

## CLINICAL REPORT

**Atypical Bullous Disease Showing Features of Both Erythema Multiforme and Bullous Pemphigoid**

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A 78-year-old man presented with multiple, centrifugal erythema, which tended to coalesce, producing polycyclic configurations. The patient developed an annular, narrow blister that was always visible along the margin of the erythema. Histology of a biopsy specimen revealed hydropic degeneration of basal cells, exocytosis of lymphoid cells, and subepidermal blister with necrosis of individual keratinocytes in the blister roof. Direct immunofluorescence studies showed a weak IgG deposition at the basement membrane zone, in a linear fashion, which was confined to the outer side of the blister. Immunoblotting of the patient's serum with human epidermal extract demonstrated circulating antibodies, which reacted to 230 kDa BP antigen 1. These findings suggest that this case is characteristic of both erythema multiforme and bullous pemphigoid and it seems likely that this condition could be a manifestation of epitope spreading, although the exact process in the development of immunological disturbances could not be elucidated. *Key words: epitope spreading; immunoblotting; immunofluorescence; 230 kDa BP antigen 1.*

(Accepted March 15, 2002.)

Acta Derm Venereol 2002; 82: 196–199.

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Epitope spreading phenomenon has been observed in a variety of autoimmune blistering or inflammatory dermatoses (1). We describe here a 78-year-old man who presented with multiple, centrifugal erythema that tended to coalesce, producing polycyclic configurations on the extensor sites of the extremities, back and buttocks. The patient always developed an annular, narrow blister along the margin of the erythema. The histology of a biopsy specimen was consistent with erythema multiforme, but immunoblotting of the patient's serum with human epidermal extract demonstrated circulating antibodies, which reacted to 230 kDa BP antigen 1. This case has the features of both erythema multiforme and bullous pemphigoid, and seems to be a possible manifestation of epitope spreading.

## CASE REPORT

A 78-year-old man was referred to us with a severely pruritic eruption on the limbs and trunk, which started 6 months earlier. He had been treated with systemic corticosteroids for 3 months at an outside hospital before his visit to our department. This produced an excellent response, but the eruption recurred one month later after the corticosteroid treatment was stopped. His general health was good, apart from mild hypertension and insomnia, for which the patient had been taking nilvadipine and estazolam for 4 years. At the time of presentation, multiple, centrifugal erythema, which tended to coalesce, producing polycyclic configurations, was present on the extensor sites of the extremities, back and buttocks (Figs 1 and 2). Along the margin of the erythema, an annular, narrow blister surrounded by a reddish flare was always visible. Mucosal changes were not found. A biopsy specimen was taken from the surrounding, just-spreading erythema on the patient's back, including the blister, perpendicularly to the long axis of the blister. In the central portion, there was a subepidermal blister with necrosis of individual keratinocytes in the blister roof (Fig. 3a). On the outer side of the blister, hydropic degeneration of basal cells, exocytosis of lymphoid cells, and perivascular lymphocytic infiltrate were present (Fig. 3b). On the inner side of the blister, regeneration of the epidermis with similar, but milder changes than those on the outer side of the blister was observed. Neither eosinophils nor neutrophils were found throughout the specimen.

Direct immunofluorescence studies showed a weak IgG deposition at the basement membrane zone in a linear fashion, which was confined to the outer side of the blister. Other immunoglobulins and complements were negative. Indirect immunofluorescence studies, using the skin split with 1M NaCl demonstrated circulating anti-basement membrane zone antibodies bound to the epidermal side to a titer of 1:40. Immunoblotting of the patient's serum with human epidermal extract, using techniques previously described (2), demonstrated circulating antibodies, which reacted to 230 kDa BP antigen 1. Furthermore, a faint band corresponding to 180 kDa BP antigen 2 could be detected (Fig. 4), but immunoblotting, using the 180 kDa BP antigen NC16a domain fusion protein, showed no reactivity.



Fig. 1. Multiple, confluent erythema on the extensor site of the lower leg.

