Necrolytic Acral Erythema: A Review of the Literature

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The estimated time to complete this activity is 1 hour.

GOAL

To understand necrolytic acral erythema (NAE) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Evaluate leading theories on the pathogenesis of NAE.
2. Identify patients who may benefit from further diagnostic testing for hepatitis C virus infection.
3. Propose treatment options for NAE.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and generalists.

CME Test and Instructions on page 316.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: May 2009.

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Necrolytic acral erythema (NAE) has been described as an early cutaneous marker for hepatitis C virus (HCV) infection. It most commonly presents as a well-defined, dusky, erythematous eruption with marked hyperkeratosis and a dark red rim associated with pruritus or burning. Necrolytic acral erythema bears microscopic and clinical resemblance to other necrolytic erythemas, including necrolytic migratory erythema (NME) and several nutrient-deficient syndromes. It is distinct, however, in its predominantly acral distribution and strong association with HCV infection.

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The pathogenesis is unknown, but a relationship to metabolic alterations has been hypothesized. Optimal therapy appears to be treatment of the underlying HCV infection using a combination of ribavirin and interferon alfa; oral zinc therapy may be an alternative but useful therapy. Cases of NAE without HCV infection suggest that more work needs to be done defining NAE and its relationship to HCV.

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Necrolytic acral erythema (NAE) is a distinct skin lesion first described in the 1990s. In 1996, el Darouti and Abu el Ela[1] described NAE on the dorsal aspects of the feet in 7 Egyptian patients with hepatitis C virus (HCV) infection. Cutaneous findings of NAE share all microscopic features and some clinical features of other necrolytic erythemas,[1] including acrodermatitis enteropathica, pellagra, necrolytic migratory erythema (NME), low biotin levels, and fatty acid deficient states.[2] Necrolytic acral erythema, however, is distinguished by its predominant acral distribution and strong association with HCV infection. Also included in the differential diagnosis are acrokeratosis neoplastica (also known as paraneoplastic acrokeratosis), psoriasis, erythrokeratoderma (also referred to as erythrokeratodermia variabilis), and nummular dermatitis. A variety of theories exist regarding the pathogenesis of NAE (Table).

Based on a search of the literature using the PubMed database (National Library of Medicine), 69 cases of NAE were reported through 2007 (65 in Egypt and 4 in the United States).[1,2,4-10] More recent cases also have been reported.[11-17] No sex predisposition has been reported thus far. El-Ghandour et al[7] described 23 Egyptian patients with NAE and the

Theories on the Pathogenesis of NAE

Reference (Year)	Theory
el Darouti and Abu el Ela[1] (1996)	Similarities exist between NAE and acrodermatitis enteropathica, pellagra, NME, low biotin levels, and fatty acid deficient states Hypoaminoacidemia and hyperglucagonemia associated with hepatocellular dysfunction may lead to epidermal protein depletion, resulting in necrolysis of epidermal cells
el Darouty and Abu el Ela[3] (1996)	Acral areas exposed to repeated trauma may potentiate the release of arachidonic acid in the presence of elevated serum glucagon levels in chronic liver disease, resulting in the typical distribution of NAE
Nofal et al[4] (2005)	Hypoaminoacidemia and hyperglucagonemia unlikely to be sole factors responsible for NAE Decreased serum albumin levels could lead to high levels of prostaglandins, thereby inducing inflammatory changes of NAE; decreased serum albumin levels also may cause a transitory deficiency in zinc or essential fatty acids in plasma
Abdallah et al[5] (2005)	Zinc has antiapoptotic properties and deficiency may contribute to NAE; decreased epidermal levels of zinc may occur despite serum zinc levels within reference range
Najarian et al[6] (2006)	Zinc deficiency and NAE are physiologically linked

Abbreviations: NAE, necrolytic acral erythema; NME, necrolytic migratory erythema.

mean age (standard deviation) was 41.7 (11.5) years (age range, 11–76 years). Discrepancies in regional prevalence exist, attributable to Egypt being a hyperendemic area for HCV infection, with an approximate prevalence in the general population of 15% to 20%,[18] or differences in HCV strains (HCV genotype 4 being the most common),[7] host susceptibility, and disease recognition.[8]

Cutaneous findings represent a substantial portion of the extrahepatic manifestations of HCV infections. In particular, cutaneous necrotizing vasculitis, lichen planus, mixed cryoglobulinemia, and porphyria cutanea tarda often are linked to HCV infection. Behçet syndrome, erythema multiforme, erythema nodosum, malacoplakia, urticaria, and pruritus also may be associated with HCV infection.[19]

