topical antimicrobial + non-adherent dressing. Detached areas: non-adherent dressings + secondary foam or synthetic membranes or allograft/ xenograft	Nd	Nd	Nd	Nd
Curtis et al.[24]	Expert consensus	Nd	Most no debridement	Petrolatum gauze; silver-containing non-adherent dressings	Nd	Nd	Nd	Nd
Wolkenstein andWilson[19]	Expert consensus	Nd	Nd	Detached skin as biologic dressing. Caution with silver-impregnated dressings in large areas	Nd	Nd	Nd	Nd
Cartotto[20]	Literature review	Nd	Routine removal of remaining epidermis	Porcine xenograft or cadaveric allograft or biosynthetic skin substitute + antimicrobial secondary dressing	Fixation staples	Nd	12-14 days	Nd

(*Continues*)

Table 2. Specific data on most used dressings for SJS/TEN in included studies *(continued)*

Reference	Study design	Materials/techniques used for dressings				Frequency of dressing changes	Time until re-epitheliazation	Pain scale
		Cleansing	Debridement	Topical therapy (% of use/ citations)	Fixation			
Rogers et al.[12]	Case–control	Soap and chlorhexidine upon admission	Mechanic debridement upon admission	Biosynthetic membrane with porcine collagen +, followed by antimicrobial mesh with nanocrystalline silver versus petrolatum ointment or silver-based dressing or greasy tulle gauze	Nd	silver-containing screen 48-72 h. Control group: Nd.	13 versus 12 days	Nd
Paggiaro et al.[13]	Systematic review	Nd	Nd	Xenograft / cadaveric allograft / amniotic membrane	Nd	Nd	Nd	Nd
Castillo et al.[4]	Narrative review	Nd	Nd	Biosynthetic dressings versus silver-impregnated fibers	Nd	weekly on average	14.16 ± 9.42 days	Biosynthetic dressings improved comfort (5/22 studies)
Richard et al.[14]	Multicentre Expert consensus	Diluted chlorhexidine (51.6%), water (22.6%), saline (12.9%), other (12.9%)	Nd	Topical antibiotics (58.1%), whirlpool baths (12.9%), topical corticosteroids (6.5%), silver foam (48.4%), biologic skin substitutes (45.2%), nanocrystalline silver mesh (32.3%), petrolatum gauze (29%), silver sulfadiazine (12.9%), and non-adherent gauze with PHMB (6.5%)	Nd	Daily (41.9%), every 3 days (22.6%), 2 days (6.5%), weekly (6,5%)	Nd	Nd
Jaller et al.[23]	Systematic review	Warm sterile water, saline, or diluted chlorhexidine (1:5000)	No consensus on surgical debridement	High-potency topical corticosteroids in non-detached skin. Topical antimicrobials or silver-impregnated dressings on denuded areas, biosynthetic skin substitutes, cryopreserved cadaveric allografts, or porcine xenografts	Nd	Depending on dressing from daily to every 7-14 days	12.5 days (biosynthetic skin with collagen versus 16 days for debridement	Nd
Lee et al.[15]	Meta analysis	Nd	Nd	Nd	Nd	Nd	17 (debridement) versus 14 days (dressing)	Nd
Dastagir et al.[21]	Case–control	Nd	Surgical	Nd	Nd	Nd	Nd	Nd
Enescu et al.[22]	Case–control	Nd	Hydrotherapeutic blister debridement (maximum of 10% BSA)	Suprathel® versus polyhexanide gel	Nd	No exchange versus daily	Nd	Nd

Nd: not described; PHMB: polyhexamethylene biguanide; BSA: body surface area.

silver absorption on detached epidermis with systemic complications in debilitated patients.

Biosynthetic dressings with a combination of collagen mesh and silicone were frequently cited in 4 (23.5%) recent studies, as they require no changes, reduce pain, and increase comfort, allowing a similar, or even shorter, re-epithelialization time when compared to traditional topical therapies[12,16,17,20].

Six (35.3%) articles mentioned the use of allografts and porcine xenografts, which are used as skin substitutes on non-infected detached epidermis, and generally do not need frequent changes[11,16,17,20]. A further option is the use of the patient's own detached epidermis as a biological dressing, a possibility mentioned by 2 (11.8%) articles: the UK guidelines and an expert consensus[16,19].

Petrolatum-based products are still often employed, as mentioned in 4 (23.5%) studies, but more commonly as emollients in areas where the skin is not yet detached[16,17,20,24]. Nevertheless, petrolatum is being progressively replaced with previously mentioned therapies. The application of petrolatum-impregnated gauzes (as a means to keep the wound moist, facilitate dressing change, and reduce pain) has not been shown to be statistically significantly beneficial over other topical therapies[10].

Fixation

Dressing fixation in SJS/TEN is an important step and should ideally be non-adhering and not cause damage to the skin[23], as the skin is fragile, and inadequate fixation may worsen the area of epidermal detachment and pain. The primary dressing, i.e., the one that is in direct contact with the wound, may or may not need to be covered by a secondary dressing. Despite its importance, out of the 17 articles in this review, 14 (82.3%) did not mention fixation at all[4,9,10,12-24], or described the use of gauzes for fixation[11,21].

Dressing change frequency

The frequency of wound dress changing was variable for each dressing. Biosynthetic skin substitutes, allografts, and xenografts usually do not require changing[12,20]. Some studies[9,21] performed daily changes, notably if there was facial epidermal detachment. However, patient discomfort is reportedly greater, when cleansing and dressing changes are more frequent. Silver-impregnated dressings were left in place for a longer interval, with changes varying from every 2 to 7 days[4,10]. In a 2018 expert consensus[14], the ideal change interval was also diverse among experts, with changes daily, every 2 or 3 days, or weekly, respectively, in 41.9%, 6.5%, 22.6%, and 6.5% weekly, and 22.6% in alternative periods.

Re-epithelialization

Time until total re-epithelialization was not mentioned in 11 (64.7%) of the selected studies[9,13,16-19,21,22,24]. On average, the time until re-epithelialization was lower than 2 weeks, regardless of the topical therapy used[4,12,20]. A 2020 systematic review[23] reported re-epithelialization time to be shorter when using a biosynthetic skin substitute with porcine collagen, with an average of 12.5 days, compared to 16 days when using paraffin gauzes with daily changes.

Mortality

Few articles associate the choice of topical therapy for SJS/TEN with mortality rates. Among selected studies, 11 (64.7%) did not mention mortality[12,14,16-20,22-24]. In the remainder, mortality was < 30% of cases, with no reduced mortality reported for any specific dressing[4,9,10,11,13,15,21].

Pain assessment

Thirteen (76.5%) studies did not mention whether a pain scale was used[9,12-14,16-20,23,24], and few studies related it to the wound dressing choice. A pain Visual Analog Scale was used to compare groups with distinct silver-based therapies in a 2014 case–control study[10]. The group using silver hydrofiber scored significantly ($p = 0.02$) better on this scale (5.75/10, standard-deviation 1.39) than the group using silver sulfadiazine (7.42/10, standard-deviation 1.31), probably as a result of decreased need of manipulation and dressing changes in the silver hydrofiber group. A 2016 case–control study[11] compared patients with porcine xenografts to patients with silver-impregnated dressings and found pain to be considerably lower for the first group (2.8 vs. 6/10 points). Another systematic review published in 2018[4] found, in five out of 22 articles that cite pain assessment, that biosynthetic dressings result in better comfort, although without altering healing time.

Discussion

The percentage of epidermal detachment in SJS/TEN has a direct relationship with mortality and worse prognosis, therefore a fundamental part of care in SJS/TEN includes local wound management and use of

proper dressings[23]. An ideal dressing should be comfortable for the patient and protect denuded skin from secondary infections, hypothermia, or fluid loss, reduce pain, avoid expansion of detachment, and promote re-epithelization[1]. Dressing change may be performed in an operative setting, under general anesthesia, considering the extreme pain[1]. It is recommended that care of SJS/TEN patients be done, whenever possible, in specialized centers or burn units, but there are no specific guidelines for dressing application and there is a great deal of variability in topical therapies used in all steps of wound care in these conditions[14].

The current systematic review highlights that there is still no established consensus on wound management in patients with SJS/TEN, especially when regarding the choice of proper dressing. A range of different dressings have been used, such as silver-based dressings, biosynthetic membranes, xenografts, allografts, and the patient's own detached skin (which may be kept in place and used as a biologic dressing). High variability in care reflects the lack of standardized guidelines and differentiation of treatment according to each center and the patient's individual characteristics.

Silver-impregnated dressings are commonly employed due to antimicrobial properties, but attention should be given to risks of systemic absorption and adverse effects, notably if used in extensive areas[19]. Biosynthetic dressings and xenografts have shown advantages regarding patient comfort, pain reduction, and need for less frequent dressing changes, and may favor re-epithelization and decrease infection risk, but scientific evidence is still scarce and unable to infer superiority for any specific class of dressing[11-13,16,17,20].

This review highlights priorities for future research in this area. There appears to be little information regarding the importance of topical treatments in SJS/TEN. Consequently, choosing the best dressing for these diseases remains a challenge. There are several options in medical literature for each step of wound management but it is not clear what initial measures should be taken by doctors and healthcare teams when admitting patients with SJS/TEN, or what subsequent measures and dressings should be performed. There was likewise no conclusion on the best way of wound cleansing and/or fixation, and whether debridement should or not be performed.

In view of this, there is a clear need for clinical trials to directly compare different available topical therapies to establish protocols that optimize clinical outcomes, decrease mortality, and improve the quality of life in patients with SJS/TEN. Until then, an individualized and multidisciplinary approach remains the most suitable means of managing these severe and potentially lethal diseases.

Our study has some strengths – it provides an updated review of an important subject for which there is a scarcity of data published in medical literature. This study, however, also has several limitations. An important one is the overall small number of studies included. Furthermore, there is a lack of studies with a higher level of evidence–for instance, there was no randomized clinical trial available that would fulfill the inclusion criteria. Another limitation is the heterogeneity of articles–different designs such as case-control studies and guidelines, for instance, do not allow direct comparison among selected studies.

Conclusion

Regarding topical therapies in the management of SJS/TEN patients, the most used dressings were silver-containing ones, followed by synthetic membranes and allografts or xenografts. However, despite miscellaneous therapeutic options, there is no consensus on an ideal protocol for SJS/TEN patients. More powerful study designs are needed to methodologically assess which are the best topical therapies in practice. In this way, considering that wound management is essential for proper healing and reduction of morbidity and mortality in SJS/TEN, further research on this subject is highly needed.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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Port J Dermatol and Venereol. **ORIGINAL ARTICLE**

Kaposi's sarcoma: a 15-year retrospective study in a Portuguese hospital

Sarcoma de Kaposi: um estudo retrospetivo de 15 anos num hospital português

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Abstract

Objectives: To characterize the demographic and clinical aspects and describe the therapeutic approaches used in patients with Kaposi's sarcoma at Hospital Garcia de Orta. **Methods:** A retrospective, descriptive, and observational study that included patients with a histological diagnosis of Kaposi's sarcoma at Hospital Garcia de Orta between March 2009 and March 2024. **Results:** A total of 55 patients were included, 43 males and 12 females, with an average age at diagnosis of 63.55 years. The majority of patients (67.3%) had lesions in a single anatomical location, mainly in the lower limbs. The most frequently observed subtype was classic (38.2%), followed by epidemic (36.4%), endemic (23.6%) and, finally, iatrogenic (1.8%). The time from symptom onset to diagnosis was longer in the endemic subtype (40.78 months). The epidemic subtype had the highest proportion of patients with systemic involvement (55%). The majority of patients (56.4%) underwent monotherapy. There was heterogeneity in the therapeutic modalities used. **Conclusion:** This study highlights there is still a considerable delay in diagnosis, underlines the evolving demographic characteristics of the disease, and emphasizes the importance of adapting treatment to the subtype and extent of the disease.

Keywords: Kaposi's sarcoma. Classification. HIV. Human herpesvirus 8.

Resumo

Objetivos: Caraterizar os aspetos demográficos e clínicos, bem como descrever as abordagens terapêuticas utilizadas nos doentes diagnosticados com sarcoma de Kaposi no Hospital Garcia de Orta. **Métodos:** Estudo retrospetivo, descritivo e observacional que incluiu os doentes com diagnóstico histológico de sarcoma de Kaposi no Hospital Garcia de Orta entre março de 2009 e março de 2024. **Resultados:** Foram incluídos 55 doentes, 43 do sexo masculino e 12 do sexo feminino, com uma média de idades ao diagnóstico de 63.55 anos. A maioria dos doentes (67.3%) tinha lesões numa única localização anatómica, principalmente nos membros inferiores. O subtipo mais frequentemente observado foi o clássico (38.2%), seguido do epidémico (36.4%), do endémico (23.6%) e, finalmente, o iatrogénico (1.8%). O tempo desde o início dos sintomas até ao estabelecimento do diagnóstico foi superior no subtipo endémico (40.78 meses), com uma média geral de 18,3 meses. O subtipo epidémico tem a maior proporção de doentes com envolvimento sistémico (55%). A maioria dos doentes (56.4%) foi submetida a monoterapia. Observou-se uma heterogeneidade nas modalidades terapêuticas utilizadas. **Conclusão**: Este estudo revela que ainda existe um atraso considerável no diagnóstico, salienta a evolução das caraterísticas demográficas da doença e realçam a importância de adaptar o tratamento ao subtipo e à extensão da doença.

Palavras-chave: Sarcoma de Kaposi. Classificação. VIH. Herpesvírus humano 8.

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Introduction

Kaposi's sarcoma (KS) is an angioproliferative neoplasm associated with human herpesvirus 8[1]. Diagnosis is based on clinical features, with histological and immunohistochemical confirmation[2]. It occurs more frequently in males[3]. The overall incidence and mortality have changed over the last few decades, with a decrease in the epidemic subtype in the last 30 years with the introduction and diffusion of antiretroviral therapy (ART)[2,3].

There are four major subtypes, which are histologically indistinguishable: classic (typical of older men from the Mediterranean region) (Fig. 1), endemic (a more aggressive form, mostly seen in young adults from sub-Saharan Africa), iatrogenic (a form seen in transplant patients or those undergoing intense immunosuppressive treatments) and epidemic (human immunodeficiency virus [HIV]-positive patients) (Fig. 2)[1,4].

The treatment of KS is heterogeneous, depending on the cause and the clinic, including local and/or systemic therapeutic strategies[4].

The aim of our study was to describe the characteristics of patients with KS diagnosed by histology at Hospital Garcia de Orta, in Portugal, over 15 years, between March 2009 and March 2024. The data collected was used to characterize the demographics of the patients. Furthermore, we also sought to understand the variations between each subtype, particularly regarding the time to diagnosis, age at diagnosis, location of the disease (whether it was confined to the skin or systemic), and the therapeutic approach used. In addition, we conducted comparisons with other Portuguese and European studies that employed similar methodologies and with overlapping years of data collection.

Material and methods

This is a retrospective, descriptive, and observational study. It included patients with a histological diagnosis of KS at Hospital Garcia de Orta in Portugal between March 2009 and March 2024. Three patients were excluded due to missing data.

The endemic subtype was assumed for patients from sub-Saharan Africa, and the epidemic subtype was assumed for patients with HIV infection, regardless of their place of birth.

Clinical and demographic data were studied (age, gender, place of birth, subtype, location of lesions, time until diagnosis, and treatment used).

Statistical analysis was carried out using IBM Statistical Package for the Social Sciences Statistics, version 29.0. The correlations between the variables were considered statistically significant if $p < 0.05$.

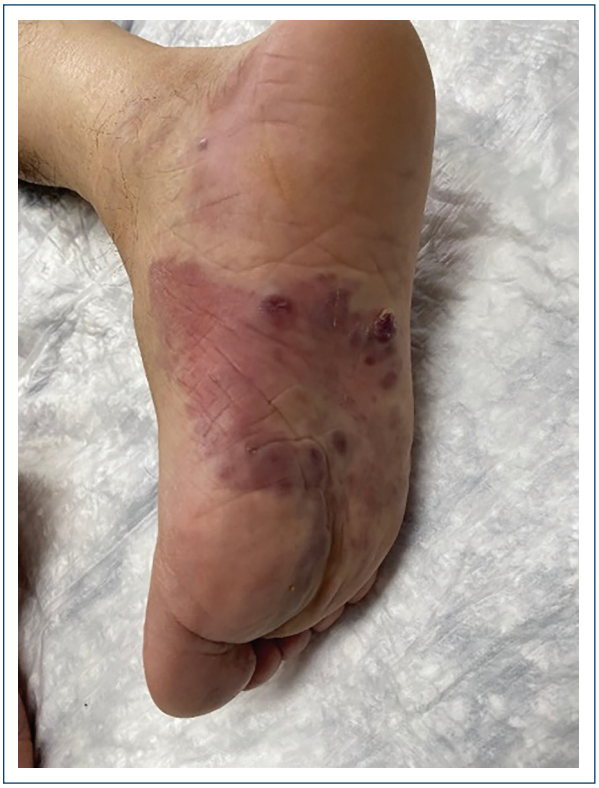

Figure 1. Classic subtype: erythematous to violaceous plaque extending across the medial plantar arch and heel, with an infiltrative component, areas of induration, and swelling. Multiple discrete ulcerated nodules with crusting are present within the plaque.

