Erythema Elevatum Diutinum Arising in the Setting of Dermatitis Herpetiformis

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Dermatitis herpetiformis is an autoimmune blistering disease characterized by granular deposits of immunoglobulin A (IgA) in dermal papillae. Erythema elevatum diutinum is a chronic form of vasculitis associated with IgA paraproteinemia. We report a patient with dermatitis herpetiformis who developed characteristic erythema elevatum diutinum lesions on the elbows and knees despite sulfone therapy. We speculate that the different patterns of IgA deposition in the skin account for the clinical manifestation of these 2 uncommon disorders.

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Erythema elevatum diutinum is characterized by firm papules and nodules occurring over extensor surfaces. Histologic changes of leukocytoclastic vasculitis are evident and associated with perivascular fibrosis.[1] Antecedent bacterial infections, collagen vascular diseases, myeloproliferative diseases, human immunodeficiency virus infection, cryoglobulinemia, Wegener granulomatosis, Crohn disease, systemic fungal diseases, and other associations have been reported.[2] Additionally, associated immunoglobulin A (IgA) paraproteinemia has been noted.[3,4] IgA also has been implicated in the pathogenesis of IgA nephropathy, Henoch-Schönlein purpura, and other systemic illnesses. Mesangial IgA deposits have been noted in ankylosing spondylitis, lupus erythematosus, hepatitis, and dermatitis herpetiformis.[5]

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Dermatitis herpetiformis presents as a widespread pruritic dermatosis. Evaluation of skin biopsy results reveals granular deposits of IgA in the papillary dermis. A link with gluten-sensitive enteropathy is noted, and there are associations with thyroid disease, rheumatoid arthritis, and lupus erythematosus (Table).[6] Individuals with dermatitis herpetiformis are thought to have an immunogenetic predisposition to the development of characteristic skin lesions.

Case Report

A 58-year-old man with a history of dermatitis herpetiformis documented by light microscopy and direct immunofluorescence results noted good control of pruritic skin lesions while taking sulfasalazine extended-release tablets 500 mg 4 times daily. Prior therapy with colchicine and dapsone had failed to provide adequate control of clinical flares over the elbows and knees. For 5 years, the patient had noted the gradual development of red firm nodules over the elbows and knees (Figure 1) and around the ankles (Figure 2). Some of these nodules rubbed against his shoes and were a source of irritation. Topical fluradrenalone tape, as well as the use of halobetasol ointment, failed to flatten these lesions or prevent further growth. Intralesional triamcinolone acetonide 20 mg/cc injected into select areas also did not lead to noticeable improvement. Shave removal of lesions led to only temporary benefit. Biopsy results revealed subepidermal cleft formation as well as numerous neutrophils within the blister cavity (Figures 3 and 4). Perivascular fibrosis was noted (Figure 5). Histologic evaluation findings supported a diagnosis of erythema elevatum diutinum occurring in the setting of dermatitis herpetiformis. Results of antiendomysial antibody tests were negative. Serum protein electrophoresis revealed an elevated β-globulin level of 1.7 g/dL (reference range, 0.8–1.2 g/dL) and an elevated IgA level of 1354 mg/dL (reference range, 81–463 mg/dL).

Diseases Associated With Dermatitis Herpetiformis[6]

Autoimmune
Dermatomyositis
Myasthenia gravis
Rheumatoid arthritis
Sjögren syndrome
Systemic lupus erythematosus
Thyroid abnormalities
Type 1 diabetes mellitus
Gastrointestinal
Gastric atrophy
Gastric hypochlorhydria
Gluten-sensitive enteropathy
Pernicious anemia
Neoplastic
Gastrointestinal lymphoma
Non-Hodgkin lymphoma

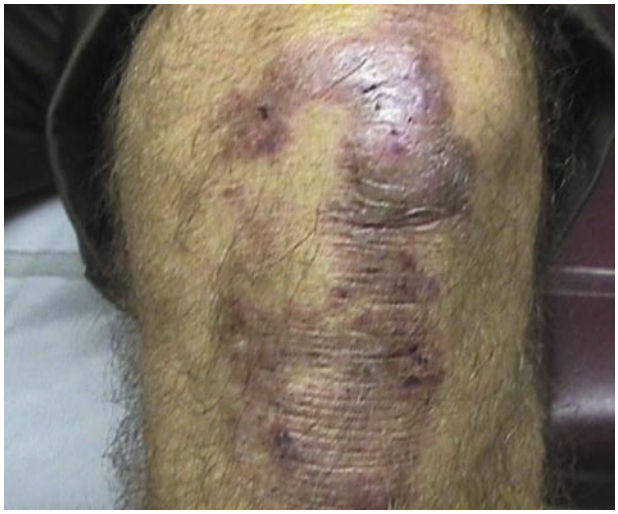

Figure 1. Erythematous nodules and excoriated pruritic vesicles on the knee.

