DOI: 10.2478/sjdv-2014-0003

Concomitant Psoriasis and Bullous Pemphigoid – a Case Report

Lidija CVETKOVIĆ JORDANOV, Lidija KANDOLF SEKULOVIĆ[1], Željko MIJUŠKOVIĆ[1], Lidija ZOLOTAREVSKI[2], Radoš ZEČEVIĆ[1]

[1]Department of Dermatology, School of Medicine, Military Medical Academy, Belgrade, Serbia
[2]Institute of Pathology and Forensic Medicine, School of Medicine, Military Medical Academy, Belgrade, Serbia

*Correspondence: Lidija Kandolf Sekulović, E-mail: lkandolfsekulovic@gmail.com

DE GRUYTER OPEN

UDC 616.517:616.527

Abstract

Concomitant occurrence of psoriasis and bullous pemphigoid was described in less than 100 cases in the literature. The co-occurrence affects the treatment approach of patients. We present a case of a 58-year-old man with psoriasis presenting with erythematous plaques, tense bullae, erosions and fever up to 39°C. Direct and indirect immunofluorescence and histopathological examination confirmed the diagnosis of bullous pemphigoid. In our case, bullous eruptions were successfully treated with oral methylprednisolone and dapsone, and psoriasis with narrowband ultraviolet B phototherapy and acitretin.

In conclusion, the etiopathogenesis of the coexistence of these two entities remains unknown, but it may be related to relatively high incidence of psoriasis and bullous pemphigoid, respectively. Both conditions are immunologically mediated and combined immunosuppressive regimens, directed at cellular and humoral immune responses, usually result in clinical improvement.

Key words

Psoriasis; Pemphigoid, Bullous; Comorbidity; Fluorescent Antibody Technique; Immunosuppressive Agents; Ultraviolet Therapy

Psoriasis is a complex, chronic, multifactorial, T-cell mediated inflammatory disease with keratinocyte hyperproliferation in the epidermis, and an increase in the epidermal cell turnover rate. Environmental trigger factors (e.g. trauma, medications, infections) in addition to immune and genetic factors, appear to play a role in the pathophysiology of clinical manifestations: sharply demarcated, erythematous plaques with silvery white scales. The most commonly affeted areas are found on the skin, scalp, elbows, knees, lumbosacral region, nails, hands and feet. Joint involvement accounts for up to 30% of all cases (1). Bullous pemphigoid is an autoimmune, subepidermal, blistering disease, which may be associated with significant morbidity, and predomonantly affects the elderly. It is characterized by multiple tense bullae arising on normal or erythematous skin, with a predilection for the groins, axillae and flexural areas. In contrast to psoriasis, bullous pemphigoid represents a distinct autoimmune condition in which the skin is the main target organ, and the role of autoantibodies against basement membrane antigens is well established (230 kD protein bullous pemphigoid antigen 1 and 180 kD protein bullous pemphigoid antigen 2, both of which are localized to the hemidesmosome).

The concomitant occurrence of psoriasis and bullous pemphigoid, as two well-characterized, chronic inflammatory skin diseases was first described in the literature in 1929 by Bloom et al. Since then, less than 100 cases were described worldwide (2). The pathogenic foundations of this phenomenon

are unknown. It may be suggested that psoriasis, as a chronic inflammatory disease, provides a particular predisposition of the immune system that, under certain circumstances leads to autoimmune response. The diagnosis relies on clinicopathologic correlation of direct and indirect immunofluorescence microscopy. Here we present a 58-year-old man with a 30-year history of plaque-type psoriasis presenting with disseminated tense bullae diagnosed as bullous pemphigoid.

Case report

A 58-year-old male with a 30-year-old history of psoriasis was admitted to the Department of Dermatology of the Medical Military Academy in Belgrade with fever (39 °C), extensive eruption of tense bullae and erosions on the trunk and extremities. Blisters and erosions appeared one year before on the trunk, and since then they spread to the extremities. The lesions were intensely pruritic, significantly affecting the patient′s quality of life. Before admission to our Clinic, the patient was treated by a general practitioner and other dermatologists with prednisone 60 mg per day, and after improvement with 20 mg per day. According to the patient's history, limited psoriasis was partially controlled with occasional mid-

