

PUVA Induced Bullous Pemphigoid in a Patient with Psoriasis

A bullous eruption in a patient with psoriasis was first described by Bloom in 1929 (as cited by Weber) (1). Since then there have been several reports of bullous pemphigoid occurring during the treatment of psoriasis, especially after ultraviolet (UV) B exposure. Comorbidity of these two diseases without treatment has also been reported (2,3).

Psoriasis is one of the most common chronic inflammatory skin diseases. Its etiopathogenesis is unknown, but nonspecific inflammatory processes and specific immunologic factors have been described. Autoimmune processes occurring within the epidermis and immunologic responses to exogenous infectious agents are suspected as causes, but not confirmed. In contrast, bullous pemphigoid (BP) represents a distinct autoimmune disease in which basement membrane zone (BMZ) molecules are most affected (4). BP is an autoimmune subepidermal bullous disease with circulating autoantibodies against BP antigen 1 (230kDa) and BP antigen 2 (180kDa). Antigen 2 is a transmembrane glycoprotein located in the hemidesmosomes and is the major antigenic

target in this disorder (5,6). The BP180 NC16a domain is considered to be the most immunogenic site (7).

The occurrence of BP in patients with psoriasis has occasionally been reported (8). Although the pathogenetic mechanism of comorbidity of psoriasis vulgaris and BP is unclear, a common immunogenetic mechanism might be involved (9). Most previously reported cases attributed the occurrence of BP in psoriasis to photochemotherapy and phototherapy (PUVA, UVA, UVB311nm), topical treatment with anthralin, tar, and as a result of systemic application of anti-TNF antibodies (10). The role of PUVA therapy in the development of BP remains unknown. George *et al.* suggested that such changes may trigger the development of antibodies which may later cross-react with proteins, such as the BP antigen, causing a bullous eruption to appear. The possibility that PUVA induces the alteration of immunologic reactivity of T-helper and T-suppressor cells, allowing the development of autoantibodies against native proteins, has also been raised (6,11).

A 55-year-old woman was referred to our department with a ten days history of bullous lesions, erosions, and exacerbated plaque psoriasis. Psoriasis was diagnosed in 1994, and various systemic and topical therapies (in combination or as single treatment)



Figure 1. Bullous lesions located on a psoriatic plaque of the upper limb.

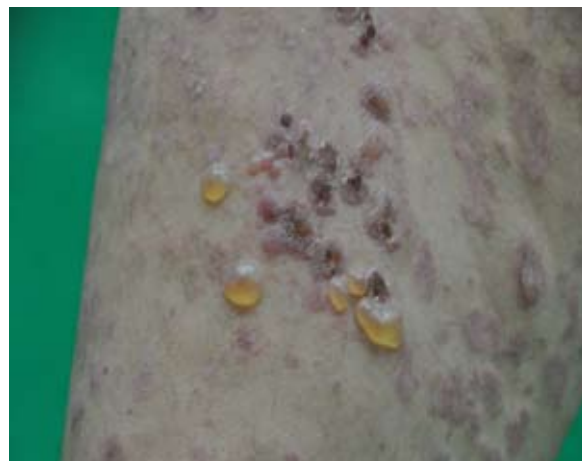


Figure 2. Bullous lesion located on a psoriatic plaque and uninvolved skin of the lower limb.

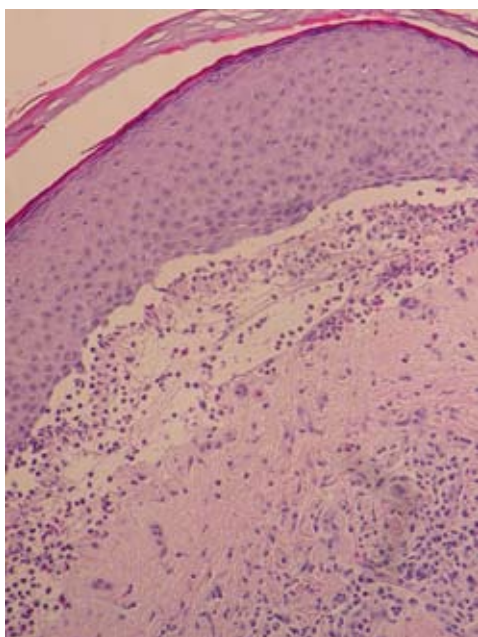


Figure 3. Subepidermal blister with eosinophils, fibrin, and neutrophils. Perivascular edema and lymphohistiocytic infiltration with eosinophils present in upper dermis (hemalaun and eosin; x 400).

were prescribed, such as topical corticosteroids, cyclosporine, and methotrexate. Three courses of PUVA therapy (cumulative dose 291 J/cm²) had been given several days before hospitalization.

