Epidermolysis Bullosa Acquisita

—A Case of a Localized Inflammatory Form—

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A 40-year-old woman had a pruritic, vesiculobullous eruption of her face for 6 weeks with no evidence of systemic disease. A biopsy showed subepidermal blisters and dermal infiltrates of neutrophilic inflammatory cells. Direct immunofluorescence demonstrated thick linear deposits of IgG and C3 along the basement membrane zone. The cleavage plane was identified to be just beneath the lamina densa. Using Western immunoblots, the patient's IgG autoantibodies were found to recognize type VII procollagen. Moderate starting doses of systemic prednisolone gave a good response for this patient with an early inflammatory form of epidermolysis bullosa acquisita. (Ann Dermatol 1:73–76, 1989)

Key Words: Early inflammatory form, Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA) is a chronic, subepidermal blistering disease of the skin and mucous membranes presenting variable clinical features. It is now regarded as a distinct entity among the autoimmune bullous dermatoses.[1-4]

For the diagnosis of this disease, in addition to the immunoultrastructural findings described in 1981[1], the target antigen in this disease has recently been identified as type VII procollagen (particularly the C-terminus) which constitutes a structural component of anchoring fibrils of human skin.[5-7] The specificity of EBA autoantibodies distinguishes EBA from all other blitering disorders of the skin except bullous systemic lupus erythematosus (BSLE) which shares the same autoantibodies.[3,8]

We report herein a case of EBA with localized inflammatory vesiculobullous lesions, in which sublamina densa blistering and serum antibodies to type VII procollagen were identified. The skin lesions responded favorably to moderate doses of corticosteroids.

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REPORT OF A CASE

A 40-year-old woman visited the dermatology clinic at Hanyang University Hospital in December 1987, with a 6-week history of a moderately pruritic blistering eruption affecting her face. The lesions had developed initially on the preauricular area and subsequently involved the forehead, upper eyelids, and cheeks. Some of the lesions subsided spontaneously but others changed into tense bullae over the ensuing weeks. The patient had taken antihistamines and had applied hydrocortisone cream to the lesions with no benefit. She was in good general health prior to developing the skin lesions. The review of systems was negative; she had no trauma-induced lesions, drug history relevant to her skin disease nor any systemic disease or infection at the time of her visit. Her family history and past medical history were non-contributory.

Physical examination revealed nothing significant except for the multiple vesiculobullous lesions over her face (Fig. 1), extending into the hairline. Most of the lesions had arisen on erythematous bases and the bullae were tense. The skin lesions ranged in size from 3 to 15 mm and the Nikolsky sign was not seen. In some areas they were serpinginous in arrangement. Skin fragility and scarring were absent. The mucous membranes were not involved.

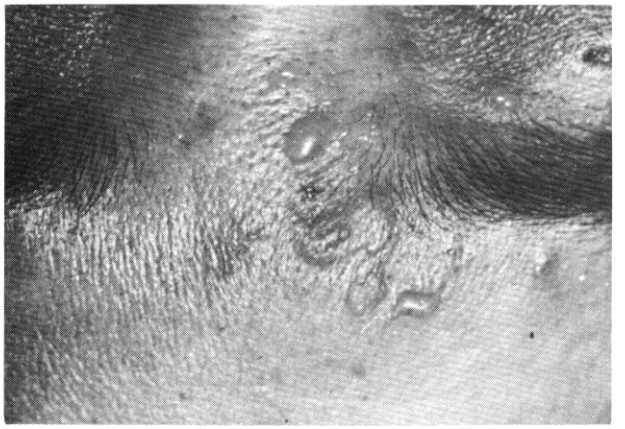

Fig. 1. Vesiculobullous lesions around the eye brow.

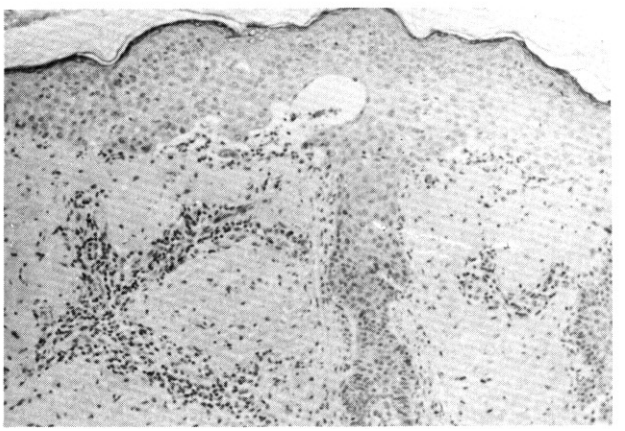

Fig. 2. Histologic examination shows subepidermal vesiculation and dermal infiltrates of inflammatory cells (H & E stain, ×100).

