Epidermolysis Bullosa Acquisita Associated with Relapsing Polychondritis: An Association with Eosinophilia?

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Epidermolysis bullosa acquisita is a blistering disorder that has been associated with other autoimmune diseases. It has not previously been associated with relapsing polychondritis (RPC). RPC is an autoimmune disorder that frequently displays peripheral eosinophilia. The eosinophil has been implicated in mediation of tissue damage and bullae formation. RPC should be added to the list of diseases seen in association with EBA.

Epidermolysis bullosa acquisita (EBA) is a rare, usually chronic blistering disorder that has been associated with systemic diseases in which autoimmune pathogenesis has been implicated.[1] It has not been described in association with relapsing polychondritis (RPC). Three clinical forms of EBA exist.[2] The classic presentation has noninflammatory acral bullae associated with trauma that heal with scarring and milia. The bullous pemphigoid-like presentation has widespread inflammatory bullae surrounded by urticarial plaques involving the trunk; these heal without scarring or milia. The cicatricial pemphigoid-like presentation has predominantly mucosal involvement. EBA is often refractory to treatment.

Case Report

A previously healthy 75-year-old white woman was hospitalized for a 3-week history of generalized weakness, arthralgias, fevers, and a nonspecific generalized red papular eruption. On physical examination, she was noted to have intense well-demarcated erythema, edema, and warmth over the cartilaginous ear bilaterally (Figure 1) and less intensely over the cartilaginous alae. Her nonspecific eruption rapidly evolved to tense bullae on edematous, erythematous urticarial bases over a 3-day period (Figure 2). There was no mucosal involvement. Throughout the hospitalization she had leukocytosis as high as 22.5 thousand/mm^3 with a peripheral eosinophilia of up to 41% and an elevated erythrocyte sedimentation rate of 10^3 mm/hour. An antinuclear antibody, c-ANCA, p-ANCA, and Lyme titer, as well as blood, skin, and cerebrospinal fluid cultures were all normal. Incisional biopsy of skin, perichondrium, and auricular cartilage demonstrated a dense inflammatory infiltrate in the perichondrium, consisting of lymphocytes, histiocytes, and admixed eosinophils, consistent with relapsing polychondritis

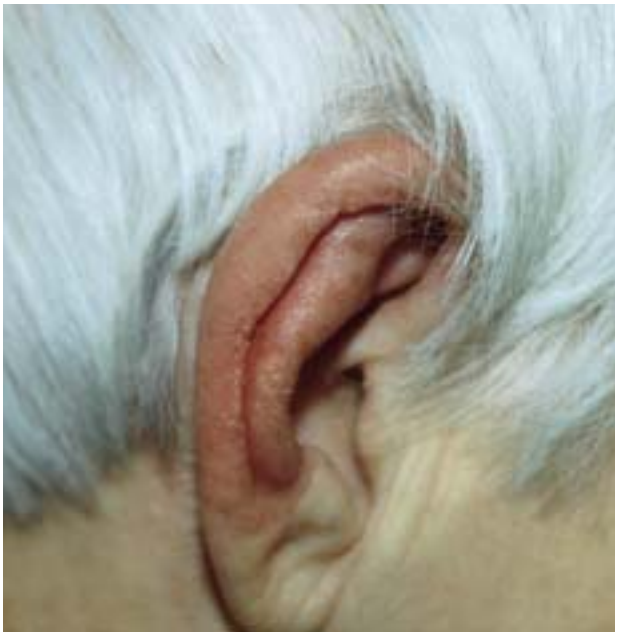

FIGURE 1. Sharply marginated erythema and edema of cartilaginous ear.

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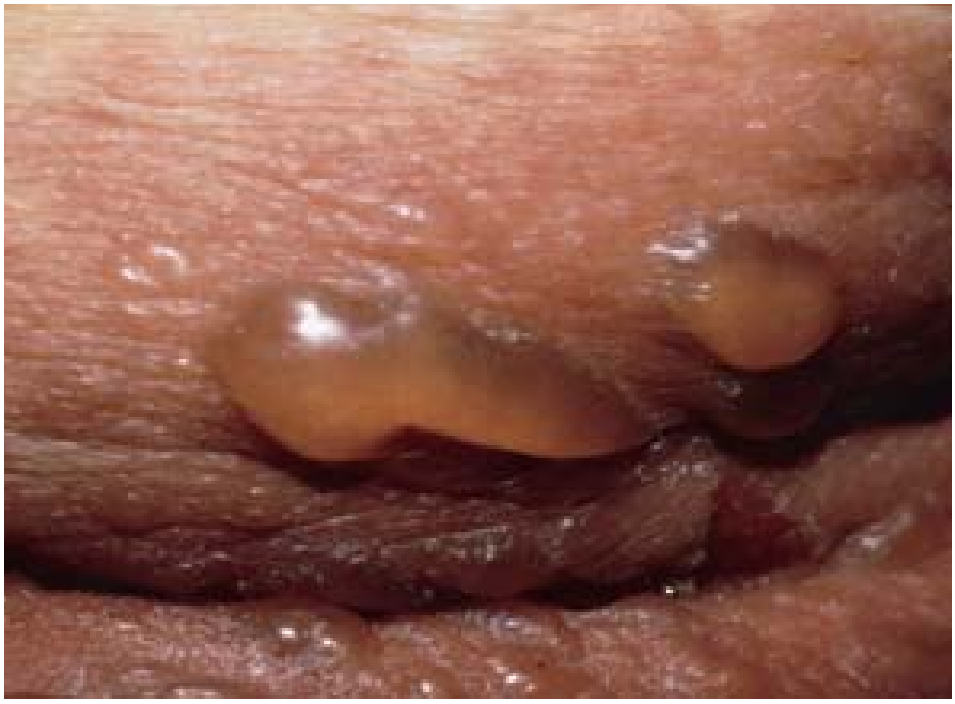

