Atypical Variant of Bullous Pemphigoid

—Prolonged Eruptions of Papulourticarial Lesions—

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A 63-year-old woman had a large number of pruritic papulourticarial eruptions on her abdomen and extremities for 6 months, with only a single tense vesicle on her arm. The biopsy specimen from a papular lesion showed foci of microvesicles at the dermoepidermal junction, and an abundance of eosinophilic infiltrate. Immunofluorescent studies showed linear deposits of IgG, IgE, and C3 at the basement membrane zone (BMZ) and circulating anti-BMZ antibodies in her serum, consistent with bullous pemphigoid.

This case can be distinguished from most of the other variant of bullous pemphigoid, particularly in the aspect of clinical presentation. It further emphasizes the concept that bullous pemphigoid represents a spectrum of bullous disease with heterogeneous clinical features. (Ann Dermatol 1:33—36, 1989)

Key Words: Bullous pemphigoid, Prolonged papulourticarial lesions

Bullous pemphigoid (BP) is a wide spectrum disease that can affect the skin and mucous membranes. Clinically, most patients with BP present with large tense bullae. However, clinical variants of vesicular,[1] erythematous,[2] localized,[3] erythrodermic,[4] nodular,[5] seborrheic,[6] and vegetans[7] forms may occur. The degree of pruritus is variable in this disorder and ranges from severe to nonexistent. The patient reported herein has an unusual variant of immunopathologically confirmed BP who presented long lasting pruritic papulourticarial lesions which were not considered to be a prodromal symptom.

REPORT OF A CASE

A 63-year-old woman visited the dermatology clinic at Hanyang University Hospital in November 1987, complaining of a pruritic papular dermatosis on her abdomen and arms. She first noted several erythematous papular eruptions on the periumbilical area 6 months before her visit. The lesions had gradually spread on her abdomen and arms over the ensuing weeks. She had noted only a few vesicular lesions developing sporadically. The patient had taken antihistamines and applied topical corticosteroids for the pruritic symptoms with some benefit. She was in good health prior to developing the skin lesions. She had no drug history relevant to her skin disease, nor did she have any systemic disease or infection at the time of her visit. Her family history and past history revealed nothing of significance.

Physical examination of this normotensive, thin woman, weighing 40 kg, was essentially unremarkable except for the pruritic skin condition. On her abdomen, inner and extensor arms, and parts of her inner thighs a large number of erythematous, relatively flat papules with a somewhat urticarial nature were dispersed (Fig.1). Each papular lesion was rather firm and measured 2 to 6 mm in diameter. Nikolsky's sign was not seen on these papular lesions. The patient had only one tense vesicle measuring 4 mm on her left forearm which initially erupted as a tiny clear vesicle on an erythematous papule. The mucous membranes were not involved, and there were no lymphadenopathies.

Histologic examination of a skin specimen obtained from a papular lesion on the abdomen showed irregular acanthosis and an occasional spongiosis of

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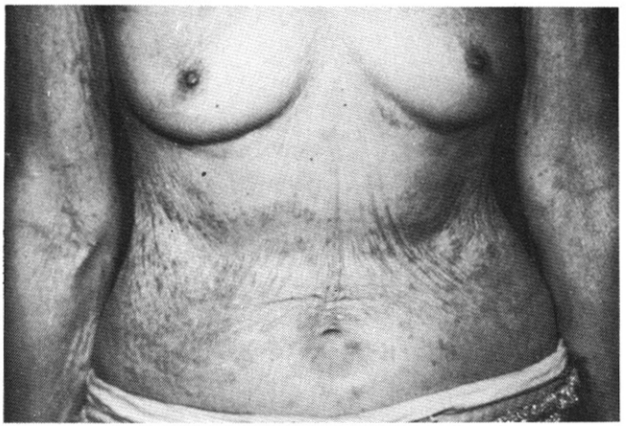

Fig. 1. A large number of erythematous papules with urticarial nature are dispersed on the abdomen and arms.

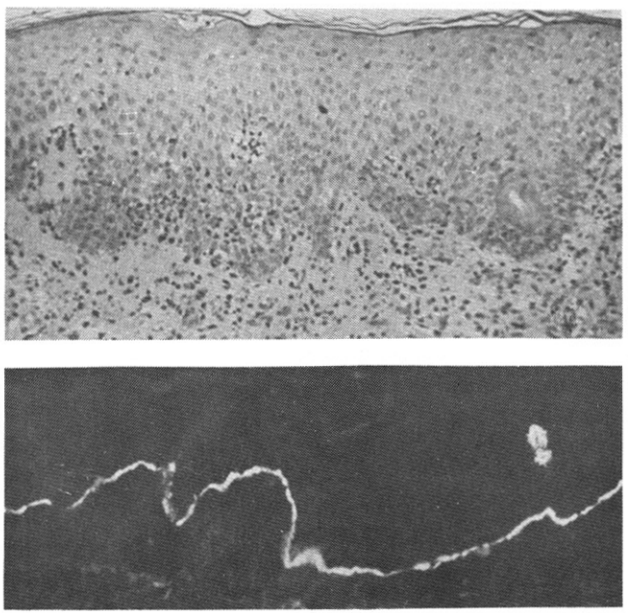

Fig. 2. Top, Biopsy specimen from a papular lesion shows irregular acanthosis and an occasional spongiosis of the epidermis with exocytosis of eosinophils and neutrophils. Subepidermal microvesicles and an upper dermal infiltrate of eosinophils are also noted (H & E stain, ×200).
Bottom, Direct immunofluorescence of a papule demonstrates a linear deposit of IgG along the basement membrane zone (×200).

the epidermis with exocytosis of eosinophils and neutrophils. Some vacuolar alterations of basal cells and subepidermal microvesicles were noted. In the papillary and upper dermis, a considerable number of eosinophilic infiltrates with perivascular eosinophils, neutrophils, and lymphohistiocytic cells were seen (Fig.2). A second specimen taken from the bullous lesion on the forearm showed a frank subepidermal blister containing many eosinophils and neutrophils.