Results

The study included a total of 55 patients, 43 (78.2%) male and 12 (21.8%) female. The age of our patients at diagnosis ranged from 26 to 92 years, with a mean age at diagnosis of 63.55 ± 18.7. The mean male age at diagnosis was 61.26 ± 17.434, and the mean female age at diagnosis was 71.75 ± 21.495. The distribution of ages at diagnosis by gender was not statistically significant ($p = 0.057$).

Over the years, there have been fluctuations in the number of KS diagnoses per year, with a statistically significant downward tendency ($p = 0,005$). The maximum number of diagnoses per year was in 2011 (Fig. 3).

The majority of patients (67.3%) presented with lesions in a single anatomical site, mainly on the lower limbs. Only 32.7% of patients had lesions in two or more locations. Table 1 shows the anatomical locations of the lesions.

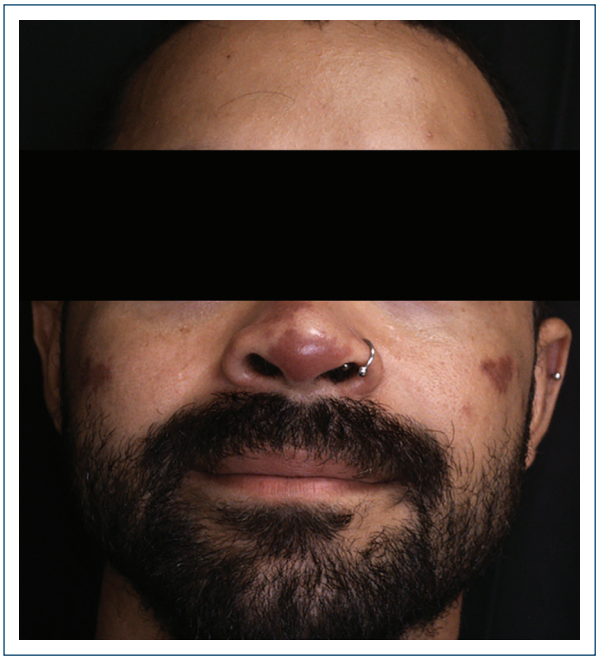

Figure 2. Epidemic subtype: multiple well-defined violaceous plaques located on the nose and cheeks.

Patients were classified into the four subtypes mentioned above: the classic subtype was the most common (38.2%), followed by the epidemic (36.4%), the endemic (23.6%) and finally the iatrogenic (1.8%) (Table 2). The only case of the iatrogenic subtype is a patient with myasthenia gravis and thymoma under high doses of systemic corticoids and rituximab. In the endemic subtype, six patients were from Cape Verde, three patients were from São Tomé e Príncipe, two patients were from Guinea-Bissau, and two patients were from Angola. Of the 20 patients with the epidemic subtype, 17 (85%) had a low TCD4 + lymphocyte count at the time of diagnosis, 2 (10%) had a normal count, and in 1 patient (5%), the count was unknown. The mean age at diagnosis was 77.9 ± 11.251 in the classic subtype, 69.0 ± 12.955 in the endemic subtype, 45.25 ± 12.315 in the epidemic subtype, and 57 in the iatrogenic subtype (Table 2). The observed differences in age at diagnosis for each subtype are statistically significant ($p < 0.001$).

The longest interval (in months) between the onset of symptoms and diagnosis was observed in the endemic subtype (40.78 ± 50.23), which exhibited a significantly longer duration than other subtypes (Table 2). The overall mean time was 18.3 months.

All patients with the classic subtype had only cutaneous involvement, just 2 patients (15.4%) with the endemic subtype demonstrated both cutaneous and visceral involvement, and the majority (55%) of patients with the epidemic subtype had both cutaneous and visceral involvement (Table 2).

Among the 55 patients included in the study, 37 (67.3%) underwent computed tomography (CT) scans, 16 (29.1%) underwent upper endoscopy, 15 (27.3%) underwent colonoscopy, and 11 (20.0%) underwent bronchofibroscopy. In terms of visceral involvement, the most common organs involved were the lungs (in seven patients), the gastrointestinal tract (in four patients), and the lymph nodes (in three patients).

About 56.4% of the patients received only one treatment, whereas 30.9% of cases necessitated the combination of multiple treatments. It is important to note that the follow-up of 7 patients (12.7%) was lost, and the treatment they received is unknown. Treatment approaches were both local and systemic and included ART, surgery, chemotherapy (CT), surveillance, radiotherapy, and cryosurgery.

The classic subtype predominantly underwent surgical intervention (10 cases), indicating a preference for localized surgical intervention in this subtype. The surveillance approach was used in two cases. The remaining cases displayed variability in treatment choice. The endemic subtype exhibited a broader therapeutic distribution, with CT alone being the most frequently applied treatment used in four cases. The epidemic subtype showed a marked reliance on ART, either alone or in combination with other treatments. ART alone was used in seven cases, whereas ART combined with CT was used in 11 cases.

Of the 55 patients, 18 died (32.7%). The mean time from diagnosis was 3.5 years, 8 of the classical subtype (38.1% within subtype), 2 of the endemic subtype (15.4% within subtype), none of the iatrogenic subtype, and 8 of the epidemic subtype (40% within subtype). The mean time (in years) from diagnosis to death was higher in the endemic subtype (6.00), followed by the classic subtype (4.63) and finally the epidemic subtype (1.75), but without statistical significance ($p = 0.146$).

Discussion

This study conducted a retrospective analysis of KS cases over a 15-year period in a hospital in Portugal. The demographic data from our study reveal an average age at diagnosis of 65.55 years (higher in men than in women), with a higher prevalence in men compared to women. These findings confirm previous studies indicating that KS is more common in men and diagnosed at older ages[3].

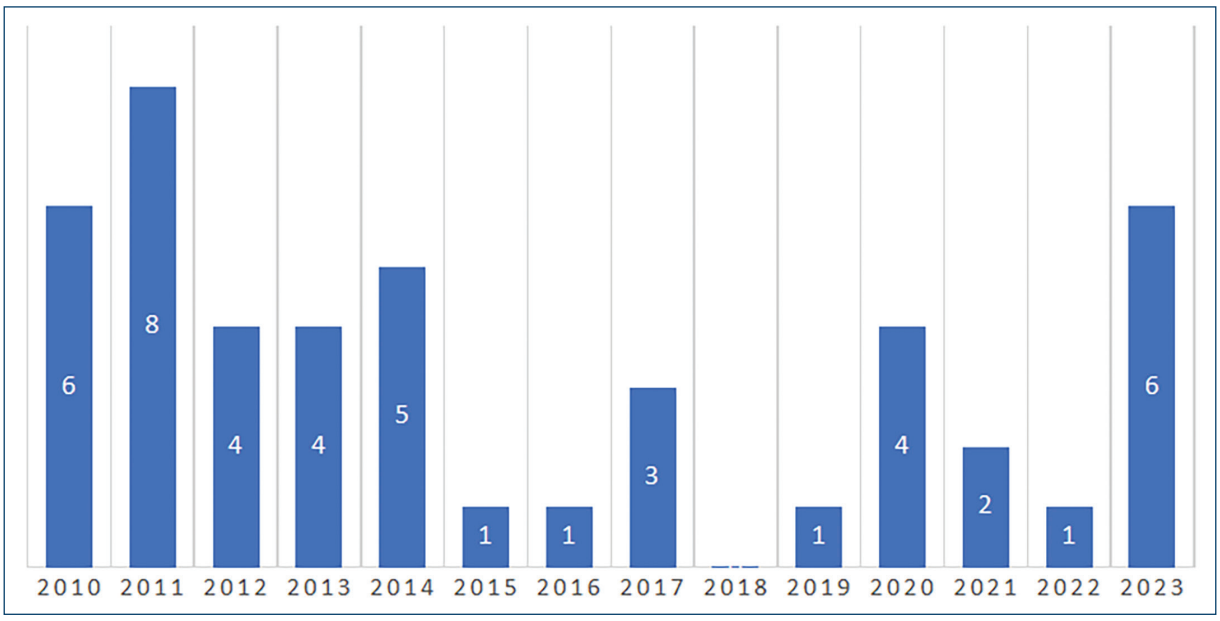

Figure 3. Number of diagnoses per year. 2009 and 2024 were not included because the data were collected from March 2009 to March 2024.

Table 1. Distribution of lesions by anatomical location

Location of lesions	n (%)	Location of lesions	n (%)
Single site	37 (67.3%)	Multiple sites	18 (32.7%)
Head and neck	3 (5.454%)	Lower limbs and trunk	7 (12.726%)
Trunk	2 (3.636%)	Lowe and upper limbs	7 (12.726%)
Lower limbs	31 (56.358%)	Hands and feet	2 (3.636%)
Genitals	1 (1.818%)	Genitals and lower limbs	1 (1.818%)
		Head, trunk, and lower limbs	1 (1.818%)

Table 2. Distribution of KS cases based on clinical and epidemiological characteristics, mean age at diagnosis, time (in months) until diagnosis, and skin and visceral involvement

Subtype	Number of cases (percentage)	Mean age at diagnosis	Time (in months) until diagnosis	Skin involvement only (%)	Skin and visceral involvement (%)
Classic	21 (38.2)	77.9 ± 11.251	8.36 ± 8.801	21 (100)	0 (0)
Epidemic	20 (36.4)	45.25 ± 12.315	10.95 ± 15.736	9 (45)	11 (55)
Endemic	13 (23.6)	69.0 ± 12.955	40.78 ± 50.23	11 (84.6)	2 (15.4)
Iatrogenic	1 (1.8)	57.0	6.0	1 (100)	0 (0)
	55			42 (76.4)	13 (23.6)

Table 3. Distribution of therapeutic modalities by subtype

Treatment	Classic	Endemic	Epidemic	Total
RT	1	1	0	2
CT	0	4	0	4
RT + CT	1	3	0	4
ART	0	0	7	7
ART + CT	0	0	11	11
Surveillance	2	1	0	3
Surgery	10	2	0	12
Cryosurgery	1	0	0	1
Surgery + cryosurgery	1	0	0	1
ART + cryosurgery	0	0	1	1
Surgery + RT	1	0	0	1
Shaving + electrosurgery	0	1	0	1
Total	17	12	19	48

RT: radiotherapy, CT: chemotherapy, ART: anti-retroviral drug.

In a retrospective study carried out by Resende et al. between January 2001 and December 2013, cases from the Egas Moniz Hospital and the Centro de Dermatologia Médico-Cirúrgica de Lisboa were analyzed. The study included 91 patients, 67% of whom belonged to the classic subtype, 30.8% to the epidemic subtype, 1.1% to the endemic subtype, and 1.1% to the iatrogenic subtype[5]. Compared to our results, the percentages of the epidemic and iatrogenic subtypes were similar. However, there was a considerable increase in the prevalence of the endemic subtype and a decrease in the classic subtype. Given that both studies used similar methodologies and were carried out in similar geographical areas (both belonging to the Lisbon metropolitan area), about a decade apart, these differences-particularly the higher proportion of endemic subtype cases in our cohort (23.6% compared to 1.1%) can be explained by the recent migratory flow.

In addition, a retrospective study conducted by Russo et al. in Italy between 1993 and 2022 analyzed 86 patients. Of these, 43.02% were classified as belonging to the classic subtype, 33.73% to the epidemic subtype, 3.49% to the endemic subtype, and 19.77% to the iatrogenic subtype[4]. Compared to our study, the Italian study reported a higher percentage of cases classified under the iatrogenic subtype. This difference can be explained by the fact that our hospital is not a transplant center, thereby limiting the number of epidemic subtype cases followed in our hospital. In the last decade, there has been a decrease in cases of iatrogenic KS, which can be explained by new-generation immunomodulators that reduce the immunosuppressive status of patients and enable the optimization of the dose of immunosuppressive medications[6].

The epidemic subtype demonstrated the highest frequency of visceral involvement in our cohort (Table 2), reflecting its aggressive clinical behavior as previously described in the literature[7]. This observation highlights the impact of immunosuppression in HIV-positive patients, contributing to more advanced and disseminated disease presentations characteristic of this subtype. The exclusively cutaneous involvement in other subtypes (classic and iatrogenic) suggests that these subtypes may have less aggressive behavior in terms of visceral dissemination, which is consistent with the expected clinical profile.

The time from the onset of lesions to diagnosis was longer in the endemic subtype. This may be attributed to the lower level of health literacy observed in this population or to greater difficulty in accessing health care.

There was a great heterogeneity in the therapeutic modalities used, which shows the great complexity of treating KS and the need to adapt the treatment to each subtype, as shown by the predominance of ART in the epidemic subtype, surgery in the classic subtype and chemotherapy in the endemic subtype (Table 3).

The preference for surgery as the primary treatment in the classic subtype reflects the option of localized therapies for lesions associated with this subtype, which generally exhibit a slower and more localized progression. In contrast, for the epidemic subtype, the majority of patients underwent a combination of ART and CT, although a notable proportion underwent ART alone. ART monotherapy in patients with disease limited to the skin can significantly reduce the size of the lesions and achieve complete remission in 35% of cases within 39 months of treatment[8]. However, in cases involving more extensive skin disease or with visceral involvement, it is necessary to combine systemic drugs such as doxorubicin or paclitaxel. The limited use of radiotherapy in our cohort may be explained by the anatomical distribution of the lesions. As radiotherapy is most effective for localized symptomatic lesions, its role is more limited in cases of widespread disease. In addition, in patients with extensive lower limb involvement, radiotherapy may be less practical. Furthermore, resource availability and institutional treatment protocols may limit the routine use of radiotherapy, and alternative local therapies, such as surgical excision, have been preferred for isolated lesions in accessible areas.

Our study has some limitations, such as being retrospective and unicentric. As it included cases from 2009 onwards, there was a lack of information, which made statistical analysis challenging.

Conclusion

This study highlights there is still a considerable delay between symptoms onset and diagnosis of SK, and that it is not homogeneous between the subtypes. Treatment should be adjusted on a case-by-case basis and adapt to the subtype and extent of the disease. For many years, systemic therapy was represented by chemotherapy, but with the emergence of translational research, it can currently count on immunotherapy and targeted therapies with promising results. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have shown promising efficacy. Combination approaches, including ipilimumab with nivolumab and pembrolizumab with lenvatinib, aim to improve disease control. Ongoing trials are also evaluating nivolumab with pomalidomide and cabozantinib, as well as dostarlimab in epidemic KS[9].

Previous presentations

This study was presented in the “23° Congresso Nacional de Dermatologia e Venereologia (2024).”

Funding

None.

Conflicts of interest

There are no conflicts of interest to declare.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution’s confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CASE REPORT

Takayasu's arteritis with involvement of small cutaneous vessels – with regard to a clinical case

Arterite de Takayasu com envolvimento de pequenos vasos cutâneos – a propósito de um caso clínico

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Abstract

Takayasu's arteritis (AT) is a vasculitis that affects large vessels. Rarely, microcirculation is involved, sometimes with cutaneous manifestations. Inflammation of small vessels of the skin can present as erythema nodosum-like lesions, granulomatous cutaneous vasculitis, among others. We describe the case of a 29-year-old woman with a diagnosis of AT confirmed by Angio-CT. She was referred to a Dermatology appointment due to a skin condition characterized by centimetric, erythematous, painful and non ulcerated nodules on the soles and inner edges of the feet. Clinical and analytical criteria of active disease were met, despite implemented corticotherapy. Cutaneous biopsy showed panniculitis and leukocytoclastic vasculitis. Autoimmune vasculitis and cryoglobulinemia panels were negative. Erythema nodosum-like subcutaneous nodules have been described in TA, possibly preceding other disease manifestations or as markers of disease activity. An early correlation with constitutional and cardiovascular symptoms may lead to earlier diagnosis and prompt control of disease activity.

Keywords: Small vessel vasculitis. Large vessel vasculitis. Cutaneous vasculitis. Granulomatous panniculitis. Takayasu's arteritis.

Resumo

A arterite de Takayasu (AT) é uma vasculite que afeta vasos de grande calibre. Raramente, atinge a microcirculação, por vezes com manifestações cutâneas. A inflamação de pequenos vasos da pele apresenta-se como lesões eritema nodoso-*like*, vasculite cutânea granulomatosa, entre outros. Descrevemos o caso de uma doente de 29 anos com diagnóstico de AT confirmado por Angio-TC. Foi referenciada à Dermatologia por dermatose caracterizada por nódulos eritematosos centimétricos, dolorosos e não ulcerados nas plantas e bordos internos dos pés. Mantinha critérios clínicos e analíticos de doença ativa apesar da corticoterapia instituída. A biópsia cutânea revelou paniculite e vasculite leucocitoclástica. O estudo de vasculites auto-imunes e crioglobulinas foi negativo. O aparecimento de nódulos subcutâneos eritema nodoso-*like* estão descritos na AT, podendo preceder outras manifestações e ser considerados marcadores de atividade da doença. Uma correlação precoce com sintomas constitucionais e cardiovasculares permitirá diagnósticos mais atempados e controlo precoce da atividade inflamatória.

Palavras-chave: Vasculite de pequenos vasos. Vasculite de grandes vasos. Vasculite cutânea. Paniculite granulomatosa. Arterite de Takayasu.

