Necrolytic Acral Erythema: An Expanding Spectrum

Analisa V. Halpern, MD; Steven R. Peikin, MD; Pascal Ferzli, MD; Warren R. Heymann, MD

Hepatitis C virus (HCV) infection is the most common chronic blood-borne viral infection in the United States. Well-described cutaneous manifestations of HCV infection include polyarteritis nodosa, porphyria cutanea tarda, type II cryoglobulinemia–associated vasculitis, pruritus, erythema nodosum, urticaria and urticarial vasculitis, lichen planus, and erythema multiforme. First described in 1996, necrolytic acral erythema (NAE) is now recognized as a cutaneous acral eruption uniquely associated with HCV infection. Most patients present with chronic, acral, erythematous, and psoriasiform lesions. Acute presentations of NAE are rare and patients may present with atypical clinical features; in these cases, suspicion for HCV infection may be delayed for weeks to months until more classic chronic lesions develop. In many cases, NAE presents before the patient has been diagnosed with HCV infection, which allows dermatologists the unique opportunity to suspect and diagnose HCV infection based on skin findings alone.

Cutis. 2009;84:301-304.

Case Report

A 50-year-old man presented to the emergency department with extensive erythroderma, flaccid bullae, and hyperkeratosis on his arms, legs, face, and trunk of 3 weeks' duration. The patient had no medical history or history of blood transfusion. He denied allergies, tobacco or alcohol abuse, and drug abuse. Physical examination revealed total body erythroderma; weepy, eroded, crusted patches and plaques over the face, ears, and neck with secondary impetiginization on the neck; scale and erosions on the mid back, elbows, and knees; and edema and desquamation of the facial skin with underlying erythema. Both psoriatic erythroderma and pityriasis rubra pilaris were considered in the differential diagnosis, and liver function studies were ordered in anticipation of starting oral retinoid therapy. The presence of mild transaminitis (alanine aminotransferase, 83 U/L [reference range, 0–48 U/L]; aspartate aminotransferase, 39 U/L [reference range, 0–42 U/L]) prompted the request for a hepatitis evaluation. Hepatitis C virus (HCV) infection (viral load, 9,350,000 IU/mL; HCV genotype 1a) was diagnosed. A skin biopsy was performed on an acute lesion from the mid upper back and demonstrated superficial parakeratosis, patchy interface dermatitis with areas of vacuolar alteration, diffuse epidermal pallor, and focal keratinocyte necrosis throughout the epidermis (Figure 1).

Follow-up physical examination revealed conjunctival injection with mild icterus; diffuse erythroderma of the face, back, abdomen, and chest; and a suggestion of confluent, targetoid, erythema multiforme–like lesions of the forearms. Hyperkeratotic erythematous plaques were present on the hands, feet, knees, legs, and abdomen. Focal swelling of the elbow and marked pitting edema (grade 2+) of the lower legs was observed. The patient's hands and feet had marked platelike and velvety hyperkeratosis, deep erythema, scattered bullae, and full-thickness epidermal fissures (Figure 2). Histologic examination of a lesion on the left palm showed hyperkeratosis, parakeratosis, and acanthosis with psoriasiform elongation of the rete ridges (Figure 3). His fingernails showed onychodystrophy with marked thickening of the nail plates and early onychomadesis (Figure 4). Laboratory evaluation was remarkable for alanine aminotransferase, 108 U/L; aspartate aminotransferase, 53 U/L; γ-glutamyltransferase, 350 U/L (reference range, 0–65 U/L); α_1-fetoprotein, 12 ng/mL (reference range, 0–6 ng/mL); zinc,

Drs. Halpern, Ferzli, and Heymann are from the Division of Dermatology, and Dr. Peikin is from the Division of Gastroenterology, all at the Department of Medicine, Cooper University Hospital–University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School, Camden.

The authors report no conflict of interest.

Correspondence: Analisa V. Halpern, MD, 100 Brick Rd, Marlton, NJ 08103 (analisa_halpern@yahoo.com).

