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Case Presentation

Necrolytic acral erythema masquerading as cellulitis

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Abstract

Necrolytic acral erythema (NAE) is a rare cutaneous sign of hepatitis C virus infection and has recently been linked to zinc deficiency. It presents as well-demarcated erythematous plaques in a sandal-like distribution on the dorsal feet with psoriasiform epidermal hyperplasia on histology. Our patient reported a 9-month history of progressive bilateral lower extremity erythema, swelling, erosions, and nail dystrophy that failed to improve despite multiple courses of antibiotics for presumed lower extremity cellulitis. Serum studies revealed zinc deficiency. This case supports the association of NAE with both HCV infection and zinc deficiency and highlights the pitfalls in the diagnosis of chronic unrecognized NAE. Suspected cases of NAE should prompt evaluation for underlying HCV and zinc deficiency to avoid treatment delay and associated complications.

Keywords: Necrolytic Acral Erythema, zinc deficiency, Hepatitis C

Abbreviation/Acronym List: NAE: Necrolytic Acral Erythema, HCV: Hepatitis C Virus

Introduction

Necrolytic acral erythema (NAE) is an uncommon cutaneous manifestation of hepatitis C virus (HCV) infection. It has been recently associated with zinc deficiency through an unclear mechanism [1]. Previous cases report a mean age of 40 years with a high prevalence of 92% in African populations [2]. First described in Egypt in 1996, the condition typically manifests as pruritic sharply demarcated erythematous to violaceous lichenified plaques on the lower extremities [3]. Clinical symptoms include pruritus, a burning sensation, and pain in 93%, 16%, and 14% of patients, respectively [2]. Herein, we present a patient with HCV and recently discovered zinc deficiency with chronic lower extremity erythema and erosion misdiagnosed as chronic cellulitis. Clinical presentation and histopathology support a diagnosis of NAE. We discuss the association of NAE with HCV and zinc deficiency and highlight the importance of early recognition and intervention to prevent misdiagnosis and secondary complications.

Case synopsis

A 61-year-old man with a history of intravenous drug use and HCV infection presented to the University of California, Davis Medical Center with bilateral lower leg erythema and pain. The patient reported his condition started 9 months prior as sores on the feet which spread to involve the legs. Subsequent erosion and pain led to multiple hospitalizations over a 6-month period and frequent IV antibiotic administration for presumed cellulitis. In the absence of improvement, a dermatology consultation was obtained. Clinical examination revealed confluent moderately well-defined erythematous to violaceous plaques with superficial erosions extending from the dorsal feet and ankles to the lower legs bilaterally. On both hands were violaceous plaques extending from the distal interphalangeal joint to the fingertip. Associated twenty-nail dystrophy was noted. Serum laboratory studies revealed zinc deficiency (38 $\mu\text{g}/\text{dL}$, reference 55-150 $\mu\text{g}/\text{dL}$).



Figure 1 a,b. (a) Violaceous plaques extend from the distal interphalangeal joint to the fingertips. (b) Confluent moderately well-defined erythematous to violaceous plaques with superficial erosions on the feet and lower legs

A 4 mm punch biopsy from the leg revealed psoriasiform epidermal hyperplasia with confluent parakeratosis and eosinophilic spongiosis. Periodic Acid-Schiff-diastrase stain was negative for dermatophytes. A diagnosis of cellulitis was made by the primary medical team and the patient was treated with cefepime and vancomycin without improvement. Upon dermatology consultation, based on clinicopathologic correlation in the setting of HCV infection, a diagnosis of necrolytic acral erythema was rendered. Systemic antibiotics were discontinued and oral zinc supplementation as well as consideration of HCV treatment was recommended. Unfortunately, the patient was lost to follow-up.