FIGURE 2. Tense bullae on urticarial plaques of abdomen.

(Figure 3). Biopsy of the early papular eruption demonstrated early focal subepidermal vesiculation with histiocytes, eosinophils, and neutrophils in the interface and interstitial infiltrate (Figure 4). Biopsy of abdominal lesional skin revealed a subepidermal bulla with neutrophils and occasional eosinophils (Figure 5); direct immunofluorescent studies on intact perilesional skin showed linear staining of C3 at the basement membrane zone. Direct immunofluorescent study on perilesional salt-split skin demonstrated linear staining of C3 on the dermal side only. Indirect immunofluorescent study was negative.

The diagnosis of EBA associated with RPC was made, and the patient was started on 60 mg of oral prednisone. In 7 days, the bullae and erythema cleared on the trunk, the erythema, edema, and tenderness of the cartilaginous ears resolved, and the weakness was much improved. Three weeks after prednisone therapy was initiated, her white blood cell count decreased to 16.1 thousand/mm^3 with only 1% eosinophils. The prednisone was tapered slowly over 5 months without any recurrence of bullae or chondritis. Ten months after prednisone was discontinued, she remains clear and healed without scarring or milia.

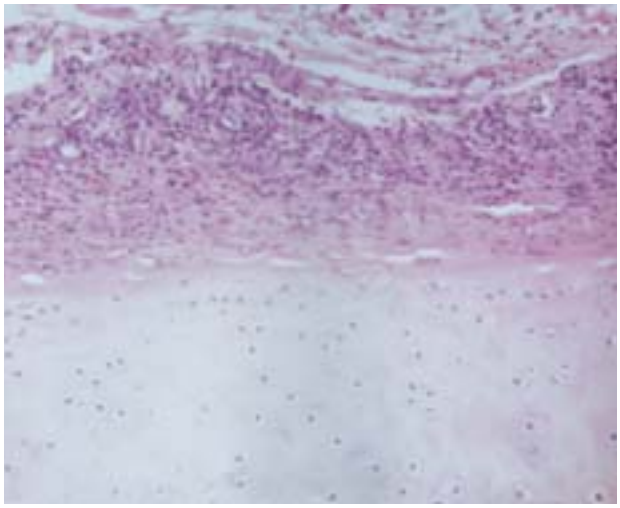

FIGURE 3. Perichondrium and auricular cartilage with a dense inflammatory infiltrate in the perichondrium, consisting of lymphocytes, histiocytes, and admixed eosinophils, consistent with relapsing polychondritis (H&E; original magnification, × 125).

Comments

EBA is a usually chronic blistering disorder that is caused by autoantibodies against type VII collagen. Type VII collagen is a major component of anchoring fibrils that play a role in adherence of the basement membrane zone to the papillary dermis. EBA has been associated with other diseases that are thought to be autoimmune-mediated.

Eosinophils are frequently observed in inflammatory infiltrates and have been implicated in the mediation of tissue damage, specifically epidermal-dermal separation. Extensive extracellular deposition of eosinophil granule proteins has been demonstrated by indirect immunofluorescence.[3] Granule products

