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 methicillin-resistant staphylococcal aureus (MRSA) sepsis. Intravenous immunoglobulins (IVIG) initially used to resolve MRSA sepsis improved the pruritus 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 antibiotics 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 circumscribed 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 230 (BP230), and bullous pemphigoid antigen 180 (BP180) and BP230.

A skin biopsy specimen from an erythematous lesion on the chest containing a vesicle 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 layer of the dermis (Figure 2b). Direct immunofluorescence (DIFF) revealed linear deposition of IgG and C3 along the epidermal basement membrane zone (BMZ; Figure 2c). Indirect immunofluorescence (IFF) 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). Methicillin-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 administered, 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...
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IB with purified human laminin-332.
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LABD. Clear detection of the 290-kDa type VII collagen by IB led to
dense neutrophil infiltration in the dermis. However, the lack of IgA
pemphigoid; each of which presents with subepidermal blisters and
suggested a possible diagnosis of dermatitis herpetiformis (DH),
Discussion
The patient’s cutaneous manifestations with severe pruritus
suggested a possible diagnosis of dermatitis herpetiformis (DH),
linear IgA bullous dermatosis (LABD), or anti-laminin gamma-1
pemphigoid; each of which presents with subepidermal blisters and
dense neutrophil infiltration in the dermis. However, the lack of IgA
reactivity in the dermal papilla and on the BMZ excluded DH and
LABD. Clear detection of the 290-kDa type VII collagen by IB led to
the final diagnosis of EBA. Our patient also had IgG autoantibodies to
the laminin alpha-3 subunit of laminin-332, which was determined by
IB with purified human laminin-332.
To the best of our knowledge, this report is the second case of EBA
with autoantibodies to both type VII collagen and the laminin alpha-3
subunit to be published [1]. However, the patient in the first case study
demonstrated mucosal manifestations, whereas our patient showed no
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 FcγRIV (the mouse counterpart of human FcγRIIIA) and
inhibited by FcγRII, indicating that equilibrium between activating
and inhibitory FcγRs plays an important role in the pathogenesis of
EBA [12]. Fc fragments in IVIG preparation could interact with both
the activating and inhibitory FcγRs to neutralize their functions.
Neutralization of the inhibitory FcγR may explain why repeated IVIGs
were required to reach clinical remission in EBA. IVIG preparations
enriched with inhibitory FcγRs or depleted of activating FcγRs would
improve the efficacy of IVIG in treating EBA.

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Figure 1: Cutaneous manifestations. (a-c) Skin lesions on the back at the first
visit. (d) Aggravated skin lesions at the onset of MRSA sepsis, and (e) at remission after 2 cycles of IVIG.

Figure 2: Results of histopathological, DIF, and IB studies. (a,b) Histopathological
features (hematoxylin-eosin stain) (a: ×100; b: ×400). (c) The results of DIF
for C3 (×100). (d) IB of normal human dermal extracts. EBA control serum
reacted with the 290-kDa type VII collagen (lane 1), and anti-laminin gamma-1
pemphigoid control serum reacted with the 200-kDa laminin gamma-1 (lane 2).
Lanes 3 and 4 reveal the IgG and IgA antibodies in the patient, respectively.
(e) IB of purified human laminin-332. The control serum of anti-laminin-332-type
MMP reacted with the 165-kDa and 145-kDa alpha-3, 140-kDa beta-3, and the
105-kDa gamma-2 subunits (lane 1), but the normal control serum showed no
positive reactivity (lane 2). Lanes 3 and 4 are for IgG and IgA antibodies in the
patient, respectively, and molecular weights are indicated in the left (d and e).
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.