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Introduction

Takayasu's arteritis (TA) is a vasculitis characterized by granulomatous inflammation, fibrosis and thickening of the wall of large and medium-sized vessels, such as the aorta and its branches[1]. The prevalence of this disease is higher in young women, especially in Asia and the Middle East[2]. Rarely, the microcirculation may also be involved, with ocular (retinopathy, uveitis, scleritis), cardiac (myocarditis) and cutaneous manifestations[2]. The prevalence of the latter is estimated to be around 2.8% to 28% of TA patients[3–7]. From a clinical and histological point of view, cutaneous manifestations can be divided into specific for TA–acute inflammatory nodules, erythema nodosum-like subcutaneous nodules, erythema induratum, pyoderma gangrenosum-like ulcers, livedo reticularis, purpuric and necrotic lesions–and nonspecific–urticaria-like lesions, erythematous macules and papules, eczematiform lesions, among others[3,8–11]. More than one type of lesion may be present in the same patient[11]. This report represents a case of small cutaneous vessel vasculitis manifesting as erythema nodosum-like subcutaneous nodules in a patient with active TA disease activity.

Case report

We report the case of a 29-year-old woman, with no previously known comorbidities. She had been diagnosed with Takayasu's arteritis 4 years prior to her Dermatology evaluation. The diagnosis was made when she developed pericarditis, differential blood pressure between the upper limbs higher than 10 mmHg, and an elevation of inflammation parameters. The diagnosis was confirmed with an angiography CT scan, which showed reduction of the caliber of the supra-aortic branches of the thoracic and the abdominal aorta.

Several immunosuppressive drugs were administered in order to control disease activity, with favorable response to an induction dose of prednisolone (1 mg/kg/day). Corticosteroid tapering and switching to corticoid-sparing drugs was attempted, but the patient was intolerant to some drugs, namely adalimumab, azathioprine and methotrexate and others failed to reduce the inflammatory activity, namely tocilizumab and infliximab. Oral prednisolone was used as maintenance therapy, however clinical criteria of active disease (Indian Takayasu Clinical Score 5) and analytical criteria (sedimentation velocity of 64 mm/h) were sustained.

The patient was referred to a Dermatology appointment due to a skin condition characterized by centimetric, erythematous, painful (particularly in the morning) and non ulcerated nodules on the soles and inner edges of both feet (Fig. 1). Lesions had subsided partially after increasing the dose of prednisolone, but had not resolved completely. Laboratory tests with blood and urine samples, specifically regarding auto-immune vasculitis and cryoglobulinemia, were negative.

Therefore, a skin biopsy of one of the nodules of the inner edge of the left foot was performed. Dermatopathology findings were compatible with leukocytoclastic vasculitis and adjacent granulomatous panniculitis (Fig. 2). It was concluded that the small vessel inflammation occurred in the context of TA, manifesting as erythema nodosum-like subcutaneous painful nodules. For the small vessel vasculitis, the patient was started on colchicine 1 mg per day and maintained a corticotherapy regimen of 15 mg of prednisolone per day with improvement of the cutaneous lesions. Even though systemic inflammation is not controlled with this dose of systemic corticosteroids, the patient refuses other biologic treatments at the moment.

Discussion

The first skin manifestations in TA were described in 1985 by Mousa et al.[12], who associated the nodular skin lesions with the systemic vasculitis in a patient with TA. Overall, dermatologic manifestations in patients with TA may result from the occlusion of large vessels –presenting as Raynaud's phenomenon and digital gangrene–or from the inflammation of small cutaneous vessels[3,9]. The latter may manifest as erythema nodosum, ulcerated nodules, pyoderma gangrenosum-like lesions, among others[3,8–11]. In North America and Europe, acute inflammatory nodules and erythema nodosum are the most prevalent skin manifestations[3], while pyoderma gangrenosum has been described more frequently in the TA Japanese population and predominantly affects the upper arms[9]. Less frequently, findings compatible with cutaneous lupus erythematosus with no systemic evidence of lupus have been reported[3].

Histologically, granulomatous or necrotizing vasculitis of small and medium vessels in the dermis and hypodermis, accompanied or not by septal and/or lobular panniculitis have been previously described[3,5,7,9,11]. Granulomatous vasculitis can be found in various types of vessels in these patients, from large to small sized

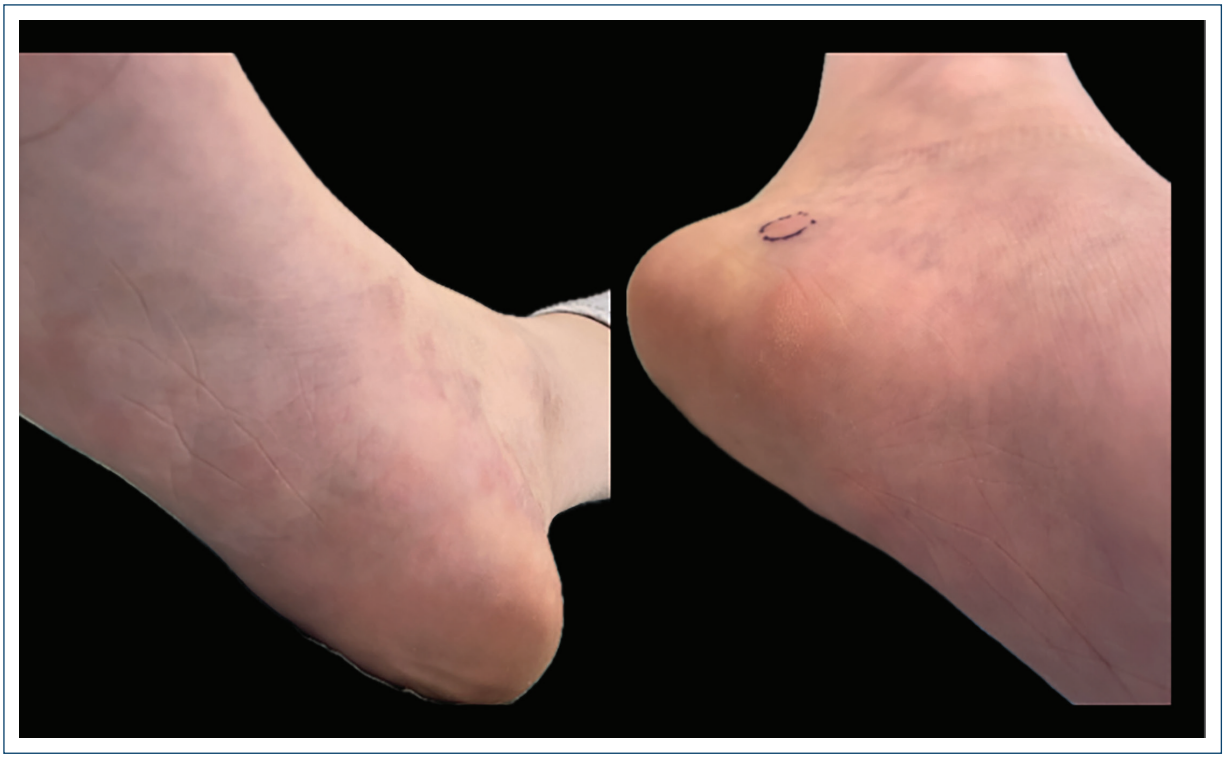

Figure 1. Erythematous nodules on the sole and inner edges of both feet. The place where the skin biopsy was performed is highlighted with a blue circle.

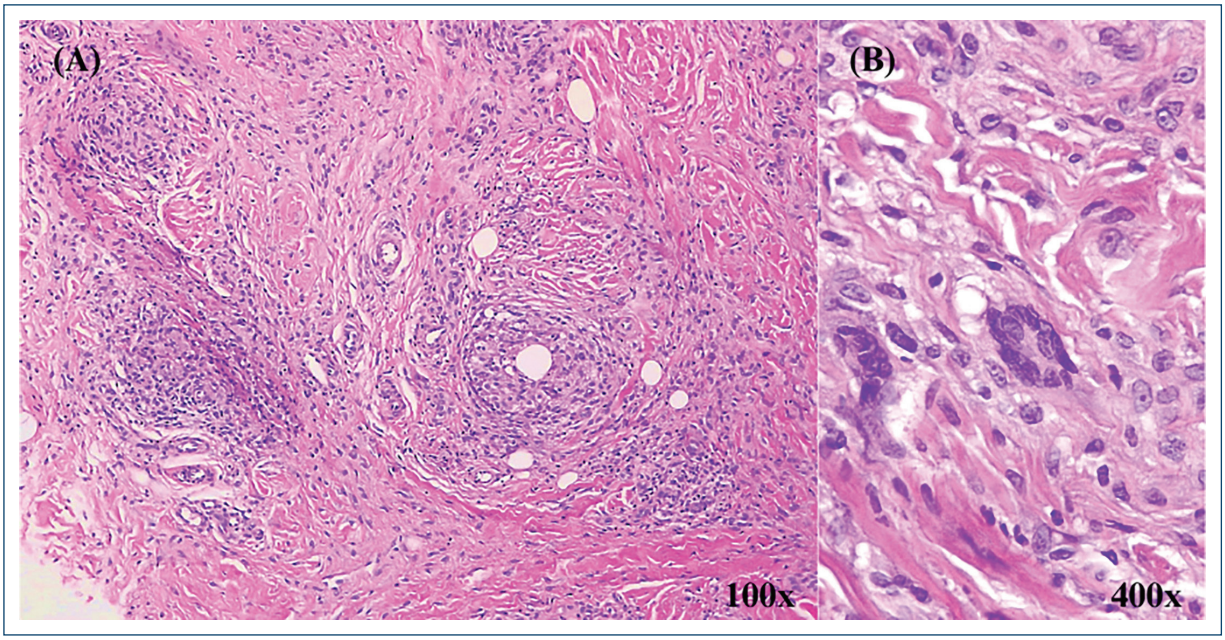

Figure 2. Histopathologic findings (H&E stain). **A:** scattered perivascular neutrophils in the deep dermis and the subcutaneous fat, as well as a lymphohistiocytic infiltrate along the lobules and septae of fat tissue, with multinucleated giant cells. **B:** higher magnification showing multinucleated giant cells in the infiltrate.

arteries, capillaries and venules[3]. Panniculitis is, in some cases, the only finding on the skin biopsy; in others, like ours, it is interpreted as a continuum of the inflammatory changes of the vasculitis found in the deep dermis into the hypodermis, particularly in erythema nodosum and subcutaneous ulcerated nodules[3].

Establishing a relation between cutaneous findings and TA may be doubtful. Francès et al.[3] suggested three arguments to sustain this association, based on the findings described in the literature, the presence of granulomatous necrotizing vasculitis of small cutaneous vessels (similar to findings on the walls of large vessels), and the chronological association between skin findings and disease activity[3]. The association is established when other etiologies have been excluded, usually by performing tests that screen for other granulomatous diseases (chest radiography, tuberculin test, anti-streptococcal antibodies, yersinia titers)[3,9].

Disease progression of TA can be divided into an initial inflammatory systemic phase and a subsequent occlusive phase with manifestations caused by the stenosis of large and medium sized arteries[13]. This evolution may not be linear, with overlap and/or inversion of the natural history of TA[13]. The appearance of cutaneous manifestations, including painful erythema nodosum-like nodules, may accompany an initial period of constitutional systemic symptoms, preceding the vessel inflammation phase of the vasculitis (sometimes several years), or manifest simultaneously with a worsening of the large vessel occlusion[3,5,11]. In Francès C, et al's[3] cohort, skin lesions were present in all disease phases, however acute and subacute nodules were more prevalent in early stages of the vasculitis, while pyoderma gangrenosum, purpuric and necrotic lesions accompanied the occlusive stage. Moreover, cutaneous lesions in TA do not appear to correlate with disease severity or location of the large vessel occlusions[5].

The painful, acute, subcutaneous nodules found in our patient are concordant with the erythema nodosum-like manifestations described in literature. Histologically, these lesions may initially be indistinguishable from classic erythema nodosum; however, later in disease progression, small cutaneous vessel vasculitis with or without panniculitis may develop and contribute to the differential diagnosis[8].

The inflammatory process of small and large vessels may correlate due to anatomical similarities between skin vessels and the *vasa vasorum* on the outer layers of the walls of large vessels[7,9]. Also, evidence suggests that both forms of inflammation respond favorably to systemic corticotherapy and other immunosuppressants, along with systemic inflammation[2,5,7,8,10,11]. Therefore, cutaneous manifestations of small vessel inflammation are considered markers of disease activity[3,9,11]. In our patient, vasculitis was not under control with the current therapy so this skin condition corroborates the existence of inflammatory activity and may be useful as a marker of response and/or flare under future therapeutic options, due to the simultaneous involvement of small, medium and large vessels.

We conclude that an early correlation between cutaneous findings and constitutional and cardiovascular symptoms of TA may lead to earlier diagnosis and a more prompt control of inflammation.

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None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CASE REPORT

Cutaneous IgG4-related disease treated with dupilumab

Doença cutânea relacionada com IgG4 tratada com dupilumab

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Abstract

We present a 59-year-old male with a prolonged history of severe, treatment-resistant pruritic dermatosis and associated systemic symptoms, including fatigue and diarrhea. Dermatologic examination revealed widespread erythematous-brownish papules and nodules, prompting a skin biopsy that showed dense infiltration by immunoglobulin G4 (IgG4)-positive plasma cells, leading to a diagnosis of IgG4-related disease (IgG4-RD). The patient was treated with dupilumab, resulting in complete skin lesion resolution and significant improvement in quality of life. IgG4-RD, a rare inflammatory disease with potential multiorgan involvement, frequently challenges diagnosis due to diverse clinical presentations. This case highlights dupilumab effectiveness as a novel therapy for IgG4-RD with cutaneous involvement, offering a promising alternative for patients who do not respond well to corticosteroids.

Keywords: Immunoglobulin G4-related disease. Cutaneous. Dupilumab.

Resumo

Reportamos o caso de um homem de 59 anos, com dermatose intensamente pruriginosa desde há 7 anos, refratária à terapêutica, e associada a sintomatologia sistémica como astenia e diarreia. Ao exame objetivo dermatológico, o doente apresentava pápulo-nódulos eritemato-acastanhados disseminados, o que motivou a realização de biópsia cutânea cujo exame histopatológico revelou infiltrado rico em plasmócitos IgG4-positivo. Admitido o diagnóstico de doença relacionada com IgG4 (DR-IgG4), o doente iniciou tratamento com dupilumab, com consequente resolução da dermatose e melhoria franca da sua qualidade de vida. A DR-IgG4, uma patologia inflamatória rara com potencial envolvimento multiorgânico, representa frequentemente um desafio diagnóstico pela sua hetereogeneidade clínica. Este caso clínico enaltece a eficácia do dupilumab na DR-IgG4 com envolvimento cutâneo, surgindo como uma alternativa terapêutica promissora na doença não respondedora a corticoterapia.

Palavras-chave: Doença relacionada com IgG4-related. Cutânea. Dupilumab.

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a rare systemic inflammatory condition characterized by tissue infiltration by IgG4-expressing plasma cells and progressive fibrosis, firstly identified in the 21st century. It occurs more frequently in middle-aged to elderly males and can synchronous or metachronously involve multiple organs[1,2]. Although the pathophysiology of IgG4-RD is not fully uncovered, studies suggest a predominance of the T helper (Th) type 2 immune response, with interleukin (IL)-4 playing a central role in the production of IgG4[3]. The disease clinical heterogeneity makes its diagnosis frequently challeging, with dermatologic manifestations appearing in a minority of cases[1]. Systemic corticosteroids are the first-line treatment; however, refractoriness and relapse on discontinuation are common[4,5]. Herein, we report a case illustrating the efficacy of dupilumab, a monoclonal antibody blocking IL-4 and IL-13 receptors, in treating cutaneous IgG4-RD, underscoring its potential role for patients who are resistant to corticosteroids.

Case report

A 59-year-old man was referred to our dermatology department due to a disseminated and extremely pruritic dermatosis with 7 years of evolution. In addition, he referred asthenia and frequent episodes of diarrhea. Fecal occult blood test was negative and thoracic, abdominal and pelvic computed tomoghrapy (CT) showed pulmonary emphysema, nodular thyroid, and prostatic calcifications. Systemic steroids provided relief, but the disease quickly relapsed on its tapering. Patient medical history was remarkable for allergic rhinitis, uncontrolled non-insulin dependent diabetes mellitus, dyslipidemia, and an episode of unilateral proptosis and diplopia 4 years before. At that time, as radiological examination demonstrated thickening of the left extraocular muscles, a diagnosis of inflammatory myositis was assumed, and the patient was treated with oral corticosteroids, resulting in clinical and imaging regression.

Dermatological examination showed a symmetric and extensive eruption affecting the face, trunk, buttocks, and upper and lower limbs, characterized by erythematous-brownish papules and papulonodules, some with crusts, amidst with excoriations and hyper- and hypopigmented macules and patches (Fig. 1). Bilateral mobile and painless cervical lymphadenopathies were palpable. Cutaneous lesions caused a debilitating pruritus (itch numeric rating scale 8/10) that markedly interfered with patient's quality of life (dermatology life quality index [DLQI] 11). The diagnoses of eczema and nodular prurigo were considered, and a skin biopsy was performed, revealing a dense perivascular and perifollicular lymphoplasmacytic infiltrate, rich in IgG4-positive cells (IgG4+/IgG+ > 40%) and eosinophils (Fig. 2). Laboratory tests showed IgG4 levels of 1570 mg/dL and immunoglobulin E (IgE) of 4563 KUI/L. The diagnosis of IgG4-RD was hence evoked, and complementary study revealed overlapping findings on body CT and colloid goiter on thyroid aspiration cytology. Treatment with dupilumab (300 mg sc every 2 weeks with a loading dose of 600 mg) was initiated as monotherapy. After 6 months, sparse cutaneous lesions were observerd and lower serum IgG4 and IgE levels (1450 mg/dL and 601 KUI/L, respectively) were noted. After 1 year of therapy, dermatosis resolution (Fig. 3), and a significant improvement of asthenia, gastrointestinal symptoms and quality of life (DLQI 0) were observed, accompanied by a noticeable decrease in serum IgG4 and IgE levels (724 mg/dL and 228 KUI/L, respectively).

