Epitope Spreading Phenomenon: A Case Report

Abstract

The concomitant occurrence of psoriasis vulgaris (PV) and bullous pemphigoid in a patient is rare. We report a 55-year-old male, with history of PV since 4 years, on irregular topical medication, who developed multiple fluid-filled lesions all over the body. A combination treatment with prednisolone, cyclosporine, and dapsone followed by methotrexate was proved suitable and effective.

Keywords: *Bullous pemphigoid, cyclosporine, dapsone, indirect immunofluorescence, methotrexate*

Keerthana Krishnaswamy, Belliappa Pemmada Raju, Leena Raveendra

Department of Dermatology, Rajarajeshwari Medical College and Hospital, Bengaluru, Karnataka, India

Introduction

Bullous pemphigoid (BP) is the most common presentation in patients having coexisting autoimmune bullous disorder and psoriasis.[1] Psoriasis is associated with metabolic syndrome, independent of its severity.[2] Although various hypotheses have been proposed for this coexistence, immunological damage at the basement membrane zone (BMZ) secondary to primary disease, damage induced by psoriasis treatment (anthralin, tar, ultraviolet B, PUVA), and the role of common immunological mechanisms in both the diseases are the important ones.[3] We report a case in view of rarity of this association.

Case Report

A 55-year-old male patient with psoriasis vulgaris (PV) for 4 years and on topical application of betamethasone valerate 0.1% ointment occasionally (once/week) over the counter, with no history of phototherapy or systemic drugs prior to this visit, presented to us with multiple tense bullae over whole of body. The bullae were insidious in onset and had gradually progressed to involve limbs, back, abdomen, trunk, neck, and scalp in a span of 3 weeks [Figures 1 and 2]. Lesions had an erythematous base, were associated with severe itching and had ruptured leaving behind raw areas. Few pustular lesions were noted over the nape of the neck. Few (five to six in number) psoriatic plaques were present over the lower back and bilateral lower limbs, the largest measuring 10 × 8 cm over the lower back. No bullae had developed on the psoriatic plaques. There was no mucosal involvement. Nikolsky's sign was negative and bulla spread sign was positive. Skin biopsy from the scaly plaque showed acanthosis with regular rete ridges. There were dilated capillaries in the papillary dermis with sparse superficial perivascular lymphohistiocytic infiltrate with few neutrophils. There was basket weave–type hyperkeratosis with focal parakeratosis which contained neutrophils and nuclear debris. Focal hypogranulosis was seen. The features were consistent with psoriasis. Biopsy from the bullae showed a subepidermal cleft containing dense neutrophilic exudates [Figures 3 and 4]. Direct immunofluorescence from perilesional (bullae) skin showed linear deposits of IgG (3+), C3c (3+), and C1q (2+) along the dermoepidermal junction. Indirect immunofluorescence (IIF) was done on salt-split study of normal skin which showed IgG band along both the epidermal side and the dermal side of the split (staining being stronger on epidermal side) [Figures 5 and 6]. Serum IgG anti BPAg-1 antibodies were positive with both 1:10 and 1:100 serum dilutions. Laboratory investigations revealed elevated fasting blood glucose levels [170 mg/dL (reference range = 70–110 mg/dL)], elevated postprandial blood glucose levels [219 mg/dL (reference range = 100–140 mg/dL)], and elevated glycosylated hemoglobin [10.4% (reference range = <6.5%)]. Other hematological and biochemical parameters were normal. The

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Address for correspondence:
Dr. Belliappa Pemmada Raju, Department of Dermatology, Rajarajeshwari Medical College and Hospital, Kambipura, Mysore Road, Bengaluru - 560 074, Karnataka, India.
E-mail: drbelliappa@gmail.com