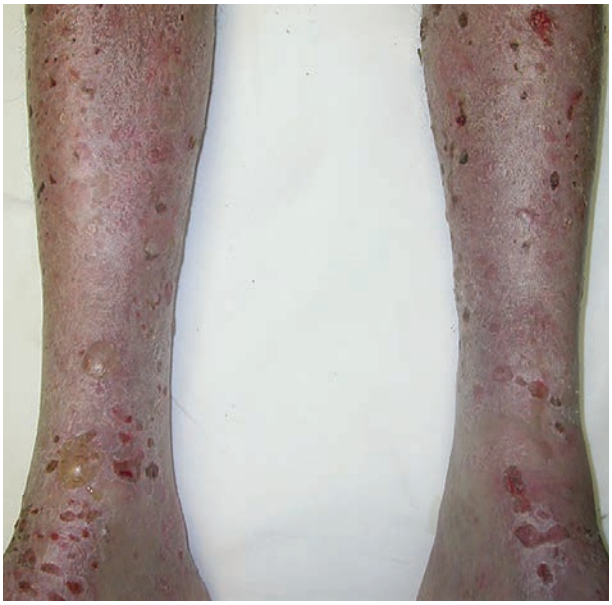

Figure 1. Tense vesicles, bullae and erosions on the lower legs

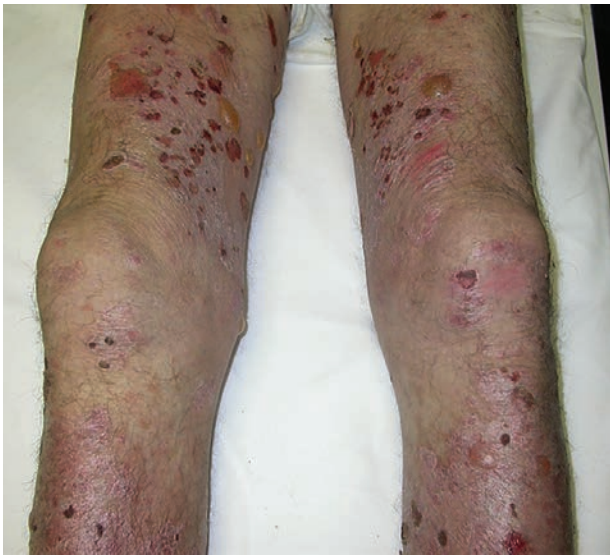

Figure 2. Tense bullae and erosions superimposed on preexisting psoriatic plaques on the thighs and lower legs