Discussion

IgG4-RD is an immune mediated condition characterized by tumefactive lesions and progressive fibrosing of affected tissues[1,6]. Its true incidence is unknown and potentially underestimated, due to lack of awareness. Although the immunopathogenesis of IgG4-RD is not entirely understood, a Th2 immune reaction is proeminent, with IL-4, IL-5, and IL-10 playing a role in stimulating the expression of IgG4 and IgE and eosinophilia. IL-4 is the key cytokine, inducing IgG4 class-switch mediated by Th follicular cells. IL-13 promotes mitochondrial dysfunction, cellular senescence, and fibrosis, but its role in the fibrosis of IgG4-RD is still under debate[2,7]. Up to 31% of patients with IgG4-RD have an atopic background, suffering from allergic rhinitis, atopic dermatitis, or asthma[1,3].

IgG4-DR can virtually affect any organ and usually follows a subacute course with relatively mild symptoms[8]. Extracutaneous presentations include tumor-like enlargement, inflammation, and fibrosis of tissue such as lacrimal and salivary glands, orbits, gallbladder, pancreas, thyroid, lungs, kidneys, and lymph nodes[4]. Asthenia and weight loss are common unspecific symptoms, while organ-specific manifestations such as diarrhea, respiratory symptoms, or xeropthalmia vary widely. Erythematous and pruritic nodules, papules,

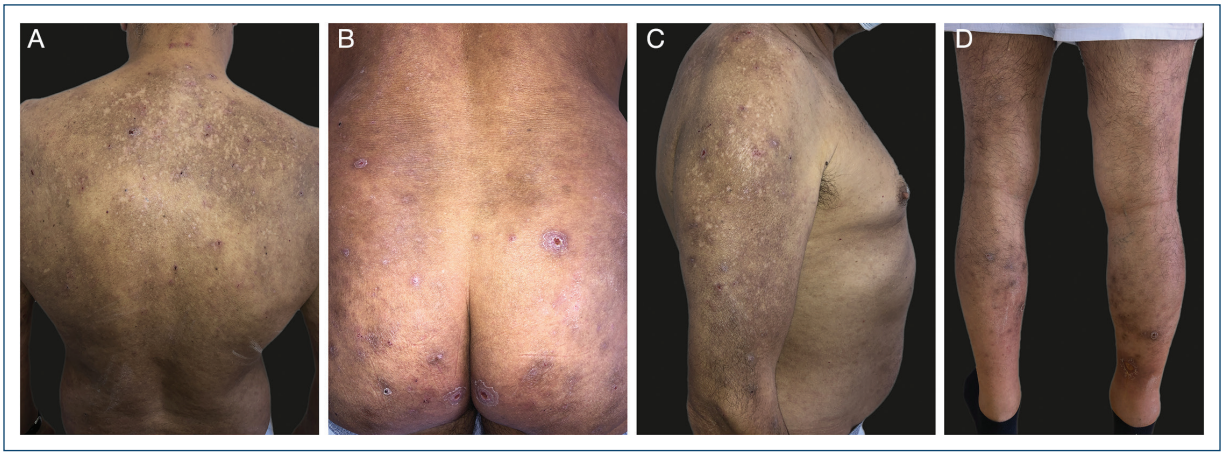

Figure 1. Baseline clinical presentation, with erythematous-brownish papules and papulonodules, excoriations and hyper- and hypopigmented macules and patches, mainly located on the **A:** trunk, **B:** buttocks and **C** and **D:** upper and lower limbs.

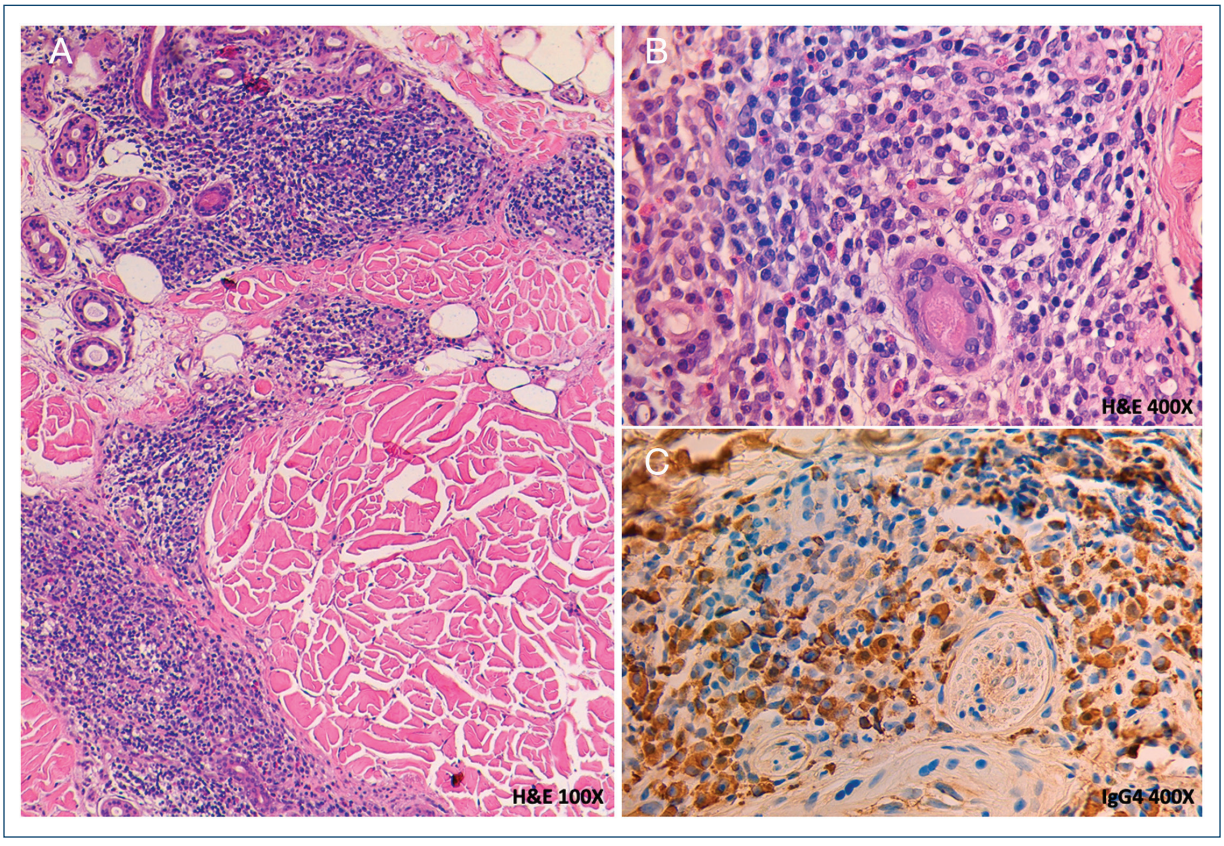

Figure 2. Histological findings on skin biopsy: dense lymphoplasmacytic infiltrate, rich in immunoglobulin G4-positive (IgG4+) cells and eosinophils.

and plaques are the most common cutaneous lesions, mainly appearing on the head-and-neck regions, but also on the trunk and extremities. Purpura and prurigo nodularis-like lesions have also been reported[9,10]. A Japanese study including 80 patients showed that skin lesions were identified in only 6.3% of IgG4-RD cases[11]. Cutaneous lesions are usually associated with systemic involvement, particularly of the orbit, lacrimal, and salivary glands[4]. Due to its clinical heterogeneity, the differential diagnosis of IgG4-RD is broad,

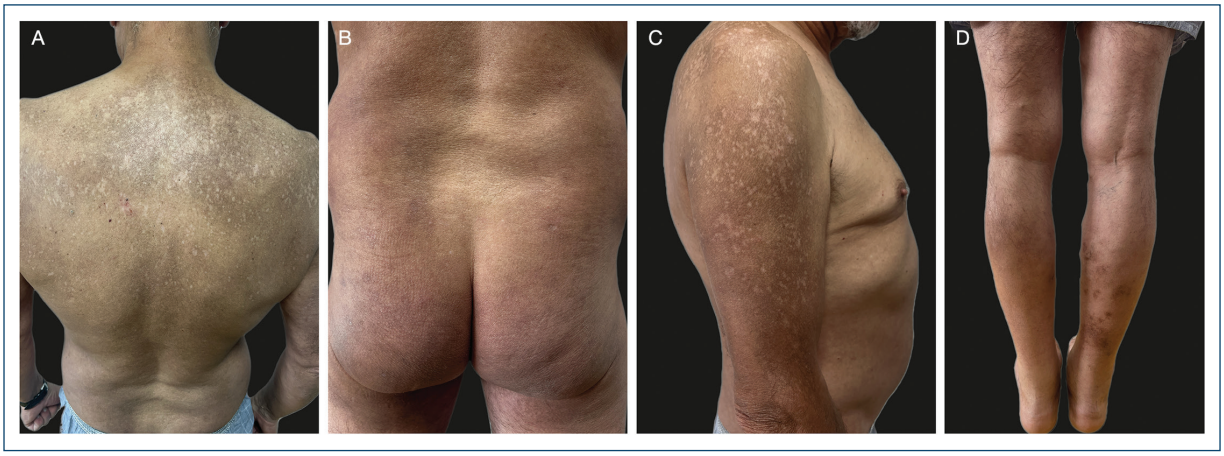

Figure 3. Significant improvement of cutaneous lesions at 1 year of therapy, with only post inflammatory hyper- and hypopigmented macules and patches remaining on the **A** and **B:** trunk, **C** and **D:** upper and lower limbs.

depending on the clinical presentation and specific sites of involvement[9].

Histopathology of affected organs shows dense lymphoplasmacytic infiltrates rich in IgG4+ plasma cells with frequent eosinophilic infiltration, storiform fibrosis, and obliterative phlebitis, the latter two seldom observed in skin biopsies[1,4,11]. Most patients present elevated serum IgG4 levels, which tends to correlate with the extent of organ involvement, hypergammaglobulinemia, elevated serum IgE (60%), and mild-to-moderate peripheral eosinophilia (34%)[1]. Comprehensive diagnostic criteria include clinically characteristic swelling or masses in single or multiple organs, serum IgG4 levels > 135 mg/dL, and histological features, namely, a ratio of IgG4+/IgG+ plasma cells > 40% on biopsy, that nevertheless is not specific as isolated and finding[1,4].

Prevention of irreversible fibrosis and organ function impairment is the major treatment goal. Systemic corticosteroids are the first-line therapy; however, relapses on discontinuation occur in up to 53% of cases[5].

Dupilumab, an IL-4 and IL-13 inhibitor, is approved for the treatment of type 2 inflammatory diseases such as atopic dermatitis, chronic prurigo, asthma, and chronic rhinosinusitis and nasal polyposis. Limited studies have demonstrated its safety and promising role in the treatment of IgG4-RD, mainly focusing on outcomes of asthma and rhinosinusitis[2,7,12,13]. Kanda M et al. reported a case series of four patients diagnosed with IgG4-related disease, predominantly affecting the submandibular and lingual glands, paranasal sinuses, and lungs, who were treated with dupilumab[2]. Similarly to our case, the two patients who underwent monotherapy with dupilumab took 3-6 months to experience a therapeutic effect.

Recent studies have focused on alternative therapies to corticosteroids, driven by a progressively deeper understanding of IgG4-RD pathophysiology. *In vitro* testing has shown that T cells from patients with IgG4-RD exhibit aberrant activation, associated with reduced expression of the inhibitory molecule CTLA4. However, in a case series of three patients diagnosed with IgG4-RD, the response to abatacept, a recombinant fusion protein of CTLA4, was inconsistent[14]. Considering the role of Janus kinases (JAK)/STAT pathway in the intracellular signaling of cytokines such as IL-4 and IL-13, JAK inhibitors may potentially mitigate chronic inflammation and tissue fibrosis in IgG4-RD. In fact, tofacitinib at 5 mg/day as monotherapy showed promising results in two patients with IgG4-RD, leading to partial or complete clinical response[15].

Studies focusing on the role of IL-13 inhibitors for the treatment of this disease are lacking. Current evidence points to a significant but problably not dominant role of IL-13 in the pathophysiology of IgG4-RD, which could justify the lack of studies with this biological agents.

Conclusion

This report highlights the efficacy of dupilumab in the treatment of cutaneous IgG4-RD, a debilitating and potentially difficult-to-treat rare condition. We further

underline the role of dermatologists in the diagnostic workup of this disease, to be considered in the presence of a persistent pruritic dermatosis with diverse systemic manifestations.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CASE REPORT

Muir-Torre syndrome: case report

Síndrome de Muir-Torre: um relato de caso

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Abstract

Muir-Torre syndrome (MTS) is characterized by the association of at least one, but often multiple, sebaceous skin neoplasms, and at least one visceral neoplasm, usually colorectal. MTS should be suspected in the presence of multiple sebaceous tumors, particularly if they appear at an early age and are in extraocular areas. We report the case of a 52-year-old man with a personal history of sigmoid colon adenocarcinoma, referred to the Dermatology department, 8 years later, due to multiple facial sebaceous tumors. Considering the clinical presentation, as well as the personal and family history, MTS was suspected and later confirmed by genetic testing. Although rare, hereditary cancer predisposition syndromes remind us of the importance of patient's global approach, especially those with cancer, allowing the early detection of potential carriers and promoting the health of their relatives.

Keywords: Muir-Torre syndrome. Lynch syndrome. Sebaceous adenoma. Colorectal carcinoma.

Resumo

A síndrome de Muir-Torre (SMT) caracteriza-se pela associação de, pelo menos, uma neoplasia sebácea e de, pelo menos, uma neoplasia visceral, sendo a colorretal a mais comum. Assim, deve suspeitar-se de SMT na presença de vários tumores sebáceos, particularmente, se estes surgirem em idade precoce e se estiverem localizados em zonas extraoculares. Relata-se o caso de um homem de 52 anos, com história de adenocarcinoma da sigmoide, referenciado a consulta de Dermatologia, 8 anos depois, por múltiplos tumores sebáceos faciais. Tendo em conta o quadro clínico, bem como os antecedentes pessoais e familiares, colocou-se a hipótese diagnóstica de SMT, que se confirmou após estudo genético. Apesar de raras, as síndromes de predisposição hereditária para cancro relembram-nos a importância do enquadramento global dos doentes, principalmente os oncológicos, detetando precocemente potenciais portadores e promovendo a saúde dos seus familiares.

Palavras-chave: Síndrome de Muir-Torre. Síndrome de lynch. Adenoma sebáceo. Carcinoma colorretal.

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Introduction

Muir-Torre syndrome (MTS) is a rare syndrome, initially described by Muir in 1967 and subsequently by Torre in 1968. It is typically characterized by the synchronous or metachronous occurrence of at least one sebaceous skin neoplasm, typically an adenoma or carcinoma, and at least one visceral malignancy, most commonly colorectal. MTS is considered an autosomal-dominant phenotypic variant of Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome), caused by mutations in DNA mismatch repair genes and leading to microsatellite instability. The most frequently mutated genes in MTS include *MLH1*, *MSH2*, *MSH6*, and *PMS2*. However, some cases of MTS have been described without microsatellite instability but with biallelic inactivation of the *MUTYH* gene (mutY homolog), causing defects in base excision repair. This subtype of MTS is called MTS type 2, has an autosomal-recessive inheritance pattern, and accounts for approximately one-third of cases. Most reported cases are related to Caucasians, probably due to a lack of epidemiologic data from Asia and Africa. MTS is more common in males, with a male/female ratio of 3:2, and the mean age at diagnosis of the first cutaneous neoplasm is 53 years[1-3].

The authors intend, with this case report, to demonstrate the importance of early diagnosis and maintenance of a high level of suspicion in the presence of multiple skin tumors, associated or not with visceral neoplasia.

Case report

We present the case of a 52-year-old male, born in Brazil, married, with three healthy children. His medical history included asthma and poorly differentiated adenocarcinoma of the sigmoid colon (stage IIIB, T3N2M0) diagnosed in 2015. For that, he underwent segmental resection of the sigmoid colon and lymphadenectomy followed by adjuvant chemotherapy. He denied taking any regular medications and had no known drug allergies. Family history is notable for a maternal grandmother and aunt with colorectal cancer diagnosed before the age of 50. Additionally, the patient's mother had liver and skin neoplasms diagnosed at the age of 68, although the specific types are unknown.

The patient presented to his primary care physician with multiple yellowish papules, spread across the face (Fig. 1), which had been evolving for several years. In Brazil, he periodically received surgical treatment or CO_2 laser therapy for these lesions. In this context, after referral to a Dermatology hospital consultation, four of these lesions were biopsied, as they were ulcerated or becoming large, concluding that they were adenomas and sebaceous hyperplasia. A nodule, mainly subcutaneous, with a violet surface and hard consistency, was also detected in the left lumbar region (Fig. 2), which, after excision and histopathological examination, revealed a keratoacanthoma. Based on the histological findings and the patient's personal history of colorectal cancer, a diagnosis of MTS was suspected. This diagnosis was subsequently confirmed by genetic testing, which revealed a large heterozygous deletion involving exons 17-19 of the *MLH1* gene.

