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Anti-p200 pemphigoid (anti-laminin-γ1 pemphigoid) demonstrating pathergy

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ABSTRACT

Anti-p200 pemphigoid, also called anti-laminin-γ1 pemphigoid, is a recently defined entity. First reported in 1996, the incidence is relatively rare, with approximately 70 reports in the literature. Clinical presentation is heterogeneous, but the disease most commonly mimics bullous pemphigoid with urticarial papules, plaques, or tense bullae on the trunk or extremities. Described here is a case with additional features of pathergy that have not yet been reported in the literature.

A 58-year-old African American female presented with a 3-week history of pruritic tense bullae over her hands and neck. There was no history of psoriasis, inflammatory bowel disease, new medications, or health status changes preceding the eruption. The patient was diagnosed with pemphigoid, despite negative direct immunofluorescence microscopy, and was placed on topical and oral steroids with temporary relief. On initial consultation, there were scattered bilateral 4-mm hemorrhagic and noninflammatory bullae with slight annular scale over the dorsal hands. In addition, there were eroded scattered papules over the anterior and posterior neck (Fig. 1). Antibodies to BP180 and BP230, as detected by enzyme-linked immunosorbent assay (EUROIMMUN, Lübeck, Germany), and porphyrin levels were within normal limits.

Skin biopsy revealed subepidermal blisters with a predominance of neutrophils, scattered lymphocytes, and eosinophils in the upper dermis. Direct immunofluorescence microscopy showed continuous strong linear deposition of immunoglobulin (Ig)G and C3 at the dermal–epidermal junction. Immunoblot studies detected IgG4 autoantibodies against p200 antigen and the C-terminus of laminin-1γ with no detection of antibodies to type VII collagen extracted from the dermis, the recombinant NC1 domain of type VII collagen, or laminin 332 extracted from the extracellular matrix of cultured human keratinocytes (Groth et al., 2011; Komorowski et al., 2013; Vafia et al., 2012; Zillikens et al., 1996). For the laminin 332, recombinant hLAMC1-cterm (amino acids 1364 to 1609; Groth et al., 2011) and dermal extract (Zillikens et al., 1996) were fractionated by SDS-PAGE, transferred to nitrocellulose membrane, and immunoblotted as reported (Groth et al., 2011). The nitrocellulose membranes were blocked with 5% dry skim milk. Human sera were diluted in TBST containing 5% skim milk powder plus 1% BSA. As a secondary antibody, horseradish peroxidase–conjugated monoclonal mouse anti-human IgG4 antibody (Southern Biotech, Birmingham, AL, USA) was used (Vafia et al., 2012). The patient developed a single pinpoint pustule at the venipuncture site and reported never having experienced this type of reaction to prior needle puncture (Fig. 2). She denied topical treatment to the area or trauma besides the biopsy.

The patient initially responded to oral and topical steroids (prednisone 60 mg/day × 4 weeks, then tapered 10 mg weekly). Doxycycline and niacinamide were added to the therapeutic regimen with no significant further improvement. After 8 weeks, recurrent disease occurred when oral steroids were tapered to less than 30 mg per day. Dapsone was initiated. Subsequently, the patient has been free of skin lesions and off any oral corticosteroids, and is currently on dapsone 150 mg daily.

Anti-p200 pemphigoid, renamed as anti-laminin γ1 pemphigoid, has a heterogeneous clinical presentation but most commonly mimics bullous pemphigoid. The differential diagnosis includes epidermolysis bullosa acquisita, linear IgA bullous dermatosis, dermatitis herpetiformis, or porphyria cutanea tarda and has even been reported presenting with an erythema gyratum repens–like appearance. Distinction from these entities is difficult clinically and histologically. In early lesions, neutrophils may predominate in all conditions (Dainichi et al., 2009; Dilling et al., 2007; Lazarova et al., 2004; Monshi et al., 2012; Rose et al., 2007; Shimizu et al., 2012).