Clinical Presentation

Necrolytic acral erythema typically precedes the diagnosis of HCV infection. In 2 studies, 44 of 53 (83%) patients with NAE presented directly to a dermatologist without a known history of HCV infection.[7,8] Classic NAE appears as well-defined, dusky red, hyperkeratotic plaques with a velvety surface often surrounded by a keratotic border. Most patients have involvement of the dorsal aspects of the feet and/or toes, but other sites include the ankles, legs, and knees, and less commonly the elbows, hands, genitalia, and buttocks.[7,8] Generally, the palms, soles, nail plates, nail beds, and distal aspects of the toes remain unaffected[8]; however, Hivnor et al[9] reported one pediatric patient with additional involvement of the palms, soles, upper thigh, and small lesions on the face and trunk. Lesions typically are described as pruritic and/or eliciting a burning sensation.[18]

Acute NAE lesions appear with prominent erythema, flaccid blisters, and foci of erosions, particularly at the margins. Chronic lesions are described as having a predominant hyperkeratotic surface, less erythema, and a characteristic dark red rim (Figure 1). Central clearing typically is not present and edema may or may not occur.[1,4] Abdallah et al[8] described the evolution of cutaneous findings of NAE according to 3 stages. The initial stage consists of a scaly erythematous papule or plaque, occasionally having a dusky or eroded center. The fully developed stage involves a well-demarcated confluence of papules increasing in diameter and thickness with adherent scale, hyperpigmentation, less erythema, and occasional pustules. The late stage shows sharply circumscribed, thinner lesions with increased hyperpigmentation that is followed by spontaneous relapse and remission.[8]

Histopathology

The histopathology of NAE generally shows mild epidermal hyperplasia; absence of the granular layer and closely adherent, compact, flat-appearing, parakeratotic scale over the epidermis; focal dyskeratosis at higher power magnification; and epidermal pallor in some cases (Figure 2). The histopathology of NAE is similar to NME.

In 2004, Abdallah et al[10] described the histopathologic features of lesions from 30 patients with NAE. Early-stage lesions demonstrated moderate regular acanthosis with variable spongiosis and inflammatory infiltrates resembling nummular dermatitis. In the fully developed stage, findings included psoriasiform epidermal hyperplasia with marked papillomatosis, as well as parakeratosis; focal hypergranulosis; occasional subcorneal pustules; epidermal pallor; vascular ectasia; papillary dermal inflammation; and necrotic keratinocytes, which can become confluent in the upper epidermis and/or track along the acrosyringium. Finally, late-stage lesions displayed minimal to moderate acanthosis and inflammatory cell infiltrate. Pigment incontinence was noted in all stages.[10]

Vacuolar degeneration in the basal cell layer also has been reported as well as blister formation[1,4]

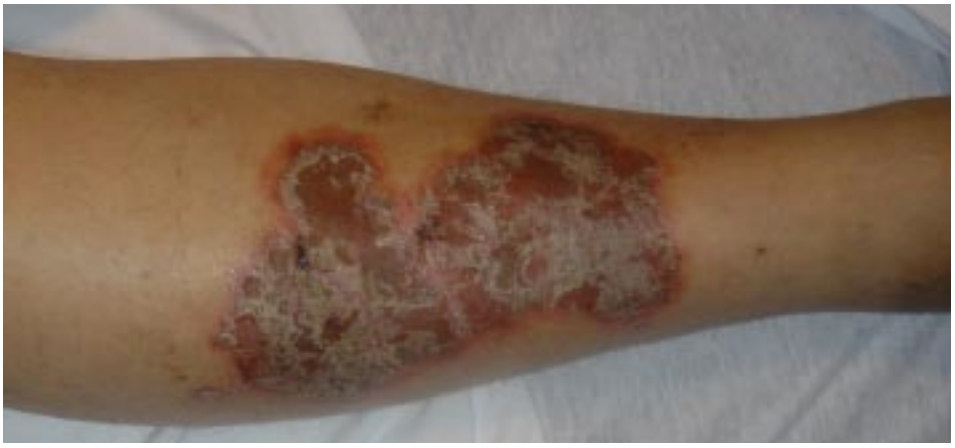

Figure 1. Well-defined, dusky, predominantly hyperkeratotic plaques on the shin demonstrate less erythema and a dark red rim characteristic of classic necrolytic acral erythema.