Despite being aware of the high number of cases of neoplasia in the family, for the first time, the patient was referred to a hospital consultation for family risk of cancer, also to study this syndrome and to screen his relatives for cancer.

Discussion

Sebaceous adenomas are the most common cutaneous tumors found in MTS and are considered the most specific marker of the disease, occurring in approximately 68% of cases. They typically present as multiple yellowish or skin-colored papules, less than 0.5 cm in diameter, scattered on the trunk, face, and scalp. Other sebaceous tumors include sebaceous epithelioma, sebaceous carcinoma, and keratoacanthoma. These tumors tend to occur at a younger age than their sporadic counterparts and may precede, occur simultaneously or follow the diagnosis of visceral malignancy[2,4]. Other muco-cutaneous findings sometimes also present in MTS are Fordyce spots (ectopic sebaceous glands) on the vestibular oral mucosa[5].

Colorectal adenocarcinoma represents more than half of all cases of visceral neoplasms associated with MTS and tends to occur proximally, unlike sporadic neoplasms. Other reported neoplasm includes urogenital neoplasia (present in approximately 25% of cases), endometrial, ovarian, urothelial, and kidney. Other cancers that are linked to MTS include those of prostate, pancreas, breast, brain, lung, gastric, small intestine, and hematological cancers[2,6,7].

Therefore, the diagnosis of MTS should be suspected in the presence of multiple sebaceous tumors, particularly if they appear at an early age and are located outside the head and neck area, especially the trunk[2,3,8]. A detailed clinical history, particularly oncologic, must be collected. As a support tool, there is the Mayo risk score, which includes the following

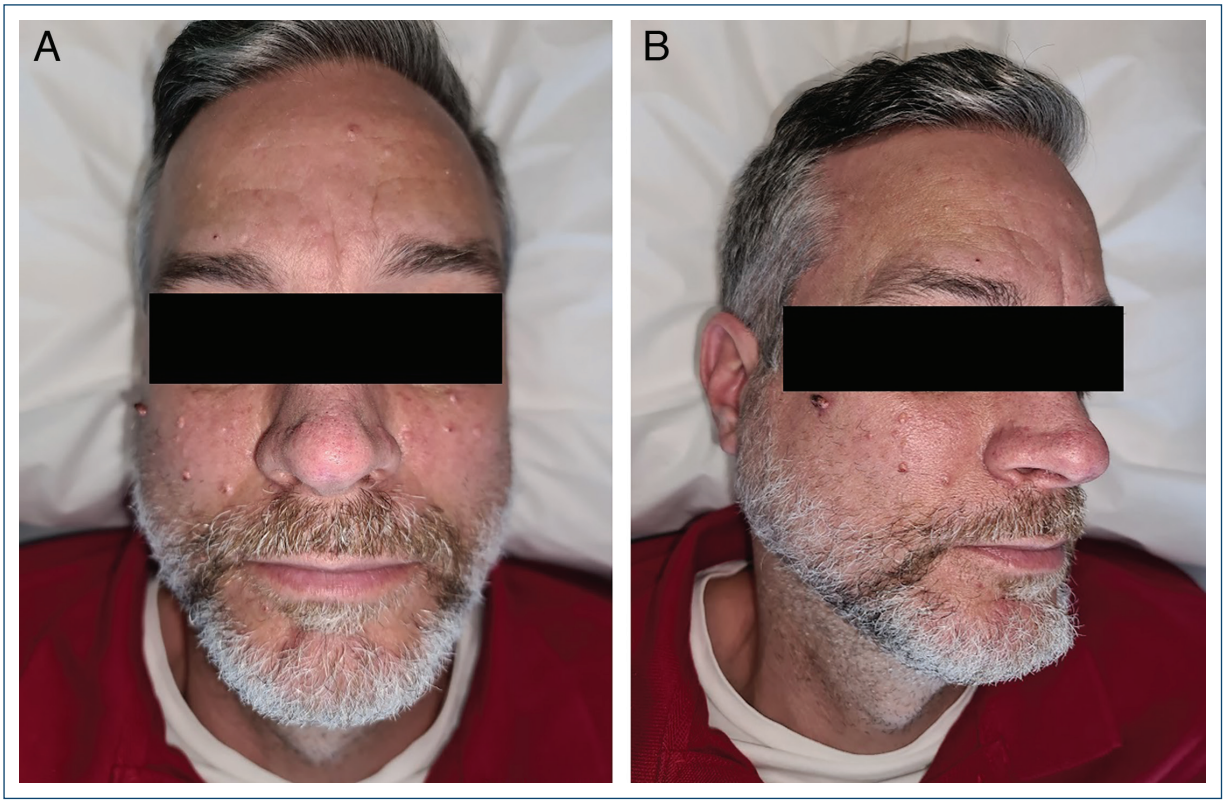

Figure 1. A-B: multiple yellowish papules spread across the face.

criteria: age less than 60 years (1 point), number of sebaceous tumors (2 points), personal history (1 point), and family history (1 point) of any Lynch-related cancers. Any patient with a total of two or more points has a high risk of having MTS and, therefore, should undergo genetic testing for germline variants screening of the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes[8,9].

This strategy was challenged by some experts due to the risk of not detecting patients with a single sebaceous neoplasm and unknown family history. Therefore, it is reasonable to consider that young patients, with only one extraocular sebaceous tumour and suspected MTS, who do not meet the Mayo risk criteria, also undergo immunohistochemical tests to detect mismatch proteins in sebaceous tumors[8,10].

Regarding cancer screening in people with MTS and their first-degree relatives, annual full-body skin examination, starting at late teens/early twenties, is recommended. Colonoscopy surveillance is recommended starting at age 25 years for *MLH1* and *MSH2*-mutation carriers, and at age 35 years for MSH6 and PMS2-mutation carriers; colonoscopy should be performed every 2–3 years, unless they have had colorectal cancer before, after which biennial colonoscopy is recommended. Upper gastrointestinal endoscopy should be considered in patients with a positive family history of gastric cancer, and Helicobacter pylori eradication is recommended in mutation carriers. Female patients should receive annual surveillance for breast, endometrial, and ovarian cancers. Therefore, annual mammography, pelvic examination, transvaginal ultrasounds, and endometrial biopsies are warranted, starting between the ages of 30 and 35. As for male patients, prostate and testicular cancer laboratory testing is also recommended. In addition, annual urinalysis and cytologic examination are recommended starting at age 30–35 years for testing for renal and genitourinary cancers. Prophylactic surgeries may be considered in high-risk individuals to reduce the cancer burden. Prophylactic colectomy should be considered in patients above 25 years with gene mutation, and prophylactic hysterectomy and bilateral salpingo-oophorectomy may be considered after childbearing is complete or at age 40[11–15].

Although rare, it is important to adopt a low threshold of suspicion for this syndrome to allow for early diagnosis and a multidisciplinary approach for appropriate treatment and follow-up, reducing patient morbidity and mortality.

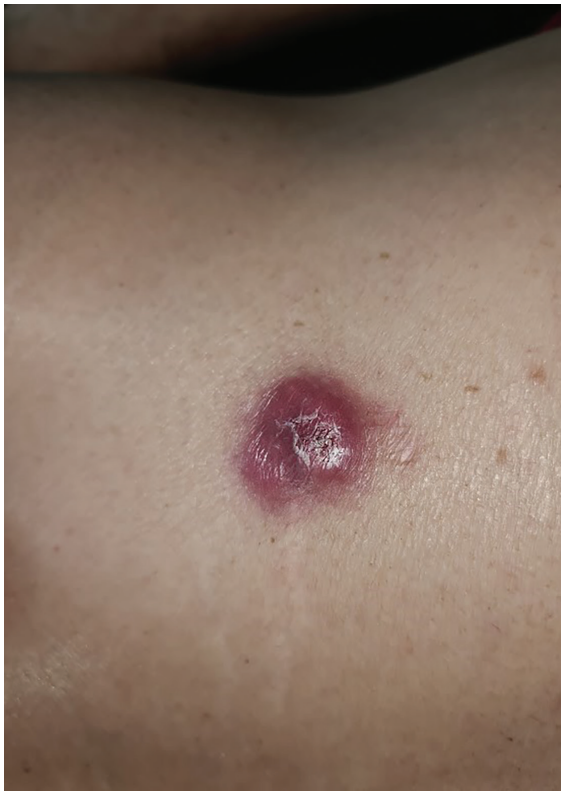

Figure 2. Violet nodule with a hard consistency, in the left lumbar region, whose histopathologic examination revealed a keratoacanthoma.

Documenting cases of genetic familial cancer syndromes makes it possible to adapt the follow-up of index patients, while also having important consequences for their relatives. All doctors involved in the care of these patients and their relatives must be included.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CASE REPORT

Terbinafine-induced generalized pustular psoriasis treated with dapsone

Psoríase pustulosa generalizada secundária a terbinafina e tratada com dapsona

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Abstract

We report the case of a 37-year-old healthy woman who developed a generalized cutaneous eruption 1 week after starting oral terbinafine. The eruption was nonspecific, composed of erythematous—violaceous patches, limited areas of epidermal detachment, and sparse sterile pustules. Initial differential diagnoses included Stevens-Johnson Syndrome (SJS) and Acute Generalized Exanthematous Pustulosis (AGEP). Systemic corticosteroid therapy was initiated, with no improvement after 2 weeks. Skin biopsies suggested a diagnosis of pustular psoriasis,and during hospitalization, the patient developed scalyplaques on her scalp, more in keeping with terbinafine-induced Generalized Pustular Psoriasis (GPP). The patient was started on cyclosporine, which proved ineffective, followed by oral dapsone, which led toa major improvement within just 2 days. This case highlights the difficulty of differentiating between SJS, AGEP, and GPP in the presence of a nonspecific drug eruption and suggests dapsone as a safe therapeutic alternative for GPP.

Keywords: Generalized pustular psoriasis. Drug eruption. Terbinafine. Dapsone.

Resumo

Descrevemos o caso de uma mulher de 37 anos, saudável,observada em contexto de urgência de Dermatologia por erupção cutânea generalizada 1 semana após o início de terbinafina oral. Clinicamente, objetivavam-se manchas eritematovioláceas, áreas limitadas de descolamento epidérmico e escassas pústulas estéreis. Foram inicialmente considerados os diagnósticos diferenciais de Síndrome de Stevens-Johnson (SSJ) e Pustulose Exantemática Generalizada Aguda (AGEP). Foi iniciada corticoterapia sistémica, sem melhoria após 2 semanas. O resultado da biópsia cutânea foi compatível com psoríase pustulosa e, durante o internamento, a doente desenvolveu lesões descamativas no couro cabeludo, estabelecendo-se assim o diagnóstico de Psoríase Pustulosa Generalizada (PPG) secundária a terbinafina. A doente iniciou ciclosporina, sem resposta, seguida de dapsona oral, com melhoria significativa em apenas 2 dias. Este caso realça a dificuldade do diagnóstico diferencial entre SSJ, AGEP e PPG perante um quadro pouco específico de toxidermia e propõe a dapsona como alternativa terapêutica segura na PPG.

Palavras-chave: Psoríase pustulosa generalizada. Toxidermia. Terbinafina. Dapsona.

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Introduction

Generalized pustular psoriasis (GPP) is a rare and aggressive subtype of psoriasis, characterized by a widespread eruption of sterile, subcorneal pustuleson a background of erythema, often associated with systemic involvement manifested as fever and leukocytosis[1]. Possible complications include sepsis and hepatic, respiratory, or renal impairment[2].

GPP can develop in patients with or without a prior history of psoriasis. While its pathogenesis is not fully understood, various precipitating factors have been reported, such as infections or drug exposure[3].

In the setting of a generalized cutaneous eruption followingdrug exposure, a comprehensive differential diagnosis is essential to distinguish among severe drug-induced dermatoses, such as Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms Acute Generalized Exanthematous Pustulosis (AGEP), or GPP. In some cases, the initial presentation of the eruption is nonspecific, and a definitive diagnosis can only be established later, making clinicopathologic correlation essential within the diagnostic algorithm[4].

The recommended first-line therapies for GPP in adults include acitretin, methotrexate, cyclosporine, and biologic agents, although there are few randomized controlled trials available to guide therapy[3].

Dapsone is a sulfone antibiotic that has been proven useful in some dermatological conditions including dermatitis herpetiformis, pyoderma gangrenosum and bullous diseases. Due to its antineutrophilic activity, dapsone can also be an effective treatment for pustular disorders, such as GPP. There is a number of case reports documenting its efficacy in the management of treatment-resistant GPP[5].

We present the case of a 37-year-old woman with an acute flare of generalized pustular psoriasis induced by terbinafine, resistant to conventional therapy and successfully treated with dapsone.

Clinical case

A 37-year-old woman presented to the Emergency Department (ED) with an erythematous generalized rash that had been rapidly progressing over the past four days. The patient had no personal or family history of skin disorders and no known history of drug allergies. One week before the eruption, she had been started on terbinafine 250 mg once daily for tinea unguium. On the first day of the rash, she sought the care of her primary care doctor and was started on deflazacort 30 mg once daily. On admission, the patient looked uncomfortable, with mild pruritus, but was apyrexial and there was no peripheral lymphadenopathy.

During the physical examination, poorly defined erythematous-violaceous patches were seen on the trunk (Fig. 1) and limbs, affecting over 50% of the body surface area (BSA). On the lower abdomen and thighs, these patches had coalesced and presented scarce, nonfollicular, pinhead pustules (Fig. 2). In some areas, there was limited epidermal detachment, with positive Nikolsky sign, affecting less than 10% of the BSA. The remainder of the patient's skin was clear, including the face, scalp, palms, soles, and mucous membranes. Upon examination of the nails, xanthonychia and distal onycholysis of the toenails on both feet were observed. The patient underwent evaluation by Ophthalmology and Otorhinolaryngology in the ED, both of which confirmed the absence of ophthalmologic or mucosal involvement.

Routine biochemical analyses, comprising renal and liver tests, were normal. Full blood count revealed a hemoglobin level of 13.5 g⁄dL (normal range 12.0-16.0 g⁄dL), with leukocytosis 17.2 × 10^9⁄L (normal range 3.6-11.0 × 10^9⁄L) and neutrophilia 15.03 × 10^9⁄L (normal range 1.30-8.80 × 10^9⁄L). Blood cultures were negative, and the chest X-ray was normal.

The initial differential diagnosis included terbinafine-induced SJS and AGEP. Hence, the patient was hospitalized for observation and initiated prednisolone 1 mg/kg/day.

A 4-mm punch biopsy was taken from the patient's thigh. Histopathological examination revealed subcorneal pustules (Fig. 3). The epidermis exhibited orthokeratosis, with sparse permeation of neutrophils in the underlying spinous layer (Fig. 4). There was no evidence of spongiosis or acantholysis, and keratinocyte apoptosis was minimal. The dermis containeda superficial perivascular lymphohistiocytic infiltrate, accompanied by frequent neutrophils that extend into the interstitium of the superficial reticular dermis. There were no observable eosinophils in the dermis nor in the epidermis, and there was also no vacuolar interface change in the epidermis. Direct immunofluorescence microscopy studies were negative. These findings were more suggestive of the diagnosis of pustular psoriasis than of AGEP, its closest histological mimic.

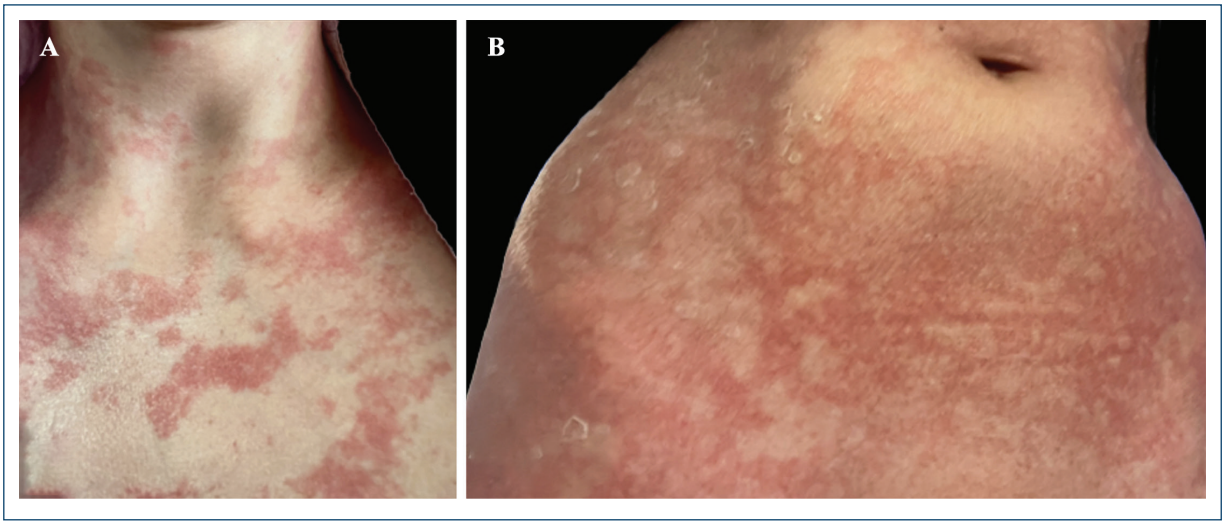

Figure 1. Poorly defined erythematous–violaceous patches on the trunk of the patient, starting from the neck **(A)** and coalescing in the lower abdomen (**B**).

