Erythema Elevatum Diutinum Mimicking Extensive Keloids

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GOAL

To describe a case of erythema elevatum diutinum (EED) that clinically mimicked extensive keloids

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the clinical presentation and lesion appearance in EED.
2. Discuss the electron microscopic and laboratory findings of EED.
3. Outline treatment options for EED.

CME Test on page 386.

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We report an unusual case of erythema elevatum diutinum (EED) that mimicked extensive keloids. A 53-year-old man presented with a 6-year history of painful, enlarging nodules over the legs, feet, arms, hands, and back. Although the clinical morphology of the lesions resembled extensive keloids, histopathologic examination confirmed a diagnosis of EED. After initiating therapy with dapsone, the patient quickly experienced dramatic improvement in the appearance of the lesions. This article details the unusual characteristics of our case and reviews the important considerations involved in the diagnosis and treatment of EED.

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Erythema elevatum diutinum (EED) is a rare form of cutaneous vasculitis that was initially described by Hutchinson in 1888.[1] An additional case was reported by Bury[2] in 1889. In 1894, Radcliffe-Crocker and Williams[3] recognized several common features shared by their case and the 2 previous cases. They suggested that this dermatosis was a unique entity and introduced the term *erythema elevatum diutinum* to describe it.[3] Since Hutchinson's initial

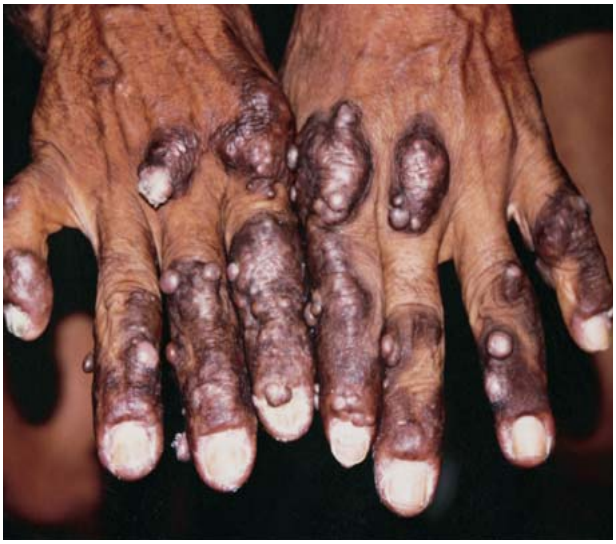

Figure 1. Numerous keloidal nodules and tumors on the dorsal fingers and hands.

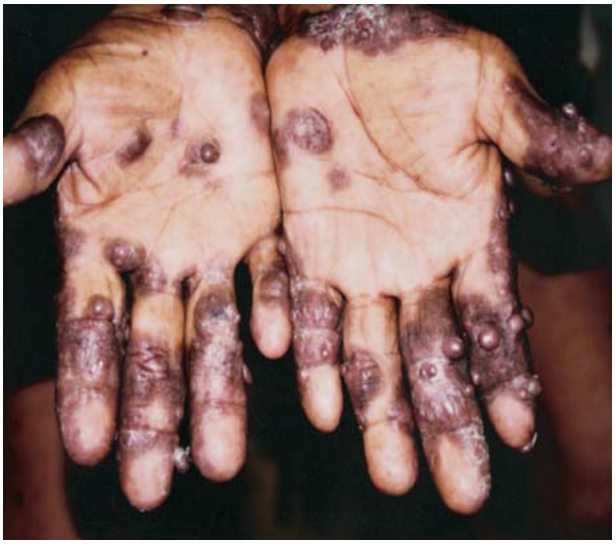

Figure 2. Numerous nodules on the fingers and palms.

description, there have been approximately 100 reported cases of EED.[4] We report a case of EED that clinically mimics extensive keloids.

Case Report

A 53-year-old Nicaraguan man presented with a 6-year history of enlarging nodules over the legs, feet, arms, hands, and back. The nodules were painful and pruritic, and there were associated arthralgias of the finger joints. New smaller, flatter lesions had recently appeared on his back. The patient denied any significant medical history, including no known history of streptococcal infection, hepatitis B, cancer, or infection with human immunodeficiency virus. His only medication was oxycodone, which he took for severe joint pain.