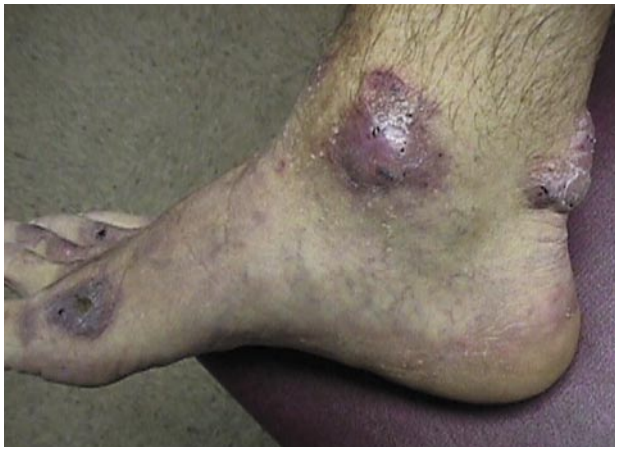

Figure 2. Erythematous firm nodules around the ankle.

Comment

The close association of IgA with dermatitis herpetiformis is well-known. Associations with antireticulum antibodies, antigliadin antibodies, and gluten-sensitive enteropathy also have been well-characterized. Erythema elevatum diutinum has been associated with IgA monoclonal gammopathy.[3,4] Because of the association with IgA, the presence of erythema elevatum diutinum in a patient with chronic dermatitis herpetiformis is not surprising. The IgA in the skin may be an epiphenomenon or may represent deposition in the skin along with other immune complexes.[7]

In previous studies, results of immunoelectron microscopy revealed IgA deposition below the basal lamina and concentrated on the microfibrillar components that surround elastin.[8,9] Although circulating immune complexes contain both IgA1 and IgA2 subclasses, skin lesions contain only IgA1, which is thought to be derived from the mucosal immune system.[8] Circulating immune complexes may play a role in the development of the characteristic skin lesions of dermatitis herpetiformis. Small bowel abnormalities may allow antigenic proteins to cross-react with IgA. The presence of antireticulum antibodies and antigluten antibodies, as well as the presence of polyclonal light chains in the skin, seems to support the presence of an underlying small bowel defect.[8]

Gluten enteropathy is present in the majority of patients with dermatitis herpetiformis, though the bowel disease is often mild or asymptomatic. In addition, antigliadin antibodies are present in 80% to 90% of patients with gluten enteropathy.[10] IgA may stimulate the alternate complement pathway through complement 3 (C3) or the membrane

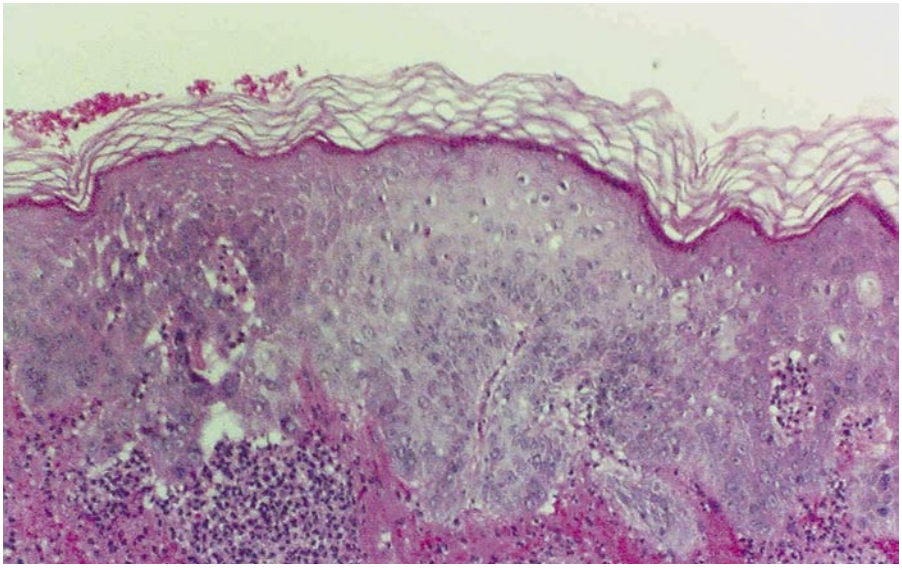

Figure 3. Biopsy results reveal stuffing of dermal papillae characteristic of dermatitis herpetiformis (H&E, original magnification ×40).

