Necrolytic acral erythema in a patient with sarcoidosis

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INTRODUCTION

Necrolytic acral erythema (NAE) is considered a rare dermatologic condition in a predominately acral distribution that commonly presents in middle-age women and African Americans.[1] The condition has reported association with hepatitis C virus (HCV) infection[1]; however, several cases have been reported in the absence of HCV, undermining a causal link to the clinical association.[2] Our clinical observation supports a conceptual model to NAE that is driven by metabolic disruption in zinc metabolism.

Abbreviations used:

HCV: hepatitis C virus
NAE: necrolytic acral erythema

CASE REPORT

A 51-year-old African-American man with a history of sarcoidosis, diabetes mellitus, and chronic hepatitis presented with an intermittently pruritic, symmetric eruption on the bilateral dorsal feet, posterior calves, medial thighs, and upper buttocks of 1-year duration. The eruption began on the lower extremities and progressed to involve feet, thighs, and buttocks. Prior treatment with oral antibiotics, topical triamcinolone 0.1% cream, and hydrophor did not improve symptoms. Review of systems was positive for chronic cough caused by pulmonary sarcoidosis. He otherwise denied gastrointestinal symptoms, weight loss, fevers, or chills. The patient was taking 10 mg/d of prednisone for management of his sarcoidosis.

Physical examination found well-demarcated, violaceous, hypertrophic plaques, with erosions and peripheral erythema on the bilateral dorsal feet, posterior calves, and medial thighs (Fig 1). An isolated similar plaque was found on the upper buttocks, centered at the gluteal cleft. Laboratory workup was significant for elevated liver function enzymes; normal ferritin, ceruloplasmin, prothrombin time, niacin, biotin, and glucagon; negative hepatitis A, B, C viral antigen or antibodies, anti-smooth muscle antibody, transglutaminase antibody, and human-immunodeficiency virus antibodies; low albumin; and mildly decreased zinc levels. Magnetic resonance elastography imaging findings were consistent with liver cirrhosis without evidence of malignancy. Colonoscopy showed a single hyperplastic polyp but was otherwise normal. Liver biopsy found moderate interface and lobular hepatitis with microgranulomas and mild fibrosis, compatible with sarcoidosis.

Punch biopsies of the left medial thigh and posterior calf (Fig 2) found psoriasiform epidermal hyperplasia, subtle papillomatosis associated with confluent parakeratosis, and a diminished granular cell layer. Neutrophils were present in the stratum corneum. Multiple foci of columnar necrosis and dyskeratosis of keratinocytes within the epidermis were also observed. Based on comprehensive clinical history and pathologic evidence, a diagnosis of NAE was made, and treatment with 220 mg zinc supplementation twice daily was initiated. Concurrently, his prednisone requirements decreased to 5 mg/day during this time. The patient subsequently experienced resolution of skin lesions, which has remained stable without relapse with zinc, 220 mg twice-daily therapy, at 2.5 years' follow-up.

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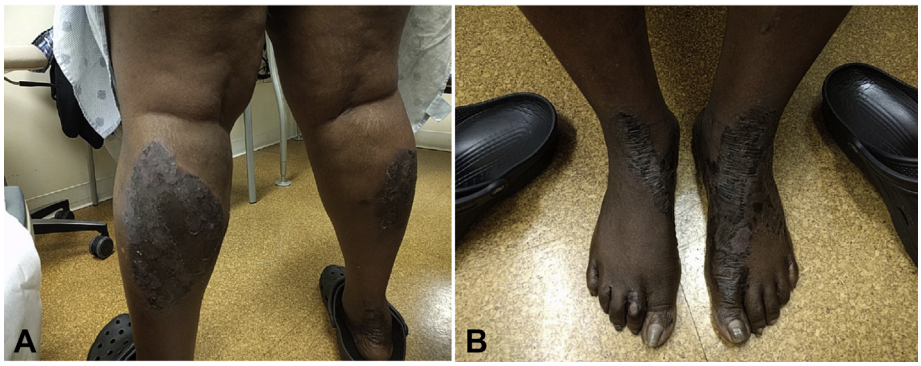

Fig 1. Well-demarcated, violaceous, hypertrophic, erosive plaques on the posterior calves (**A**) and dorsal feet (**B**).