Results of the following laboratory tests were either within normal limits or negative: complete blood count, urinalysis, liver and renal function tests, plasma protein electrophoresis, and antinuclear antibody. Immunologic evaluations were: IgG, 1,699 mg/dl (778–1794); IgA, 665 mg/dl (80–413); IgM, 101 mg/dl (37–254); and IgE, 368 IU/ml (less than 175). Serum complement levels were normal. Computed tomographic scans of the chest and abdomen, upper gastrointestinal endoscopy, and gallium scintigraphy of the whole body were undertaken to rule out underlying neoplasm, all results showing no significant abnormality.

The patient was instructed to stop taking nivaldipine and estazolam, because it could not be ruled out that they might play some role as precipitating factors. Although he followed this instruction for a week, the eruptions increased in number and 40 mg prednisolone daily was therefore started, resulting in complete clearing of the eruption within 3 weeks. Immunoblotting examination of his serum was performed 4 months after starting corticosteroids, showing similar results to those before starting corticosteroids, although a band at 230 kDa became faint (Fig. 4). The doses of prednisolone were tapered, and the patient has remained in



Fig. 2. Polycyclic erythema on the patient's back. Along the margin of the erythema, an annular, narrow blister surrounded by a reddish flare is always visible.

remission for 2 years, taking 8 mg prednisolone daily, although a small number of new lesions have appeared at 2- or 3-week intervals on the extensor sites of the extremities, without any particular trigger factors. A repeat biopsy specimen revealed the same histological and immunofluorescence findings as before. Topical clobetasol propionate has subsequently been added, showing favorable effects, although eruptions have tended to occur at the previously affected sites. The patient suffered from labial herpes 2–3 times a year, but without producing any aggravating effects.

## DISCUSSION

The following clinical features in our patient resembled erythema multiforme: extensor sites of extremities were most frequently affected, and individual erythematous plaques increased in size centrifugally. In addition, histological features, such as hydropic degeneration of basal cells and subepidermal blister with necrosis of individual keratinocytes in the blister roof were consistent with erythema multiforme. A weak, linear C3 deposition at the basement membrane zone, which was confined to

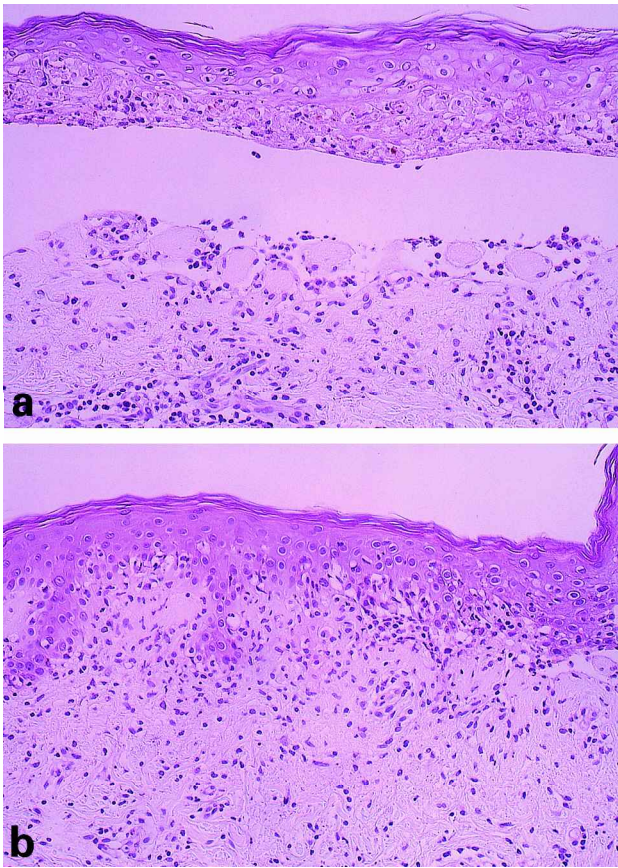


Fig. 3. Central portion of the lesion with a subepidermal blister (a). Outer side of the blister (b) shows hydropic degeneration of basal cells and exocytosis of lymphoid cells. (HTX – eosin stain × 50).