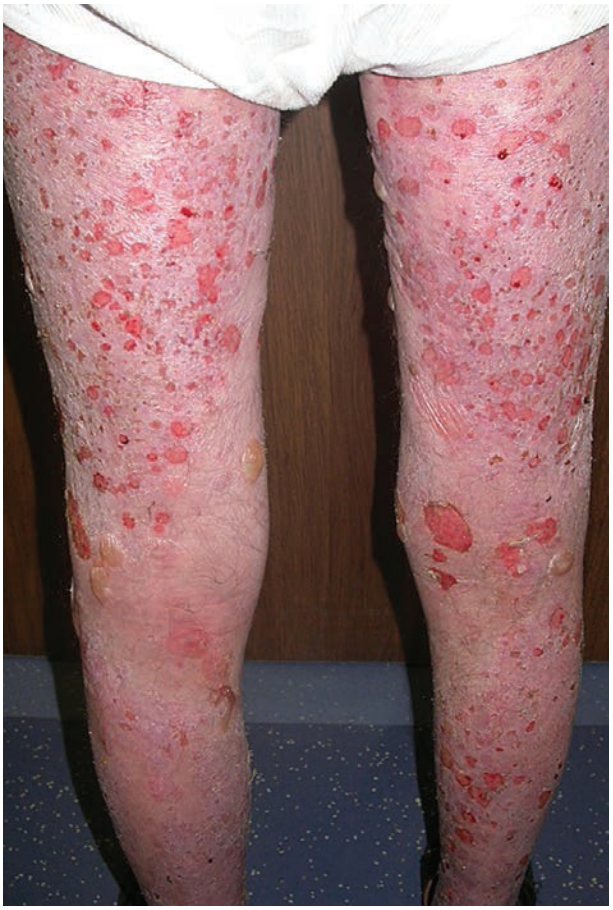

Figure 3. Multiple, extensive erosions and tense bullae on the lower extremities

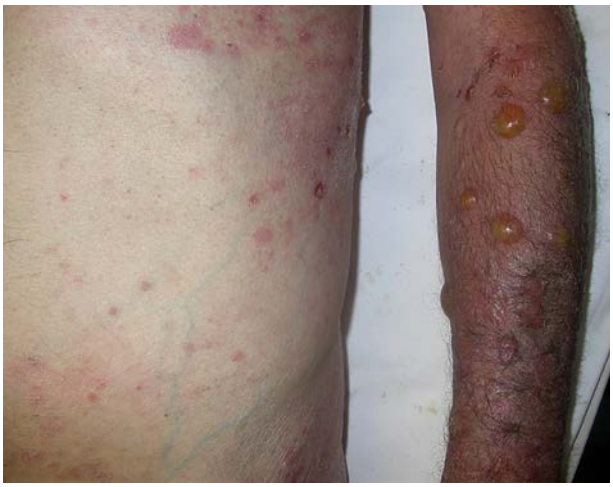

Figure 4. Blisters on the left forearm

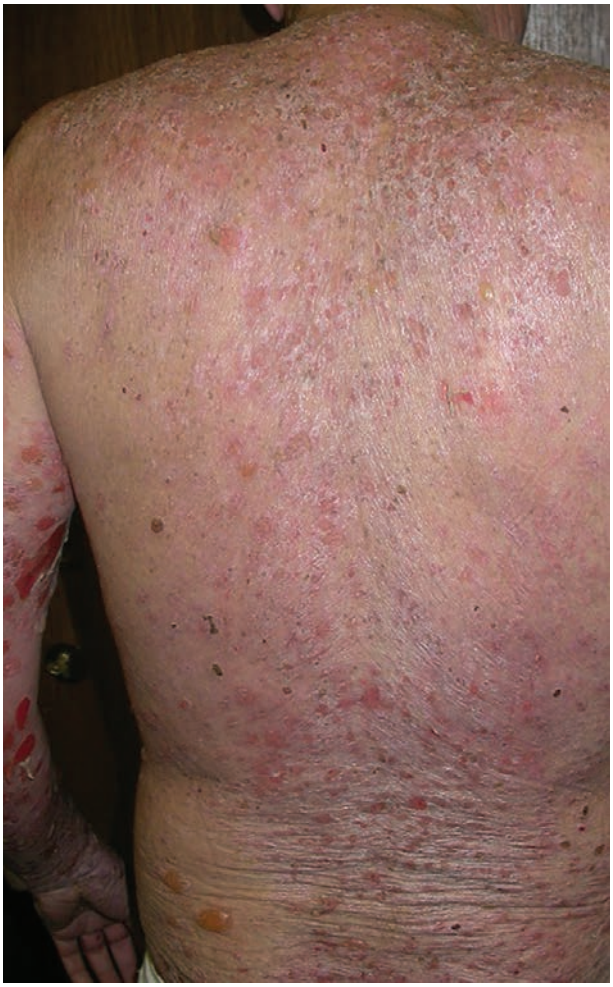

Figure 5. Tense bullae and erosions on the back and right arm, partially superimposed on preexisting psoriatic plaques in the sacral area

to-high-potency topical corticosteroids. The patient was otherwise healthy. There was no family history of psoriasis or autoimmune diseases.

He reported occasional alcohol consumation.

Physical examination revealed tense bullae and erosions on the trunk, lower and upper extremities, (Figures 1-4) partially superimposed on the pre-existing psoriatic erythematous plaques on the forearms and lower legs (Figure 5). The face and mucous membranes were spared. He had a fever up to 39°C.

Laboratory tests revealed increased sedimentation rate, C-reactive protein and fibrinogen, neutrophilia, hyperbilirubinemia, megaloblastic anemia and elevated levels of liver enzymes - alanine aminotransferase and aspartate aminotransferase. Hepatitis B surface antigen (HbsAg), anti-HCV (hepatitis C virus) antibodies, serum creatinine, urea, uric acid, lipids and urine analysis were within physiological limits. The diagnosis of sepsis was established by an infectologist, based on microbiology isolation of staphylococcus aureus in blood cultures and affected lesions.

X-ray of the heart and lungs showed no pathological findings. Ultrasonography of the upper abdomen and pelvis showed hepatomegalia with a bright echostructure.

Pathohistology analysis was performed on skin specimens. Two skin biopsies were taken for histopathology and immunofluorescence examinations. The first biopsy specimen, obtained from a psoriatic lesion, showed psoriasiform hyperplasia with parakeratosis, neutrophils and dilated capillaries in the dermis (Figure 6); the second biopsy specimen obtained from the border of a fresh bulla revealed epidermis separated from the dermal tissue, with serum exudate and a large group of neutrophils and eosinophils (Figures 7 and 8). Direct immunofluorescence from the perilesional skin revealed linear, continuous C3 and IgG deposits along the basement membrane zone. Indirect immunofluorescence assay demonstrated circulated IgG autoantibodies against the dermal-epidermal junction (titer 1 : 320).

Specialist consultations established the following diagnoses: sepsis and alcocholic liver injury (by an infectologist) and megaloblastic anemia (by a hematologist).