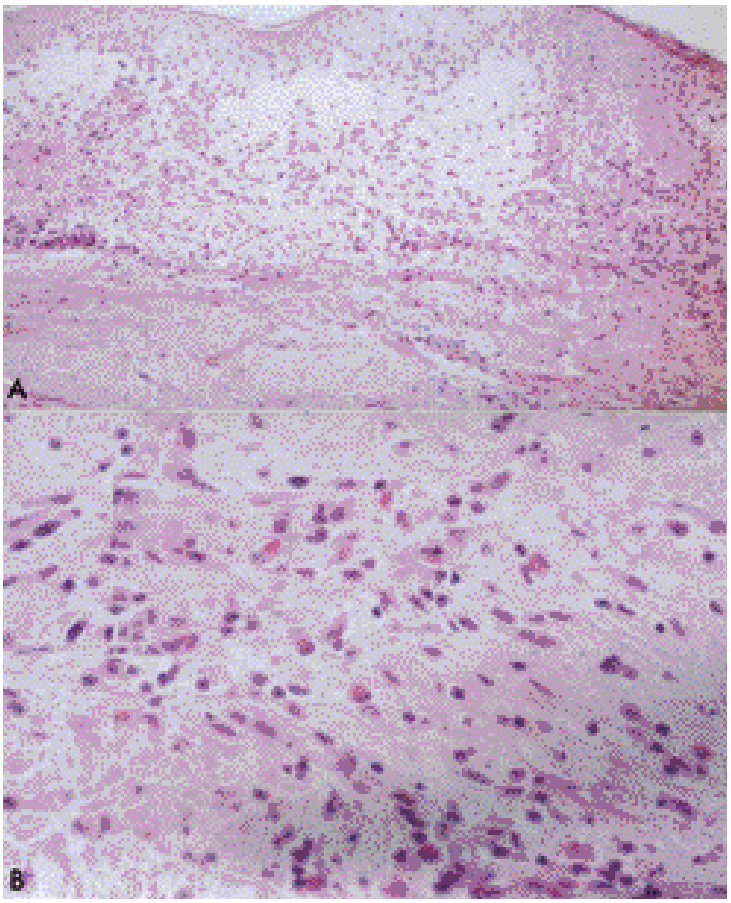

FIGURE 4. *A*, Focal subepidermal vesiculation with histiocytes, eosinophils, and neutrophils in the interface and interstitial infiltrate (H&E; *A,* original magnification, × 125. *B,* original magnification, × 400).

released by the neutrophil and eosinophil may mediate epidermal-dermal separation.[4] Gammon *et al*[5,6] demonstrated that *in vitro* neutrophils and eosinophils adhere to the basement membrane zone and cause epidermal-dermal separation.

Clinically and on routine histopathologic examination, EBA may be indistinguishable from bullous pemphigoid. Immunoelectron microscopy was not performed due to its unavailability at our institution; we recognize that this would be the gold standard in differentiating bullous pemphigoid from EBA. Gammon *et al*,[7] however, demonstrated that these two entities could be reliably distinguished through direct immunofluorescence on salt-split skin.[7] In our case, this study aided in the diagnosis of EBA. We hypothesize that the pronounced peripheral eosinophilia and thus tissue eosinophilia associated with RPC mediated the EBA clinically. Once her eosinophilia resolved, so did the clinical signs of EBA. Ward *et al*[8] reported a case of eosinophilia associated with the use of granulocyte-macrophage colony-stimulating factor unmasking EBA. Their case, like ours, was negative on indirect immunofluorescence; this is not unexpected since only 50 to 65% of patients with EBA have circulating antibodies.[9]

We believe that RPC should be added to the list of autoimmune diseases associated

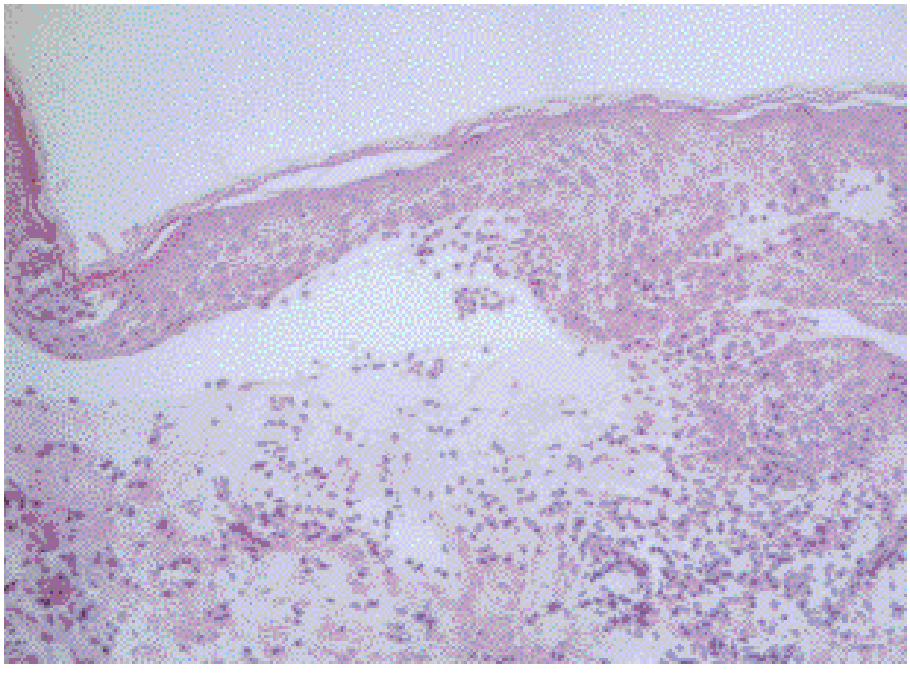

FIGURE 5. Subepidermal bulla with neutrophils and occasional eosinophils (H&E; original magnification, × 125).

with EBA. We further hypothesize that in predisposed individuals, eosinophilia may mediate bullae formation and clinical expression of disease.

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