Necrolytic acral erythema is a novel member of the necrolytic erythema family found exclusively in patients with hepatitis C virus (HCV) infection. Acrally distributed, dusky, erythematous plaques with vesiculation evolve into hyperkeratotic lesions resembling psoriasis. Given the prevalence of chronic HCV infection, necrolytic acral erythema probably is a commonly encountered entity misdiagnosed as an inflammatory dermatosis. The paucity of case reports in the United States is likely the result of unfamiliarity with the condition and its viral association. We report a case of necrolytic acral erythema and review the literature summarizing its diagnosis, pathogenesis, and treatment.


Necrolytic erythemas are skin diseases of variable etiology sharing similar clinical and histopathologic characteristics. Causes of necrolytic erythemas include nutritional deficiency, hepatic cirrhosis, neoplasm, and hepatitis C virus (HCV) infection. When correctly identified, necrolytic erythemas allow early detection of serious underlying disorders; therefore, physicians should be cognizant of these diagnoses, especially in patients with lesions unresponsive to topical steroids.

Case Report
A 42-year-old woman with a medical history of human immunodeficiency virus, HCV infection, hypothyroidism, and hypertension was referred by her primary care physician for evaluation of a pruritic eruption of 1 year's duration involving the arms, hands, legs, feet, and back. Further inquiry revealed that the lesions caused substantial burning and were unresponsive to daily applications of over-the-counter emollients. Her medications included epoetin alfa, hydrochlorothiazide, interferon alfa, lamivudine, levothyroxine sodium, losartan potassium, nelfinavir mesylate, and zidovudine.

On physical examination, there were numerous well-demarcated erythematous plaques with superficial erosions and serosanguineous crust on her buttocks and dorsal aspects of the hands and feet (Figure 1). A skin biopsy specimen from the left leg was consistent with psoriasis and the patient was started on clobetasol propionate ointment 0.05%. At her 3-month follow-up, the lesions persisted and a second biopsy specimen was obtained from the distal right hand. The section demonstrated psoriasiform hyperplasia, parakeratosis, loss of the granular cell layer, clusters of dyskeratotic cells, and a moderately intense superficial and mid-dermal perivascular mononuclear cell infiltrate (Figure 2). Necrolytic acral erythema was diagnosed and the patient was prescribed oral zinc. The lesions continued to progress despite treatment.

Comment
In 1996, el Darouti and Abu el Ela1 described 7 Egyptian patients with lesions resembling necrolytic migratory erythema that demonstrated an acral predominance, periorificial sparing, and a uniform association with HCV infection. They designated the condition necrolytic acral erythema and outlined the morphologic, histologic, and serologic findings to differentiate it from other necrolytic erythemas (Table 1).1-5

Necrolytic acral erythema presents with burning and pruritic, dusky, erythematous plaques with vesiculation and/or hyperkeratosis predominantly on the dorsal surfaces of the hands and feet. Hyperkeratotic lesions may simulate psoriasis, but symptomatology and palmoplantar sparing help to exclude the diagnosis. Vesicular lesions may resemble necrolytic
migratory erythema but lack its annular and migratory distribution.

The unifying histologic pattern of necrolytic erythemas is psoriasiform hyperplasia and necrolytic acral erythema shares this characteristic.\(^1\) Other commonalities include papillomatosis, hyperkeratosis, parakeratosis, a perivascular mononuclear cell infiltrate, and a focal absence of the granular cell layer. Focal keratinocyte necrosis and basal vaculopathy have been used as specific identifiers, but they were later found to occur in only 26.7% and 13.3% of cases of necrolytic acral erythema, respectively.\(^1,6\) The lack of pathognomonic histology requires clinical-pathologic correlation and a high index of suspicion to make the diagnosis.

Chronic HCV infection is the sine qua non for diagnosis and has been described in all patients with necrolytic acral erythema to date. Most case reports

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**Figure 1.** Left leg (A) and right foot (B) with well-demarcated erythematous plaques with superficial erosions and serosanguineous crust.

**Figure 2.** Biopsy specimen demonstrating psoriasiform hyperplasia, parakeratosis, loss of the granular cell layer, clusters of dyskeratotic cells, and a moderately intense superficial mid-dermal perivascular mononuclear cell infiltrate (H&E, original magnification ×20).
Necrolytic Acral Erythema

Table 1.
Necrolytic Erythemas and Associated Diseases

<table>
<thead>
<tr>
<th>Necrolytic Erythemas</th>
<th>Associated Disease(s)</th>
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<tbody>
<tr>
<td>Acrodermatitis enteropathica</td>
<td>Zn(^{2+}) (zinc) deficiency</td>
</tr>
<tr>
<td>Necrolytic acral erythema</td>
<td>Hepatitis C virus</td>
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<tr>
<td>Necrolytic migratory erythema</td>
<td>Glucagonoma syndrome</td>
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<td>Pellagra</td>
<td>Niacin deficiency</td>
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originated in Egypt, presumably because of the 18.5% to 25.8% seropositivity rate for HCV. In contrast, the estimated prevalence rate in the United States is 1.6% and 81% of these patients have chronic infection, which represents approximately 3.2 million Americans at risk of hepatocellular carcinoma, cirrhosis, and related comorbidities. The importance of recognizing necrolytic acral erythema is underscored by the observation that 87% of patients with the condition are unaware of their HCV status. In these instances, antiviral therapy can be initiated earlier, which has been shown to improve patient outcomes.