On examination, extensive psoriatic plaques, vesicles and tense blisters up to 3 cm in diameter, filled with clear fluid, located on both the normal skin and psoriatic lesions were observed all over the body. The highest intensity of bullous skin lesions was found in the upper limbs and lower limbs (Fig. 1 and 2). No lesions were observed on the face or on the mucous membranes.

Routine laboratory tests such as biochemical tests, complete blood count, and urinalysis were normal. Chest radiography and abdominal ultrasonography, tumor markers CEA, and AFP showed no abnormalities.

Two biopsy specimens were taken from psoriatic and bullous lesions for histopathologic examination, and one biopsy was taken from a perilesional bullous area located on the right forearm for a direct immunofluorescence test (DIF). Histopathologic examination revealed a subepidermal blister with eosinophils, fibrin, and neutrophils. Perivascular edema and lymphohistiocytic infiltration with eosinophils was observed in upper dermis (Fig. 3). DIF test showed linear C3c deposits at the dermal-epidermal junction (Fig. 4). C3c was present at both the epidermal and dermal sides of BMZ in salt-split skin examination (Fig. 5).

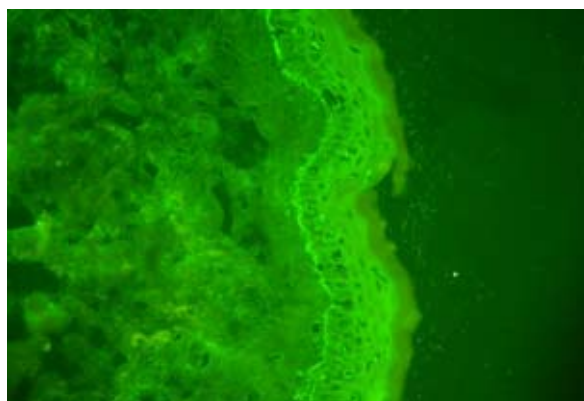


Figure 4. Direct immunofluorescence (DIF) study of uninvolved skin showing linear deposits of C3c at the dermal-epidermal junction.

Indirect immunofluorescence study (IIF) was done using monkey esophagus substrate and demonstrated IgG antibasement membrane zone antibodies (Fig. 6).

Enzyme-linked immunosorbent assay (ELISA) confirmed high titers of anti-BP180 (>200 E/ml) and anti-BP230 (140 E/ml) with negative results for anti-envoplakin, anti-Dsg1, anti-Dsg3, and anti-Col7A antibodies.

After BP was diagnosed, the patient received prednisolone orally at a dose of 50 mg daily (0.8 mg/kg body weight). After 1 week, during skin control examination there were no new lesions, and the existing ones were reduced. Prednisolon was gradu-

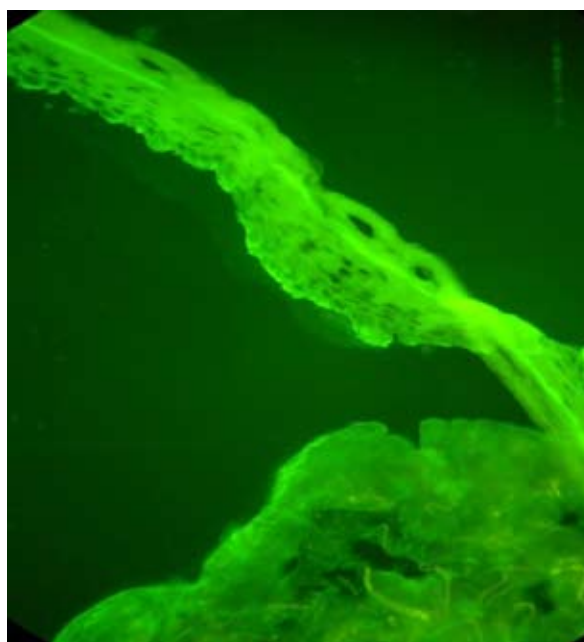


Figure 5. Salt-split skin test showing C3c deposits at the epidermal and dermal sides of the substrate.