On examination, there were numerous hyperpigmented, tumorous nodules and plaques distributed over the fingers and hands (Figures 1 and 2), lateral aspects of the feet, elbows, and extensor forearms (Figure 3), and the back (Figure 4). There was associated swelling of the joints of the fingers. Numerous smaller nodules were also scattered on the back. Three punch biopsies were performed and all revealed vasculitis, granulation tissue, and fibrosis consistent with EED (Figures 5 and 6). A serum protein electrophoresis was normal.

The patient was started on dapsone at 100 mg per day. After only 1 week, there was dramatic improvement in the appearance of the lesions and in his joint pain.

Comment

EED may occur at any age and affects males and females equally.[5] The clinical presentation of EED is characterized by a wide spectrum of morphological variants. Typically, EED initially presents as soft, violaceous papules, plaques, and nodules. Early lesions may display petechiae or purpura.[6] As the lesions age, they become hard, round-to-oval, brownish-yellow nodules. The nodules have smooth surfaces and are freely moveable from the underlying tissues. Vesicle formation, erosions, and ulceration may be observed as well.[7] There may be associated pain,[8] paresthesias,[9] or pruritus.[5] Less commonly, widespread arthralgias may be present.[5,7,9] However, in many cases the lesions are asymptomatic.

The lesions typically present symmetrically on the extremities, especially the extensor and periarticular surfaces. This distribution may be supported by the theory that EED might be induced by trauma.[5,6,10,11] The most commonly affected areas are the dorsal hands and feet, elbows, knees, buttocks, and the skin overlying the Achilles tendon.[12] Involvement also has been described on the palms, fingers, nails, soles, toes, and auricle.[9,13,14] The trunk and mucous membranes are almost always spared. When lesions resolve, residual hyperpigmentation or hypopigmentation and loss of underlying collagen may occur.[7,15]

Our case is unusual in 2 ways. First, the clinical morphology of the lesions mimicked extensive keloids, an occurrence that, to our knowledge, has not been reported. Second, the lesions were so widespread that truncal involvement was also prominent. The patient's severe arthralgias were not unexpected due to the extent of the disease.

Histologically, early lesions of EED show leukocytoclastic vasculitis and capillary proliferation. Fibrin and polymorphonuclear leukocytes are seen within vessel walls, and there is prominent endothelial

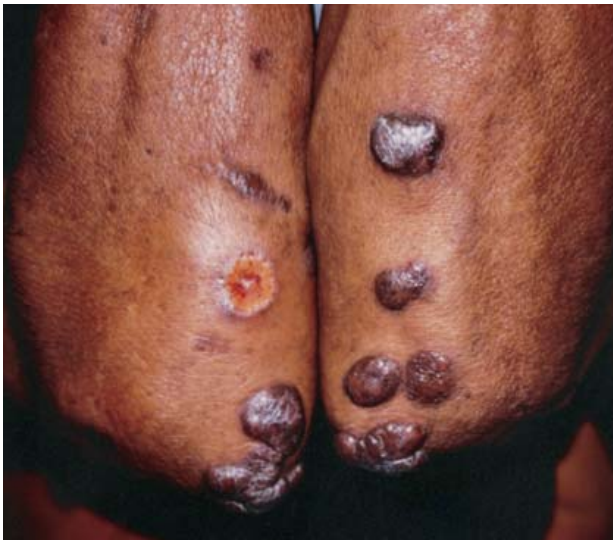

Figure 3. Keloidal nodules on the extensor surface of the arms and elbows.