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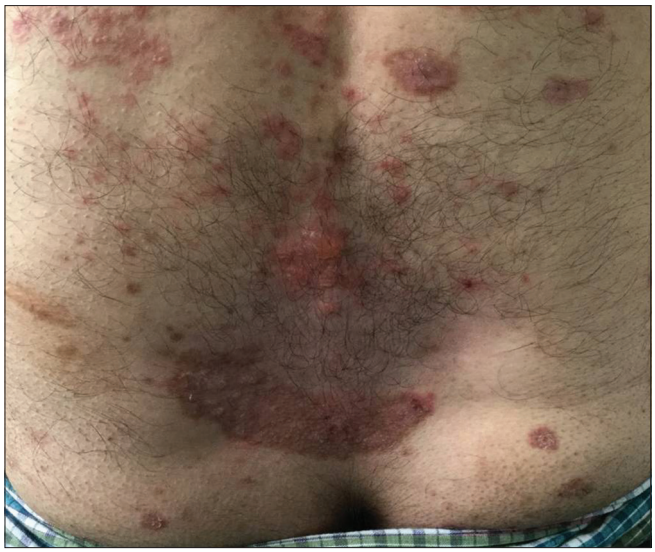

Figure 1: Psoriatic plaque and bullous pemphigoid bullae over lower back

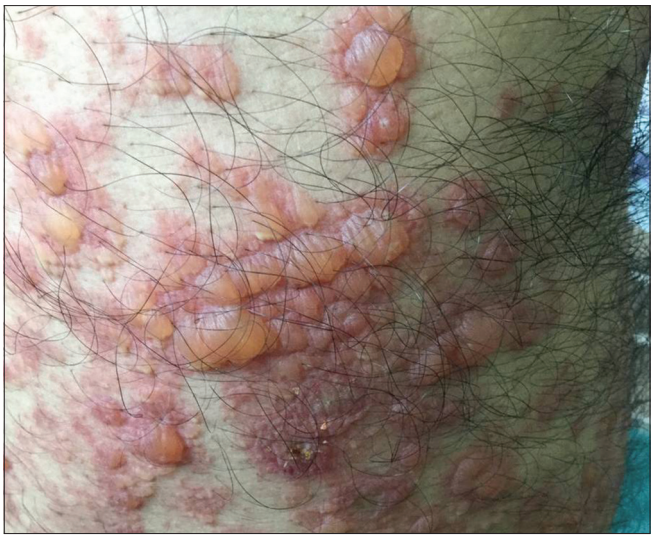

Figure 2: Multiple bullae over left infra axillary area and left lateral abdominal wall

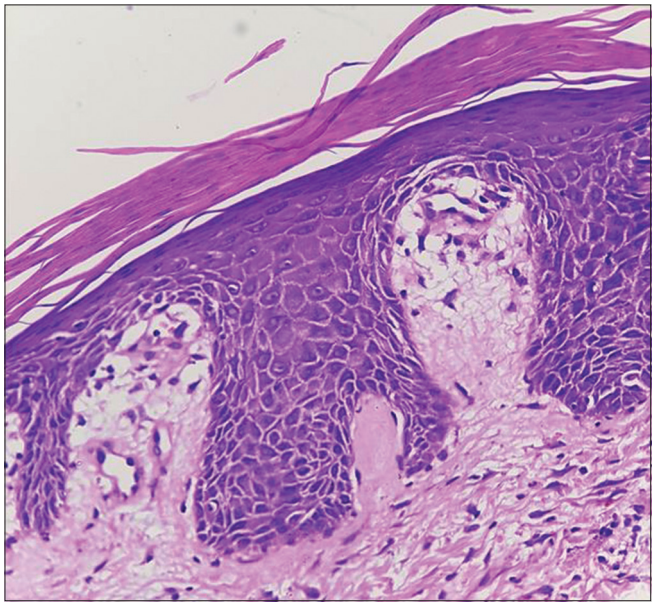

Figure 3: Acanthosis with regular rete ridges. Dilated capillaries in the papillary dermis with sparse superficial perivascular lymphohistiocytic infiltrate with few neutrophils. Basket weave–type hyperkeratosis with focal parakeratosis (hematoxylin and eosin, ×40)