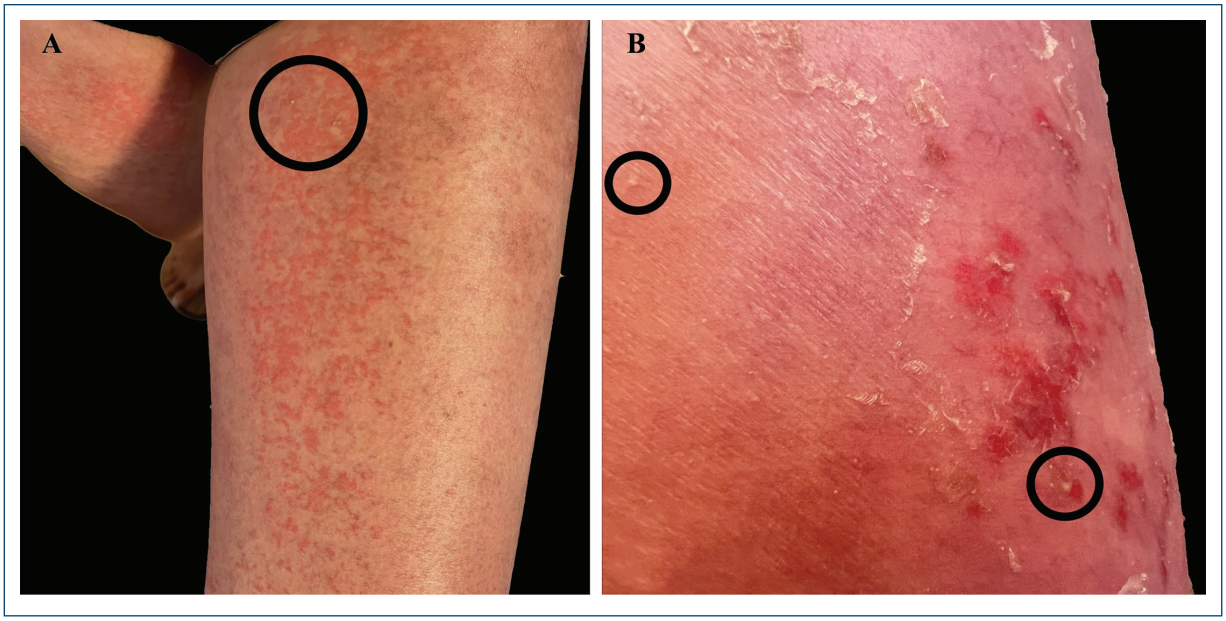

Figure 2. Erythematous coalescing patches on the thighs (**A**) of the patient presenting with some epidermal detachment (**B**) and scarse, nonfollicular, pinhead pustules (black circles).

After two weeks of systemic corticosteroid therapy, no clinical improvement was noted. Additionally, during the hospitalization, the patient gradually developed few thick silvery scaly plaques on her scalp. Thus, the clinical diagnosis was nowfelt to be more in keeping with terbinafine-induced GPP. Cyclosporine 3 mg/kg/day was started, as well as slow corticosteroid tapering, but there was no response after four days of therapy. After excluding glucose-6-phosphate dehydrogenase (G6PD) deficiency, the patient was switched to dapsone 100 mg daily, and within 2 days the eruption was almost cleared. The patient was discharged on the third day, maintaining dapsone on an outpatient basis, and a complete clearance was seen after 2 weeks.

One month later, the patient made the decision to stop the treatment on her own, and 2 days later the

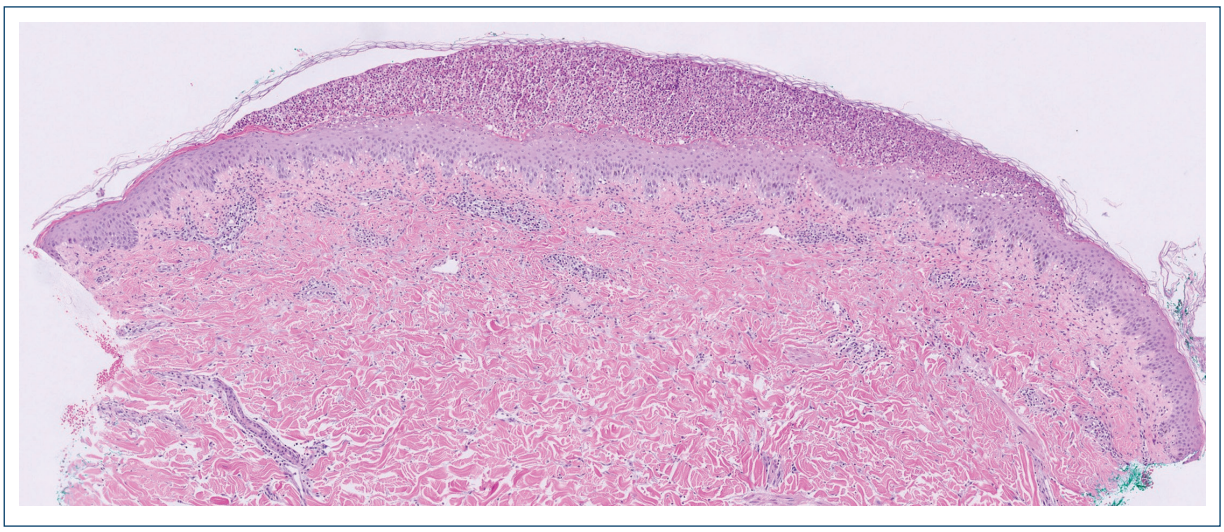

Figure 3. Histopathology of a thigh lesion skin biopsy revealed a subcorneal macropustule.The dermis contained a superficial perivascular lymphohistiocytic infiltrate accompanied by multiple neutrophils that extend into the interstitium of the superficial reticular dermis. Hematoxylin and eosin, 50×.

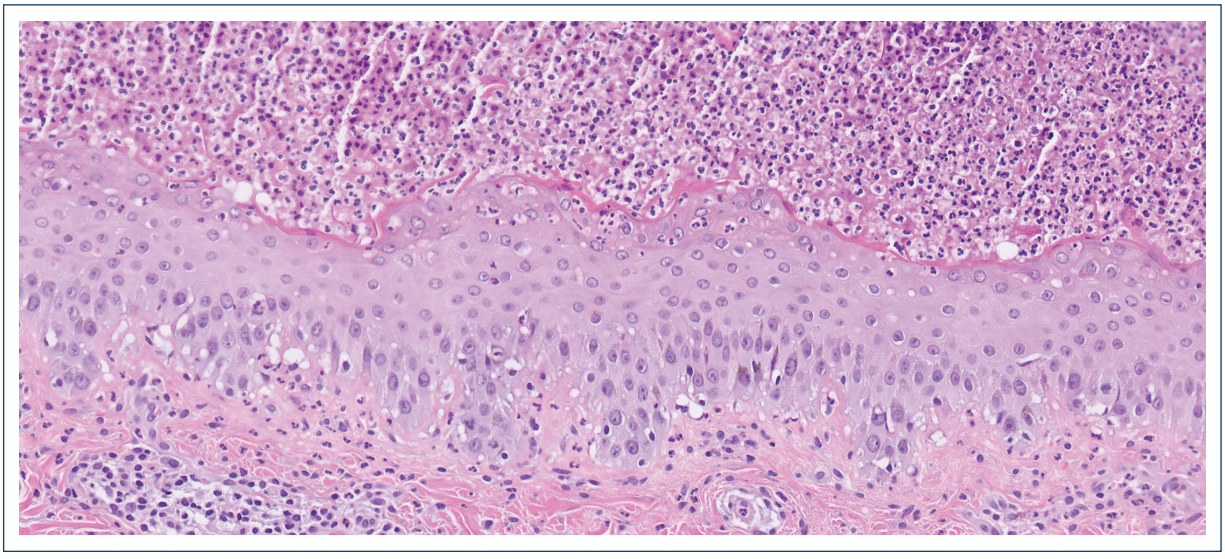

Figure 4. Histopathology of a thigh lesion skin biopsy revealed permeation of neutrophils in the spinous layer. There was no evidence of spongiosis or acantholysis, and keratinocyte apoptosis was minimal. Hematoxylin and eosin, 200×.

eruptionrelapsed. Dapsone was reintroduced, leading to a new resolution of the rash within just 3 days. At the 3-month follow-up, the patient's skin remained clear. Dapsone was tapered to 50 mg daily and, after another month, 50 mg every other day. Throughout this period, no adverse effects were observed, and regular laboratory tests, including complete blood counts, showed no abnormalities. Dapsone was discontinued after 5 months of therapy, and the patient remained in remission at the 8-month follow-up.

Discussion

As with many medications, oral terbinafine carries the potential foradverse skin reactions, varying from

mild maculopapular reactions to severe drug eruptions, such as GPP[6].

The challenge demonstrated in this case lies in differentiating between SJS, AGEP, and GPP in the presence of a nonspecific drug-induced rash exhibiting characteristics of all three conditions upon admission.

Initially, the patient presented with some areas of epidermal detachment, and the possibility of an early SJS had to be considered given the severity and possible complications of this condition. Thus, systemic corticosteroid therapy was instituted along with close monitoring of the eruption's progression. However, the lack of mucosal lesions and clinical stability prompted us to reconsider the diagnosis.

Considering the presence of sterile pustules, albeit sparse, along with leukocytosis and neutrophilia, the possibility of AGEP was also evaluated. However, AGEP typically resolves within a few weeks following the cessation of the causative drug, whereas our patient did not show any improvement while on systemic prednisolone over the course of two weeks. Moreover, the leukocytosis and neutrophilia could be interpreted in the context of prior use of deflazacort.

As it is described in the literature, a GPP diagnosis often becomes more evident asdisease progresses[7], and indeed, our patient developed typical psoriatic plaques on her scalp during hospitalization. Additionally, the skin biopsy results further reinforced the diagnosis of GPP. Although AGEP and GPP demonstrate considerable histopathologic overlap, both presenting in the pattern of a pustular dermatosis, this case revealed an absence of dermal eosinophils, vacuolar interface change, and eosinophilic spongiosis, all of which can be used as criteria[8] to help favoring GPP. Finally, the toenail alterations upon admission could already be a sign of psoriasis. It is, in fact, common to misdiagnose nail changes as onychomycosis when they may be attributed to other underlying conditions. Thus, performing a mycological examination is crucial for an accurate diagnosis.

Among the available first-line therapies for GPP, cyclosporine was initiated due to its rapid onset of action, with clinical improvements documented in the literature occurring within the first days of therapy[4]. However, our patient did not show any sign of improvement over the course of 4 days of cyclosporine. Following this lack of response, we decided to switch to oral dapsone based on multiple case reports demonstrating its efficacy in treatment-resistant GPP[5]. Dapsone is a readily available drug associated with fewer side effects and not as immunosuppressive as other conventional agents[9]. Given that the patient was of child bearing age, acitretin was not a viable option.

In this case, a significant response to dapsone was observed within a few days of therapy. This was further corroborated when the patient discontinued dapsone, leading to recurrence of the skin lesions, and achieved resolution once again within just 3 days upon resuming the medication.

Dapsone's efficacy in GPP and other sterile pustular dermatoses can be explained by its mechanism of action targeting neutrophils, which involves theinhibitionof the myeloperoxidase system, as well as the suppression of neutrophil adhesion and chemotaxis[5,10]. Side effects of oral dapsone include methemoglobinemia, hemolytic anemia, neutropenia, and agranulocytosis. A G6PD deficiency should always be ruled prior to starting dapsone and regular monitoring with a complete blood count should be performed. Less commonly, dapsone may also cause hepatitis, renal toxicity and hypersensitivity reactions[9].

The clinical course of GPP can be unstable with frequent flares, either precipitated by re-exposure to known triggers or occurring without an identifiable cause[2]. Regarding our patient, although dapsone was discontinued after 5 months, continued patient monitoring is essential and re-exposure to terbinafine should be avoided. In the event of a recurrence, dapsone could be restarted considering the excellent response.

In conclusion, this case highlights the challenge in differentiating between SJS, AGEP, and GPP when presented with a drug-induced generalized, nonspecific, pustular skin eruption. Additionally, it supports the use of dapsone as an effective, readily available, and safe therapeutic option for treating GPP.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's

confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CASE REPORT

Lenalidomide and its impact on exanthematous reactions: a case report

Lenalidomida e seu impacto em reações exantemáticas: um relato de caso

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Abstract

Lenalidomide is a drug used mainly in the treatment of multiple myeloma and myelodysplastic syndrome. Despite its therapeutic benefits, lenalidomide can cause several adverse effects, including exanthematous reactions that can appear unexpectedly and cause discomfort to the patient. These skin reactions can be mild or severe and sometimes require the discontinuation of the lenalidomide treatment. In this case study, we will present the case of an 86-year-old man with a history of multiple myeloma who was on his fifth cycle of lenalidomide 10 mg and dexamethasone 20 mg, who was seen at the Health Center for constipation after two visits to the emergency department. During the consultation, the objective examination revealed a scattered maculopapular rash, probably secondary to lenalidomide. Timely assessment and guidance in these situations can be crucial to the patient's prognosis. Anamnesis is one of the fundamental pillars of medical diagnosis.

Keywords: Anamnesis. Adverse effects. Exanthema. Hypersensitivity. Late onset. Lenalidomide.

Resumo

A lenalidomida é um medicamento utilizado principalmente no tratamento do mieloma múltiplo e síndrome mielodisplásica. Apesar dos seus benefícios terapêuticos, a lenalidomida pode causar vários efeitos adversos, incluindo reações exantemáticas que podem aparecer de forma inesperada e causar desconforto ao paciente. Estas reações cutâneas podem ser leves ou graves e, em alguns casos, requererem a interrupção do tratamento com lenalidomida. Relatamos o caso de um homem de 86 anos, com antecedentes de mieloma múltiplo cumprindo o 5˚ ciclo de lenalidomida 10 mg e dexametasona 20 mg, avaliado no Centro de Saúde por quadro de obstipação após duas idas ao serviço de urgência. No decorrer da consulta, na realização do exame objetivo identificou-se um exantema maculo-papular disperso, provavelmente secundário à lenalidomida. A avaliação e orientação atempada nestas situações pode ser crucial no prognóstico do doente. A anamnese é um dos pilares fundamentais do diagnóstico médico.

Palavras-chave: Anamnese. Efeitos adversos. Exantema. Hipersensibilidade tardia. Lenalidomida.

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Introduction

Lenalidomide is a medication that belongs to the immunomodulatory agent's class, analogous to thalidomide, which has gained prominence in the treatment of different types of cancer, namely multiple myeloma and myelodysplastic syndrome. This medicine works by modulating the immune system and inhibiting tumor growth. It is often used in combination with other therapeutic agents to increase the effectiveness of the treatment.

In treating multiple myeloma, lenalidomide has been shown to be effective in reducing disease progression and increasing patient survival. In clinical studies, the combination of lenalidomide with dexamethasone or other agents, such as bortezomib, has been associated with significantly higher response rates, leading to an improvement in patients' quality of life and prognosis[1,2].

In the context of myelodysplastic syndrome, lenalidomide has been used to reduce the need for blood transfusions in patients with this condition, contributing to an improvement in anemia and patients' quality of life[3]. However, it is important to remember that lenalidomide can cause side effects such as fatigue, nausea, diarrhea, anemia, and thrombocytopenia, so monitoring patients during treatment is essential[1,3].

The prevalence of hypersensitivity reactions to lenalidomide varies between 6% and 43%, with a predominance of morbilliform, urticarial, and maculopapular rashes, which occur more frequently in the 1st month of treatment[4].

Due to its therapeutic importance and potential side effects, lenalidomide should be prescribed and monitored by specialized health professionals, who can adjust the dose and manage adverse reactions. Patients must follow medical advice and report any unusual or worrying symptoms during treatment, and proper clinical follow-up is crucial to ensure the efficacy and safety of the treatment.

Case report

An 86-year-old male patient diagnosed with multiple myeloma, on his 5th cycle of lenalidomide 10 mg and dexamethasone 20 mg, was evaluated at the Health Center for constipation after two visits to the emergency department, where he was treated with a laxative and discharged. During the consultation, the objective examination revealed a maculopapular rash scattered all over the body, sparing the face, with confluent plaques, which disappeared on digitation, as well as petechiae on the palate, not reported by the patient (Fig. 1).

In fact, when questioned, the patient confirmed the presence of skin lesions in the anterior region of the thighs, with a week's evolution, which gradually extended distally, involving the abdominal region, the back, and the anterior part of the trunk, without any other associated manifestations, namely pruritus, nausea or vomiting.

The patient was once again referred to the emergency department with the initial suspicion of Stevens-Johnson syndrome and was admitted to the Internal Medicine department for study and investigation.

During hospitalization, laboratory tests were conducted, revealing that only cytomegalovirus immunoglobulin M (IgM) tested positive. He was treated with oral prednisolone 20 mg for 3 days and oral hydroxyzine 25 mg for 5 days, with concomitant suspension of lenalidomide for 15 days. Clinically, he remained apyretic at all times, with a resolution of constipation and positive progression, with an almost total resolution of the skin lesions and limited to the distal third of the lower limbs at the time of discharge.