Laboratory studies, including a complete blood cell count with differential, were within the normal ranges except for a 21% reading of eosinophils. The erythrocyte sedimentation rate was elevated to 44 mm/hr. A urinalysis, stool examination, and roentgenogram of the chest were normal. The pattern of serum protein electrophoresis, the values of liver, thyroid, and kidney function tests, fasting blood sugar level, serum concentration of immunoglobulins (G,A, and M), serum total hemolytic complement (CH50), C3 and C4 concentrations, ASLO, VDRL, antinuclear antibody, alpha-1 antitrypsin level, and C-reactive protein were all within the normal limits or negative. The serum examination for cryoglobulin was positive, and the serum IgE level was slightly elevated to 620 IU/ml. Intradermal skin tests with recall antigens of PPD and Trichophyton showed positive reactivities.

A preliminary diagnosis of bullous pemphigoid was made, and confirmed by immunofluorescence (IF) studies. The patient was treated with a regimen of systemic prednisolone (25mg/day) and azathioprine (75mg/day), as well as antipruritic topical preparations. The skin lesions soon subsided without scarring and she became symptom free in 3 weeks. Three months later, when clinical remission of the skin lesions was evident, she could manage with only a minimum dose of prednisolone and 50 mg of azathioprine a day.

IF Studies

Direct and indirect IF studies were performed according to the established procedures,[8] using commercially obtained monospecific fluorescein-conjugated antisera (Meloy Laboratories, Inc., Springfield, VA, U.S.A.). Direct IF studies of papular and peribullous specimens demonstrated linear deposits of IgG, IgE, and C3 along the basement membrane zone (BMZ) (Fig.2). The intensity of IgE staining was weaker than IgG, but recognizable. Indirect IF studies of the serum, using normal human flank skin as the substrate, detected anti-BMZ IgG and IgE antibodies, at a titer of 1:40 and 1:10 respectively. The patient did not have IgA class autoantibody to the BMZ.

Another system of indirect IF studies, using 1.0 mol/L sodium chloride split intact skin preparations

as substrates,[9] demonstrated that the serum anti-BMZ IgG and IgE were bound only to the epidermal side, the roof of the plane of separation. In vitro C3 IF staining was also carried out using a 2-step method described previously,[10] and the serum C3 fixing titer was found to be 1:80.

DISCUSSION

Nearly one half of the patients with BP have prodromal symptoms. It is often forgotten that BP may start as a nonspecific rash which may have urticarial or occasionally eczematous eruptions that can last for a few weeks or even for several months before the appearance of blisters.[11,12] Clinical characteristics of the individual varieties of the BP spectrum, as mentioned above, may differ considerably from the classical bullous form and from each other.

There have been a few cases reported in the literature of patients having prolonged pruritus with nonbullous papular or eczematous lesions which were recognized as fully evolved manifestations of BP per se.[13] The relationship of this uncommon variant of BP to the classic BP is not presently known. With this patient we found serum anti-BMZ antibodies of IgG, and IgE, which can be detected even less frequently in this disease,[14] and a significant titer of in vitro C3 fixing activity. There was also peripheral blood eosinophilia. But these findings are not remarkable features.[14,15] Assuming that BP is a primary immunologic disease in which the anti-BMZ antibody it responsible for the formation of skin lesions, ultrastructural localizations and biologic properties of the pemphigoid immune complexes or immunochemical characterization of the involved antigen(s) might be necessary to determine the relationship of this unusual variant of BP to its classic type.

There are a host of chemical mediators which can be involved in the inflammatory response induced by anti-BMZ antibodies;[16-22] complement products (anaphylatoxin, chemotcatic factors, etc.), mast cells, and perhaps, IgE anti-BMZ antibody generated products (eosinophilic chemotactic factor, histamine, leukotriens, high molecular weight neutrophil chemotactic factor, prostaglandins, etc.), eosinophilic mediators (lysosomal enzymes, major basic proteins, reactive oxygen intermediators), neutrophilic mediators (lysosomal proteolytic enzymes, reactive oxygen intermediators), activated lymphocyte mediators (lymphotoxin, eosinophil colony stimulating factor), and nonspecific tissue factors (plasmin, kinin, substance P, etc.). Possible relavancy regarding the pathomechanism of the unusual pruritic papulourticarial eruptions in this patient with BP might also be explained by the prominence of certain kinds of chemical mediators, and/or some modified biologic interactions between these factors. Similarly, constitutional variations in the local production of these mediators could be one determinant of the heterogeneity or atypicality of the clinical features.

In our opinion, the above case may be only an occasionally encountered variant in the BP spectrum, and persons who are initially seen with atypical chronic papular or urticarial eruptions should be examined for the possibility that their disease may be BP.

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