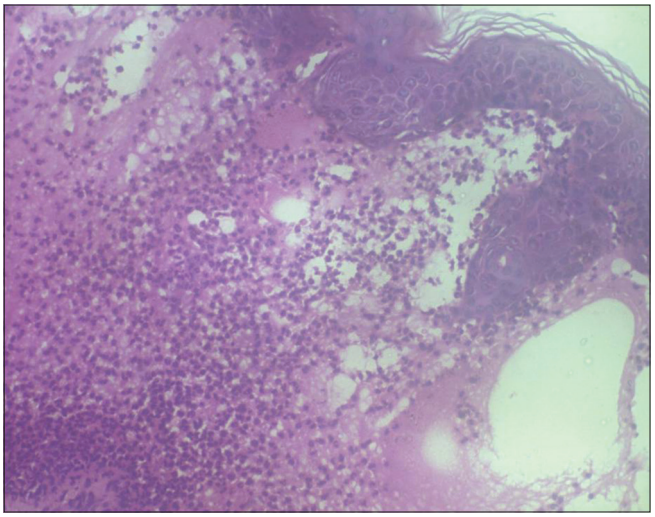

Figure 4: Subepidermal bulla containing dense neutrophilic exudates (hematoxylin and eosin, ×40)

patient was diagnosed with diabetes mellitus incidentally and was not on any hypoglycemic drugs prior to this visit.

The patient was started on the treatment as shown in Table 1.

Discussion

The coexistence of autoimmune bullous diseases and psoriasis was first reported as early as 1929.[4,5] In India, the first case was reported in 2012.[6] The most prevalent bullous disorder in patients with psoriasis and autoimmune bullous diseases is bullous pemphigoid.[1] The presence of the damage to basement membrane zone in patients with psoriasis may induce the generation of various anti- basement membrane zone antibodies. However, the concept of "epitope spreading," whereby tissue damage from a primary inflammatory process causes the release and exposure of a previously "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 in patients having psoriasis.[7] Epitope spreading can result from injuries in inflammatory dermatoses and other inflammatory diseases. Psoriasis can be associated with bullous pemphigoid and pemphigoid-like blistering disease. Psoriasis is a chronic inflammatory and hyperproliferative skin disease characterized histopathologically by dermal and epidermal inflammatory infiltration. These inflammatory cells include neutrophils, activated T cells and macrophages (a professional

Table 1: Course of treatment given

Time of visit	Lesion status	Treatment given	Remarks
At admission	Both psoriatic plaque and bullous lesions	1. Oral prednisolone 40 mg/day for 2 weeks tapered to 30 mg/day for next 2 weeks followed by 20 mg/day for subsequent 2 weeks 2. Oral cyclosporine 150 mg/day 3. Subcutaneous injection of human insulin according to sliding scale	
6th week	Both lesions subsided [Figure 7]	1. Oral prednisolone 10 mg/day 2. Oral cyclosporine 150 mg/day	On further tapering of oral prednisolone to 10 mg on alternate day, new bullae appeared, so dose of 10 mg/day was maintained
5th month	Exacerbation of psoriatic lesion; no bullous lesion	1. Oral cyclosporine 150 mg twice daily 2. Oral prednisolone 10 mg/day 3. Oral hypoglycemic drugs	Patient had stopped oral cyclosporine by himself 15 days prior to visit
7th month	Few psoriatic lesions and few bullae over bilateral thighs	1. Oral cyclosporine 100 mg twice daily 2. Oral prednisolone 10 mg/day 3. Oral dapsone 100 mg/day	
10th month	Psoriatic erythroderma, no bullous lesions	1. Oral prednisolone 10 mg/day gradually tapered and stopped 2. Oral cyclosporine 100 mg twice daily gradually tapered and stopped 3. Oral methotrexate 15 mg/week was started 4. Oral dapsone was stopped	Dapsone was stopped and methotrexate was started
12th month	Both lesions subsided	1. Oral methotrexate 15 mg/week	Patient is now on following treatment and is in remission