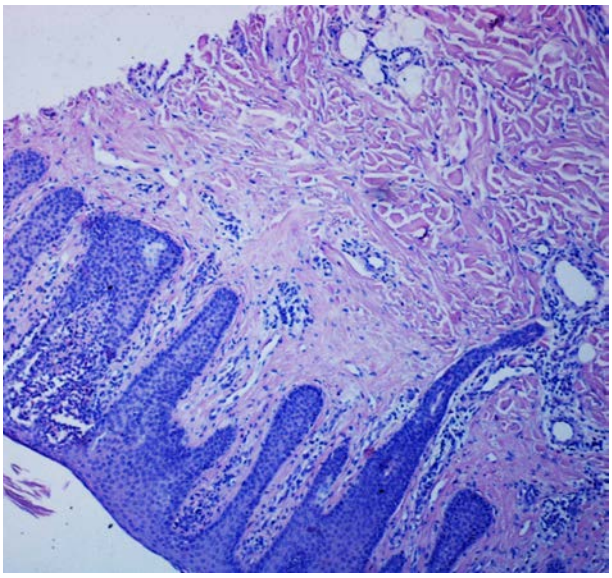

Figure 6. Psoriasiform hyperplasia with parakeratosis and neutrophils and dilated capillaries in the dermis (HE x 5)

A combination of methotrexate and corticosteroids was considered as the first choice treatment, but it was contraindicated due to the history of alcochol consumption, elevated transaminases and enlarged liver, estimated by ultrasonography. The patient was treated with systemic antibiotics: cefprozil 1g/6h i.v. and ciprofloxacin 200 mg/12h during two weeks; cefuroxime tbl. 500 mg were introduced

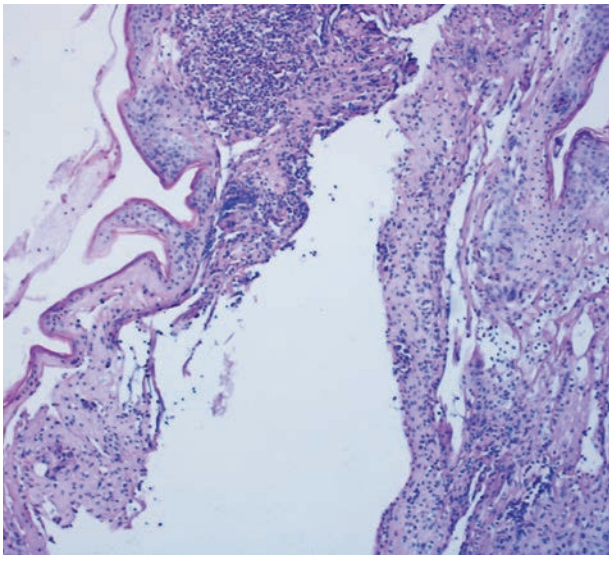

Figure 7. Epidermis separated from the dermal layer (HE x 5)

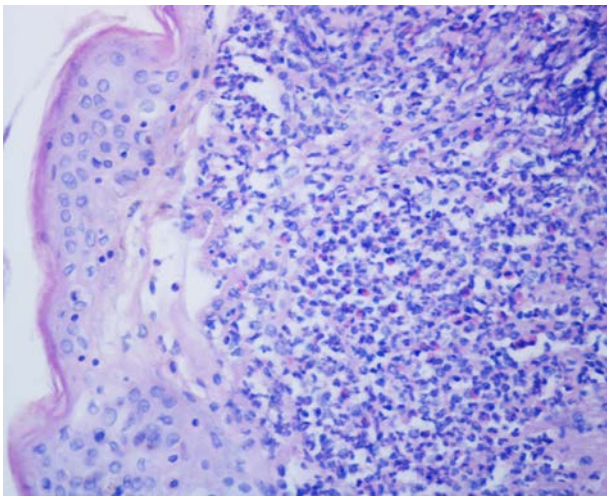

Figure 8. Epidermis separated from the dermal layer: serous exudate of serum with large group of neutrophils and eosinophils (HE x 20)

twice a day for one week. At the same time, oral methylprednisolone was initiated at an initial dose of 60 mg/day. The dosage was reduced to 40 mg/day after two weeks, and diaminodiphenyl sulfone (dapsone) 100 mg/day was added. After 12 weeks of treatment, skin lesions resolved almost completely (absence of bullae and PASI <5), so methylprednisolone was slowly tapered to 24 mg daily, and dapsone was reduced to 50 mg daily.

After 8 months of follow-up, the patient was almost lesion free, but new erythematous plaques were obsered on his forearms and lower legs. Narrowband UVB (NB UVB) phototherapy was given, which proved to be effective for psoriasis treatment, but may aggravate bullous pemphigoid. The patient was irradiated twice weekly for six months, and methylprednisolone and dapsone were continued at the above dose. Complete remission of psoriasis with small single bullae was observed at monthly follow-ups (Figure 9).

