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Chilblain lupus: A rare form of cutaneous lupus erythematosus — A case report

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Abstract

Chilblain lupus erythematosus is a rare, cold-induced form of chronic cutaneous lupus that can occur in both genetic and sporadic forms. It is characterized by acral skin lesions and is commonly associated with autoimmunity and type I interferon pathway activation. Diagnosis is based on clinical features and histological findings. While topical and systemic therapies can be effective, the disease is often chronic and relapsing. We describe a case of a 48-year-old woman with chilblain lupus erythematosus who achieved almost complete clinical remission following treatment with hydroxychloroquine and methotrexate.

Keywords

dermatology, immunology, inflammatory dermatoses, chillblain

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Introduction

Chilblain lupus erythematosus (CHLE) is a rare, chronic variant of cutaneous lupus erythematosus (CLE), presenting as painful, violaceous, or erythematous lesions on acral areas—such as the fingers, toes, ears, and nose—typically triggered and/or worsened by cold exposure. CHLE can occur as a primary skin condition or in association with systemic lupus erythematosus (SLE), and may have either a familial or sporadic origin. Lesions are typically pruritic, sometimes painful, erythematous to violaceous, and may ulcerate in chronic or severe cases. The condition is more common in women and may precede or accompany other forms of lupus. Up to 20% of patients with CHLE may eventually meet criteria for SLE.[1–5] Diagnosis is primarily clinical but supported by histopathological examination showing perivascular lymphocytic infiltrate, interface dermatitis, and dermal mucin deposition. Direct immunofluorescence may reveal deposits of immunoglobulins and complement at the dermo-epidermal junction.[5,6] Familial forms of CHLE are associated with mutations in selected genes including TREX1, SAMHD1, and TMEM173, all of which are involved in nucleic acid sensing and type I interferon signalling.[7–10] These genetic mutations lead to chronic type I interferon activation, contributing to autoimmunity.[8–10] Management includes protection from cold, topical corticosteroids, and calcineurin inhibitors. Systemic therapies such as hydroxychloroquine, methotrexate, or other immunosuppressants may be required for refractory disease.[10–12] JAK inhibitors have shown promise, particularly in familial interferonopathy-related.[1,7,9] However, complete disease remission is uncommon, and relapses are quite frequent.[5]

Case report

A 48-year-old woman with a history of chronic spontaneous urticaria and Raynaud's phenomenon came to our attention due to nodular lesions localized on the toes, which arose in 2015 and had a chronic relapsing course and worsening during the winter period. The lesions were associated with a burning sensation, and she reported an inability to warm her

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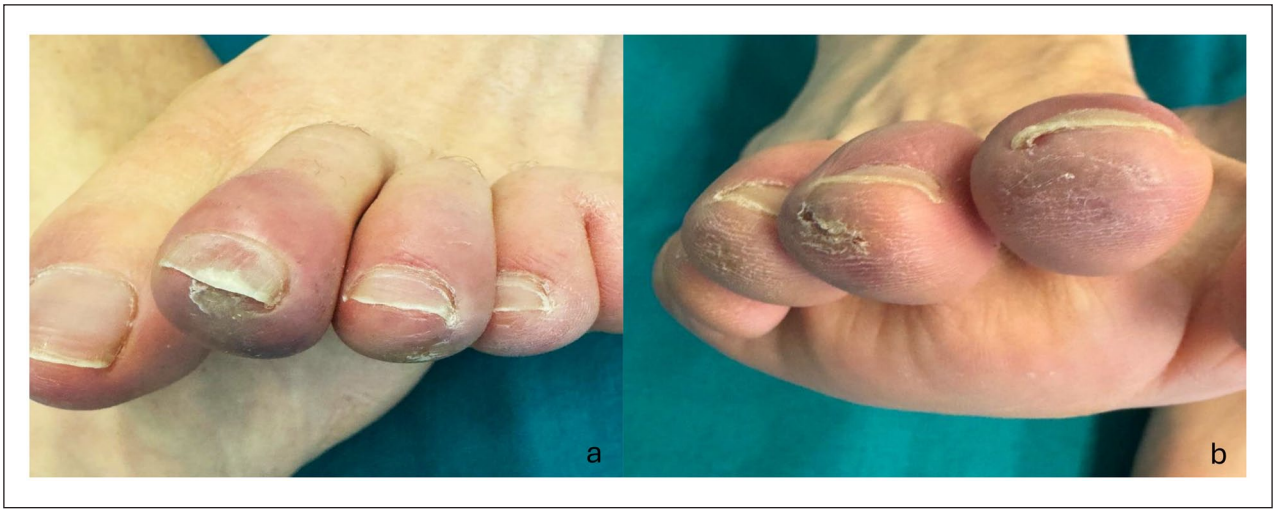

Figure 1. a) Erythrosquamous plaques and livid nodules at the tips of the left toes. (b) Violaceous patches at the tips of the right toes.

