Necrolytic Acral Erythema Associated With Hepatitis C

Effective Treatment With Interferon Alfa and Zinc

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Background: Necrolytic acral erythema is a recently described necrolytic erythema that is unique in its exclusive acral location and strong association with hepatitis C.

Observation: We report the first case of necrolytic acral erythema in the United States. The patient is a 43-year-old black woman who presented with a 4-year history of tender, flaccid blisters localized to the dorsal aspect of her feet. Serum zinc and glucagon levels were normal. Serum antibodies were positive for hepatitis C, and a liver biopsy specimen showed chronic hepatitis. She was successfully treated with interferon alfa-2b and zinc. We review all previously reported cases.

Conclusions: Necrolytic acral erythema is a distinct entity. In a review of the literature, most patients were between 35 and 55 years of age, although 1 patient was 12 years old. Five of 8 patients were female. Four of 7 patients described previously were treated with variable success using oral zinc sulfate and amino acids, whereas 2 were successfully treated with interferon alfa. All patients were infected with hepatitis C. Necrolytic acral erythema appears to be a skin disorder linked to infection with hepatitis C virus that responds to treatment with interferon alfa and oral zinc.


ECROLYTIC acral erythema belongs to the family of necrolytic erythemas that include necrolytic migratory erythema, acrodermatitis enteropathica, pellagra, and essential fatty acid deficiencies. These entities are similar clinically and histologically but differ in etiology. Necrolytic acral erythema was first described in 1996 by El Darouti and El Ela1 in Egypt in 7 patients with active hepatitis C infection. In this article, we review the literature and report a new case of necrolytic acral erythema, which was effectively treated with interferon alfa-2b and oral zinc.

REPORT OF A CASE

A 43-year-old black woman with a medical history of atopic dermatitis, asthma, and allergic rhinitis was referred to our clinic in June 1996 with a 4-year history of a recurrent, pruritic, erythematous, papular eruption associated with blisters involving the feet and ankles. When the superficial blisters eroded, the areas became tender and painful. Previous biopsy specimens were interpreted as lichen simplex chronicus and erythema multiforme; the results of direct immunofluorescence were negative. Factitial dermatitis had also been considered. The patient had been treated unsuccessfully with a variety of topical, intralesional, and systemic corticosteroids and hydroxychloroquine sulfate, acyclovir, and Unna boots. Medications included the following: prednisone, 40 mg/d; hydroxychloroquine sulfate, 200 mg twice daily; valacyclovir hydrochloride, 500 mg twice daily; lorazepam; allergic hyposensitization injections; fluticasone propionate; and albuterol inhalers.

On physical examination, large, painful, partially eroded violaceous patches were noted on the proximal half of the dorsal aspect of the feet extending over the medial and lateral malleolar aspects; 2+ to 3+ pedal edema was present (Figure 1). The patient's skin was otherwise clear. Laboratory studies indicated normal erythrocyte sedimentation rate and normal blood cell count with differential except for an elevated leukocyte count of 17.1×10^9/L (reference range, 3.7-10.4×10^9/L) with a left shift. Antinuclear antibodies and cryoglobulins were not detected. Chemistry values were normal except for a decreased albumin level of 31 g/L (reference range, 36-47 g/L) and an elevated cholesterol level of 5.85 mmol/L (226 mg/dL) (reference range, 2.59-5.18 mmol/L [100-200 mg/dL]). Liver en-
zyme levels were elevated: aspartate aminotransferase, 73 U/L (reference range, 10-35 U/L); alanine aminotransferase, 126 U/L (reference range, 5-37 U/L); and lactate dehydrogenase, 276 U/L (reference range, 100-190 U/L). The patient tested seronegative for hepatitis A and B virus but positive for hepatitis C virus. This was confirmed by an immunoblot assay for hepatitis C virus and a liver biopsy specimen that showed mild fibrosis and features of chronic hepatitis. Serum glucagon level was 163 ng/L (reference range, 25-250 ng/L); zinc level was 12.70 µmol/L (reference range, 10.71-22.95 µmol/L); and long chain fatty acid levels were slightly elevated. A biopsy specimen of the right ankle showed hyperkeratosis, parakeratosis, superficial necrosis, pallor, intercellular edema, and regenerative and/or inflammatory cytologic atypia in the epidermis. The underlying dermis revealed telangiectasia, extravasation of red blood cells, and a perivascular sparse lymphocytic infiltrate (Figure 2). These findings were thought to be consistent with a necrolytic erythema.