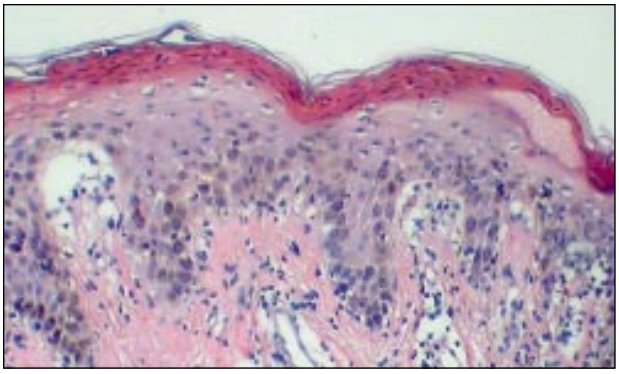

Figure 1. A biopsy specimen from an acute lesion on the mid upper back demonstrated superficial parakeratosis and patchy interface dermatitis with areas of vacuolar alteration. Diffuse epidermal pallor and focal keratinocyte necrosis were found throughout the epidermis (H&E, original magnification ×40).

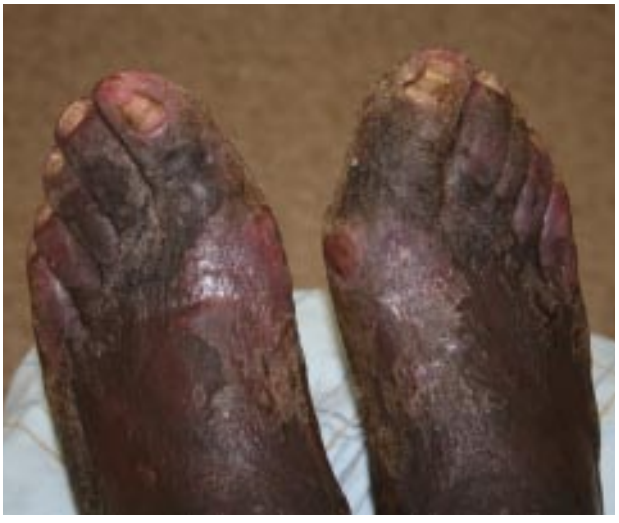

Figure 2. Dorsal aspect of the feet showing velvety hyperkeratotic plaques and toenail involvement.

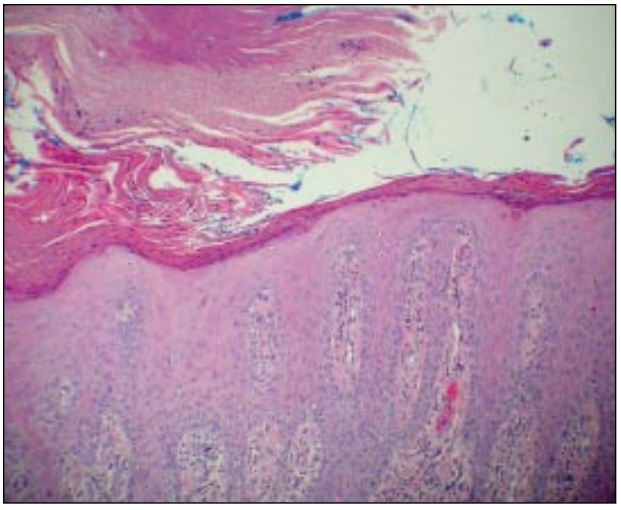

Figure 3. A biopsy specimen from a chronic lesion on the left palm showed hyperkeratosis, parakeratosis, and acanthosis with psoriasiform elongation of rete ridges. Scattered necrotic keratinocytes are present as well as a perivascular mononuclear infiltrate and mild spongiosis (H&E, original magnification ×40).

161 µg/dL (reference range, 70–150 µg/dL); glucagon, less than 50 pg/mL (reference range, 50–200 pg/mL); serum albumin, 3.2 g/dL (reference range, 3.2–5.0 g/dL); and normal SS-A/Ro (Sjögren syndrome antigen A) and SS-B/La (Sjögren syndrome antigen B) antinuclear antibody patterns. Test results for human immunodeficiency virus were negative.