There are records in the literature of dose-dependent delayed reactions, the immunological mechanism of which is poorly understood[5,6].

After discussing the case with the hospital's Hematology department, the patient was discharged with a diagnosis of exanthema, probably secondary to lenalidomide, having restarted treatment with the drug in question at a dose of 5 mg/day 15 days after its suspension.

Discussion

Cutaneous delayed hypersensitivity reactions to lenalidomide represent a significant challenge in the treatment of patients with multiple myeloma and myelodysplastic syndrome[7]. Lenalidomide, an immunomodulatory drug used in these conditions, can trigger exaggerated immune responses in some individuals, leading to severe complications, although most eruptions are mild to moderate in severity.

Among the most feared manifestations of skin reactions is DRESS syndrome, a systemic and potentially fatal allergic reaction that can arise as a result of exposure to the drug[8]. Generalized skin rashes, hyperpyrexia, lymphadenopathy, and possible involvement of organs such as the liver, kidneys, and lungs characterize this syndrome.

Stevens-Johnson syndrome, another potential complication of hypersensitivity reactions to lenalidomide,

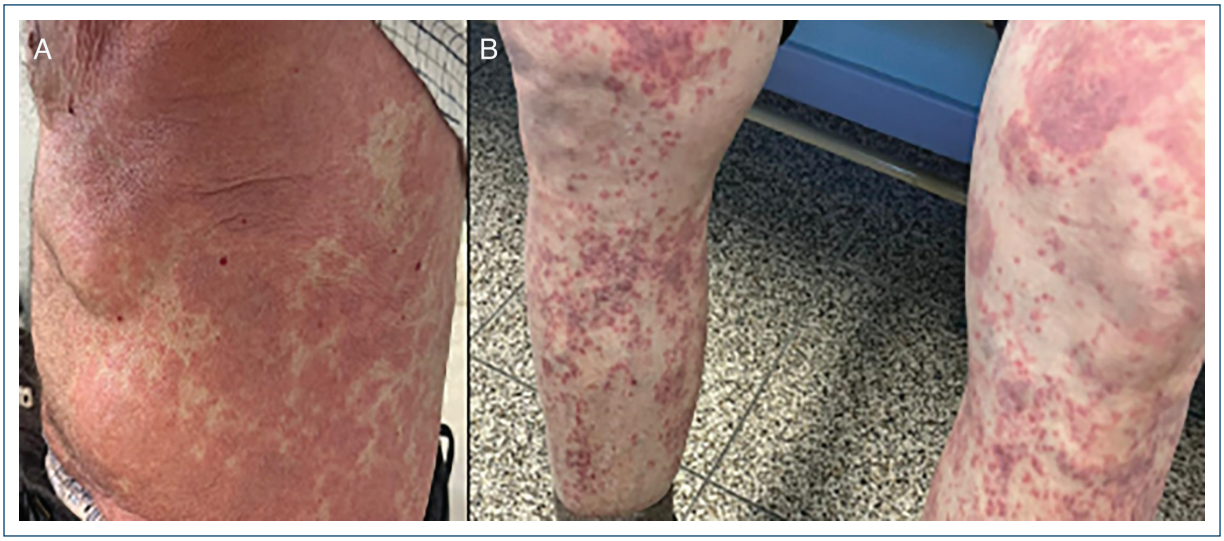

Figure 1. A and **B:** maculopapular rash scattered all over the body.

presents with painful lesions and severe skin rashes, with case reports of dose-dependent late-type reactions[9]. This condition can progress to Toxic Epidermal Necrolysis, which is the most severe form of the skin reaction, is characterized by extensive desquamation of the skin and mucous membranes.

The treatment of DRESS, Stevens-Johnson syndrome, and toxic epidermal necrolysis is complex and requires a multidisciplinary approach[10]. Immediate suspension of medication, the use of corticosteroids, and close patient monitoring are standard measures in managing these conditions.

Given the potential risks associated with late skin reactions to lenalidomide, desensitizing the patient to this medication can be an essential strategy to minimize the risk of adverse reactions. Desensitization involves the gradual and controlled administration of lenalidomide, allowing the patient's immune system to adapt to the presence of the drug[11].

Anticipation and early recognition of the signs and symptoms of adverse skin reactions to lenalidomide are essential for effective and safe intervention. Patient education about possible side effects and open communication with the healthcare team is essential to ensure patient safety and well-being during treatment with lenalidomide.

Anamnesis is one of the fundamental pillars of medical diagnosis. Through an excellent clinical interview, it is possible to gather all the necessary information about the patient's symptoms and background so that an accurate diagnosis and effective treatment can be carried out.

Conclusion

Due to the growing number of patients under the use of lenalidomide for the treatment of hematologic conditions, such as multiple myeloma, it is extremely important that healthcare professionals are alert to the possibility of severe cutaneous adverse reactions. Lenalidomide is known for its effectiveness in treating these diseases. However, patients who use it are subject to developing rashes, dermatitis, and other allergic skin reactions. It is, therefore, essential that the doctor closely monitors possible exanthematous reactions in patients being treated with lenalidomide and is prepared to discontinue the drug if adverse reactions occur. The safety and well-being of patients must be a priority in any medical treatment, and proper management of possible skin reactions is essential to ensure the success of treatment with lenalidomide. In fact, in this case, the reason for the consultation and its organized and objective exploration led to the accidental finding of the rash and its appropriate and rapid management. One of the pillars of general practice is also the holistic approach, which allows us to assess a patient as a whole and not just focus on the symptoms or pathologies they mention in the consultation.

Author contributions

C. Vieira-Maia: Main contributor for the conception, design, acquisition, analysis, and interpretation of data for the work. She also drafted the work, gave final approval

of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. J.E. Ramos: He contributed to the conception and design of the work. He also helped draft the work, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A.C. Morgado: She contributed to the conception and design of the work. She also helped draft the work, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Ethical considerations

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Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CASE REPORT

Erythema *induratum* secondary to *Pseudomonas aeruginosa* bacteremia in an elderly patient: a rare case report

Eritema induratum secundário a bacteriemia a Pseudomonas aeruginosa em doente idoso: relato de um raro caso clínico

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Abstract

Erythema *induratum* (EI) is a rare form of panniculitis, often associated with tuberculosis but which can be linked to other infections or idiopathic. We report a case of an atypical presentation of EI secondary to *Pseudomonas aeruginosa* bacteremia. An 84-year-old man with chronic kidney disease on hemodialysis was admitted for left leg cellulitis and *Pseudomonas aeruginosa* bacteremia. Despite antibiotic therapy, he developed nontender, erythematous nodules on his left leg. Histopathology revealed a mixed-pattern panniculitis consistent with EI. Targeted antibiotic therapy led to overall improvement. EI typically presents in adult women and rarely in elderly men. Differential diagnosis included infectious panniculitis, erythema *nodosum* and ecthyma *gangrenosum*. Negative microorganism stainingand a favorable antibiotic response confirmed the diagnosis. This case highlights a rare association of EI with infection by *P. aeruginosa* and emphasizes the importance of comprehensive diagnostic evaluation in atypical clinical presentations.

Keywords: Erythema *induratum*. *Pseudomonas aeruginosa*. Nodular vasculitis. Panniculitis.

Resumo

O eritema *induratum*é uma forma rara de paniculite, frequentemente associada à tuberculose, mas que também pode ser secundária a outras infeções ou ser idiopática. Apresentamos um caso de uma manifestação atípica de eritema *induratum*-secundário a bacteriemia por *Pseudomonasaeruginosa*. Um homem de 84 anos, com doença renal crónica sob hemodiálise, foi internado por celulite da perna esquerda e bacteriemia a *Pseudomonasaeruginosa*. Apesar da terapêutica antibiótica, desenvolveu nódulos eritematosos e indolores na perna esquerda. A histopatologia revelou um padrão misto de paniculite, consistente com o diagnóstico de eritema *induratum*. A terapêutica antibiótica direcionada levou a uma melhoria global do quadro clínico. O eritema *induratum*apresenta-se tipicamente em mulheres adultas, sendo raro em homens idosos. O diagnóstico diferencial incluiu paniculite infeciosa, eritema nodoso e ectima gangrenoso. A coloração negativa para microrganismos e a resposta favorável à terapêutica antibiótica confirmaram o diagnóstico. Este caso destaca uma associação rara entre o eritema *induratum*e infeção por *Pseudomonas aeruginosa*, sublinhando a importância de uma avaliação diagnóstica abrangente em apresentações clínicas atípicas.

Palavras-chave: Eritema *Induratum*. *Pseudomonas aeruginosa*. Vasculite nodular. Paniculite.

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Introduction

Erythema *induratum* (EI), also known as nodular vasculitis, is a rare form of panniculitis characterized by erythematous nodules typically located on the lower limbs. Initially described as a hypersensitivity reaction to *Mycobacterium tuberculosis* (EI of Bazin)[1,2], EI can also be associated with other diseases, drugs, or be idiopathic[2].

This case report describes an unusual presentation of EI secondary to *Pseudomonas aeruginosa* bacteremia in an elderly patient with multiple comorbidities. This is a unique presentation that highlights the diverse etiologies of EI and the diagnostic challenges it presents.

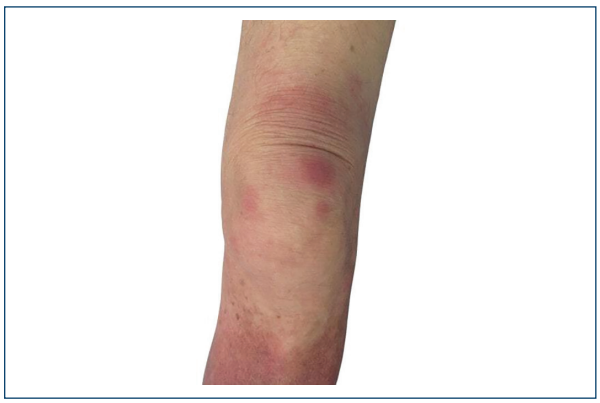

Figure 1. Physical examination revealing edema, slight erythema, and five nontender, erythematous, centimetric nodules distributed in a sporotrichoid pattern on the anterior aspect of the upper third of the left leg and knee.

Case presentation

An 84-year-old man with a history of chronic kidney disease on hemodialysis, cerebrovascular disease, atrial fibrillation, hypertension, hyperuricemia, and diabetes was admitted to the Nephrology Department due to left leg cellulitis and bacteremia caused by *Pseudomonas aeruginosa*.

After six days of hospitalization under targeted antibiotic therapy, dermatology was consulted due to persistent inflammatory lesions on the affected limb. Examination revealed edema, slight erythema, and increased local temperature, with five nontender, erythematous, centimetric nodules distributed in a sporotrichoid pattern on the anterior aspect of the upper third of the left leg and knee (Fig. 1). Differential diagnosis included infectious panniculitis and erythema *nodosum*.

A deep skin biopsy of one nodule was performed. Histopathological examination (Fig. 2) revealed a mixed-pattern panniculitis, with a marked mixed inflammatory infiltrate, multiple neutrophils, abscess formation, multinucleated giant cells, leukocytoclasia, cytosteatonecrosis, focal granuloma formation, and some vessels with fibrinoid necrosis, with negative staining for bacteria, mycobacteria and fungi, favoring the diagnosis of EI.

Complementary investigation for etiological study revealed elevated inflammatory markers (erythrocyte sedimentation rate of 68 mm/1st hour, c-reactive protein 3.25 mg/dL), a normal chest X-ray, negative serologies for human immunodeficiency virus, syphilis, hepatitis B and C, and a negative interferon-gamma release assay (IGRA) test.

The diagnosis of EI of Whitfield (or nodular vasculitis) secondary to *P. aeruginosa* infection was made. The patient showed overall improvement with targeted antibiotic therapy, including 17 days of piperacillin/tazobactam and 14 days of amikacin. The skin nodules ulcerated, giving place to painless superficial ulcers, with good response to local wound care.

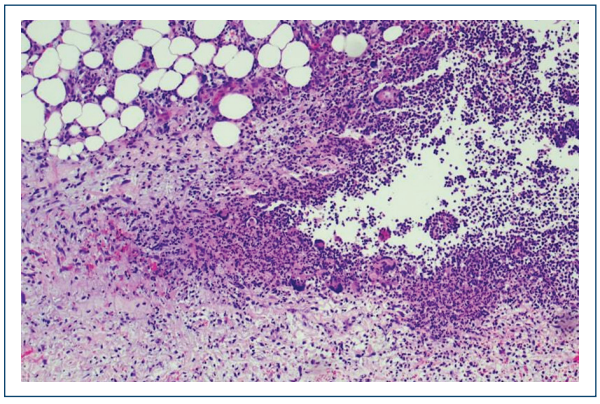

Figure 2. Histopathological examination (hematoxylin & eosin, 100x) of a deep skin biopsy revealing a mixed-pattern panniculitis, with a marked mixed inflammatory infiltrate, multiple neutrophils, abscess formation, multinucleated giant cells, leukocytoclasia, cytosteatonecrosis, focal granuloma formation, and some vessels with fibrinoid necrosis.

Given the absence of symptoms associated with the skin lesions, the good response to local treatment, and the resolution of the associated infection, the patient remains under clinical surveillance and complete healing is expected.

Discussion

Erythema *induratum* is traditionally classified into three subtypes: associated with tuberculosis (Bazin

Table 1. Summary of the reported cases of infectious panniculitis secondary to *Pseudomonas aeruginosa*

Author and year	Patient's gender and age	Clinical presentation
Gosnell H et al. 2021	Male, 57 years	Diffuse, erythematous subcutaneous nodules, and several necrotic ulcerations surrounded by erythematous halos, on the abdomen, upper, and lower extremities
Yendo et al. 2022	Female, 44 years	Erythematous nodules on the upper back, chest, face, arms, and breasts
Penz et al. 2010	Female, 72 years	Ulcers on the right leg and a nodule on the right thigh
Moyano et al. 2011	Female, 63 years	Erythematous nodules, some with pustules on the surface
Bagel et al. 1986	Female, 56 years	Erythematous subcutaneous nodules, pustules, and hemorrhagic blisters on the extremities
Patterson et al. 1989	ND	No information available
Roriz et al. 2014	Female, 80 years	Multiple ulcers on the right lateral malleolus and inflammatory nodules on the left thigh
Roriz et al. 2014	Male, 50 years	Inflammatory nodules on the left leg, with some infracentimetric cutaneous ulcers
Roriz et al. 2014	Female, 70 years	Inflammatory nodules on the right limb
Aleman et al. 1999	ND	Erythematous subcutaneous nodules on the posterior surface of the right leg
Picard et al. 2011	Female, 82 years	Multiple painful red-purple nodules on the right leg and inguinal lymphadenopathy
Saito et al. 2024	Male, 11 months	Erythema in the right abdomen and left lower leg

type), associated with other diseases or drugs (Whitfield type), and idiopathic. Latent or active tuberculosis is the most commonly reported identifiable cause[1,2]. Differentiation between these subtypes relies on clinical history, physical examination and complementary investigations, as clinical and histological findings alone are indistinguishable[2].

Erythema *induratum* typically affects adult women and presents with subcutaneous erythematous nodules on the posterior aspect of the lower legs, which can ulcerate and heal with scarring and lipoatrophy[1,2]. Systemic symptoms are generally absent[2]. Diagnosis requires an incisional biopsy for histopathological and microbiological examination to exclude infectious panniculitis[2,3].

The histopathological hallmark of EI is a lobular panniculitis with necrosis and a mixed granulomatous infiltrate with vasculitis[1,2]. The inflammatory infiltrate is mixed, containing lymphocytes, plasma cells, histiocytes, neutrophils, and eosinophils, with extravascular foci of fibrinoid necrosis[2,4]. The vasculitis may involve various vessel types in the subcutaneous septa and/or lobules[2].

Treatment primarily involves addressing the underlying disease, together with symptomatic treatment including nonsteroidal anti-inflammatory drugs, rest, elevation, and compression[1,2]. Successful treatment of the underlying condition usually leads to the resolution of EI[1,2,4].

In the described clinical case, the leg nodules subsided along with the improvement of the systemic infection following antibiotic administration, suggesting that EI was caused by *P. aeruginosa* infection. This diagnosis was supported by the negative IGRA test and negative microbiological stains, excluding tuberculosis and infectious panniculitis, respectively. However, the location of the nodules on the anterior leg and knee, and the fact that the patient was an elderly man, are atypical for this diagnosis, posing a diagnostic challenge.

The main differential diagnosis considered was infectious panniculitis secondary to *P. aeruginosa*, a rare cause. In our case, despite negative histopathological stains, skin cultures were not performed. Another important differential diagnosis to consider in the context of *Pseudomonas bacteremia*was ecthyma *gangrenosum*, but the absence of blister formation or necrotic ulcers ruled out this option.

The patient shows a favorable clinical evolution, with resolution of the underlying infection, progressive healing of the leg ulcers, and no recurrence of nodules.

Literature reports 12 cases[3,5-9] of infectious panniculitis secondary to *P. aeruginosa* (Table 1). However, to

our knowledge, this is the first reported case of EI secondary to P. aeruginosa, and it's therefore important to highlight the clinical presentation and management of this rare cause of EI.

