Symposium - Vesicobullous Disorders

Bullous pemphigoid

Sujay Khandpur, Parul Verma

Department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:
Dr. Sujay Khandpur, Department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi, India.
E-mail: sujay_khandpur@yahoo.com

ABSTRACT

Bullous pemphigoid (BP) is a relatively common autoimmune vesicobullous disease encountered in India. It is a subepidermal bullous disorder most commonly seen in the elderly and manifests as tense blisters on urticarial base, predominantly over flexures, and is associated with pruritus. The diagnosis can be confirmed by histology, direct and indirect immunofluorescence. Several new diagnostic techniques have also been developed. Treatment of BP is based on the extent and rate of progression of the disease. Several topical and systemic anti-inflammatory and immunosuppressive agents have been used with variable results.

Key words: Bullous pemphigoid, clinical features, management, India

INTRODUCTION

Bullous pemphigoid (BP) is a subepidermal blistering skin disease that usually occurs in the elderly population and is characterized by large tense blisters with immunopathological findings of linear deposits of C3 and IgG at the basement membrane zone.

Little is known about the epidemiology of BP. Previous studies have reported incidence between 0.2 and 3 per 100,000 person years.[1] In UK, a regional study estimated an incidence of 1.4 per 100,000 person years. Epidemiological data from India are lacking. Pemphigus vulgaris is more commonly encountered than BP in India.

It primarily affects elderly individuals in the fifth to seventh decade of life, with average age of onset being 65 years. BP in childhood has been reported from various countries including India.[2] There is no known ethnic, racial, or sexual predilection.

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PATHOPHYSIOLOGY

The pathogenesis of BP is characterized by tissue-bound and circulating IgG autoantibodies against two components of the hemidesmosome of stratified epithelia, BP 230 kD (BPAg1) and BP 180 kD (BPAg2, COL17). BPAg1 is a cytoplasmic protein involved in the anchorage of intermediate filaments to the cytoskeleton. BPAg2 is a transmembrane adhesion molecule with several collagenous extracellular domains. Antibodies to BPAg2 appear to be important in subepidermal blister formation. BPAg1 may have a secondary role, and its exact function in the pathogenesis is not fully defined.[3] Autoantibodies against alpha 6 integrin and laminin-5, two other skin basement membrane components, have also been identified in BP.[4]

IgG autoantibodies bind to the basement membrane which activates complement and inflammatory mediators. Activation of the complement system is thought to play a critical role in attracting inflammatory cells to the basement membrane. These inflammatory cells release proteases, which degrade hemidesmosomal proteins leading to blister formation. Eosinophils are characteristically present in the blisters as demonstrated by histopathologic analysis, although their presence is not an absolute diagnostic criterion. Cytokines and chemokines like eotaxin, IL16 and IL2 also play an important role.

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The early urticarial phase in BP seems to be associated with IgE, and IgE autoantibodies against COL17 (BP180Kd Ag) are detected in 86% of untreated BP patients.[5] Iwata *et al.*[5] reported that the presence of IgE autoantibodies against COL17 was associated with a severe form of BP, and these patients required more intensive and longer treatment period for remission and higher dose of prednisolone.

CLINICAL MANIFESTATIONS

BP may present with several distinct clinical presentations and the onset may be either subacute or acute. The characteristic skin lesion is a large tense blister arising on erythematous base or on normal skin. These lesions are most common in the lower abdomen, inner or anterior thighs and flexor forearms, although they may occur anywhere. The bullae are usually filled with clear fluid but may be hemorrhagic. Significant pruritus is frequently present. In some patients, blisters arise after persistent urticarial lesions, and in some, urticarial lesions are the sole manifestations of the disease. Oral and ocular mucosal involvement rarely occurs. The bullae usually heal with post-inflammatory pigmentary changes and there is no scarring or milia formation.

The vesicular form manifests as groups of small tense blisters, often on an urticarial or erythematous base. The vegetative form is very uncommon, with vegetating plaques in intertriginous areas of the skin, such as the axillae, neck, groin and inframammary areas. This form of BP closely resembles pemphigus vegetans. Rare nodular form termed as pemphigoid nodularis has clinical features that resemble prurigo nodularis, with blisters arising on normal-appearing or nodular skin. Localized BP is infrequent, but has been documented following radiotherapy, in surgical wounds, secondary to trauma or burns and peristomal lesions. Localized BP affecting the pretibial, oral or vulvar region has also been described. Balachandran and Rai[6] from India described localized BP on breast. Mehta and Balachandran[7] reported localized flexural BP in the axillae and groins in a 63-year-old Indian male agriculturist.