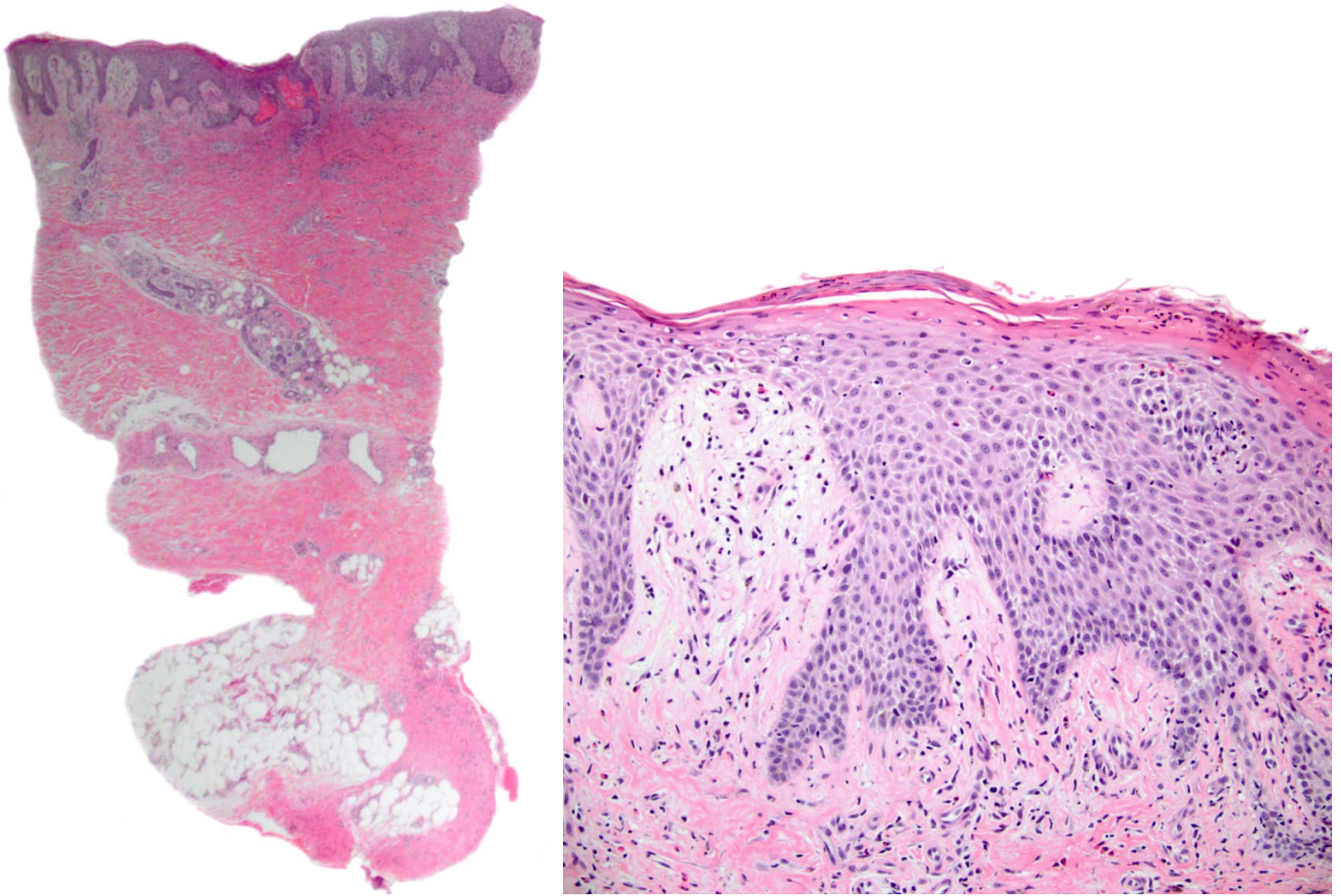


Figure 2. Low power magnification of a biopsy from the leg reveals psoriasiform epidermal hyperplasia(hematoxylin & eosin stain: 4X).

Figure 3. High power magnification of a biopsy from the leg reveals psoriasiform epidermal hyperplasia with hypogranulosis and confluent parakeratosis (hematoxylin & eosin stain, 40X).

Discussion

Necrolytic acral erythema is a rare cutaneous manifestation of HCV infection and has recently been associated with zinc deficiency [1]. It has been reported worldwide in Pakistan, India, and the United States with the majority of cases emerging from Egypt. This may relate to the high prevalence of HCV in Egypt (up to 20%) compared to worldwide (3%). One recent cohort study suggests a 1.7% prevalence of NAE in HCV infected individuals [4].