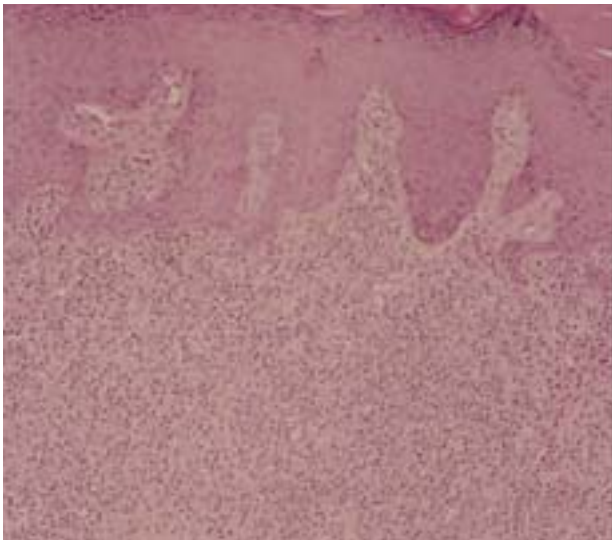

Figure 5. Dense, mixed dermal infiltrate with a predominance of neutrophils and areas of fibrosis (H&E, original magnification ×40).

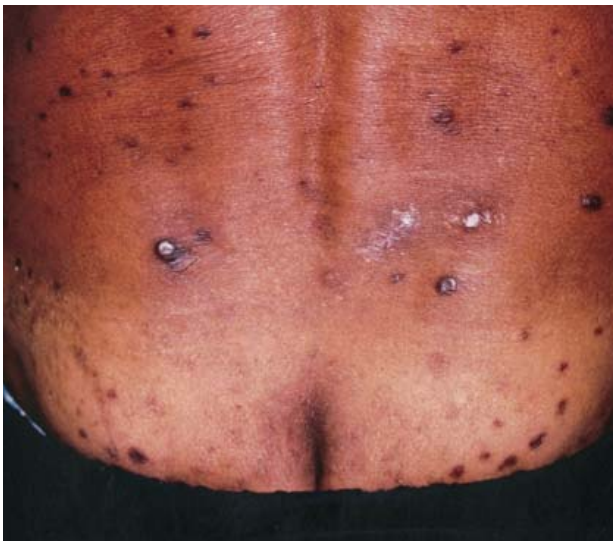

Figure 4. Numerous nodules on the back.

swelling. Older lesions additionally show dermal aggregates of neutrophils and histiocytes, fibrosis, and areas of granulation tissue. There are numerous dermal Langerhans cells in both early and late lesions.[6,16] Very mature lesions show fibrotic replacement of the dermis characterized by a marked proliferation of fibroblasts, an increased number of collagen fibers,[7,17] and only small foci of leukocytoclastic vasculitis.[18]

Electron microscopy reveals prominent lipid inclusions within histiocytes in late lesions, and smaller inclusions in keratinocytes, mast cells, and lymphocytes.[16] The location of these lipid deposits has been the subject of some controversy. Urbach et al[19] first noticed these prominent lipid collections extracellularly and proposed the descriptive term *extracellular cholesterolosis*. However, Kanitakis et al[16] suggest that the term *extracellular cholesterolosis* is a misnomer because subsequent ultrastructural studies have shown large intracellular lipid deposits and an absence of extracellular ones. The preponderance of evidence suggests that most of the lipid deposits are present within cells, but a small amount of lipid may be present extracellularly as a result of the degeneration of lipid-laden cells.[16,17,20]

Laboratory findings associated with EED include elevated erythrocyte sedimentation rate,[7,21,22] positive C-reactive protein,[15,21] elevated serum IgA levels,[5,13,15,23,24] and positive streptokinase-streptodornase skin tests.[4,5]

The pathogenesis of EED has not been fully elucidated. Many authors have suggested that EED is a disease that is initiated by the deposition of immune complexes in small cutaneous vessels. This immune complex deposition is thought to result in the activation of the complement cascade, which in turn stimulates the migration of neutrophils to the cutaneous vasculature. These neutrophils then release enzymes that cause the vascular damage that characterizes EED. It has been proposed that this immune complex deposition is the result of an Arthus-type reaction to streptococcal antigens.[5] This hypothesis is supported by the well-documented association between EED and streptococcal infection. A significant number of patients with EED have evidence of concurrent rheumatic fever or streptococcal infection.[4,13,23,25] Moreover, in patients with EED, the intradermal injection of streptococcal antigens will induce the formation of lesions at sites that were previously uninvolved.[5,23,25]