separating a necrotic upper epidermis from viable subjacent epidermis, specifically in early lesions. In addition, electron microscopy of 5 biopsy specimens demonstrated clumped tonofilaments in keratinocytes but failed to detect any viral particles or HCV RNA by reverse transcriptase–polymerase chain reaction.[7]

Pathogenesis and Treatment

The exact cause of NAE is unknown, but a metabolic alteration due to HCV infection is likely. Based on similar microscopic and clinical features, many hypotheses of the pathogenesis pertain to nutrient deficiencies, as with other necrolytic erythemas. Postulated mechanisms of pathogenesis include hepatocellular dysfunction, hypoaminoacidemia, hyperglucagonemia, hypoalbuminemia, diabetes mellitus, and zinc deficiency.[4]

Two studies have noted a relationship between activity of underlying HCV infection in terms of liver enzymes and severity of skin disease[1,4]; however, one study found no association.[8] Hepatocellular dysfunction with associated hypoaminoacidemia and hyperglucagonemia also has been proposed to play a role in the development of NAE.[20] Low serum amino acid levels may result in epidermal protein depletion leading to necrolysis.[1,4,21]

In a study by Nofal et al,[4] 3 of 5 patients were found to have hypoaminoacidemia; however, little to no improvement was noted after amino acid treatment, regardless of initial serum amino acid levels. Similarly, el Darouti and Abu el Ela[1] reported temporary improvement of skin lesions in 3 of 7 patients with hypoaminoacidemia after treatment with amino acid therapy; however, lesions recurred while patients were still receiving amino acid treatment. These findings have led to speculation that hypoaminoacidemia and hyperglucagonemia unlikely are the sole factors of NAE.[1,4]

Elevated serum glucagon levels may yield greater amounts of arachidonic acid and its metabolites, which could induce the inflammatory changes of NAE.[4,22] el Darouty and Abu el Ela[3] proposed that acral areas exposed to repeated trauma, along with elevated serum glucagon levels occurring with chronic liver disease, may potentiate the release of arachidonic acid, resulting in the typical distribution of NAE. Glucagon levels and their effect on metabolism seem to disrupt the body's homeostasis[22] and affect the development of NAE. The absence of lesions in other areas subjected to trauma challenges this theory.[7] In addition, among 3 reported studies, only 2 of 7 patients with NAE had elevated serum glucagon levels.[2,4,9]

Necrolytic migratory erythema associated with glucagonoma syndrome often is compared to NAE based on strikingly similar histopathologic features. Elevated serum glucagon levels provoke multiple nutrient and vitamin B deficiencies that likely result in NME.[23] It is uncertain if a similar mechanism occurs in NAE. It has been suggested that NAE is a variant of NME rather than a distinct entity.[4] Nonetheless, NAE is unique in its invariable association with HCV infection and acral distribution.

Decreased serum albumin levels also may be a factor in the development of NAE. Albumin sequesters fatty acids released from tissue membranes, making them inaccessible to further degradation to metabolic products such as prostaglandins.[24,25] In addition, albumin is the main carrier of zinc and essential fatty acids in plasma, and decreased serum albumin levels may cause transitory deficiency in 1 or more of these nutrients,[26] which could play a role in the development of NAE. Hypoalbuminemia

