Successful Treatment of Intravenous Immunoglobulins in a Patient with Intractable Epidermolysis Bullosa Acquisita with Autoantibodies to Type VII Collagen and Laminin Alpha-3

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Abstract

Epidermolysis bullosa acquisita (EBA) is a blistering disease caused by autoantibodies to type VII collagen, a major component of anchoring fibrils at the dermal-epidermal junction. Here, we report a case of inflammatory EBA with a unique antibody profile showing reactivity to laminin alpha-3 as well as type VII collagen. The patient's cutaneous lesions were refractory to dapsone, prednisolone, betamethasone, and double filtration plasmapheresis, which led to a catheter-mediated mexitellic-resistant staphylococcal aureus (MRSA) sepsis. Intravenous immunoglobulins (IVIG) initially used to resolve MRSA sepsis improved the pruritis and skin manifestations of EBA, and clinical remission of EBA was achieved after only two cycles of IVIG. The mechanism for the concurrence of antibodies to type VII collagen and laminin alpha-3 and the potential mode of action of IVIG in EBA are discussed.

Keywords: Epidermolysis bullosa acquisita; Type VII collagen; Laminin alpha-3; Intravenous immunoglobulins; Sepsis; Epitope spreading

Case Report

A 48-year-old Japanese male presented with a 1 year history of progressive blistering skin lesions on the face, trunk, and extremities, which were treated with topical corticosteroids and antihistamines but showed no clinical improvement. On physical examination, severely pruritic erythemas and vesicles were diffusely distributed all over the body, most of which were eroded because of scratching (Figure 1a). The erythematous rashes showed a variety of morphological patterns, such as erythema with circumferential vesicles and erosions, crater-like erosions, flaccid bullae, and concentric erythemas with a wood-grain-like appearance (Figures 1b and 1c). Oral and conjunctival mucosal lesions were absent. The patient had no medical history, and the results of laboratory examinations were within normal ranges, except for mild hypercholesterolemia. Enzyme-linked immunosorbent assays showed negative results for all desmoglein 1 (Dsg1), Dsg3, bullous pemphigoid antigen 180 (BP180) and 230.

Skin biopsy specimen from an erythematous legion on the chest containing a vessel showed subepidermal blistering and dense infiltration of neutrophils, eosinophils, and histiocytes in the superficial dermis (Figure 2a). The infiltrated cells were condensed in the papillary dermis (Figure 2b). Direct immunofluorescence (DIF) revealed linear deposition of IgG and C3 along the epidermal basement membrane zone (BMZ; Figure 2c). Indirect immunofluorescence (IIF) demonstrated circulating IgG anti-BMZ antibodies at a titer of 1:160, which bound to the dermal side of 1M NaCl-split normal human skin (data not shown).

Immunoblot (IB) analysis of normal human dermal extracts revealed that IgG antibodies in the patient serum reacted with a 290-kDa protein band with the same mobility as an epidermolysis bullosa acquisita (EBA) antigen (type VII collagen; Figure 2d). IB of purified human laminin-332 (epiligrin or laminin-5) also detected IgG reactivity with the 165-kDa and 145-kDa forms of the alpha-3 subunit of laminin-332, which were also recognized by a positive control serum from a patient with anti-laminin-332-type mucous membrane pemphigoid (MMP) (Figure 2e). Other IB analyses of normal human epidermal extracts, the recombinant proteins of NC16a and the C-terminal domains of BP180, and a concentrated HaCaT cell culture supernatant showed no positive reactivity (data not shown).

The patient was initially treated with dapsone (50 mg/day), which dramatically improved his pruritus, but failed to suppress the development of the erythemas and vesicles. Gradual increase in levels of liver transglutaminases led to cessation of dapsone. Because both pruritus and skin lesions were refractory to subsequent oral prednisolone (40 mg/day) or betamethasone (6 mg/day), double filtration plasmapheresis (DFPP) was performed. However, after 3 cycles of DFPP, the patient abruptly developed a high fever, showed deterioration of liver function, and showed increase in levels of white blood cells (12,800 cells/µL, normal<9,000 µL) and C-reactive protein (15.7 mg/dL, normal<0.3 mg/dL). Mexitellic-resistant staphylococcal aureus (MRSA) was detected from a blood specimen and from a catheter inserted into the subclavian vein. Therefore, MRSA sepsis caused by catheter contamination was diagnosed.

Concomitantly, cutaneous manifestations were aggravated, and edematous erythemas and flaccid bullae developed on the entire body (Figure 1d). Nikolsky's sign was positive. In addition, mucosal lesions appeared on the tongue and lips. To treat the sepsis, intravenous immunoglobulins (IVIG, 400 mg/kg/day, 5 consecutive days) and levofloxacin were administrated, which resolved the sepsis and improved the cutaneous lesions. A month after the second cycle of IVIG, all vesicles and erosions were epithelialized, leaving milia formation...
mucosal lesions at the early stage, when antibodies to laminin-332 were positive. It is unclear why our patient did not show mucosal lesions in spite of the presence of autoantibodies to laminin-332 (one of the autoantigens for MMP).

The concurrence of antibodies to type VII collagen and laminin alpha-3 suggests the heterogeneity of EBA. Considering the fact that NC-1 domain, a major antigenic site in type VII collagen binds to the beta-3 subunit of laminin-332, intermolecular epitope spreading may generate antibodies to laminin alpha-3 [1-8]. Therefore, initially “hidden” laminin-332 epitopes became “exposed” by an anti-type VII collagen response to evoke a secondary autoimmune response to the juxtaposed laminin alpha-3 protein.

Because the IIF titer of anti-BMZ antibodies was unchanged at the onset of MRSA sepsis, deterioration of skin lesions, and development of mucosal lesions were not considered as aggravation of EBA disease activity. Production of staphylococcal toxins or superantigen-induced T cell activation was suggested to cause the deterioration of the mucocutaneous lesions. Thus, IVIG was used for the treatment for sepsis, resulting in improvements of both sepsis and mucocutaneous lesions.

Several lines of evidence indicate that IVIG is effective in the treatment of EBA. A recent study reported that repeated IVIG (mean 23.1 cycles) resulted in discontinuation of concomitant therapies (corticosteroids, dapsone, and others), and that IVIG monotherapy led to long-term remission [9]. Other reports also showed that several cycles induced a sustained clinical remission [10]. In our case, although cutaneous lesions were refractory to dapsone, prednisolone, betamethasone, and DFPP, only 2 cycles of IVIG induced clinical remission. We speculated that DFPP performed before IVIG decreased anti-BMZ autoantibodies, which reduced the number of IVIG cycles required.

Recent studies on Fc gamma receptors (FcγRs) provided a rationale for the use of IVIG to treat EBA [11]. In experimental EBA model studies using targeted mice for each FcγR, an EBA phenotype was induced by FcγRIIIA antibodies, which reduced the number of IVIG cycles required. Neutralization of the inhibitory FcγR may explain why repeated IVIGs were required to reach clinical remission in EBA [11]. In experimental EBA model studies using targeted mice for each FcγR, an EBA phenotype was induced by FcγRIIIA antibodies, which reduced the number of IVIG cycles required.
domain of type VII collagen binds to the beta3 chain of laminin 5 via a unique subdomain within the fibronectin-like repeats. J Invest Dermatol 112: 177-183.