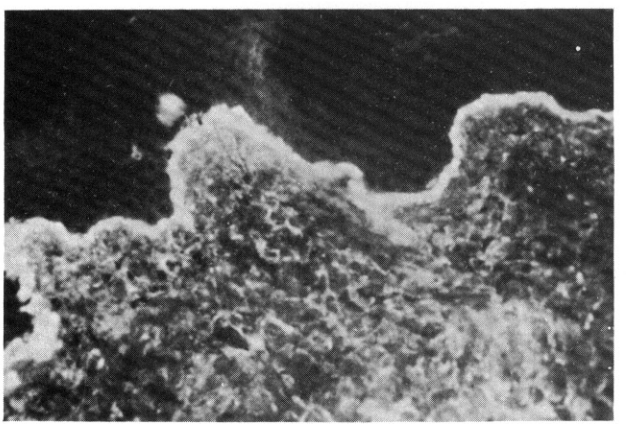

Fig. 3. Direct immunofluorescence of perilesional skin demonstrates a thick linear deposit of IgG along the basement membrane zone (× 200).

A biopsy specimen taken from a peribullous area showed subepidermal vesicles containing a few neutrophils and nuclear dust. Around the foci of microvesicles, mild infiltrates of neutrophils and

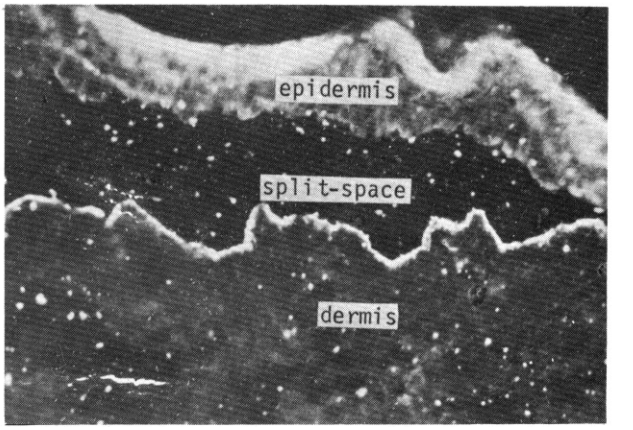

Fig. 4 Indirect immunofluorescence with salt split-skin substrate discloses binding of IgG anti-BMZ antibodies only to the dermal side of the separation (×200).

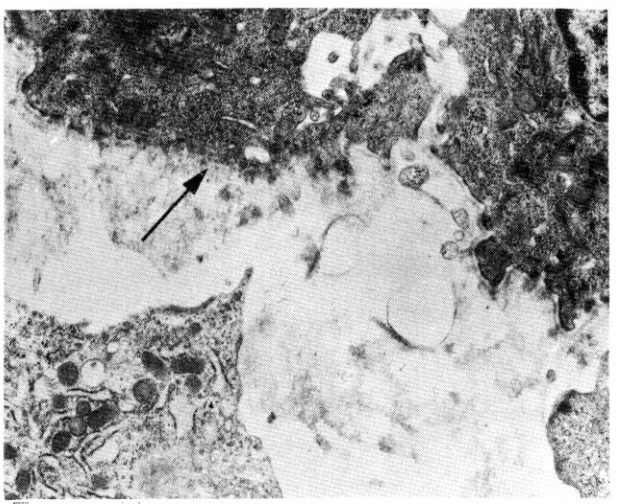

Fig. 5. The cleavage plane is seen immediately below the lamina densa. Focally, it is destroyed (arrow), which might be caused by neutrophil-induced damage (×10,000).

nuclear dust were noted. In the upper and middermis there was a moderate degree of perivascular infiltrate composed of neutrophils, lymphohistiocytic cells, and occasional eosinophils (Fig. 2).

Laboratory data were as follows: A complete blood count with differentials was within the normal ranges. The erythrocyte sedimentation rate was 25 mm/hr. Urinalysis, stool examination for occult blood, and roentgenogram of the chest were normal. The pattern of serum protein electrophoresis, the values of liver and thyroid function tests, blood levels of urea nitrogen and creatinine, 24-hour urinary creatinine clearance, fasting blood glucose level, serum concentration of immunoglobulins, ASO titer, VDRL, latex fixing rheumatoid factor, and urinary porphyrin were all within the normal limits or were negative. The

serum total hemolytic complement (CH50), C3 and C4 concentrations were in the normal ranges. A lupus erythematosus cell preparation was negative. Antinuclear antibodies on HEp-2 cells, antinative DNA antibodies using Crithidia luciliae assay, and Ro-antibodies using immunodiffusion were negative. The serum examination for cryoglobulin was positive.

Immunofluorescence, Electron Microscopic and Immunoblot Studies

Direct immunofluorescence (IF; antisera from Meloy Laboratories Inc., Spring-field, VA, U.S.A.) of perilesional skin showed thick linear deposits of IgG (Fig. 3) and C3 and less intense deposits of IgA and IgM along the basement membrane zone (BMZ). Another specimen from normal-appearing extensor forearm skin was negative. Indirect IF of the serum, diluted up to 1:10, using normal human flank skin as the substrate was negative. When indirect IF studies were performed with sodium chloride split-skin preparations as the substrate, the serum anti-BMZ antibodies of IgG class found to be bound only to the dermal side at a titer of 1:16 (Fig. 4). In vitro C3 staining was also carried out using a 2-step method,[9] and the serum yielded a positive result.