Two months after phototherapy was discontinued, the patient had discrete psoriasis eruptions. Since the patient reported alcochol abstinence, reevaluation of alcocholic liver injury revealed that transaminases were at normal levels. Treatment with acitretin (25 mg daily) was initiated with dapsone that was increased to 100 mg daily, and methylprednisolone was reduced to 24 mg per day

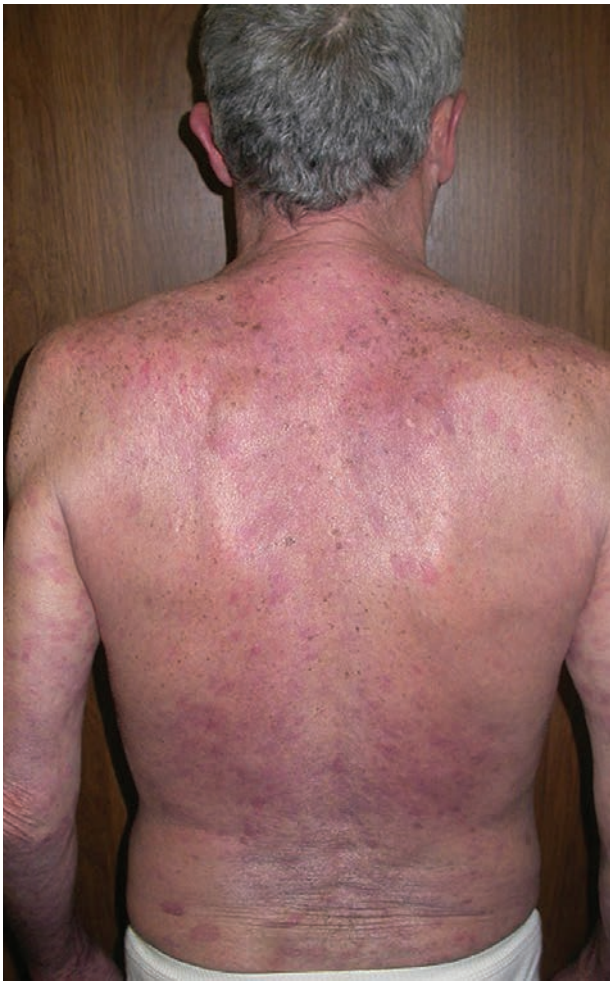

Figure 9. Hyperpigmented macules on the normal back skin

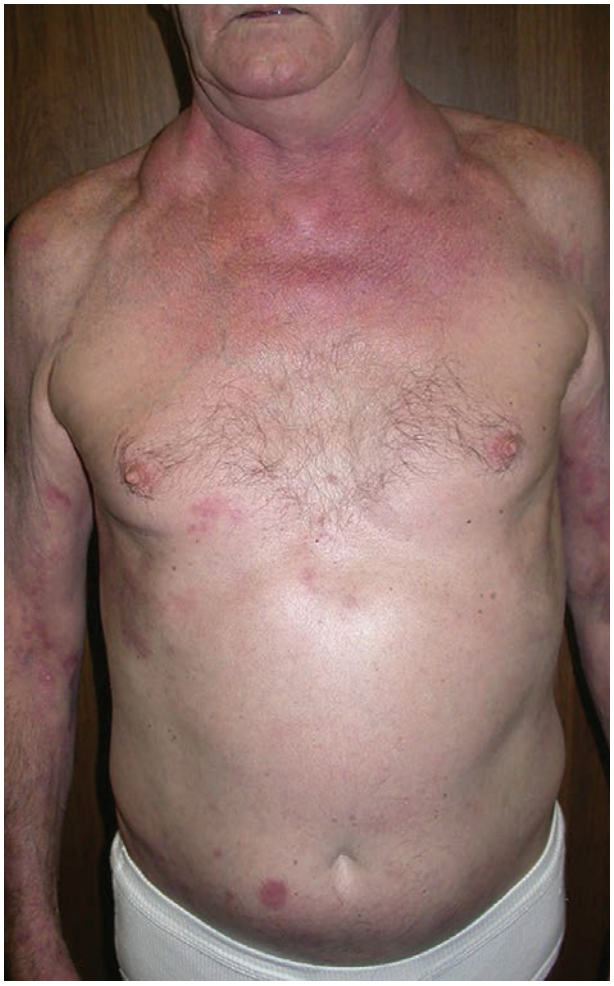

Figure 10. Hyperpigmented macules on the trunk and arms

3 times weekly. At 9 month follow-up, there was no relapse of bullous pemphigoid or psoriasis (Figure 10). The treatment was well-tolerated: a limited elevation in serum lipids (cholesterol 6,4 mmol/l; triglycerides 4,1 mmol/l) was the only side effect, without observed increment of transaminases.