The patient's erythroderma marginally improved with oral corticosteroids and topical triamcinolone acetonide. After initial presentation, the patient was maintained on a slow prednisone taper (40 mg tapered to 10 mg) over 4 months. After a substantial flare at the lower dose, the dosage was increased to 20 mg daily, which the patient then self-tapered to 5 mg over the following 3 months. Corticosteroids were discontinued altogether 10 months after initial presentation because of the development of cataracts.

For social reasons, the patient was not evaluated by the gastroenterology service until nearly 9 months after diagnosis of HCV infection. Liver biopsy specimens showed grade 4 cirrhosis without evidence of hepatocellular carcinoma. Physical examination 9 months after diagnosis was remarkable for extensive desquamative erythroderma of the hands and feet that involved the palms and soles (Figure 5). The nails were shedding. The patient was treated with interferon alfa, ribavirin, and oral zinc sulfate supplementation with marked improvement of the skin condition.

Comment

First described by el Darouti and Abu el Ela[1] in 1996, necrolytic acral erythema (NAE) is considered a unique cutaneous marker of HCV infection. Classically, lesions involve the dorsal aspects of the hands and feet but can involve the thighs, arms, face, trunk, genitals, palms, soles, and nails. Early lesions show erythematous papules or dusky erythematous plaques and flaccid bullae. Chronic lesions show well-demarcated, velvety or finely mamillated, violaceous to erythematous, hyperkeratotic plaques that may resemble erythrokeratodermia or psoriasis. Over time, lesions develop hyperpigmentation and scaling becomes progressively less marked; however, the lesions retain a striking demarcation.[2] Histopathologically,

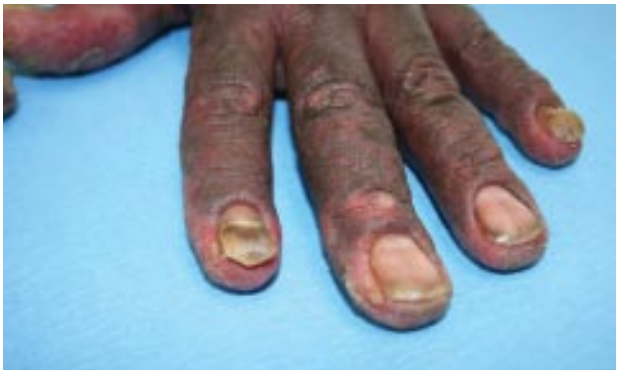

Figure 4. Onychodystrophy and onychomadesis of the fingernails.

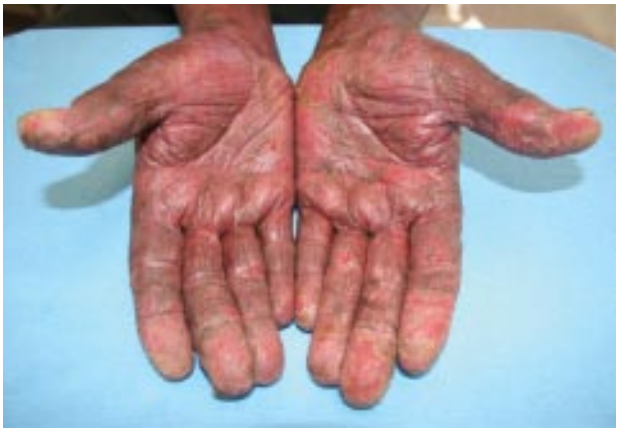

Figure 5. Extensive erythroderma and desquamation of the palms.

early lesions may be indistinguishable from other necrolytic erythemas showing pallor and confluent necrosis of the upper epidermal layers, while more advanced lesions show a thick corneal layer, psoriasiform epidermal hyperplasia, focal basal vacuolization, focal individual keratinocyte necrosis, and a variable superficial perivascular mononuclear infiltrate.[3]