Based on a longitudinal study by Abdallah et al, NAE develops in three stages [3]. It begins as a scaly erythematous papule with a deep red center that later develops into the second stage, a sharply defined erythematous to violaceous lichenified plaque with scale. In the final stage, lesions demonstrate increased pigmentation and progressive thinning with crusting and erosion, as demonstrated in the current case. Disease remission may occur spontaneously. Common sites of involvement include the dorsal feet, legs, and knees [1]. Although previous reports indicate the palms, soles, nail bed, and nail plate are usually uninvolved in NAE, a study by Bentley et al suggests NAE may include pitting of the nails and palmoplantar involvement similar to psoriasis [5]. Biopsy of NAE typically reveals psoriasiform epidermal hyperplasia with papillomatosis and parakeratosis [6]. Keratinocyte necrosis and superficial pallor of the epidermis may also be seen. Bentley et al also suggested that a lack of classic histology should not preclude a diagnosis of NAE.

NAE may be clinically challenging to differentiate from psoriasis, eczematous dermatitis, and several nutrient-linked dermatitides [3, 7]. These conditions are included in the differential diagnosis of NAE. In contrast to the typical silver scale of psoriasis, NAE often has a darker scale with an erythematous rim [3]. Histologically, one distinguishing feature of NAE as compared to psoriasis and eczematous dermatitis may be the presence of necrotic keratinocytes, which are absent in the latter diagnoses [7]. Clinical and laboratory data are helpful in differentiating nutrient-linked cutaneous conditions from NAE. Acrodermatitis enteropathica, associated with an inborn error resulting in zinc deficiency, displays more erosion and indistinct borders compared to NAE, although there may be significant clinical overlap, particularly in cases of NAE with associated zinc deficiency [3]. Pellagra, resulting from niacin (Vitamin B3) deficiency, consists of an erythematous eruption typically on the head, upper chest, and distal arms along with neurologic and gastrointestinal symptoms. Pancreatic glucagonoma can present with psoriasiform plaques, called necrolytic migratory erythema. However, this condition tends to favor flexural surfaces rather than the acral distribution seen in NAE. Unlike in cases of glucagonoma, patients with NAE have normal glucagon levels [5].

NAE is considered to be a part of the nutrient-linked disorders called necrolytic erythemas [8]. However, there is controversy regarding a link between NAE and zinc deficiency. Some authors believe the decreased skin and serum levels of zinc may be related to HCV infection [1, 9]. Although several studies have shown improvement after administration of oral zinc [7, 9], others report no response [3]. One study reported improvement from oral zinc therapy despite normal plasma zinc levels [7]. Hence, treatment with oral zinc may be beneficial despite normal serum zinc levels. According to one paper, zinc sulfate supplementation at a dose of 220 mg by mouth twice a day should be first line therapy for NAE [2].

Other attempted treatments of NAE include topical tar and oral tetracycline, which showed no benefit; corticosteroids, oral amino acid supplementation, and intralesional triamcinolone injections resulted in minimal improvement in a subset of patients [3, 5]. Parenteral interferon therapy has been reported to lead to resolution of NAE in select cases [7]. Topical tacrolimus ointment has also been shown to be effective [10].

Herein, we present a case of extensive persistent and progressive necrolytic acral erythema masquerading as lower extremity cellulitis. NAE is a rare cutaneous manifestation of HCV infection. This case supports the association of NAE with HCV infection and zinc deficiency. It also highlights potential diagnostic and therapeutic delays and secondary complications, which can ensue if NAE persists unrecognized and untreated. Cases of suspected NAE warrant evaluation for underlying HCV and zinc deficiency followed by timely management. Additional long-term studies are needed to determine effective and standard treatments for NAE.

Table 1: Summary of Necrolytic Erythemas

Disease	Key Clinical Features
Necrolytic Acral Erythema	Associated with zinc deficiency and hepatitis C[8]; well-demarcated, erythematous & violaceous, plaques on the dorsal feet [3].
Acrodermatitis Enteropathica	Associated with zinc deficiency, Crohn’s Disease, AIDS, and malnutrition [8]; Typically occurs in infancy as periorificial, acral, and perineal erythematous patches with erosion [3, 11]; Diarrhea, failure to thrive, and alopecia may accompany cutaneous signs.
Necrolytic Migratory Erythema	Associated with zinc deficiency and glucagonoma [8]; Scaly, crusting, erythematous patches favoring flexural areas, such as the groin and intergluteal cleft [12]; Cheilitis and glossitis may be present.
Pellagra	Associated with niacin deficiency, malnutrition, and carcinoid syndrome [8]; Scaly, hyperpigmented patches in a photodistributed pattern on the head, neck, and distal arms [3]; Neurological and gastrointestinal symptoms are additional features.

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