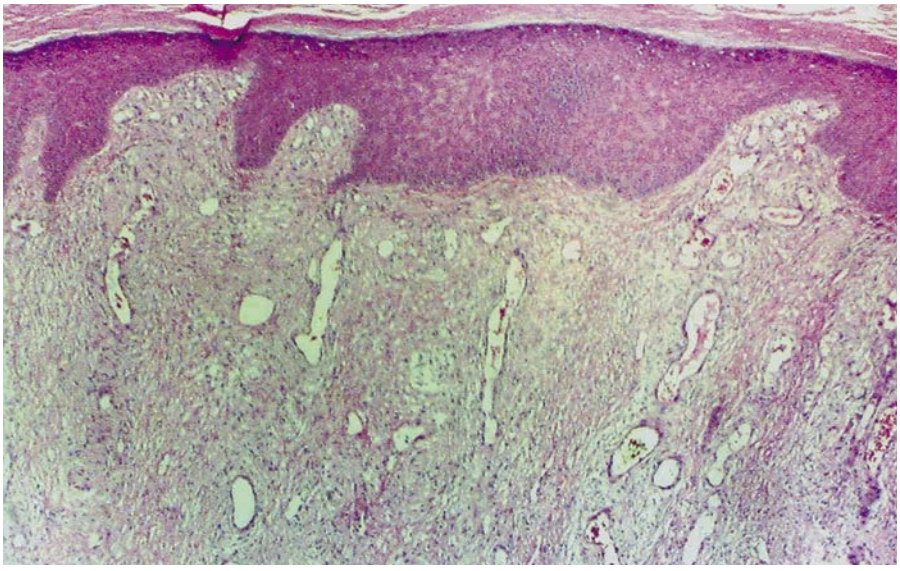

Figure 4. Fibrosis is noted in the dermis and surrounds the blood vessels (H&E, original magnification ×10).

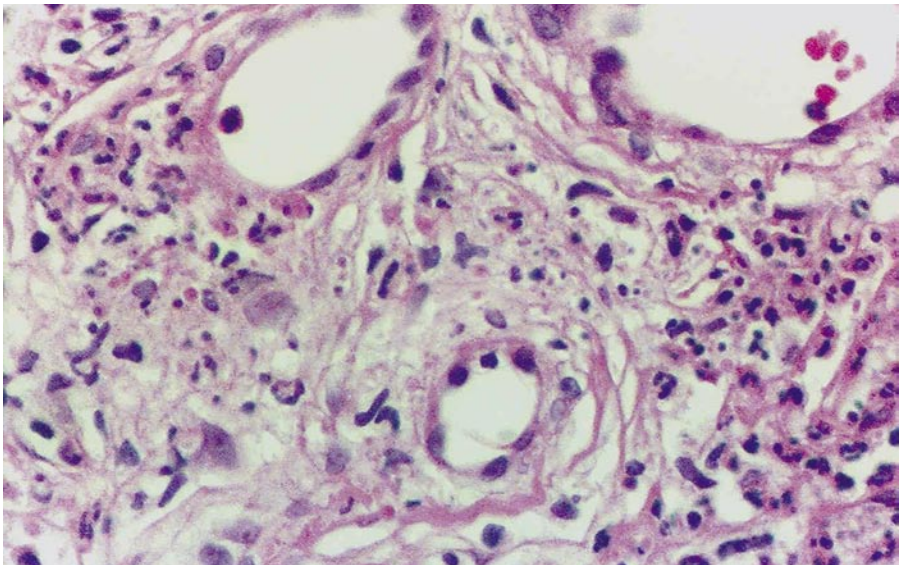

Figure 5. Leukocytoclasis and perivascular fibrosis surround the blood vessels (H&E, original magnification ×40).

attack complex by acting on C5. C5a is extremely potent in stimulating neutrophil chemotaxis and may explain why biopsy of a typical lesion reveals a prominent neutrophilic infiltrate. Immune complexes within the basement membrane zone region may trigger a cascade that eventuates into a blister or the formation of the chronic vasculitis of erythema elevatum diutinum. These lesions may show collections of neutrophils in the papillary dermis that mimic dermatitis herpetiformis. Histologic differences include the more diffuse neutrophilic infiltrate of erythema elevatum diutinum that involves the entire dermis and is centered around blood vessels compared with the papillary dermal involvement of dermatitis herpetiformis. We would like to alert clinicians to the unique association of erythema elevatum diutinum and dermatitis herpetiformis, and we suspect that further research will find common inflammatory pathways in both of these disorders.

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