the outer side of the bulla, was found by direct immunofluorescence. This area was at the edge of the plaque where the lesion was beginning to spread. Thus, although the intensity of staining was weak, the immunofluorescence results seem to be significant. Immunoblotting of the patient's serum with human epidermal extract demonstrated autoantibodies directed against 230 kDa BP antigen 1. Therefore, based on the immunological investigations, this case seems to be associated with bullous pemphigoid. Although there was an additional faint band at 180 kDa BP antigen 2, the patient's serum showed no reactivity with the NC16a domain fusion protein, which is considered to be an immunogenic site of 180 kDa BP antigen (3). Reactivity with this protein was demonstrated in 80% of bullous pemphigoid by Matsumura et al. (4). One possible explanation for this result might be that his serum reacted to another epitope in 180 kDa BP antigen other than the NC16a domain.

Several cases of bullous pemphigoid clinically mimicking erythema annulare centrifugum or erythema multiforme have been reported elsewhere (5, 6). These cases differ from our case in that histological findings showed typical features of bullous pemphigoid, in addition to immunological findings. These are likely to be bullous pemphigoid merely having atypical clinical features.

## Epidermal Extract

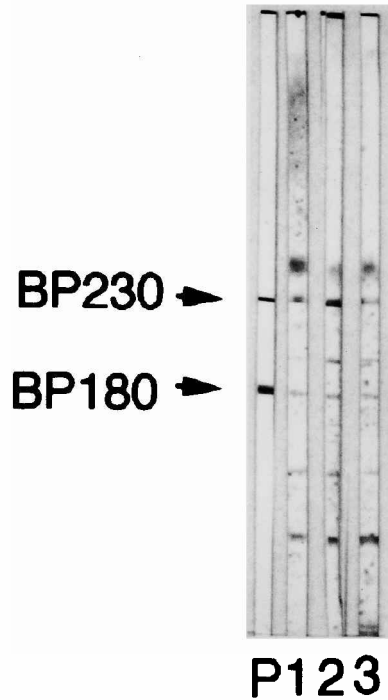


Fig. 4. Immunoblot analysis of the serum using human epidermal extract. P indicates the lane of generalized bullous pemphigoid serum. Lane 1: patient's serum taken 10 days before starting corticosteroids; Lane 2: patient's serum just before starting corticosteroids; Lane 3: patient's serum 4 months later. Lanes 1, 2, and 3 show reactivity with 230 kDa BP antigen 1, as well as a faint band at 180 kDa BP antigen 2.

Histological features in our case, such as hydropic degeneration of basal cells and necrosis of individual keratinocytes suggest that cell-mediated immune responses played an important role for the development of skin lesions. However, as mentioned above, the results of the immunofluorescence and immunoblotting studies lend support to the persistent production of the autoantibodies directed against the protein components of the basement membrane zone. Recently, the phenomenon of "epitope spreading" has been observed in a variety of autoimmune blistering or inflammatory dermatoses (1). This phenomenon was defined as a specific autoreactive lymphocyte response to endogeneous epitopes, which are distinct from and non-cross-reactive with the disease-inducing epitopes, on the proteins secondary to the release of such self protein during a chronic autoimmune or inflammatory response (7). As pointed out by Bowen et al. (8), it is difficult to detect the sequential development of autoantibody arrays in human disease, because screening for autoantibodies in patients is usually not performed until clinical signs and symptoms of a disease are well manifested. Although the exact process in the development of immunological disturbances could not be elucidated in our case, presumably the chronic basement membrane zone injury caused by cell-mediated

immune response exposed basement membrane zone proteins to the autoreactive lymphocytes, leading to an autoimmune reaction to the BP antigen.

#### ACKNOWLEDGEMENT

We express our thanks and gratitude to Masayuki Amagai, MD, for his advice in evaluating this patient and for performing the immunoblotting analysis.

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