Both clinically and histologically, NAE can mimic other necrolytic erythemas and papulosquamous disorders, most commonly those associated with nutrition deficiency or malignancy. The differential diagnosis of NAE includes necrolytic migratory erythema (NME), acrodermatitis enteropathica/zinc deficiency, biotin or fatty acid deficiency, pellagra, acrokeratosis paraneoplastica, hypertrophic lichen planus, and psoriasis.[4] The disease most commonly mistaken for NAE is NME, a necrolytic erythema classically associated with the glucagonoma syndrome secondary to pancreatic islet cell neoplasia. Of interest, NME without glucagonoma, pseudoglucagonoma syndrome, has been reported in patients with impaired liver function and chronic active hepatitis, and it has been suggested that NAE may in fact be an acral variant of NME.[5,6]

Several pathophysiologic mechanisms for the development of NAE have been proposed, including hypoalbuminemia and hypoaminoacidemia secondary to elevated glucagon levels often seen in patients with liver dysfunction. Low amino acid levels (seen in both NAE and NME) may lead to epidermal protein depletion resulting in necrosis of keratinocytes.[1] Laboratory evaluation in suspected cases of NAE should include hepatitis panel and liver function tests as well as serum glucagon levels and serum zinc levels to rule out NME and acrodermatitis enteropathica. Other laboratory studies include serum albumin and total protein, amino acids, biotin, essential fatty acids, and nicotinamide/vitamin B_3.[1]

Most patients who receive combination interferon alfa and ribavirin for HCV infection show marked improvement and often complete clearance of the cutaneous eruption several months after treatment initiation. Hivnor et al[7] described a pediatric patient with NAE whose skin disease improved with interferon and ribavirin despite a persistently elevated HCV viral load. Interestingly, zinc supplementation has been shown to benefit some patients, even if serum zinc levels are within reference range.[8,9]

This case report illustrates the variability in presentation of NAE, especially in patients with acute lesions that develop prior to an HCV diagnosis. Early lesions may not be limited to the classically described acral psoriasiform eruption. In the proper setting, a differential diagnosis of NAE should be included in patients who present with erythroderma and flaccid bullae with involvement of body sites not commonly associated with NAE, namely the trunk, face, thighs, arms, palms, soles, and nails. Several conditions traditionally have been considered distinct entities under the umbrella of necrolytic erythemas. These conditions may represent similar diseases that lie on a spectrum of variable presentations attributable to a common pathophysiologic pathway. As more cases of this uncommon manifestation of HCV infection are recognized and reported, further information will help to delineate this disease spectrum.

REFERENCES

1. el Darouti M, Abu el Ela M. Necrolytic acral erythema: a cutaneous marker of viral hepatitis C. *Int J Dermatol.* 1996;35:252-256.
2. Abdallah MA, Ghozzi MY, Monib HA, et al. Necrolytic acral erythema: a cutaneous sign of hepatitis C virus infection. *J Am Acad Dermatol.* 2005;53:247-251.

3. Abdallah MA, Ghozzi MY, Monib HA, et al. Histological study of necrolytic acral erythema. *J Ark Med Soc*. 2004;100:354-355.
4. Khanna VJ, Shieh S, Benjamin J, et al. Necrolytic acral erythema associated with hepatitis C: effective treatment with interferon alfa and zinc. *Arch Dermatol*. 2000;136:755-757.
5. Marinkovich MP, Botella R, Datloff J, et al. Necrolytic migratory erythema without glucagonoma in patients with liver disease. *J Am Acad Dermatol*. 1995;32:604-609.
6. Nofal AA, Nofal E, Attwa E, et al. Necrolytic acral erythema: a variant of necrolytic migratory erythema or a distinct entity? *Int J Dermatol*. 2005;44:916-921.
7. Hivnor CM, Yan AC, Junkins-Hopkins JM, et al. Necrolytic acral erythema: response to combination therapy with interferon and ribavirin. *J Am Acad Dermatol*. 2004;50(suppl 5):S121-S124.
8. Abdallah MA, Hull C, Horn TD. Necrolytic acral erythema: a patient from the United States successfully treated with oral zinc. *Arch Dermatol*. 2005;141:85-87.
9. Najarian DJ, Lefkowitz I, Balfour E, et al. Zinc deficiency associated with necrolytic acral erythema. *J Am Acad Dermatol*. 2006;55(suppl 5):S108-S110.