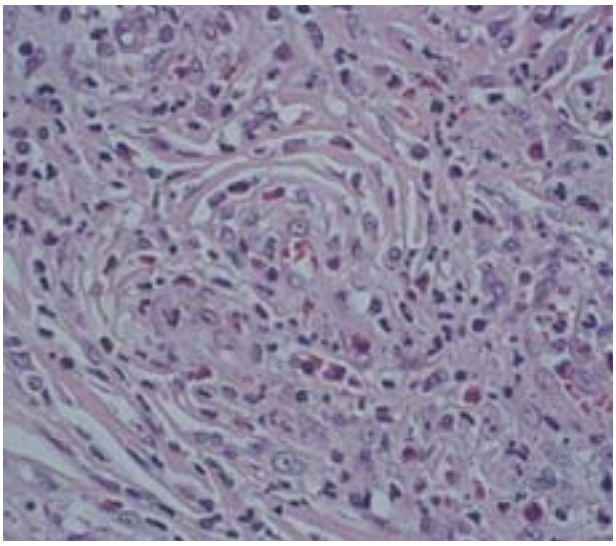

Figure 6. Leukocytoclastic vasculitis (H&E, original magnification ×400).

EED also has been associated with IgA gammopathy. Of the 26 cases of EED reported by Wilkinson et al[5] and Yiannias et al,[26] 31% (8) were associated with IgA paraproteinemia. The paraproteinemia occurred in the setting of IgA monoclonal gammopathy or myeloma. Furthermore, there have been several reports of patients with EED without evidence of clonal gammopathy but with elevated levels of IgA.[5,23]

EED also has been reported in association with many other diseases. A significant number of patients with EED have hematologic abnormalities including B-cell lymphoma, hairy cell leukemia, myelodysplasia, myeloma, mixed cryoglobulinemia, polycythemia vera, and hypereosinophilic syndrome.[26] In addition, gastrointestinal diseases such as ulcerative colitis,[10] Crohn's disease,[27] and celiac disease[22] have been observed in conjunction with EED. Infectious diseases that are associated with EED include hepatitis B,[28] streptococcal infections,[4,13,23,25] and HIV infection.[4,12,18,29-32]

Dapsone is the treatment of choice for EED. Numerous reports have detailed dramatic clinical improvement following the initiation of dapsone therapy. Complete healing of lesions generally occurs within weeks to months of starting therapy.[33-35] Despite these favorable results, dapsone does have some limitations. Because dapsone is a suppressive rather than curative therapy, withdrawal of dapsone usually results in prompt and severe recurrence of disease.[7] Furthermore, nodular lesions with significant fibrosis respond poorly to dapsone. Dapsone also is limited by potential adverse effects of methemoglobinemia, hemolysis, and agranulocytosis.[36] The process by which dapsone suppresses EED is not completely understood. Proposed mechanisms include stabilization of neutrophilic lysosomes,[37] interference with deposition of complement,[7] inhibition of myeloperoxidase,[36] and blockage of integrin-mediated neutrophil adherence.[36]

Other medications that have shown to successfully suppress EED include niacinamide,[28] phenformin,[38] colchicine,[39,40] and sulfapyridine.[5] Excision and intralesional steroids have been used for cases of limited disease.

Appropriate treatment of associated diseases is also important in the management of EED. Flares of EED tend to coincide with exacerbations of the associated disease. This phenomenon has been observed in those cases associated with HIV infection,[19] celiac disease,[22] and streptococcal infection.[4] EED is a chronic condition and, if left untreated, the lesions will persist for years with intermittent periods of remission. The longest reported duration of illness is 39 years.[5] In this case, the rapid improvement of our patient due to dapsone was not expected given the chronicity of the disease but highlights the sometimes unpredictable clinical behavior of EED.

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