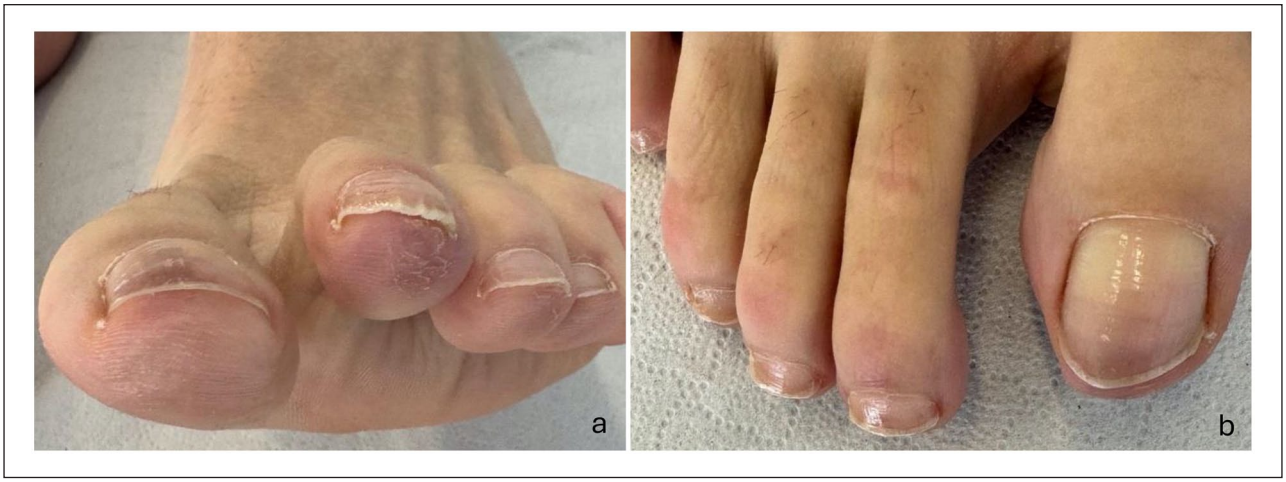

Figure 2. Left (a) and right (b) toes after 6 months of treatment with methotrexate in combination with hydroxychloroquine.

feet despite wearing thick socks. She was not taking any medications apart from oral antihistamines. Physical examination revealed erythematous to violaceous lesions on the toes with overlying light scaling (Figure 1(a) and (b)). Laboratory tests revealed slightly elevated antinuclear antibodies (titer 1:160, granular pattern), positivity for anti-Smith antibodies (28.60 Chemiluminescent Units), negativity for anti-RNA antibodies, and absence of cryoglobulins and cold agglutinins. Complement levels (C3 and C4) were within normal limits. Skin biopsy revealed a mild perivascular lymphocytic infiltrate, interface dermatitis with vacuolization of the basal layer, scattered necrotic keratinocytes in the lower epidermis, and increased dermal mucin. Nailfold capillaroscopy showed severe peripheral microangiopathy, giant capillary loops, and microhaemorrhages. Based on clinical, histological, and immunological findings, a diagnosis of CHLE was made. Initial treatment with hydroxychloroquine (200 mg twice daily) and tacrolimus 0.1% ointment, along with conservative measures (e.g. warmth protection), resulted in partial improvement. Methotrexate was then used as an add-on treatment at 12.5 mg/week. Within 6 months, the patient achieved almost complete clinical remission of all lesions, which has remained stable for 6 months to date (Figure 2(a) and (b)).

Discussion

CHLE is a rare variant of cutaneous chronic lupus erythematosus characterized by cold-induced acral lesions that can be resistant to standard therapy. Although its pathogenesis is not fully understood, type I interferon signalling appears to play a central role, particularly in familial cases associated with mutations in DNA-sensing pathways. This case illustrates a favourable outcome in a patient with CHLE who was refractory to hydroxychloroquine but responded well to low-dose association with methotrexate. Clinicians should maintain a high index of suspicion for CHLE in patients presenting with cold-induced acral lesions and systemic immunosuppression

should be considered when topical treatments and antimalarial agents fail. The differential diagnosis includes several conditions with overlapping clinical features. Perniosis represents a benign inflammatory response to cold that can closely resemble CHLE, but typically occurs in the absence of systemic autoimmunity. Furthermore, lupus pernio is a cutaneous manifestation of sarcoidosis, usually affecting the face and nasal region with violaceous plaques or nodules, and is not precipitated by cold exposure. Cryoglobulinemia should also be considered, as it involves the deposition of cryoprecipitable immunoglobulins, leading to cold-sensitive vasculitic lesions. Lastly, cold panniculitis presents with tender, erythematous to violaceous subcutaneous plaques at sites of cold exposure usually the tighs and buttocks but in contrast to CHLE, these lesions are self-limited and typically resolve within a few weeks. This case highlights that hydroxychloroquine and topical tacrolimus may be partially effective, but recurrences are common. Second-line systemic therapies mainly include immunomodulators and immunosuppressants, such as prednisone and mycophenolate mofetil, which are considered when patients fail to respond to or cannot tolerate first-line medications. However, treatment options for patients with CHLE may be limited by variable efficacy and patient comorbidities. Methotrexate, a folate antagonist with immunomodulatory effects, has been reported to be effective in recalcitrant CLE, including cases of CHLE, which three out of four of them showed a clear clinical improvement at weekly doses ranging from 10 to 25 mg.[13] In our case, methotrexate association with hydroxychloroquine led to complete remission of CHLE. Although many patients experience a relapsing course, early diagnosis and escalation to systemic immunomodulation can help prevent chronic lesions and potential progression to SLE. Given the role of interferon in CHLE pathogenesis, future therapeutic directions may include the use of targeted agents such as JAK inhibitors, particularly in familial or genetically confirmed interferonopathies.

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Consent for publication

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