Based on clinicopathologic correlation, the diagnosis of necrolytic acral erythema associated with hepatitis C infection was made. The patient began oral therapy with zinc sulfate, 220 mg twice daily, with some clinical improvement noted within 5 weeks. At this time, subcutaneous injections of interferon alfa-2b, 3 × 10^6 U three times weekly, were administered in addition to the zinc. Within the following 3 weeks, the patient had a marked decrease in tenderness and edema, and most lesions had cleared, except for a 1 × 3-cm “C-shaped” erosion above the left lateral malleolus and a few scattered satellite erosions. At 6 months, all lesions had resolved. In addition, liver enzyme test results returned to normal. Therapy was discontinued at this time. Three and a half years after treatment, the patient has had no recurrence of lesions. Furthermore, liver function test results have remained normal, and although hepatitis C serologic testing was never repeated, there has been no clinical evidence of recurrence or complications from the viral infection.

Our review of the literature shows our patient to be the first case report since the original description of 7 cases by El Darouti and El Ela.1 We summarize the clinical data in the Table. Of the 8 cases reported to date, most patients were between the ages of 35 and 55 years, although one 12-year-old child was also affected. Five of the 8 patients were female. Clinically, all patients exhibited erythematous to violaceous patches with superficial necrosis in early lesions, and later lesions tended to be hyperkeratotic plaques with a rim of dusky erythema. All patients shared an acral distribution with a predilection for the lower extremities. Glucagon levels were normal in our case and had not been measured in prior patients. Serum zinc levels were normal in all patients in whom they were measured, although therapy with oral zinc sulfate in dosages ranging from 60 to 440 mg/d was effective to varying degrees in 5 patients, including ours. Administration of oral amino acids showed an unclear response. Interferon alfa therapy was extremely effective in 2 previously described patients and in our case. In 1 case, interferon alfa alone resulted in almost complete clearance of lesions. In the other 2 cases, the addition of interferon alfa to oral zinc resulted in total clearance. These results suggest that interferon alfa alone may be sufficient to treat necrolytic acral erythema or may enhance the effect of oral zinc.

The necrolytic erythemas comprise a group of dermatoses that share similar clinical and histologic findings. Several necrolytic erythemas have been described and are associated with altered serum levels of various factors: necrolytic migratory erythema with high levels of glucagon, acrodermatitis enteropathica with low zinc levels, pellagra with niacin deficiency, and low biotin and fatty acid levels in the syndromes of their deficiencies. Al-
though necrolytic migratory erythema is most commonly associated with a glucagon-secreting alpha cell tumor of the pancreas, it has also been described in patients without glucagon-secreting tumors. Most commonly, necrolytic migratory erythema without glucagonoma is associated with impaired hepatic function.

Necrolytic acral erythema differs from other necrolytic erythemas in its exclusively acral distribution of lesions and universal association with hepatitis C infection. Recognition of this association is of particular importance because the distinct cutaneous findings of necrolytic acral erythema most often precede the diagnosis of hepatitis C infection, and, therefore, necrolytic acral erythema is a cutaneous marker for systemic disease.

The incidence of hepatitis C infection worldwide is rising. Hepatitis C infection has been associated with leukocytoclastic vasculitis, cryoglobulinemia, lichen planus, porphyria cutanea tarda, erythema nodosum, erythema multiforme, urticaria, pruritus, malakoplakia, and polyarteritis nodosa. Treatment with interferon alfa has been reported to be effective in some cases of vasculitis,

cryoglobulinemia, lichen planus, and porphyria cutanea tarda. Our patient represents the first case of necrolytic acral erythema in the United States. Awareness of necrolytic acral erythema is important not only for accurate dermatologic diagnosis but also because of the potential for earlier diagnosis and treatment of hepatitis C infection.

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REFERENCES