

PUVA-induced Bullous Pemphigoid in Psoriasis

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ABSTRACT The association between psoriasis vulgaris and bullous pemphigoid is due to the still unclear autoimmune process. The common disease site is the dermo-epidermal junction or basal membrane zone (BMZ), with specific alterations for both diseases. Photochemotherapy (PUVA) is one of the therapeutic modalities for psoriasis and can trigger production of autoantibodies against antigens in the BMZ in patients with subclinical bullous pemphigoid. Furthermore, PUVA therapy can alter the immunological milieu and hence can contribute to the expression of bullous pemphigoid in patients with psoriasis. We observed a bullous eruption compatible with bullous pemphigoid in a psoriatic patient treated with PUVA. We speculate that the cumulative dose of PUVA sufficient for triggering blister formation is individually determined.

KEY WORDS: psoriasis; PUVA; bullous pemphigoid

INTRODUCTION

There are reports in the literature concerning the association between psoriasis vulgaris and autoimmune bullous diseases such as pemphigus vulgaris (1), pemphigus herpetiformis (2) pemphigus foliaceus (3), bullous pemphigoid (4), linear immunoglobulin A (IgA) bullous diseases (5), and epidermolysis bullosa acquisita (6). Another bullous disease that targets the 200k Da molecule (anti-laminin γ 1 pemphigoid) (7,8) as well as the so-called psoriasis bullosa acquisita were recently added to that list (9). The autoimmune process is common for all these diseases. It not only provokes blister lesions on psoriatic skin but also affects normal-appearing skin. Sometimes the trigger for these associations are therapeutic modalities for psoriasis itself. The exact pathogenic mechanism for the expression of a combination of psoriasis vulgaris with another autoimmune bullous disease is not well understood. We report a case of a man with long-standing plaque psoriasis who developed bullous

pemphigoid in the early course of PUVA therapy. This case is an example of the appearance of bullous pemphigoid in a patient who already suffers from psoriasis vulgaris, as well as the individual effect of the cumulative dose of UVA as a potential trigger.

CASE REPORT

We present a case of 58-year-old male with a history of chronic plaque psoriasis of more than 20 years. Four years ago he was briefly treated with methotrexate (MTX) 15 mg/weekly for a generalized episode of psoriasis, but the therapy was discontinued because of lack of compliance by the patient. He applied therapy for psoriasis irregularly, not including UVB and PUVA therapy. He was admitted to our Department with worsening psoriatic lesions, and PUVA therapy was an indication. Prior to PUVA initiation, we obtained laboratory analyses (including a complete blood count and basic metabolic panel)



Figure 1. A few early bullae on the anterior aspect of the upper arm and a large psoriatic plaque in regression on the lateral side of the trunk.

and performed ophthalmological examination of the patient, echosonography of the abdomen for possible hepatic lesions, chest radiography, and testing for AFP and CEA tumor markers. All findings were unremarkable. Indirect immunofluorescence (IIF) test was not performed. After a cumulative PUVA dose of 33.6 J/cm² he developed a solitary bullous lesion on his left arm restricted to the psoriatic plaque in regression (Figure 1). The Nikolsky sign was negative. Two days later there were multiple large tense blisters on his trunk and extremities that were not limited only to the psoriatic plaques but were also distributed over the normal-appearing skin. There was no mucosal or ocular involvement. The patient had not taken other medications. A biopsy specimen obtained from the border of a bulla that had arisen on psoriatic skin showed changes consistent with psoriasis vulgaris and subepidermal bulla formation that contained eosinophils. There was an inflammatory infiltrate with lymphocytes and eosinophils in the superficial dermis (Figure 2). Direct immunofluorescence testing from perilesional, healthy (non-psoriatic) skin revealed linear, homogeneous immunoglobulin G (IgG) and C3 deposits along the epidermal basement membrane zone (Figure 3).

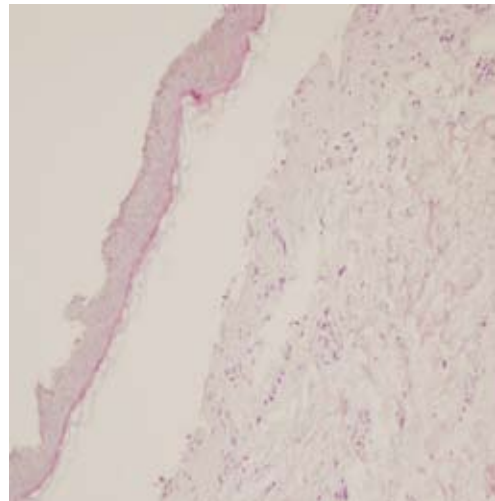


Figure 2. Subepidermal blister formation containing a few eosinophils. Complete dermoepidermal separation and "naked" dermal papillae. Inflammatory infiltrate with lymphocytes and eosinophils in superficial dermis.