Discussion

In 1929, Bloom et al. were the first to report on the simultaneous occurrence of psoriasis and bullous pemphigoid. Since then, less then 100 cases were described worldwide (2). Psoriasis has consistently been associated with many cutaneous and systemic conditions. Recent epidemiological studies have shown that psoriasis patients are prone to develop cardiovascular and other metabolic syndromes. On the other hand, a variety of cutaneous disorders may be associated with psoriasis (3). Since the initial description of the coexistance of bullous pemphigoid and psoriasis, several autoimmune bullous diseases associated with psoriasis have been reported in the literature. These include pemphigus vulgaris, pemphigus foliaceus, pemphigus herpetiformis, linear bullous dermatoses, cicatricial pemphigoid and, epidermolysis bullosa acquisita (3). Amoung these, bullous pemphigoid is the most frequently reported condition to be associated with psoriasis. It is more common among men than women, with an average age of onset at 63 years. In most cases psoriasis preceded the development of bullous pemphigoid, with an average time interval of 20 years, between the two conditions (4). Our patient, with an interval

of 30 years was well within this range. Also, bullous pemphigoid seems to occur in patients with psoriasis at a younger age than sporadic bullous pemphigoid (2).

The etiologic and trigger factors responsible for co-occurrence of psoriasis and bullous pemphigoid remain unknown. Since the coexistence was seen in patients who received a wide range of treatment for psoriasis, as well as in untreated patients, it is difficult to incriminate a single agent as a potentially causative factor in the development of bullous pemphigoid. A reduced barrier function of the psoriatic epidermis, combined with the irritant effects of therapies administered for psoriasis, such as anthralin, tar and ultraviolet light, psoralen ultraviolet A (PUVA), narrowband UVB irradiation, together with a low grade immunologic basal memmbrane zone (BMZ) insult, may precipitate blister formation (5). Our patient was previously treated only with local corticosteroids. Recently, cases of bullous pemphigoid developing after efalizumab therapy (anti-tumor necrosis factor treatment) of psoriasis have been described (6).

Changes at the BMZ in psoriasis itself may be responsible for precipitating the bullous disease. The presence of chronic inflammation, trafficking of activated lymphocytes and abundance of antigen presenting cells in psoriasis could unmask, expose or alter BMZ antigens, giving rise to autoantibody production (7). Electron microscopy studies have shown a focal discontinuity and reduplication of the basal lamina in psoriasis. The concept of „epitopic spreading“ whereby tissue damage from a primary inflammatory process can cause the release and exposure of a previosly „sequestered“ antigen, leading to a secondary autoimmune response against the newly released antigen, may provide us with a unifying explanation for the development of subepidermal bullous disorders (8). Such changes in structure may result in altered antigenicity of BMZ and keratinocytes, and subsequent generation of antibodies. Kobayashi et al. (4) described blistering that occurred only on psoriatic lesions. They postulated that bullous pemphigoid antigens are unmasked in psoriatic lesions through enzymatic degradation of the BMZ, and thus become accessible to circulating antibodies. Despite this assumption, blistering on both the psoriatic and normal-appearing skin was observed in other patients, including our case.

The autoimmune nature of bullous pemphigoid has been confirmed with the identification of IgG antibodies to bullous pemphigoid antigen 1, a 230-kd protein and bullous pemphigoid antigen 2, a 180-kd molecular weight transmembrane protein, both of which are localized on the hemidesmosome. These antigens account for 90% of patients with bullous pemphigoid (15). Bullous pemphigoid with psoriasis is typically associated with autoantibodies against type XVII collagen – bullous pemphigoid antigen 2, with the main antigenic site occurring within the noncollagenous 16a (NC16a) domain (9). Although specific autoantibodies operate in bullous pemphigoid, the significance of autoimmune mechanism and target autoantigens is only postulated in psoriasis. Circulating autoantibodies against components of the Malpighian layer and stratum corneum have been detected in the serum of psoriatic patients (10). The disregulation ot T-cell activity in psoriasis might result in the induction of specific antibodies to basement membrane antigens (4). Psoriasis has been historically considered as T-helper type-1 (Th1 type) immune mediated disease. However, recent studies have etablished that Th17 is the primary pathogenetic subset; this subset of T-cell also plays a key role in autoimmunity (5). Psoriasis has been associated with other autoimmune diseases such as discoid and systemic lupus erythematosus, miasthenia gravis, Sjögren syndrome, Crohn's disease, ulcerative colitis, vitiligo, Hashimoto thyreoiditis (11). No association with malignant conditions has been noted (11).

It was shown that UVB light can induce autoimmune phenomena characteristic of bullous pemphigoid. Furthermore, the basal cell layer known as the germinative compartment, is critically UV light sensitive (5). PUVA and retinoid therapy have been shown to modulate the glycocalyx and the expression of bullous pemphigoid and pemphigus antigens in nonlesional skin as well as in keratinocyte culture and have been found to decrease the expression of adhesion molecules on circulating and tissue-infiltrating T-lymphocytes. In support of these

observations, bullous pemphigoid has been observed in patients with other PUVA treated diseases, such as mycosis fungoides (5). In our patient, during and after the NB UVB phototherapy, the skin lesions were not aggravated by NB UVB phototherapy, possibly attributable to the concomitant corticosteroid and dapsone therapy.