The pathogenesis of necrolytic acral erythema is largely unclear, though various treatment responses suggest a multifactorial etiology. The essential role of HCV is apparent because substantial and sustained remission of cutaneous lesions occurs in patients responsive to antiviral therapy; in addition, necrolytic acral erythema has not been reported with other cirrhotic conditions (eg, alcoholism, hepatitis B virus), which excludes chronic liver damage as the sole cause. In the setting of HCV infection, a direct correlation exists between severity of cutaneous disease and degree of hepatic damage.

Ribavirin was successful in one patient whose viral load remained elevated during therapy, suggesting an immunomodulatory mechanism. The active metabolite, ribavirin monophosphate, has anti-inflammatory and antiviral properties through inhibition of an enzyme required for purine synthesis. Mycophenolate mofetil, an effective immunosuppressant used for psoriasis and transplant medicine, inhibits the same enzyme lending support to an immunomodulatory role. Necrolytic acral erythema is consistently unresponsive to topical steroids, making a wholly inflammatory etiology unlikely.

Zinc may play a causative role given the variable responses to supplementation reported in the literature. The divalent cation inhibits apoptosis and is a cofactor in DNA and RNA replication, protein synthesis, and hepatic mobilization of vitamin A. Zinc deficiency reduces serum transport proteins that may impair nutrient delivery to tissues, such as vitamin A, transported by a retinol-binding protein and prealbumin complex, which is required for healthy epidermal proliferation and differentiation. The aforementioned mechanisms of zinc deficiency are established in acrodermatitis enteropathica, a congenital zinc malabsorption syndrome, but also may contribute to the lesions of necrolytic acral erythema, even though serum zinc levels often are within reference range. Although purely speculative, zinc supplementation, even in the absence of overt deficiency, may help resolve necrolytic acral erythema lesions by enhancing nutrient delivery and promoting healthy epidermal growth.

Necrolytic acral erythema most closely resembles necrolytic migratory erythema, and hypoaminoacidemia is common in both. Amino acid supplementation has been shown to clear the lesions of necrolytic migratory erythema yet is largely ineffective in necrolytic acral erythema. Some patients with necrolytic acral erythema have slightly elevated glucagon levels; however, this finding may be caused by reduced clearance secondary to ongoing liver dysfunction. Although the precise mechanism is unclear, hypoaminoacidemia may deplete epidermal protein stores, resulting in keratinocyte necrosis. Immunocomplex mechanisms underlie many of the extrahepatic manifestations of HCV infection (Table 2), but evidence for involvement in necrolytic...
acral erythema is lacking. In some HCV-associated cutaneous conditions, direct expression of HCV RNA has been found, but this viral parasitism has not been observed in necrolytic acral erythema. HCV infection is lymphotrophic and may signal leukocyte activation, resulting in the mononuclear cell infiltrate seen in tissue specimens.

**Conclusion**

Necrolytic acral erythema is a unique cutaneous manifestation of active HCV infection marked by dusky erythematous plaques with vesiculation and/or hyperkeratosis in a dorsal acral distribution. It is the only pathognomonic sign of HCV infection; therefore, dermatologists and primary care physicians should be familiar with the diagnosis. The condition often resembles psoriasis, and the diagnosis should be considered in any patient with acral lesions unresponsive to topical steroids. A reasonable evaluation includes serology for viral hepatitides, markers of hepatic inflammation and synthetic function, zinc, serum amino acids, and glucagon. As in our patient, a biopsy cannot be used to exclude the diagnosis because lesions are dynamic and the histology will vary depending on the stage of evolution.

The pathogenesis resembles necrolytic migratory erythema and pseudoglucagonoma, yet it is likely modulated by the presence of HCV infection, resulting in the predominantly acral distribution and focal keratinocyte necrosis. The most efficacious treatment is resolution of the underlying infection, though other modalities, including ribavirin and zinc, exhibit some, albeit minimal, effect. A thorough understanding of the pathophysiology is imperative if tailored and directed treatments are to be developed. Perhaps retinoids or mycophenolate mofetil (both useful in treating psoriasis) will prove useful by normalizing cellular proliferation and modulating immunologic hyperactivity.

Numerous questions remain unanswered. What is the incidence of necrolytic acral erythema in chronic HCV infection and is there a genotypic association? Why are lesions predominantly localized on dorsal acral surfaces? Does hepatitis C viral replication play a direct role in lesion initiation and evolution? Regardless, it is clear that necrolytic acral erythema deserves its autonomy in the necrolytic erythema family.

**REFERENCES**

Necrolytic Acral Erythema