Considering all these findings, the primary diagnosis (psoriasis) was changed to PUVA-induced bullous pemphigoid in psoriasis. PUVA therapy was withdrawn. After a test dose of 2.5 to 5.0 mg MTX followed by a blood count 5 days later, the therapy with MTX at a dose of 10 mg/week was started with folic acid supplementation, along with topical steroids. There were no new blisters after two weeks of therapy, and mild improvement of the plaque psoriatic lesions was noted. After 4 weeks of treatment, remission of psoriasis with residual hyperpigmentation was observed along with healing of blisters and erosions without scarring or milia formation. During the follow-up period of one year with tapering of the MTX dose, no relapses of both conditions, psoriatic and bullous, were registered.

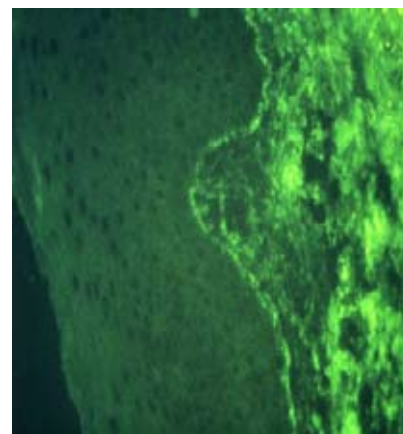


Figure 3. Direct immunofluorescence of perilesional skin revealed linear-homogeneous, band-like IgG and C3 deposits along the epidermal basement membrane zone.

DISCUSSION

Association between psoriasis and subepidermal bullous diseases was reported for the first time by Bloom in 1929 (10). In 1985 Grattan (11) described the coexistence of psoriasis vulgaris and bullous pemphigoid without treatment.

The main disease site in the pathogenesis of bullous pemphigoid is the basement membrane zone (BMZ). There are changes in the BMZ that are due to psoriasis vulgaris itself. As was discovered by Alvin J. Cox (12), basal lamina in psoriasis vulgaris has shown reduplication and focal discontinuity. The onset of blisters, primarily on psoriatic plaques, was due to changes of the basal lamina of psoriatic lesions that can expose, alter, or unmask its antigens (13). Bullous pemphigoid lesions limited to psoriatic plaques were developed because antigens at these sites were unmasked through enzymatic degradation of the BMZ (14). Despite that, herniation of basal keratinocytes in the lamina densa (14) takes place, providing easier access to antibodies and can thus initiate autoimmunity (15). All these events are independent of UVA light and can be sufficient to provoke subepidermal blisters limited to psoriatic skin. These hypothetical steps in the pathogenesis of bullous pemphigoid in patients with psoriasis does not explain bullous lesion on clinically healthy, non-psoriatic skin. They can, however, explain rare reports of the occurrence of bullous pemphigoid in psoriatic individuals without using anti-psoriatic systemic therapy (16,17). Among anti-psoriatic systemic therapeutics, photochemo (PUVA) is most commonly suspected of triggering bullous pemphigoid. It was suggested that PUVA may precipitate bullous pemphigoid by immunological alteration of the epidermal antigens. The result is formation of complement-binding anti-BMZ antibodies leading to bullous skin lesions (18). Washio *et al.* (19) suggested alteration of the BMZ antigenicity by UV radiation that might lead to exposing or releasing altered antigens and consequently stimulation of autoantibody production. Danno *et al.* hypothesized that alteration of the membrane markers by PUVA might be due to the reaction of PUVA and membrane glycoproteins (20). Bullous pemphigoid antigen (BPAG) (230kDa BP antigen) as an intracellular plaque protein and BPAG2 (180kDa BP antigen) as a transmembrane collagenous protein take part in forming hemidesmosomes. Kitajima *et al.* (21) noted that BPAG2 internalization takes part in weakening the hemidesmosomes. This is especially important when basal cells enter mitosis, because there is a process of reconstruction of hemidesmosomes during mitotic activity that would be difficult to achieve if there is a shortage of BPAG2 due to its internalization. On the

other hand, the effect of PUVA-inducing interruption/blockade of the mitotic activity in cells is well known. This shortage of BPAG2 and the antiproliferative effect of PUVA inevitably leads to subepidermal blister formation.

From the immunological point of view, bullous pemphigoid is regarded as a Th2-mediated disease. During PUVA therapy there is a switch in cytokine expression from Th1 to Th2 (22). This new immunological milieu in patients with subclinical bullous pemphigoid, patients with hidden susceptibility, might lead to clinical expression of bullous pemphigoid. PUVA, UVA, and UVB have already been described as a possible mode of therapy that can provoke bullous pemphigoid formation (23-25). This was the case in our patient treated with PUVA therapy. Regarding the cumulative dose of UVA sufficient to induce bullous pemphigoid in psoriasis, Bernadas *et al.* (26) presented a patient who had developed bullae after receiving a cumulative dose of UVA of 673 J/cm² and UVB of 2.96 J/cm². In contrast to that case report, our patient developed bullous pemphigoid after the administration of a cumulative dose of UVA of only 33.6 J/cm² and without previous UVA or UVB phototherapy.

CONCLUSION

We speculate that the cumulative dose of UVA which is sufficient to provoke blisters on psoriatic plaques in susceptible patients is individually determined.

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