Infectious agents are also possible triggering factors in the development of bullous pemphigoid. Tomasini et al. (10) speculated on the role of streptococcal infections in the pathogenesis of both psoriasis and bullous pemphigoid. These organisms may increase the production of possibly pre-existing molecules against surface antigens of keratinocytes, which may lead to the development of blisters. Other infections, such as hepatitis C, have been described in linear IgA dermatosis with concomitant psoriasis (12). In addition, infections may trigger immunologic reactions against basement membrane structures which have been altered or disruptured by the inflammatory mechanisms of psoriasis or its treatment. A common genetic predisposition for psoriasis and bullous pemphigoid has not been eluciadated. Although the latter is associated with HLA-B57, Cw6, C7, DR4 and DR7, no distinct association has been found for bullous pemphigoid (13).

Several therapeutic modalities have been described for the treatment of coexisting psoriasis and bullous pemphigoid. Immunosuppressive drugs proved to be effective in both diseases. Roeder C. et al. (14) described the combination of acitretin, which is well established in the treatment of severe psoriasis, and azathioprine, often used as a combination agent to treat bullous pemphigoid. Other therapeutic options include low dose methotrexate, cyclosporine, erythromycin in combination with etretinate (14), or tetracycline in combination with nicotinic acid or dapsone (4).

Oral treatment with fumaric acid showed a good clinical response in both psoriasis and blister formation (4). Two independent cases of psoriasis associated with bullous pemphigoid have been successfully treated with azathioprine and cyclosporine (15). Mycophenolate mofetil monotherapy (2000 mg per day) has proven to be effective (16). Systemic steroids should be avoided to prevent pustular psoriasis upon dose modifications (17). Franceso Cusiano et al. (18) described a patient in whom remission of bullous pemphigoiod was obtained with etanercept used as a single drug therapy. TNF-α antagonists may be used as an effective alternative therapy for coexisting bullous pemphigoid and psoriasis, since corticosteroids may induce a relapse of psoriasis and other well-known side effects and traditional systemic therapies are often associated with organ toxicity. In the literature, two cases of bullous pemphigoid (19, 20) treated with etanercept are described, both coexisting with psoriasis; the first achieved remission using etanercept when the steroid dose was lowered (19), the second patient was given etanercept for psoriasis after being completely cured of bullous pemphigoid with rituximab (20). Methotrexate used in low doses (10 mg weekly) (3) is effective in the treatment of BP-associated psoriasis, but, our patient could not tolerate MTX due to alcocholic liver disease. NB UVB phototherapy was an option, and, surprisingly, without outbreak of bullous pemphigoid; a complete clinical clearing of both diseases was achieved, with addition of dapsone and oral methylprednisolone. Subsequently, after NB UVB was discontinued, the patient continued receiving dapsone and oral methylprednisolone and acitretin was initiated. A limited elevation in serum lipids (cholesterol - 6,4 mmol/l; triglycerides - 4,1 mmol/l) was the only side effect seen. In our case, combination of NB UVB phototherapy with dapsone and oral corticosteroids was highly successful in suppressing lesions of both diseases. Our experience encourages further trials of this combination treatment in patients suffering from psoriasis and bullous pemphigoid.

Conclusion

In conclusion, the etiopathogenesis of the coexistence of psoriasis and bullous pemphigoid, remains unknown and may be related to relatively high incidence of both diseases. Further investigations may shed more light on the pathophysiological mechanism of this phenomenon. The majority of patients with psoriasis and bullous pemphigoid report a serious impairment of their quality of life and they also feel

that current treatment, although often effective, does not provide a satisfactory long-term solution. Due to the fact that both conditions are immune-mediated, combined immunosuppressive regimens, directed at cellular and humoral factors, usually result in clinical improvement. Thus, the challenge is to find appropriate, specific, safe and effective long-term treatment solution.

Abbreviations

PASI - psoriasis area and severity index
NB UVB - Narrowband UVB
PUVA - psoralen ultraviolet A
BMZ - basal membrane zone
Th1 type - T-helper type-1
HLA – human leukocyte antigen

References:

