Clinical Features of Epidermolysis Bullosa Acquisita

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Epidermolysis bullosa acquisita (EBA) is an autoimmune blistering disease of the skin occurring mostly in middle-aged persons with characteristic skin lesions of inflammatory vesiculobullae and mechanobullae lesions. Separation of the skin occurs at the dermoeidermal junction (DEJ) initiated by an immune process involving the anchoring fibrils (AF) which have a role in the normal adherence of the epidermis and the dermis. Patients with EBA have autoantibodies of IgG to type VII collagen which is the main component of AF.

An electron microscopic picture of normal DEJ is shown in figure 1, and the antigen site of this disease (AF) is noted at the upper-most part of the dermis.

In EBA, a biopsy specimen shows subepidermal bulla with a variable degree of dermal infiltrates. Immunofluorescence (IF) demonstrates a linear deposit of IgG. The pattern of immune deposits along the DEJ is similar to that of bullous pemphigoid. However, the linear fashion is thicker and coarser. When examined by the indirect method with a semi-horizontal section of normal human skin substrates the same patterns can be observed: a fine linear deposit with bullous pemphigoid antibodies and a slightly coarser linear pattern with EBA antibodies. With salt-split skin substrates, the serum autoantibodies of IgG are found to be bound only to the dermal side, the AF zone (Fig. 2). This immunopathologic study can provide a diagnostic finding. Transmission electron microscopic examination reveals the blister to be localized just beneath the lamina densa, the site of the immune deposit.

In immunoblot analysis of the patient's serum against the dermal extracts, serum antibodies are found to recognize type VII collagen of 290/145 kD (Fig. 3). This is a confirmatory technique (with antibody-positive sera) in the diagnosis of EBA.

EPIDEMIOLOGY

It has been thought that EBA does not have any predilection for race. According to published papers from western countries, EBA is considered to be less common than bullous pemphigoid, but may be as common as cicatricial pemphigoid and linear IgA bullous dermatosis. It appears that in the United States, France, and Germany the incidence of EBA is very low, and perhaps lower than one-tenth of the incidence of bullous pemphigoid. In Japan, Dr Nishikawa of Keio University mentioned that EBA is very rare, and only countable cases of the disease could be seen during recent years. However, in our experience with Korean patients, it seems that EBA is more common than bullous pemphigoid, which is in contrast to many other countries of the world (among Korean people, the prevalence of bullous pemphigoid is somewhat lower than among white people).

Epidemiologic data on EBA throughout the world is scant. It seems that EBA is more prevalent in Korea, even though reliable statistics are not currently available. During the last 7 years, I have seen 12 patients with EBA at Hanyang Uni-
University Hospital. However, during the same period, I have seen only 8 patients with bullous pemphigoid.

When considering the immunogenetic background which may be related to the development of anti-type VII collagen autoantibody, it would seem that HLA DR2 and some other genes may be more closely linked (in white & Black population). Immunogenetic studies with Korean patients with EBA are under investigation, and will be publicized within a few years.

CLINICAL CHARACTERISTICS OF CUTANEOUS DISEASE

Skin and Mucous Membrane Lesions
As we know there are clinical variants of EBA.

The clinical findings of EBA may be similar to bullous pemphigoid or to hereditary forms of epidermolysis bullosa. In the spectrum of clinical presentation of the disease, we may see an inflammatory bullous eruption (Fig. 4), non-inflammatory mechanobullous lesions (Fig. 5), and a mucosal lesion-dominant disease (Fig. 6). These different clinical presentations may be due to the heterogeneity of some biological characteristics of the tissue bound EBA immune complexes, and possibly to some undefined tissue factors.
Inflammatory bullous lesions

Inflammatory lesions seem to be more prevalent than the mechanobullous phenotype among those patients with EBA. They may be localized or widespread with no apparent predilection sites (Fig. 7). Most of the patients with inflammatory lesions do not have skin fragility and the lesions tend to heal without scarring in contrast to those having non-inflammatory mechanobullous lesions. There are also transitional forms with combined features of inflammatory and non-inflammatory bullous lesions.

Occasionally we may see patients with localized bullous lesions as in a woman who had bullous lesions scattered only on the face (Fig. 8). The clinical appearance of those lesions on the exposed site was somewhat similar to the bullous eruptions of systemic lupus erythematosus (SLE), but the patient did not meet the criteria for the diagnosis of SLE. Inflammatory facial lesions in this patient regressed completely with oral prednisolone in a few months without recurrence during the next 4 years. This case can be regarded as an unusual localized variant of EBA.

Non-inflammatory mechanobullous lesions

As seen in Figure 9, a woman presented an 8-year history of skin fragility with recurring mechanobullous lesions, especially around the joints. Recurrent lesions resolved with crusts and bleeding, leaving multiple scars with pigmentation about the joints. On the scalp she had superficial scarring alopecia (Fig. 10). Among other pa-
patients, a man had typical trauma-induced lesions on the leg (Fig. 5).

**Mucosal lesions**
Patients often have mucosal lesions on the oral cavity; erosion or tense bulla on the tongue (Fig. 6). Associated findings of asymptomatic esophageal erosions can be seen. Besides the oral cavity and esophagus, mucosal lesions can be found in the nasal, conjunctival, pharyngeal, laryngeal, anal, genital, uterine cervix, and even on the urinary bladder. Uncommonly, a patient with a web-like stenosis of upper esophagus or tender erosions on the cervix with subepithelial blisters can be noted. Mucosal lesions and resultant scarring in those sites may lead to functional impairment such as esophageal stenosis or even the loss of vision, similar to those of cicatricial pemphigoid.

**Subtle Differences in the Morphology of Bullae between EBA and Pemphigoid**
In EBA, inflammatory vesiculobullous lesions are considered to be the most common skin manifestation. When examining these lesions more closely, we may see subtle differences in the morphology of bullae between EBA and bullous pemphigoid.

The bullous lesions of bullous pemphigoid are mostly round-shaped or oval, with occasional circinate configurations (Fig. 11). However, in EBA many inflammatory lesions appear to be less round, serpiginous, or somewhat geographic (Fig. 12).
The ultrastructural locations of the antigenic moieties in bullous pemphigoid and EBA are different, as well as the levels of cleavage by the primary pathologic event in each disease are different. These differences in antigenic sites and the primary levels of cleavage in each disease, as well as the consideration of the architectural microenvironment of the skin, suggest that the clinical features in each bullous disease could be different. An examination of the morphology of individual inflammatory lesions may aid in making an early provisional diagnosis of EBA in many patients.

**Course**

There are very few long-term studies with patients. It seems that there may be a chronological relationship between the two phases, early inflammatory and late non-inflammatory phase, in the majority of patients. There may also be a period of transition among patients who can have both inflammatory and non-inflammatory lesions. A number of reports indicate that patients with EBA may be at risk for SLE and vice versa. These data suggest that it may be prudent to closely follow patients with EBA suspecting the development of SLE.

**TREATMENT AND PROGNOSIS**

A number of drugs have been used including corticosteroids, dapsone, azathioprine, cyclophosphamide, cyclosporine, and colchicine. In my experience, the response to treatment using these drugs is unpredictable in many cases.

The prognosis of EBA depends on several variable factors, including the duration, activity, and severity of the disease and its complications. The duration varies from less than a year to more than 10 years. Overall, the period lasts for at least several years in most patients. The severity of EBA depends on the extent of involvement, the degree of skin fragility, and the complications that arise from scarring such as stenosis and blindness. The disfigurement, functional impairment, and chronicity of the disease may lead to significant emotional and physical morbidities.

**REFERENCES**