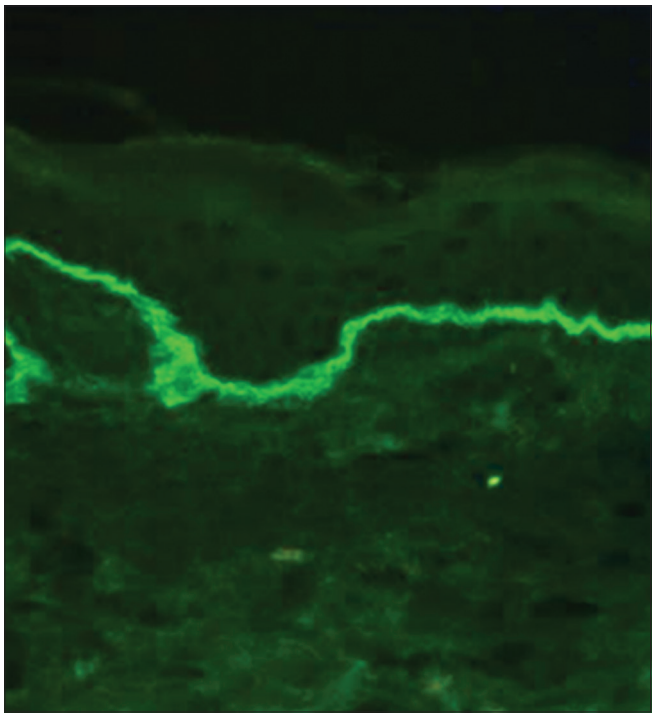

Figure 5: Direct immunofluorescence (DIF) from perilesional skin showing linear deposits of IgG (3+), C3c (3+), and C1q (2+) along the dermoepidermal junction

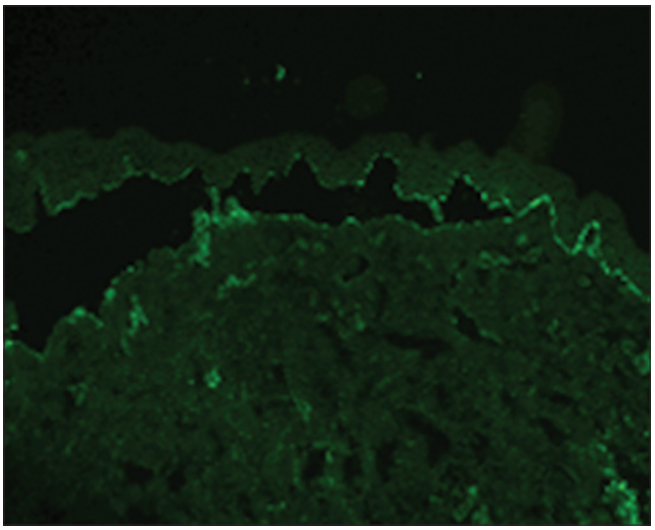

Figure 6: Indirect immunofluorescence (IIF) on salt-split study of normal skin showing IgG band along both epidermal and dermal sides of the split (staining being stronger on epidermal side)

antigen-presenting cell), and perivascular dendritic cells. In addition to the inflammatory and hyperproliferative characteristics, psoriatic skin is easily injured with even gentle removal of scale over a psoriasis lesion resulting in dermal bleeding, the so-called Auspitz sign. Furthermore, neutrophil elastase, identified along the basement membrane zone of psoriatic lesional skin, could play a role in the destruction of the epidermal–dermal junction. One could envision that the combination of psoriatic injuries caused by chronic inflammation, the trafficking of activated lymphocytes, and the abundance of antigen presenting cells could expose basement membrane zone components to

autoreactive lymphocytes and induce autoimmunity against these basement membrane zone components, such as the bullous pemphigoid antigens. Such autoimmune reaction may then subsequently lead to autoimmune disease bullous pemphigoid.[7] IL-1 is essential for the initiation and formation of psoriatic lesions, and certain cytokines such as IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, tumor necrosis factor-α, and interferon γ are involved in bullous pemphigoid.[8,9] Thus, a common cytokine network may play a crucial role in the coexistence of autoimmune bullous disorder and psoriasis.

Patients with psoriasis appear to be at higher risk for developing diabetes mellitus and cardiovascular disease. This could likely be due to the effects of chronic inflammatory changes, in particular the secretion of proinflammatory cytokines.[10] Salt-split test in bullous pemphigoid reveals staining of IgG on the epidermal side (roof pattern) of the split. Occasionally, a combined pattern (both "roof" and "floor") may be seen in BP; this may be due to recognition of additional epitopes toward the carboxy-terminal (C-terminal) of BP180 molecule. Similar to our case, Arbache *et al*.[11] reported 3% (1/33) of patients with bullous pemphigoid showing IgG deposits in both epidermal and dermal sides on indirect immunofluorescence, and a study by De *et al*.[12] showed 2 (14.3%) out of 14 (100%) patients with bullous pemphigoid showing mixed pattern of IgG deposits on indirect immunofluorescence. Indirect immunofluorescence on salt-split skin in Laminin γ1 Pemphigoid (p-200 Pemphigoid) shows a dermal-binding (floor) pattern.[13] Therefore, a diagnosis of BP was considered in our patient. However, further immunoblotting studies need to be done to confirm the exact diagnosis.