Conclusion

This case report emphasizes the importance of considering EI in the differential diagnosis of inflammatory skin lesions in patients with *P. aeruginosa* bacteremia. Comprehensive clinical evaluation, histopathological examination and exclusion of common infectious agents are crucial for accurate diagnosis and management. The successful resolution of the patient's skin lesions with appropriate antibiotic therapy highlights the importance of treating the underlying cause in EI. This case adds to the limited literature on nontuberculous etiologies of EI and emphasizes the need for awareness of its diverse presentations and etiologies.

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Conflicts of interest

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Ethical considerations

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DERMATOLOGY IMAGES

Skin ulcers due to *Serratia marcescens* mimicking a neutrophilic dermatosis of the hand

Úlceras cutâneas por Serratia marcescens mimetizando dermatose neutrofílica da mão

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A 74-year-old woman with prior history of hypertension medicated with enalapril presented to the Dermatology department due to recurrent ulcerated lesions on the right hand for the last 7 years. A previous skin biopsy was compatible with neutrophilic dermatosis of the hand, and the patient was treated with topical corticosteroids without significant change. An extensive analytical study, including autoimmunity, infectious serologies and protein electrophoresis, was unremarkable.

Physical examination revealed six ulcers on the lateral aspect of the second finger and dorsum of the right hand and wrist (Fig. 1).

A skin biopsy of the edge of an ulcer showed a dermal polymorphic infiltrate with suppuration (Fig. 2). No infectious agents were found using hematoxylin-eosin and special stains.

Serratia marcescens (*S. marcescens)* was isolated from cultures of the base of an ulcer. Fungi and acid-fast bacilli specific cultures were negative. The patient was treated with trimethoprim-sulfamethoxazole (800/160 mg twice daily) with clinical improvement after 2 weeks and complete remission in 6 weeks (Fig. 3). No relapse was observed during 15 months of follow-up.

Serratia marcescens (*S. marcescens)* is a gram-negative anaerobic bacillus from the Enterobacteriaceae family[1]. Skin infections caused by *S. marcescens* are rare and mainly occur in immunocompromised patients[2-4]. In the last years, more attention has been paid to this pathogen in Dermatology, given its increasing incidence and complex antibiotic resistance profile[1].

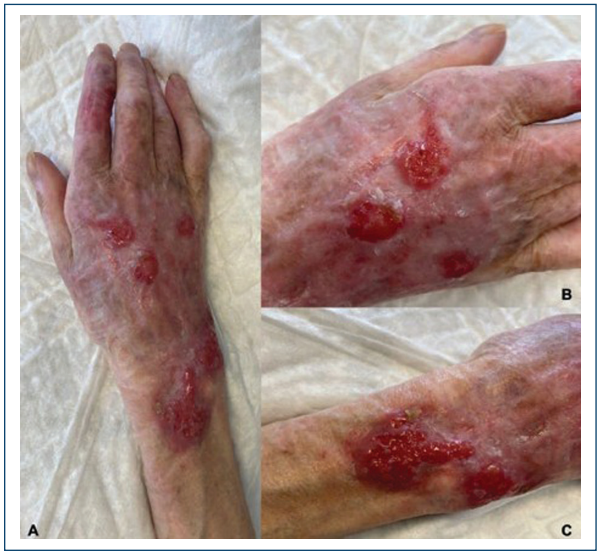

Figure 1. A, **B**, and **C:** skin ulcers of the dorsum of right hand and wrist; **B** and **C:** close images showing ulcers with a violaceous infiltrated border.

Here we describe a case of multiple hand ulcers resembling neutrophilic dermatosis. This similarity was previously described in a case mimicking pyoderma gangrenosum[5,3]. Diagnosis of pyoderma gangrenosum

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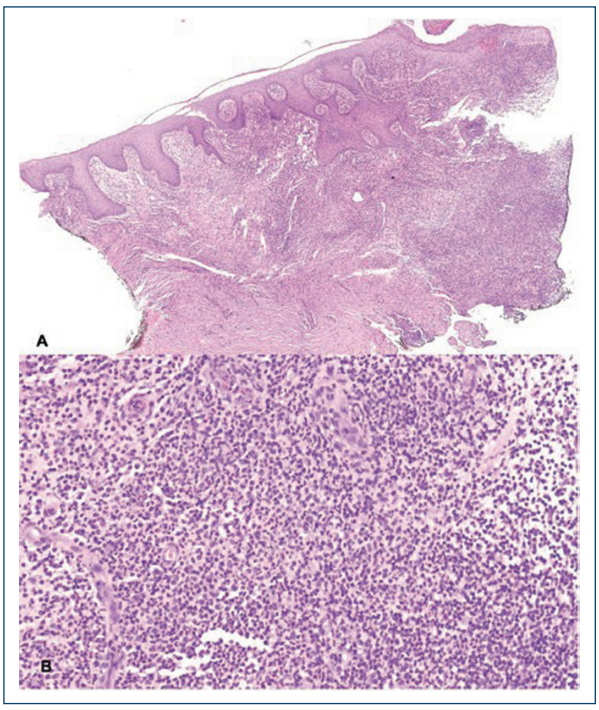

Figure 2. **A** and **B:** hematoxylin-eosin-stained sections at 50× and 200×, respectively. **A:** superficial ulcer and dense infiltrate on the dermis; **B:** close-up of the inflammatory infiltrate showing predominance of neutrophils.

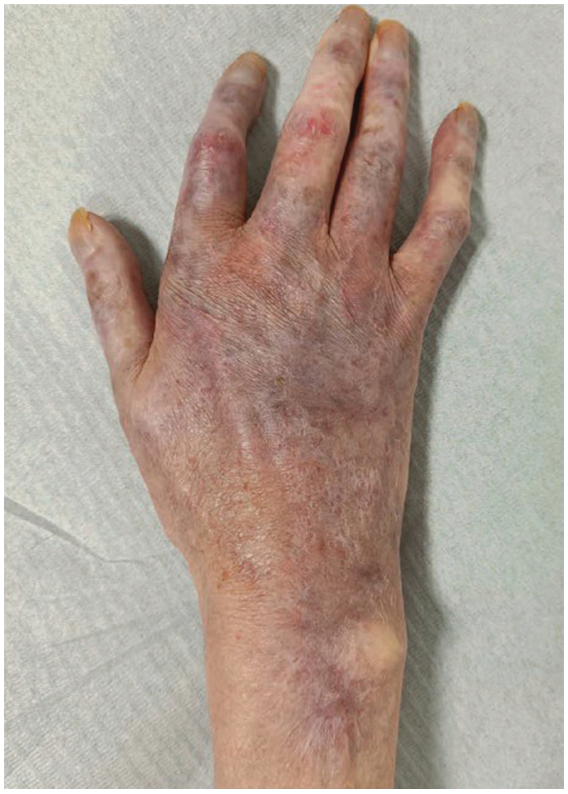

Figure 3. Complete healing of the ulcers 6 weeks after treatment with trimethoprim-sulfamethoxazole.

implies the exclusion of other conditions, namely infections[5]. This case highlights the importance of performing cultures in ulcers, specifically when facing treatment failure.

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Conflicts of interest

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Ethical considerations

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DERMATOLOGY IMAGES

Exuberant, infiltrative, and disfiguring form of mucocutaneous leishmaniasis

Forma exuberante, infiltrativa e desfigurante de leishmaniose mucocutânea

*Leandro de Oliveira-Bispo[1], Laís Büttner-Sartor[1], Gabriella Di Giunta-Funchal[2], Barbara Hartung-Lovato[1,3], and Gustavo Moreira-Amorim[1,3]**

[1]Sector of Dermatology, Santa Teresa Hospital, Santa Catarina State Secretary for Health, São Pedro de Alcântara; [2]Polydoro Ernani de São Thiago University Hospital, Santa Catarina Federal University, Florianópolis; [3]Faculty of Medicine, South Santa Catarina University, Palhoça. Santa Catarina, Brazil

We report a case of a 54-year-old male with mucocutaneous leishmaniasis, confirmed by press imprinting smear (positive for amastigote forms). He was originally from an endemic region for leishmaniasis americana in northern Brazil and had a history, from 10 years ago, of a single ulcerated lesion on his upper arm that cured spontaneously. In the last 6 months, he started with throat pruritus that progressed into verrucous violet plaques covering more than 50% of his face (Fig. 1). We performed a skin biopsy for imprinting, cultures, and histopathology, that identified amastigotes (Figs. 2 and 3). Cutaneous leishmaniasis is a noncontagious infectious disease endemic in some regions of Brazil that can affect skin and mucous membranes[1]. It is transmitted by different species of mosquitoes that carry the promastigote form of leishmania parasites in their gut and inoculate them into the skin of the human host. These promastigotes are phagocytosed and transform into amastigotes and multiply themselves. Initially, there is usually a single painless ulcer with framed borders that heals itself spontaneously[1,2]. Depending on the parasite and the immune response of the host, years after the first lesion disappears, the

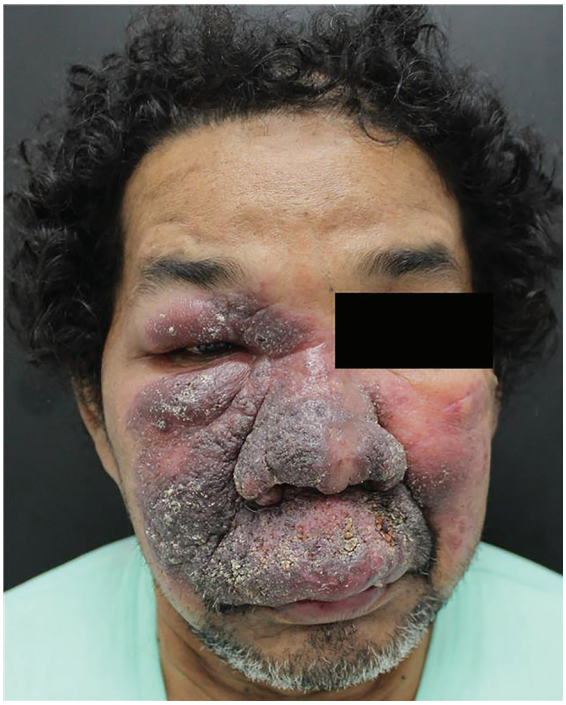

Figure 1. Violet verrucous plaques, on an erythematous base and diffuse edema of the base.

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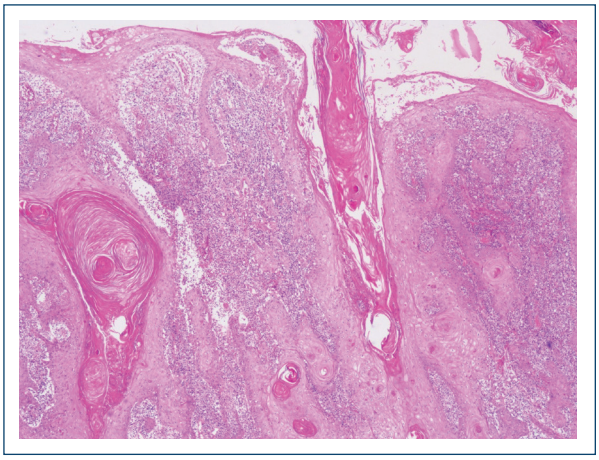

Figure 2. Hematoxylin and Eosin (H&E) staining, 10x. Pseudocarcinomatous epithelial hyperplasia, with dense, chronic inflammatory infiltrate, extending to the deep reticular dermis.

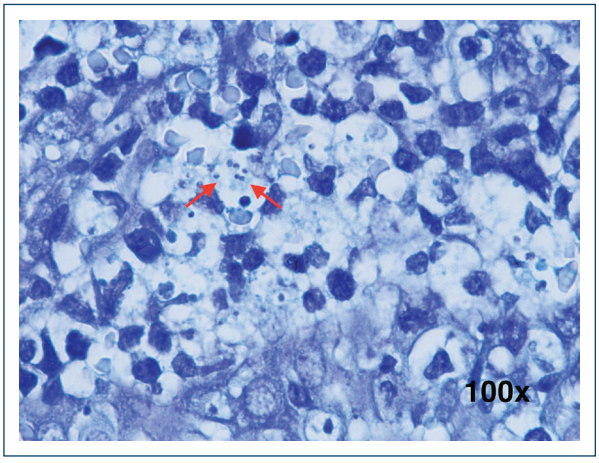

Figure 3. Giemsa staining, 100x. The arrows point to the presence of amastigote forms inside the histiocytes.

disease might recur. The mucocutaneous form of the disease is usually caused by an intense immunopathological response and is more prevalent in immunocompromised patients[3]. It can present as plaques or verrucous lesions and may cause destruction of the lips, palate and nasal septum. Therefore, differential diagnoses should include sporotrichosis, leprosy, deep mycosis and even squamous cell carcinoma[1-3]. Patient failed treatment with pentavalent antimony, requiring a full course of liposomal amphotericin B, with apparent clinical cure after 6 months. This case highlights the importance of recognizing the clinical aspects in early stages of the disease to avoid permanent sequelae.

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Conflicts of interest

None.

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DERMATOLOGY IMAGES

Malignant melanoma: clinical and digital dermoscopy combined with colour doppler skin ultrasound

Melanoma maligno: clínica e dermatoscopia digital combinada com ecografia cutânea com padrão doppler colorido

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The diagnosis of malignant melanoma using digital dermoscopy, combined with cutaneous ultrasound employing color Doppler imaging, is a powerful approach for the early detection of the tumor and subsequent therapeutic management. It provides a real-time, qualitative assessment of the direction and velocity of blood flow, allowing for the identification of flow abnormalities such as turbulence, blockages, or abnormal flow patterns.

A 67-year-old male, phototype 2, Dutch patient came to the clinic with a dark brown, asymmetric lesion of the left arm with 15 mm largest diameter and 1 year of evolution (Fig. 1). The clinical history reported no significant sun exposure, but the patient had also a nodular tumor on his back.

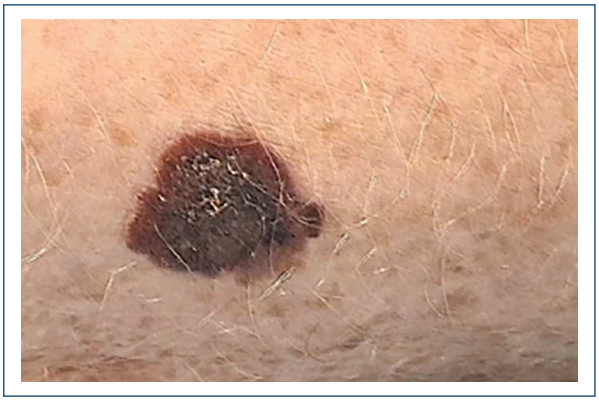

Figure 1. Asymmetric dark brown tumor.

Dermatoscopy revealed disorganized and irregular pigment network, with dark brown to black dots and globules scattered across the lesion with a central area showing whitish, structureless zones, whitish streaks and shiny vascular structures (Fig. 2).

A GE ultrasound machine with a high-frequency probe (20 HZ) with color Doppler revealed increased blood flow within the lesion. The irregular and chaotic branching of the vessels is a hallmark of tumor neovascularization. The velocity scale indicates blood flow, at relatively low velocities typical of tumors where newly formed vessels may be tortuous or inefficient. The underlying hypoechoic area represents the melanoma itself, which is typically less echogenic (darker) on ultrasound compared to surrounding tissue. The surrounding tissue and vessels may also be compressed or displaced by the tumor supporting the notion of an invasive lesion (Fig. 3).

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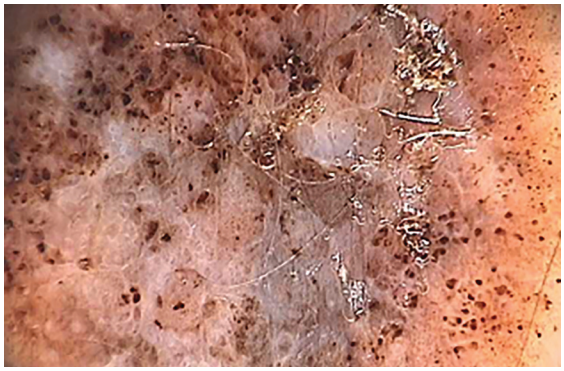

Figure 2. Irregular dark brown to black dots and globules scattered across the lesion.

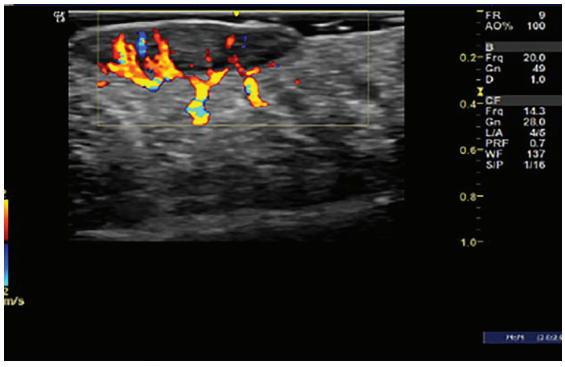

Figure 3. Irregular and chaotic branching vessels.

Based on the clinical, dermoscopic and echographic assessments, a clinical diagnosis of malignat melanoma was made[1-3].

Histopathological analysis revealed nodular melanoma with a maximum thickness of 0.65 mm. The absence of lymphovascular permeation, neurotropism, satellitosis or regression, as well as ulceration, was noted. Mitotic activity of 1 atypical mitosis figure/mm^2.

According to the AJCC staging system, this lesion is classified as T1a, and the patient was treated with a surgical margin of 1 cm.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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