

Bullous Pemphigoid with Permanent Loss of the Nails

Sir,

We describe here an unusual case of bullous pemphigoid (BP), with permanent loss of all the toe nails and some of the finger nails.

CASE REPORT

A 60-year-old woman was admitted to our hospital with extensive bullous eruptions over her entire body. On initial examination numerous tense blisters, varying in size from several mm to 50 mm in diameter, were seen on the extensor surface of the extremities and the abdominal wall in particular. All bullae were on the erythematous base. Pigmentation and depigmentation were intermingled and scars and numerous milia were also seen. Because of severe pruritus, there were many excoriations on the skin. The patient's toe nails were almost completely missing (Fig. 1) and her finger nails were partially missing. There were finger-tip size erosions on the buccal mucosa.

Laboratory investigations were normal, except for eosinophilia and a high level of serum IgE (1,371 IU/ml) and fasting blood sugar (10.3 mg/ml). Abdominal CT, chest CT and Ga scintillationigraphy did not detect any internal malignancy. Ophthalmological examination revealed no abnormality.

Histopathological examination of the skin biopsy from the bullous lesion showed a subepidermal blister containing eosinophils. No acantholysis was found. Lymphoid cells and eosinophils were densely infiltrated in the perivascular area of the upper dermis, with melanophages intermingled.

Direct immunofluorescence (DIF) studies performed on perilesional skin biopsy specimens revealed linear deposition of IgG, IgM, C3 and C1q along the basement membrane zone (BMZ). No IgA deposition was detected. Indirect immunofluorescence (IIF) studies were performed to assay for the presence of circulating anti-BMZ antibodies in the patient's serum, using normal human skin and 1 M NaCl-split normal human skin as the substrates. The patient's IgG bound to a BMZ of normal human skin. The IgG bound to the epidermal side of salt-split normal human skin, similar to that observed in BP serum, but did not react with the dermal side (Fig. 2).

Electron microscopy revealed that clefts between the basal cells and the lamina densa. Underneath the keratinocytes the lamina densa had disappeared in some areas and the lamina densa was detached from the keratinocytes and was split in several areas. Plasma cells and macrophages were infiltrated in the dermis. The macrophages phagocytosed a large amount of melanosome, or debris, from the cells. Lamina densa was present beneath the keratinocytes; however,



Fig. 1. The patient's toe nails are missing.

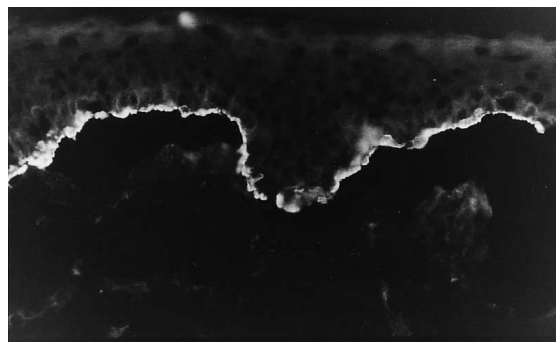


Fig. 2. Indirect immunofluorescence microscopy on 1 M salt-split normal human skin. The patient's IgG bound to the epidermal side of the salt-split normal human skin, but did not react with the dermal side.

in some areas the keratinocytes projected to the dermis without the presence of lamina densa.

In order to study the molecular weight of the antigen protein, immunoblot analysis was performed (1). SDS-polyacrylamide gel electrophoresis (SDS-PAGE) was performed according to Lamini's method, using a 6% separative gel (2). Proteins extracted from human epidermis, bacterial expressed glutathione-S-transferase fusion proteins of the 180-kDa BP antigen (GST-BP 180) (3) and the NC-16a domain of BP-180 (4) were used. The results of the immunoblot analysis of normal human epidermal extracts are shown in Fig 3. The patient's serum IgG reacted with 180 kDa normal human epidermal protein. Control BP serum reacted with 180 and 230 kDa epidermal antigens. Normal human sera did not react with any specific proteins (data not shown). The patient's serum reacted with the N-terminal domain of BP 180, NC 16a domain (non-collagenous 16a domain, sA), which had been proved to be a pathogenic epitope of BP. The C-terminal domain of BP 180, 4575 (BP-180 C-terminal truncations with length of 49 amino acids) did not react with the patient's serum.

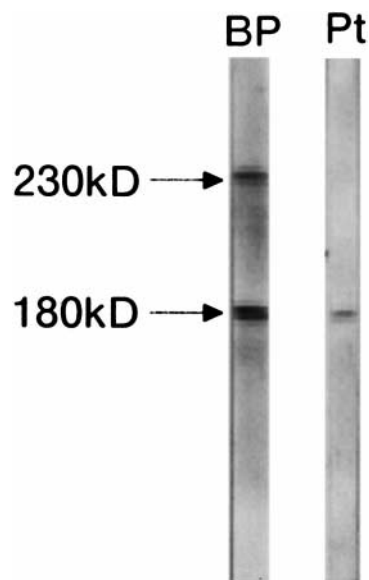


Fig. 3. Immunoblot of the epidermal extracts. Our patient's serum reacted with 180 kDa protein (Pt). Control bullous pemphigoid (BP) serum reacted with 180- and 230-kDa BP antigens.

DISCUSSION

At first we suspected that the patient suffered from epidermolysis bullosa acquisita (EBA), because of the characteristic features described above. This was excluded, however, by IIF and electron microscopy. The serum auto-antibody bound the site recognized by BP sera. Clinically, we have rarely observed milia formation, scarring and nail loss in BP patients. A small number of cases with pemphigoid with nail dystrophy and pterygium formation have been reported (5–8). Barth et al. showed linear deposits of IgM and C3 at the membrane zone of the nail (5). The changes in the nails are thought to be due to an immunological reaction with anti-BP antigen. Recently, Sinclair et al. have described the target antigens in the BMZ of the nail (9). The study demonstrated that the proximal nail fold, the nail matrix, the nail bed and the hyponychium expressed 220 and 180 kDa BP antigens and 64 integrin, as did the skin. If the adhesion structure of the nail is the same as the structure of the skin, what factor induced the nail fragility and loss?

Patients with EBA have blisters and erosions that characteristically heal with scarring, milia formation and nail fragility. On immunoblot analysis, EBA sera reacted with 290 kDa protein extracted from the dermis (10, 11), alpha chain of type VII collagen.

Deep destruction of the BMZ may have been caused by many inflammation cells infiltrating the lesion. For milia formation or nail loss, damage of the lower part of the hemidesmosome structure is required. However, the patient did not have auto-antibodies against the C-terminal domain of BP180. She might have had auto-antibodies, which we could not detect, against components of hemidesmosome other than the N-terminal domain of BP180. The severity of the cutaneous lesions might have been induced by undetected auto-antibodies. Alternatively, the proteins of the nail matrix might have been different in some way from those of the epidermis and the patient may have had specific auto-antibodies to these. Inflammatory infiltration of the upper dermis in the lesion might have an important role in the destruction of the BMZ, together with the action of auto-antibodies. Whether the patient had BP with a unique appearance or had a novel autoimmune bullous disease should be elucidated by further clinical research.

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Accepted April 21, 1999.

Yumi Namba¹, Hiroko Koizumi¹, Masanobu Kumakiri¹, Takashi Hashimoto², Tsutomu Muramatsu³ and Akira Ohkawara¹
Departments of Dermatology, ¹Hokkaido University School of Medicine, Kita 15 Nishi 7, Kita-ku, Sapporo, 060-8638 (E-mail: hkoizumi@med.hokudai.ac.jp), ²Kurume University School of Medicine, Kurume and ³Nara Medical University.