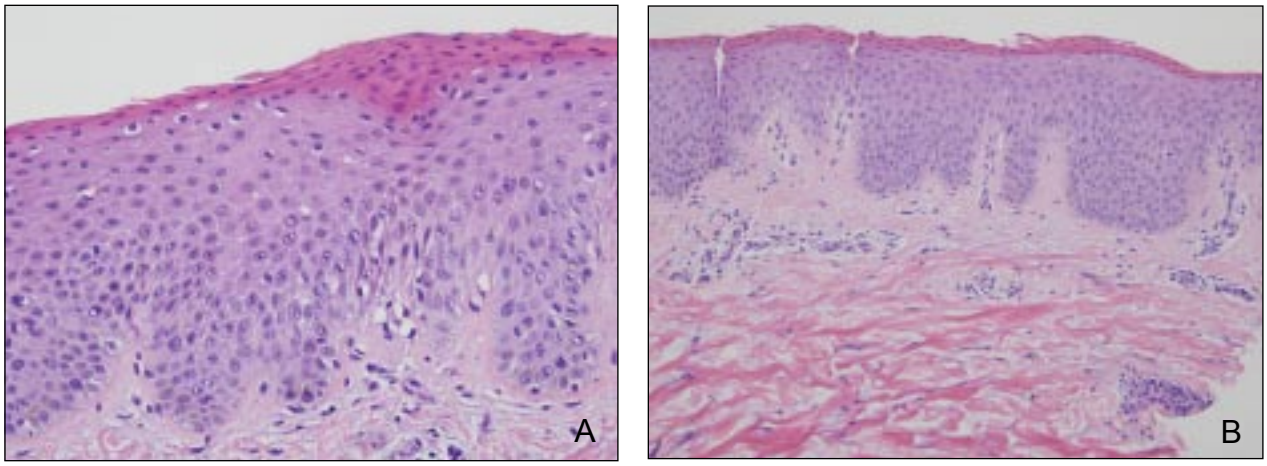

Figure 2. Histopathology of a plaque of necrolytic acral erythema showing epidermal pallor, acanthosis, and parakeratosis (A and B)(H&E; original magnifications ×400 and ×100, respectively).

was noted in 2 patients in case reports by Khanna et al[2] and Hivnor et al,[9] while Nofal et al[4] and El-Ghandour et al[7] reported hypoalbuminemia in 2 of 5 and 3 of 23 patients, respectively.

In one study, 4 of 5 patients were found to be diabetic.[4] Comorbid diabetes mellitus has been reported among cases of NAE.[1,5,8] Mason et al[27] found that while patients with liver disease are known to have a higher prevalence of glucose intolerance, there is some evidence suggesting HCV infection may be an additional risk factor for the development of diabetes mellitus. Additionally, in a cohort of patients with diabetes mellitus, 4.2% (25/596) were found to be infected with HCV compared to 1.6% (6/377) of controls (P=.02).[27] The role, if any, of diabetic cutaneous microangiopathy[28] in the development of NAE needs clarification.[4]

Zinc deficiency is thought to be an important factor in the development of NAE based on similarities to another necrolytic erythema, acrodermatitis enteropathica. Although zinc deficiency has been detected in a few cases of NAE,[4,6] serum zinc levels have been within reference range in the majority of cases.[1,2,5,7,9] Despite this finding, several authors have demonstrated partial to near complete resolution of signs and symptoms with empiric zinc therapy.[1,2,4,6,7,9] One case report of a patient from the United States reported complete resolution of plaques followed by exacerbation of signs and symptoms when the dosage of zinc sulfate was reduced. Oral zinc therapy may be a less toxic treatment option for patients with NAE who are ineligible for or do not respond to antiviral therapy.[5]

The role of zinc, especially in patients with serum zinc levels within reference range, remains unknown. Decreased serum zinc levels may be a late indicator of zinc deficiency. Thus, skin manifestations of zinc deficiency may occur despite having serum zinc levels within reference range.[29] Biochemically, apoptosis plays a role in the pathogenesis of acrodermatitis enteropathica,[30] and Zalewski et al[31] proposed that an intracellular pool of chelatable zinc blocks apoptosis.

Interferon alfa monotherapy was effective in clearing NAE lesions in 2 patients[1,8] and in 1 patient whose condition was refractory to combined amino acid and zinc treatment.[1] The addition of interferon alfa to oral zinc therapy resulted in total clearance in 1 patient.[2] These results suggest that interferon alfa alone may be sufficient to treat NAE[1,8] or may enhance the effect of oral zinc administration. Complete resolution was confirmed in 1 pediatric patient in response to hyperalimentation and combination interferon alfa and ribavirin therapy, despite persistence of detectable viral load and continued hepatic and renal insufficiency.[9] Similarly, another study using combined antiviral therapy reported either substantial improvement or complete remission of lesions among 4 patients, regardless of virologic response.[7] Based on the literature, the optimal therapy for NAE appears to be combination antiviral therapy.

Conclusion

As case reports continue to surface, it is crucial to recognize NAE as an early cutaneous marker for HCV infection. It has been noted that patients typically present to the dermatologist unaware they are infected with HCV and may have underlying liver disease. Therefore, screening for HCV in patients with NAE can potentially lead to early detection and treatment of HCV before irreversible liver damage occurs. Recently, reports have noted NAE without HCV infection, suggesting that more work needs to be done defining NAE and its relationship to HCV.[13,17]

Several areas requiring further investigation include the incidence of NAE among patients with HCV infection; the reason for acral distribution; and the connection between HCV infection, metabolic alteration, and cutaneous lesions.

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