1. Bolognia JL, Rizzo Jl, Rapini RP. Dermatology. 2nd edition. St. Louis: Mosby Elsevier; 2008; 1. p. 1221-2.
2. Jankowski M, Czajkowski R, Scibior K, Schwartz RA. Coexistence of psoriasis vulgaris and vitiligo with bullous pemphigoid: a case report. Int J Dermatol. 2013 Oct 18.
3. Rao R, Gupta A, Yuris F, Handettu S, Chandrashekar B. Coexistence of psoriasis and bullous pemphigoid. Indian Dermatol Online J. 2012; 3(2): 119-21.
4. Wilczek A, Sticherling M. Concomitant psoriasis and bullous pemfigoid: coincidence or pathogenic relationship? Int J Dermatol 2006; 45:1353-7.
5. Barnadas MA, Gilaberte M, Pujol R, Agusti M, Gelpi C, Alomar A. Bullous pemphigoid in a patient with psoriasis during the course of PUVA therapy: study by ELISA test. Int J Dermatol. 2006; 45: 1089-92.
6. Duo TA, Buffard V, Andre C, Ortonne N, Revuz J, Bagot M, et al. Efalizumab-induced bullous pemphigoid. J Am Acad Dermatol. 2010; 62:161-2.
7. Cooke N, Jenkinson H, Wojnarowska F, McKenna K, Alderdice J. Coexistence of psoriasis and linear IgA disease in a patient with recent herpes zoster infection. Clin Exp Dermatol. 2005; 30:643-5.
8. Chan LS, Vanderlugt CJ, Hashimoto T, Nishikawa T, Zonne JJ, Black MM, et al. Epitope spreading: lessons from autoimmune skin diseases. J Invest Dermatol. 1998; 110:103-9.
9. Yasuda H, Tomita Y, Shibaki A, Hashimoto T. Two cases of subepidermal blistering disease with anti-p200 or 180-kD bullous pemphigoid antigen associated with psoriasis. Dermatology. 2004; 209:149-55.
10. Tomasini D, Cerri A, Cozzani E, Berti E. Development of pemphigus foliaceus in a patiet with psoriasis: a simple coincidence? Eur J Dermatol. 1998;8:56-9.
11. Grunwald MH, David M, Feuerman EJ. Coexistence of psoriasis and bullous diseases. J Am Acad Dermatol. 1985;13(2 Pt 1):224-8.
12. Takagi Y, Sawada M, Yamauchi M, Amagai M, Niimura M. et al. Coexistence of psoriasis et linear IgA bullous dermatosis. Br J Dermatol. 2000;142:513-6.
13. Aytekin S, Inalöz HS, Harman M, Akdeniz S, Deveci E, Inaloy SS, et al. Coexistence of psoriasis and bullous disorders. Eur J Dermatol. 1999;12:185-7.
14. Roeder C, Driesch PV. Psoriatic erythroderma and bullous pemphigoid treated successfully with acitretin and azathioprine. Eur J Dermatol. 1999;9:537-9.
15. Burnett PE. Bullous pemphigoid and psoriasis vulgaris. Dermatol Online J. 2003; 9(4):19.
16. Rallis E, Anyfantakis V. Coexistent psoriasis and bullous pemphigoid responding to mycophenolate mofetil monotherapy. Skinmed 2008;7(2):101-2.
17. Kirtschig G, Chow ET, Venning VA, Wojnarowska FT. Acquired subepidermal bullous diseases associated with psoriasis: a clinical, immunopathological and immunogenetics study. Br J Dermatol. 1996; 135:738-45.
18. Cusano F, Iannazzone SS, Riccio G, Piccirillo F. Coexisting bullous pemphigoid and psoriasis successfully treated with etanercept. Eur J Dermatol. 2010;20:520.
19. Yamauchi PS, Lowe NJ, Gindi V. Treatment of coexisting bullous pemphigoid and psoriasis with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol. 2006; 54(3 Suppl 2): S121-2.
20. Saraceno R, Citarella L, Spallone G, Chimenti S. A biological approach in a patient with psoriasis and bullous pemphigoid associated with losartan therapy. Clin Exp Dermatol. 2008; 33:154-5.

Udružena pojava psorijaze i buloznog pemfigoida – prikaz slučaja

Sažetak

Uvod. U literaturi je opisano manje od 100 slučajeva udruženosti buloznog pemfigoida i psorijaze. Istovremeno prisustvo ova dva klinička entiteta kod istog pacijenta zahteva kompleksan terapijski pristup.
Prikaz slučaja. Prikazujemo pacijenta starosti 58 godina sa dugogodišnjom evolucijom psorijaze, koji je primljen u Kliniku sa diseminovanim eritematoznim plakovima, bulama, erozijama i znacima sepse. Direktnim i indirektnim imunofluorescentnim testom i histopatološkim pregledom potvrđene su dijagnoze buloznog pemfigoida i psorijaze. U našem slučaju, bulozni pemfigoid je uspešno lečen metilprednizolonom i dapsonom, a psorijaza nb UVB terapijom i acitretinom.

Zaključak. Etiološki faktori i patogenetski mehanizmi koji utiču na udruženost buloznog pemfigoida i psorijaze još uvek su nepoznati. Obe bolesti su imunološki posredovane, tako da kombinovana imunosupresivna terapija, usmerena ka humoralnom i celularnom odgovoru, može da dovede do kliničkog poboljšanja.

Ključne reči

Psorijaza; Bulozni pemfigoid; Komorbiditet; Fluorescentni test na antitela; Imunosupresivni lekovi; Ultravioletna terapija