Necrolytic Acral Erythema

A Patient From the United States Successfully Treated With Oral Zinc

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Background: Recently, necrolytic acral erythema (NAE) has been described as a cutaneous marker for hepatitis C virus (HCV) infection. Only 2 cases have been reported in the United States. Successful remission has been induced only with interferon therapy with or without ribavirin.

Observations: We describe a 46-year-old, HCV-positive African American woman with well-defined, dusky, erythematos plaques on the dorsa of the feet, Achilles tendons, legs, knees, and elbows. Histologic examination revealed confluent upper epidermal necrosis, acanthosis, papillomatosis, and superficial and deep perivascular inflammation. She was diagnosed as having NAE. We induced successful disease remission with oral zinc administration. This is the third NAE case reported in the United States and the first report of disease remission with oral zinc therapy alone.

Conclusions: Since its initial description in Egypt, more cases of NAE are being reported in the United States. Increased awareness of this entity is crucial. Oral zinc might represent a less toxic alternative therapeutic option for patients with NAE.

Arch Dermatol. 2005;141:85-87
other punch biopsy specimen from the leg demonstrated parakeratosis, irregular acanthosis, papillomatosis, and superficial and deep perivascular inflammatory infiltrate.

Based on clinicopathologic correlation and the patient’s positive HCV status, her skin disease was diagnosed as NAE. Despite her normal plasma zinc level (74 µg/dL; normal range, 70-150 µg/dL), the patient was treated empirically with 220 mg of oral zinc sulfate twice daily. The plaques resolved gradually over 8 weeks, leaving postinflammatory hyperpigmentation with complete resolution of symptoms (Figure 2A). Except for papillary dermal melanophages, histologic examination showed no significant abnormality (Figure 2B). Reduction of the zinc sulfate dose by the patient to once daily was followed by exacerbation of signs and symptoms.

**COMMENT**

Approximately 4 million Americans (1.8%) are infected with HCV, which is the most common cause of chronic liver disease in the United States. Hepatitis C virus infection rarely causes acute manifestations, may remain silent for years, and may present for the first time with advanced liver disease. Cutaneous manifestations, including porphyria cutanea tarda, leukocytoclastic vasculitis–induced mixed cryoglobulinemia, lichen planus, and NAE, are clues for diagnosis of HCV infection.

As described in earlier reports, NAE presents with well-defined, tender, dusky, erythematous plaques on the dorsa of the feet. The centers of the plaques thicken with disease progression, acquiring a velvety appearance, and are surrounded by a rim of erythema. Necrolytic acral erythema may resemble eczematous dermatitis clinically and may demonstrate spongiosis histologically. In contrast to eczematous dermatitis, NAE is well defined, has a characteristic distribution, does not respond to topical corticosteroids, and shows keratinocyte necrosis histologically. Clinically, the scale seen in NAE is darker and more verrucous than the typical silvery white scale of psoriasis. Plaques of NAE are surrounded by a characteris-
tic erythematous rim. In the absence of necrotic keratinocytes, NAE may be easily confused with psoriasis histologically. In addition to the typical distribution, association with HCV and the occurrence of pain and itching also differentiate NAE from psoriasis. In addition to psoriasis and eczematosus dermatitis, NAE should be differentiated from lichen simplex chronicus, hypertrophic lichen planus, acrokeratoelastoidosis, and acrokeratosis paraneoplastica.

Complete remission of NAE has been reported with parenteral interferon therapy in 3 cases.\textsuperscript{1,2} A recent case report demonstrated clearance of NAE coinciding with addition of ribavirin to interferon therapy despite lack of virological response.\textsuperscript{3} Oral zinc used either as monotherapy or in combination with oral or parenteral amino acid therapy resulted in only slight improvement in previous reports.\textsuperscript{1,2} To the best of our knowledge, the present study is the first to report complete remission induced by oral zinc therapy.

The exact mechanism of action of oral zinc therapy in this patient despite her normal plasma zinc level is unexplained. It has been proposed that overtly decreased serum zinc levels are a late sign of zinc deficiency, and that skin manifestations of zinc deficiency may occur despite normal plasma zinc levels.\textsuperscript{5} Low epidermal zinc levels despite normal plasma findings have been shown in acne, psoriasis, and Darier disease with no clear pathogenetic role.\textsuperscript{6} A similar mechanism might be functioning in NAE. Mori et al\textsuperscript{7} showed that apoptotic cell death plays a role in the pathogenesis of acrodermatitis enteropathica, a disease with pathologic features similar to NAE. In vivo models have shown that high concentrations of extracellular zinc suppress apoptosis by repressing the activation of endonuclease, the enzyme responsible for DNA fragmentation, and that deprivation of cellular zinc induces apoptosis both in vivo and in vitro.\textsuperscript{8} In addition to its antiapoptotic effect, zinc supplementation in therapeutic doses has an anti-inflammatory, immunostimulant, antiviral, and antioxidant effect. Zinc supplementation also improves the results of interferon therapy in patients with HCV.\textsuperscript{9}

As all patients with NAE described in the literature were also infected with HCV, NAE remains the only diagnostic cutaneous marker for HCV infection. All dermatologists must be aware of the clinical and histologic features of NAE, given its association with HCV and possible diagnosis of liver disease by skin manifestations. Oral zinc therapy represents a less toxic therapeutic option for patients with NAE not eligible for or not responding to antiviral therapy.

Accepted for Publication: May 13, 2004.

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REFERENCES