On transmission electron microscopy, peribullous skin disclosed that the blister was localized just beneath the lamina densa (Fig. 5), and a somewhat diminished numbers of anchoring fibrils were recognized. In the roof of the blister, a few electron dense amorphous materials were dispersed. The lamina densa was focally destroyed, perhaps as a result of the neutrophilic inflammatory process.

In Western immunoblot examinations of the patient's serum (performed by Dr. Gammon at the University of North Carolina, U.S.A.) against several preparations of type VII procollagen, the serum IgG autoantibodies were found to recognize type VII procollagen (Fig. not available).

Treatment and Course

The patient was initially treated with dapsone, 100 mg a day, for 2 weeks without improvement of the skin lesions. Then prednisolone, 30 mg a day, was substituted and the lesions cleared completely in a week. After 3 weeks of prednisolone therapy, when clinical remission was evident, the dosage was gradually decreased over the next 3 months to a dose of 10 mg a day. At that time the patient stopped taking her medicine, and after one week, the same vesicular eruption reappeared on her face. Repeated systemic review and laboratory examinations revealed nothing of note. Prednisolone was restarted in a dose of 20 mg daily and the new lesions subsided within a few days. The dosage of prednisolone was slowly tapered to a maintenance dose of 5mg every other day. As of March 1989, 16 months after the initial eruption, she still maintains good general health and is free of any skin disease or scars.

DISCUSSION

The patient had inflammatory vesiculobullous lesions localized on the face, similar to that of BSLE,[10,11] but she did not fulfill any one of the American Rheumatism Association's criteria[12] for the diagnosis of SLE on repeated examinations. A diagnosis of EBA was made by Western immunoblot assays of the serum autoantibody which recognized type VII procollagen.

Clinical features of EBA are heterogeneous and may have inflammatory bullous lesions that mimic bullous pemphigoid or noninflammatory mechanobullous lesions fitting the classic description of this disease with features of skin fragility, bullae and erosions at sites of trauma, which result in scarring and milia formation.[1,4,13,14] Transitional forms or patients with combined features have also been noted.[13,14] These different clinical presentations may be due to the heterogeneity of the biologic characteristics of tissue bound EBA immune complexes. In some patients, the lesions are noninflammatory from their onset;[3] but many patients seem to develop their diseases with erythematous papuloplaques or inflammatory vesiculobullous eruptions.[3,13,14] Most of the patients with early inflammatory leisons do not show skin fragility and the lesions tend to heal without scarring or milia, as shown in our patient. Since there may be a chronologic relationship between the two phases (early inflammatory and late noninflammatory),[3,4] the extent of the disease is variable in different patients; and permanent remission has not been well documented, it is hard to predict when and to what extent our patient will eventually develop the classic features of EBA until further follow-up.

In contrast to the classic form of the disease which is often resistant to a variety of therapeutic modalities, the regimen of moderate starting doses of systemic prednisolone is considered to be effective for this patient who had early localized lesions and low

titer of serum autoantibodies. Noninflammatory mechanobullous lesions do not appear to be due to a complement-mediated inflammatory process, but rather to a direct interruption of affinity between the type VII procollagen and other matrix molecules (such as fibronectin) by autoantibody deposition at this site.[7,15] For this condition, cyclosporine could be used to suppress the pathologic reaction, as reported previously.[16,17]

With regard to the clinical and histologic heterogeneity, it appears that there are situations when the diagnosis must be confirmed by recently developed criteria with immunoelectron microscopy (IEM), or Western immunoblotting against the EBA antigen. In fact there have been cases of EBA[13,14] misdiagnosed as bullous pemphigoid, and cases of pemphigoid[18-20] with one or more classic features of EBA such as healing with scars, trauma-induced lesions, and skin fragility. Even recently, Gammon et all.[21] Observed electron microscopic findings of lamina lucida cleavage in several patients of EBA with inflammatory skin lesions. If IgG containing immune deposits are found on or beneath the lamina densa by direct IEM, this is consistent with the diagnosis of EBA, but BSLE or porphyria cutanea tarda must be ruled out by other means.[1,8,21] The application of immunoblot technique, although it has limited availability, utilizing patient's serum with circulating EBA autoantibodies will provide an even more definitive diagnosis than direct or indirect IEM. However, BSLE should still be ruled out. By this method one may directly demonstrate labelling of the 290 kD and 145 kD EBA antigen bands extracted from human basement menbrane. In view of the variable clinical presentations observed in the spectrum of EBA, we hope that this case report may aid in the early diagnosis and better management of similar cases encountered by other clinicians.

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