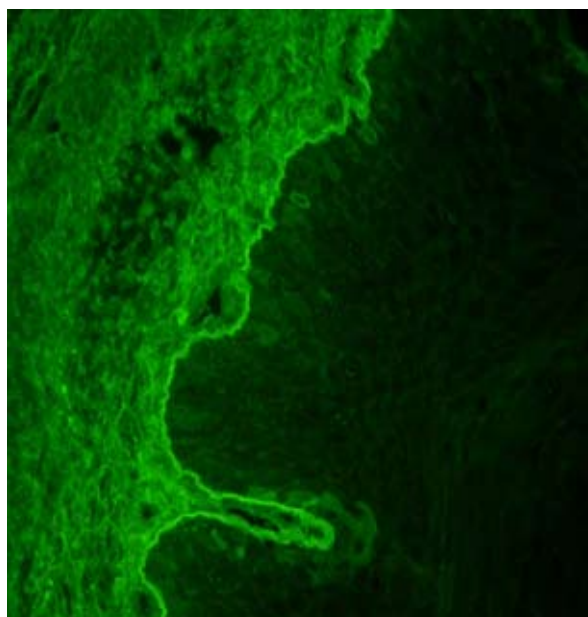


Figure 6. Indirect immunofluorescence (IIF) test on monkey esophagus substrate showing IgG antibasement membrane zone antibodies (titer 1:2560).

ally reduced (10 mg every week) until the skin lesions disappeared completely. Residual psoriatic plaques were treated with 1% hydrocortisone ointment simultaneously.

Bullous pemphigoid is sometimes considered a marker of oncogenesis, but patients with BP are mostly elderly, with a high base rate of cancer incidence. In our patient additional studies did not confirm tumor presence. She also did not receive any drugs that can contribute to the development of the disease (mainly diuretics and antihypertensives). PUVA-therapy applied during psoriasis treatment was the most likely BP induction factor. Skin lesions as a result of possible UVA overdosage were excluded. Histopathology and immunofluorescence clearly showed that our patient suffered from BP. UV radiation was most obvious trigger of bullous pemphigoid in our patients.

Comorbidity of the two diseases supports the hypothesis that autoimmunity has a partial role in the etiology of psoriasis. There have been several reports about the coexistence of these two diseases. It has been reported that UV radiation and an irritation therapies used in the treatment of psoriasis may lead to bullous pemphigoid. In predisposed cases psoralen together with UVA therapy causes the deposition of antibasement membrane zone antibodies through immunological alterations (2,3).

Exposure of psoriatic lesions to ultraviolet radiation (UVR) likely triggered to production of BP autoantibodies as a result of BP antigen configuration changes or as a secondary phenomenon demonstrat-

ed that BP180kD and alpha-6 integrin interaction is not only mediated by the BP epitope but is necessary for hemidesmosome formation (12,13). One possibility is that UVR may alter BMZ antigenicity and production of antibodies against the BMZ molecules (14).

UVR is known to induce or aggravate several autoimmune bullous diseases. The precise mechanism by which this radiation induces blistering is not well understood, but several possible mechanisms have been proposed. One is release or activation of bound antigen and/or the inducement of antibody fixation by UV radiation (15). This concept was proposed on the basis of in vitro studies using serum from a patient with BP in which UVB radiation generated by a hot quartz lamp and high-dose radiographs led to increased binding of antibodies to the BMZ (15).

Other proposed mechanisms include the activation of intracellular signaling pathways after binding of antibodies and increased production of inflammatory mediators such as interleukins (IL-1, IL-8), tumor necrosis factor-alpha (TNF- α), and granulocyte macrophage colony-stimulating factor (GM-CSF) (16,17). However, no definite mechanism of action for UVR induced blistering has been proposed. It is well known that psoralen-UVA (PUVA) therapy can itself induce acral bullous lesions, which cannot be attributed to immunologic causes, therapy overdose, or excessive psoralen uptake. It is more likely that the blistering is induced by direct damage to the dermo-epidermal junctional caused by the combination of UVA radiation and psoralen (15,18-20).

In treatment of psoriasis, we should avoid the use of systemic corticosteroids; the treatment of choice for comorbidity of psoriasis and BP is methotrexate. Even if the observed anti-inflammatory effect is short-term, long-term side effects far outweigh the benefits. In our case, we decided to apply short oral course of systemic corticosteroids because of rapid exacerbation of BP lesions with only single psoriatic plaques. The clinical result was very satisfactory, and we did not observe psoriasis exacerbation after discontinuation of prednisolone therapy. Proper treatment in such clinical cases should be decided individually, taking into account history of the disease, clinical course of psoriasis, and existing concomitant diseases.

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