Immunofluorescence studies usually demonstrate linear IgG and C3 deposits along the dermal-epidermal junction in both bullous pemphigoid and anti-laminin γ1 pemphigoid. In 2009, Dainichi et al. (2009) identified the autoantigen in anti-laminin-γ1 pemphigoid

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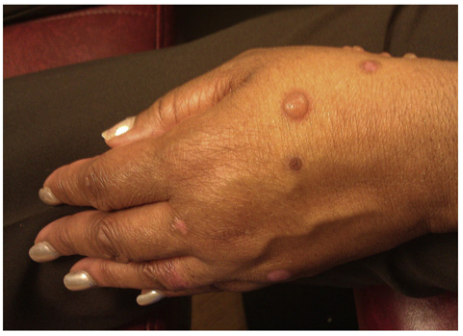

Fig. 1. Anti-p200 pemphigoid. Scattered hemorrhagic and noninflammatory bullae with slight annular scale over bilateral dorsal hands.

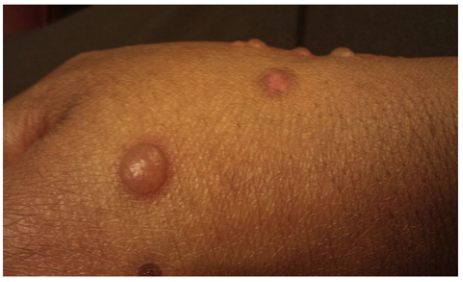

Fig. 2. Anti-p200 pemphigoid. Solitary pinpoint pustule at the venipuncture site.

as an acidic noncollagenous N-linked glycoprotein of the lower lamina lucida with a molecular weight of 200 kDa, laminin-γ1, clearly differentiating it from other autoantigens in pemphigoid diseases. The C-terminus of laminin-γ1 is the immunodominant region of the protein and activity of the disease may be monitored by enzyme-linked immunosorbent assay–detecting autoantibodies targeting this domain (Groth et al., 2011).

Unlike bullous pemphigoid, patients tend to develop anti-p200 pemphigoid at a younger age. Associations with psoriasis vulgaris in Japanese patients and use of penicillin have been reported, but no other disease correlations have been documented. However, evidence of epitope spread and progression to mucosal involvement with the development of other autoantibodies during the course of the disease has been reported (Wozniak et al., 2006; Wozniak et al., 2011). Little information exists regarding long-term outcome of these patients. One case report has followed a patient for 5 years after diagnosis with no associated morbidity or mortality (Wozniak et al., 2011).

Pathergic phenomenon is a well-described hypersensitivity reaction comprised of development of a papule or pustule hours at a site of trauma within 24 to 48 hr. This phenomenon is noted in several distinct dermatological entities, including Beçhet's, pyoderma gangrenosum, Sweet's syndrome, neonates with Down's syndrome, myleoproliferative disorders, non-Hodgkin's lymphoma, chronic myeloid leukemia treated with interferon α, pemphigus vulgaris, and eosinophilic folliculitis. However, pathergy has not been associated with any of the reported forms of pemphigoid (Wozniak et al., 2006; Hsu et al., 2005). Histopathologic studies of pathergy have shown recruitment of neutrophils with variable immunoglobulin deposition and leukocytoclasia (Baker et al., 2011; Gilhar et al., 1989; Jorizzo et al., 1985). Our patient declined the biopsy of the pathergy lesion, which resolved during oral steroid treatment.

The intense neutrophilic infiltrate noted in some cases of p200 pemphigoid may explain the presence of pathergy in our case, and its occurrence in other cases may have been overlooked. We speculate that, in fact, pathergy may be more common in other neutrophilic bullous diseases, but is missed because of the many bullae and vesicles already present at the time of diagnosis. A vesicle triggered by needle stick may be overlooked because of the many surrounding lesions. Our patient's lesions were acral and did not involve the antecubital fossae, thus the pathergic lesion was easily detected. Though there is no histopathologic correlation to prove pathergy versus another form of Koebnerization in this case, there is also no consensus in the literature of a distinct dermatopathologic pattern. Akmaz et al. (2000) evaluated the sensitivity of the histologic pattern in the detection of pathergy versus clinical detection and determined that clinical evaluation was as sensitive.

The clinical significance of pathergy in our patient is unknown, but its association may help with earlier diagnosis of this rare immunobullous disease.

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