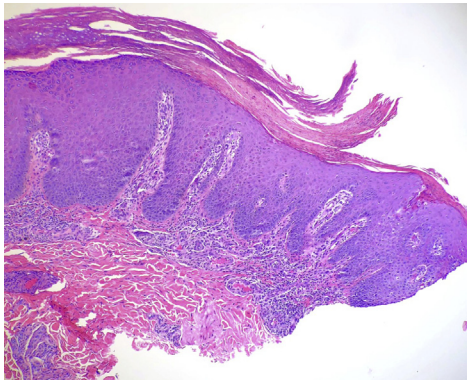

Fig 2. Biopsy of the left medial thigh shows psoriasiform epidermal hyperplasia, parakeratosis, and regions of focal keratinocyte necrosis evident on histopathology.

DISCUSSION

Zinc functions biologically in cell growth, development, and differentiation. In keratinocytes specifically, zinc is important for wound healing, cellular survival, and inhibition of inflammation, offering a biological rationale to the chronic inflammatory and necrotic pathology of NAE when deficient.[3] Rather than a causal relationship with HCV, NAE may instead be driven by a zinc deficiency that ultimately mediates development of the dermatologic condition. Although hepatic dysfunction can be commonly triggered by HCV, sarcoidosis is the likely cause in our patient, which may have led to his mildly low zinc serum levels.

Zinc levels in active NAE skin lesions have been found to be significantly lower than unaffected skin of the same patient, reinforcing a possible role for zinc in NAE pathophysiology.[4] Additionally, zinc monotherapy has shown clinical improvement in NAE patients with and without zinc serum abnormalities, suggesting a critical role for zinc in the pathophysiology of NAE regardless of serum evidenced deficiency. Although many patients with NAE have normal zinc serum levels, the protein-bound zinc that is found in plasma comprises only 0.1% of total body zinc, meaning an abnormal zinc value is a rather delayed sign of deficiency.[3] Other theories behind NAE pathophysiology and hepatocellular dysfunction are rooted in hyperglucagonemia as the predominate source of dermatologic necrosis.[5] The interplay between low zinc levels and other metabolic abnormalities induced by hepatocellular dysfunction may likely all contribute to NAE development; however, the necessity versus sufficiency of the specific elements in this pathogenesis conceptual model remains unclear.

Moist cases reported in literature unresponsive to zinc supplementation alone also had concurrent liver dysfunction. However, once the underlying etiology of the metabolite deficiency was addressed with treatment, such as with interferon-α therapy and ribavirin for HCV clearance, the lesions improved.[6,7] NAE should thus be treated with both zinc supplementation and therapy that addresses the underlying source of deficiency.[1,2,4,5]

To our knowledge, the only reported case with normal liver function that did not respond to zinc therapy was a case of woman with systemic lupus erythematosus and associated nephritis managed on daily steroid therapy.[8] Her low baseline zinc levels were likely caused by her chronic kidney disease. Unfortunately, she was reportedly given zinc supplementation only until serum levels normalized, which was likely subtherapeutic. As her NAE reportedly resolved with prednisone discontinuation, relapsed during a high-dose pulse therapy course of prednisone for an systemic lupus erythematosus flare, and quickly resolving thereafter, steroid therapy may have been another contributing factor. Because steroid receptors require functionality of a zinc-finger motif, a biologically plausible explanation may be that an increased transcription of steroid receptors may

further decrease available zinc stores for other critical functions such as reproductive health, immune status, and wound repair. In fact, a prior study found that daily steroid use can decrease serum zinc levels.[9] In our patient, zinc supplementation alongside prednisone dose lowering may have contributed to NAE resolution and maintenance.

Therapies used for NAE that do not directly address the zinc deficiency or the underlying abnormality, such as phototherapy or steroid therapy, may result in mild or temporary improvement but evidence of treatment efficacy with long-term follow-up is limited.[1]

NAE should be considered in middle-age patients presenting with lower extremity erosive plaques and consistent histopathologic features, particularly in a setting of hepatocellular dysfunction and despite seronegative results for HCV and normal zinc abnormalities. Early recognition is important to resolve a chronic, distressing inflammatory dermatologic condition. Additionally, a new diagnosis of NAE may even signal further workup of liver disease if not previously identified.

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