Other rare variants include the erythrodermic[8] and acral form. BP after PUVAsol therapy in a 60-year-old psoriatic patient has been described from India. The patient had been receiving 20 mg of 8-methoxypsoralen followed by sun exposure for nearly 2 weeks when he developed vesiculobullous lesions on the anterior abdominal wall that became generalized in 1 week. The diagnosis was confirmed by histopathology and direct immunofluorescence (DIF).[9]

BP of childhood is rare, with approximately 50 cases reported worldwide, 15 of which were infants aged <1 year.[10] Marked acral involvement was the chief clinical presentation in infants. The age of onset in childhood BP varied from 2.5 months to 14 years. Childhood BP often follows a benign course, with disease duration of <1 year. Childhood BP has been reported from India in a 5-year-old boy presenting with severely pruritic urticarial rash on the trunk, face, perineal area and proximal limbs, associated with occasional blistering. Lesions resolved with dapsone (75 mg/day) alone on the 4th day and no new lesions appeared after the 7th day.[2]

PRECIPITATING FACTORS

Most cases of BP occur sporadically without any obvious precipitating factors. However, there are several reports of precipitation of BP by ultraviolet (UV) light, either UVB or Psoralen with ultraviolet A (PUVA),[11] radiation therapy,[12] percutaneous endoscopic gastrostomy,[11] thermal burn,[13] amputation stump,[14] incisional hernia scar,[15] and injection or an adhesive dressing.[16] In these cases, BP remained localized to traumatized site or became generalized.[17] BP has also been reported in association with other autoimmune diseases like diabetes mellitus and pernicious anemia, chronic inflammatory skin diseases such as lichen planus and psoriasis, and various malignancies. Medications that have been associated with BP-like disease include furosemide, non-steroidal anti-inflammatory drugs (NSAIDs; ibuprofen), captopril, phenacetin, penicillamine, etarnacept, and systemic antibiotics.[18] Tibolone (a selective tissue estrogenic activity regulator that has progestogenic, some androgenic and estrogenic effects) induced BP has been reported from India in a 51-year-old postmenopausal woman who was prescribed this agent as an alternative to estrogen replacement therapy for the treatment of climacteric symptoms.[18]

ASSOCIATION OF BULLOUS PEMPHIGOID WITH MALIGNANCY

The relationship between BP and malignancy is a matter of debate, even though there are many case

reports of BP associated with malignant tumors such as renal cell carcinoma, gall bladder malignancy, colon, breast and parotid malignancy and leukemia. A large population study from USA and Sweden suggested no relationship between BP and internal malignancy. However, there have been contradictory findings from other countries, especially in Asia. Ogawa *et al*.[19] reported that in Japanese population, there was higher incidence of malignancy among patients with BP than controls (5.8% vs. 0.61%). Outside Asia, Chorzelski *et al*.[20] reported an 11% incidence of cancer among 110 BP patients. While there are reports suggesting the absence of any clinical or immunological signs that can be used to predict the development of a neoplasm, some authors have proposed possible predictors of internal malignancies in patients with BP. For example, from a morphological point of view, bullae on gyrate erythema or recalcitrant nature of disease were reported to be associated with internal malignancy in BP. In addition, a correlation between negative indirect immunofluorescence (IIF) test and internal malignancy has been found.

DIAGNOSIS

The diagnosis of BP is confirmed by histologic and immunopathologic investigations. Histopathology from lesional skin demonstrates a subepidermal blister. The inflammatory infiltrate is typically polymorphous, with an eosinophilic predominance. Mast cells and basophils may be prominent early in the disease course. Tzanck smear shows only inflammatory cells.

DIF studies on normal appearing perilesional skin within 2 cm of a lesion demonstrate *in vivo* deposits of IgG antibodies in 90–95% of cases and C3 in 100% cases at the basement membrane zone. IgG deposits are rarely present in the absence of C3, but presence of IgA, IgM and IgE has been described.[21] This pattern of immunoreactants is not specific to BP and may be seen in cicatricial pemphigoid and epidermolysis bullosa acquisita. BP can be differentiated from these conditions by the salt-split technique in which patient's skin biopsy sample is incubated in 1 mol/l salt solution prior to performing DIF. This process induces cleavage through the lamina lucida. DIF on salt-split skin reveals IgG on the blister roof (epidermal side of split skin) in BP. In a study from India, Satyapal *et al*.[22] evaluated salt-split technique of immunofluorescence in BP. Thirty-two cases of BP were subjected to DIF and IIF using normal and salt-split skin. DIF positivity of 100% was noted with both routine and salt-split methods. Additional immunoreactants were also noted with DIF on salt-split skin in five cases; patterns of fluorescence with salt-split skin were roof (40.6%), floor (9.4%) and combined roof and floor (50%). On IIF, positivity was almost doubled with salt-split technique (68%) as compared to routine method (36%).

IIF studies document IgG (subclass IgG4) circulating autoantibodies in the patient's serum that target the skin basement membrane component. Circulating autoantibodies are detected in 60–80% of cases on IIF.[20] The antibody titer (detected by IIF) does not correlate with disease course. Daneshpazhooh *et al*.[23] compared the antibody titers of blister fluid and serum in patients with subepidermal immunobullous diseases and concluded that IIF sensitivity on blister fluid is no more than that on serum, but the performance of this test on blister fluid in addition to serum may reduce the number of false-negative results of IIF found using either of these two substrates alone. Zhou *et al*.[24] concluded that blister fluid can be used as an alternative to serum for IIF in subepidermal immunobullous diseases.

