Chilblain Lupus Erythematosus Presenting With Bilateral Hemorrhagic Bullae of Distal Halluces

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To the Editor:
A 20-year-old man with no notable medical history presented to our dermatology clinic for evaluation of mildly painful, hemorrhagic bullae on the bilateral halluces of 1 month’s duration. On initial presentation the patient reported the lesions developed after wearing a new pair of tight-fitting shoes, suggesting a diagnosis of trauma-induced bullae. The patient was instructed to wear loose-fitting shoes and to follow up in 6 weeks to assess for improvement. At follow-up the bullae had resolved with residual violaceous patches on the bilateral distal halluces. He additionally developed a faint retiform erythematous patch on the left distal toe (Figure 1). The patient also had reticulate erythematous patches on the dorsal aspects of the hands extending to the forearms and legs resembling livedo reticularis. The patient was unsure if the skin lesions were triggered or worsened by cold exposure and reported that he smoked half a pack of cigarettes daily. At this time, the differential diagnosis still included trauma; however, there was concern for either embolic, thrombotic, or connective-tissue disease. A 4-mm punch biopsy of the left distal hallux demonstrated basal vacuolar interface dermatitis with superficial and deep perivascular inflammation and deep periadnexal mucin deposition (Figure 2) consistent with lupus dermatitis.

Serologic workup revealed increased antinuclear antibody titers of 1:320 (reference range, <1:40) and anti-Ro/Sjögren syndrome antigen antibodies of 86 (reference range, <20). There was no elevation in anti–double-stranded DNA, anti-Smith, antiribonucleoprotein, or anticardiolipin antibodies. Complement levels also were within reference range. Furthermore, the patient denied a history of Raynaud

PRACTICE POINTS
• Up to 20% of patients with chilblain lupus erythematosus (CHLE) will develop systemic lupus erythematosus (SLE), necessitating close long-term follow-up.
• Medications such as antihypertensives, antifungals, chemotherapeutic agents, and tumor necrosis factor α inhibitors have been reported to trigger CHLE.
• Chilblain lupus erythematosus is less responsive to traditional antimalarial agents commonly used to treat SLE.
• Management of CHLE includes physical protection from cold environments, calcium channel blockers, topical and systemic steroids, and pentoxifylline, among other treatment modalities.
phenomenon, photosensitivity, oral ulcers, joint pain, shortness of breath, pleuritic chest pain, arthritis, blood clots, or any other systemic symptoms. Additional evaluation by the rheumatology department did not support criteria for systemic lupus erythematosus (SLE). In the context of the clinical presentation, histologic findings, and serologic markers, a diagnosis of chilblain lupus erythematosus (CHLE) was made. He was counseled on sun protection and smoking cessation and declined systemic therapy citing concern for side effects. Follow-up with the dermatology and rheumatology departments was advised.

Cutaneous lupus erythematosus (CLE) comprises various forms of lupus, including acute cutaneous lupus, subacute cutaneous lupus, and chronic cutaneous lupus. Chilblain lupus erythematosus is a rare subset of chronic CLE that first was described in 1888 and is characterized by tender violaceous papules and plaques that typically present in an acral distribution (ie, fingers, toes, nose, cheeks, ears). The skin lesions often are triggered or exacerbated by cold temperatures and dampness. As the lesions evolve, they can ulcerate, fissure, become hyperkeratotic, or result in atrophic plaques with scarring. A subset of patients also may have concurrent Raynaud phenomenon. Up to 20% of patients will eventually develop SLE, especially those patients with concurrent discoid lupus erythematosus, warranting close long-term follow-up. Serologic studies can reveal antinuclear antibodies, anti-Ro/Sjögren syndrome antigen antibodies, rheumatic factor, and anti–double-stranded DNA antibodies. Hypergammaglobulinemia also is a common finding in patients with CHLE, affecting more than two-thirds of patients. Typical features of CHLE seen on histopathology include interface dermatitis, perivascular lymphocytic infiltrate, apoptotic keratinocytes, lichenoid tissue reaction, and increased dermal mucin.

Chilblain lupus erythematosus most commonly presents sporadically; however, there is a familial form that has been previously described. Sporadic CHLE usually occurs in middle-aged females, in contrast to familial CHLE, which presents in early childhood. The pathogenesis of the sporadic form is poorly understood, but it is thought to be stimulated by vasoconstriction or microvascular injury provoked by cold exposure. Furthermore, hypergammaglobulinemia and the presence of autoantibodies may contribute to the pathogenesis by increasing blood viscosity. The familial form is caused by heterozygous mutations in either TREX1, a gene encoding the 3′ to 5′ repair exonuclease 1, or SAMHD1, the gene encoding for SAM domain and HD domain 1. TREX1 is an intracellular deoxyribonuclease that has specificity for single-stranded DNA. It is hypothesized that a deficiency in TREX1 leads to the accumulation of nucleic acids, which activate innate immune sensors and lead to a type I interferon response that favors the development of autoimmunity.

Several drugs including thiazides, terbinafine, calcium channel blockers, angiotensin-converting enzyme inhibitors, and chemotherapeutic agents have been reported to trigger CHLE. Tumor necrosis factor α inhibitors have been shown to precipitate CHLE. Of note, drug-induced CHLE usually is limited to the skin and has not been shown to progress to SLE. Lebeau et al described a patient with breast cancer and preexisting CHLE that flared while the patient received docetaxel therapy, suggesting that certain drugs may not only induce but also may aggravate CHLE.

Many of the therapies that are effective in SLE such as antimalarial agents (ie, chloroquine, hydroxychloroquine) often are less efficacious in treating the lesions of CHLE. However, these patients often can be managed successfully by physical protection from the cold environment. Calcium channel blockers such as nifedipine also have been implicated, as they counteract vasoconstriction, which is thought to contribute to the pathogenesis of CHLE. Topical and systemic steroids also have been used to treat CHLE. Dapsone and pentoxifylline
are other treatment modalities that have been effective in select cases of CHLE.\(^5\) Boehm and Bieber\(^7\) reported near resolution of CHLE with mycophenolate mofetil in an elderly woman with skin lesions that had been refractory to systemic steroids, antimalarial agents, azathioprine, dapsone, and pentoxifylline, suggesting that mycophenolate mofetil may be a therapeutic option for recalcitrant cases of CHLE. Local immunosuppressive agents such as tacrolimus also can be considered in treatment-refractory disease.

Chilblain lupus erythematosus is a rare chronic form of CLE that typically occurs sporadically but also has a familial form that has been described in several families. It most commonly is observed in middle-aged women, but we describe a case in a young man. Although CHLE typically does not respond well to traditional lupus therapies used in the management of SLE, good effects have been observed with cold avoidance, calcium channel blockers, and topical or oral steroids. For treatment-refractory cases, mycophenolate mofetil and other immunosuppressive agents have been shown to be effective.

REFERENCES