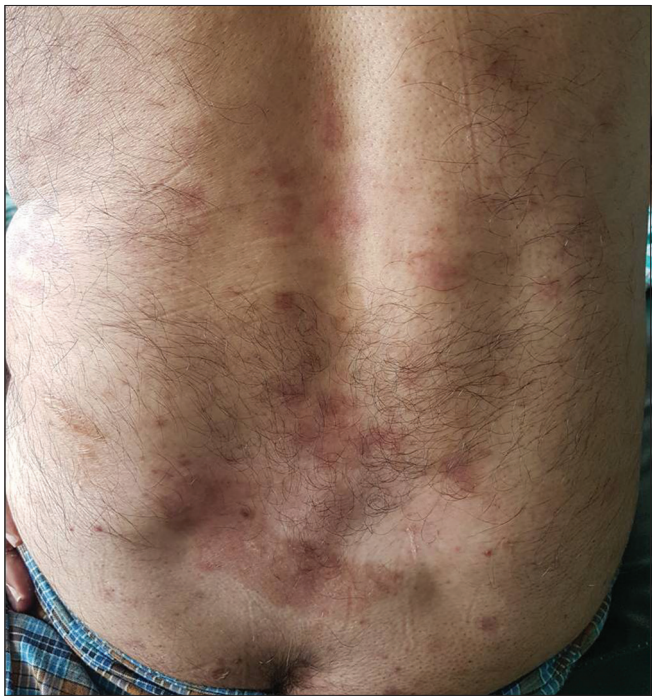

Figure 7: Both psoriatic and bullous lesions subsided at sixth week follow-up

Two cases of coexisting bullous pemphigoid and psoriasis vulgaris treated with oral methotrexate have been reported from India to our knowledge.[3,6] In view of the rarity of these two common dermatological disorders occurring in the same patient and difficult to treat when coexisting together, we considered prednisolone and cyclosporine combination based on few published reports [Table 2].[14-16] In a series of 145 cases of coexistence of autoimmune bullous diseases and psoriasis, 45% of cases were controlled by systemic corticosteroids with or without cyclosporine and no psoriatic lesions were exacerbated by tapering of systemic corticosteroids.[1] In our patient, at 7th month follow-up, dapsone was added due to recurrence of bullous lesions. Various drugs, alone or in combination such as cyclosporine,[17] dapsone,[18] methotrexate,[19] ustekinumab,[20] IV immunoglobulin,[21] mycophenolatemofetil,[22] azathioprine,[23] and acitretin,[24] have been used successfully to treat bullous pemphigoid with psoriasis.

Conclusion

We report a rare case of coexisting bullous pemphigoid and psoriasis vulgaris with type 2 diabetes mellitus. Here, bullous pemphigoid showed IgG deposits in both epidermal and dermal sides on IIF of salt-split study. A combination therapy of systemic steroid, cyclosporine, and dapsone

Table 2: Studies reporting use of prednisolone and cyclosporine as therapeutic option for treatment of psoriasis vulgaris and bullous pemphigoid coexisting together

Authors	Age/sex	Duration of psoriasis (years)	Type of psoriasis	Associated disorder	Systemic treatment	Response
Onsun *et al*.[14]	31 years/male	25	Chronic plaque psoriasis	Type 2 diabetes and hypothyroidism	Oral prednisolone and oral cyclosporine	Complete remission within 3 months
Takahashi H *et al*.[15]	57 years/male	15	Psoriatic erythroderma	Nil	Oral prednisolone (30 mg/day) and oral cyclosporine (100 mg/day)	Both lesions disappeared within 2 weeks
Bianchi L *et al*.[16]			Psoriatic erythroderma	Mild dilatative cardiomyopathy	Oral cyclosporine (3 mg/kg/day) and oral deflazacort (12 mg/day)	Both lesions disappeared within 3 weeks

followed by methotrexate proved suitable and effective in our case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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