Direct and indirect immunoelectron microscopy ultrastructurally localizes *in vivo*–bound IgG autoantibodies to the binding site at the basement membrane.

Immunoblotting or Western blotting demonstrates reactivity of IgG in the sera of BP patients, with proteins extracted from healthy human skin. The sensitivity of immunoblotting varies. As shown by Labib *et al*.,[25] BP230 antigen positivity was seen in 75% of BP cases, whereas BP180 antigen positivity was seen in 50%.

Immunoprecipitation also demonstrates reactivity with BP230 and BP180. Unlike immunoblotting, immunoprecipitation is performed with native rather than denatured protein and is more sensitive.

Enzyme-linked immunosorbent assay (ELISA) analyzes the BP antigen-specific IgG autoantibodies in the patients' sera by using various lengths of recombinant proteins of the BPAg1 or BPAg2 antigens. In several reports, ELISA has been demonstrated to be highly sensitive and specific. ELISA kits are now available commercially. An ELISA based on BP180 demonstrates sera reactivity in greater than 90% of BP patients. Atzori *et al*.[26] evaluated ELISA in 17 BP

patients and concluded that it is a sensitive, easy and quick tool; autoantibody titers correlate with disease severity and it is useful to monitor treatment response. In another study by Chan *et al*.,[27] the sensitivity of traditional diagnostic techniques, i.e. DIF (91%) and IIF (96%), were comparable with that of the newer techniques, i.e. immunoblot analysis (100%) and ELISA (96%).

Immunohistochemistry on formalin-fixed skin sections in BP has been used to examine C3 deposition along the epidermal basement membrane zone. Pfaltz *et al*.[28] investigated the expression of C3d in formalin-fixed, paraffin-embedded tissue of autoimmune bullous dermatoses and found C3d immunohistochemistry to be a valuable tool in the diagnosis of BP with a sensitivity of 97%. Chandler *et al*.[29] showed linear basement membrane deposition of C4d in formalin-fixed, paraffin-embedded tissue in 7/9 cases of DIF proven BP.

In India, histopathology and immunofluorescence (DIF and IIF) studies are routinely used for the diagnosis of BP. Direct and indirect immunoelectron microscopy, Western blotting, ELISA and immunohistochemistry have not been used.

TREATMENT

The goal of therapy is to decrease blister formation, promote healing of blisters and erosions, and achieve the minimal dose necessary to control the disease process. Therapy must be individualized for each patient, keeping in mind the pre-existing conditions and other patient-specific factors.

Localized BP often can be treated successfully with topical steroids alone. More extensive disease, which is often more difficult to control, is usually treated with systemic anti-inflammatory and immunosuppressive agents, oral corticosteroids being the mainstay of treatment. Oral prednisone/prednisolone doses range from 0.3 to 1.25 mg/kg body weight/day, which usually controls disease within 1–2 weeks; the dose is then progressively tapered. Morel and Guillaume,[30] comparing different doses of prednisolone (0.75 mg/kg/day vs. 1.25 mg/kg/day), did not find any statistical difference in the groups compared for effectiveness. There were more adverse effects associated with the higher prednisolone dose. Pulsed corticosteroids including methylprednisolone (0.5–1 g i.v. over 2 hours daily for 5 days), dexamethasone (100 mg in 500 ml 5% dextrose i.v. over 2–3 hours for 3 consecutive days) and betamethasone in suprapharmacological doses are also used. In India, dexamethasone is the preferred steroid for pulse therapy. It is either administered alone (DP) or combined with cyclophosphamide (DCP).[31]

Several studies have suggested the use of concomitant immunosuppressive agents to achieve a corticosteroid-sparing effect.[32] The most frequently used agent is azathioprine (0.5–2.5 mg/kg body weight/day). Other studies have reported successful use of cyclophosphamide, methotrexate, cyclosporine A, combination tetracycline/minocycline along with nicotinamide and, more recently, mycophenolate mofetil (MMF). Burton *et al*.,[33] who compared prednisone with prednisone and azathioprine, found a 45% reduction in the cumulative dose of prednisone taken by the azathioprine treated group during a 3-year period. In a randomized controlled trial, patients received either 0.5 mg/kg of methylprednisolone with 2 mg/kg of azathioprine sodium once daily or 0.5 mg/kg of methylprednisolone once daily with 1000 mg of MMF twice daily (2 g/day). MMF and azathioprine demonstrated similar efficacy, and similar cumulative corticosteroid doses were required in both treatment arms to control disease. However, MMF showed a significantly lower liver toxicity profile than azathioprine.[34]

In a retrospective analysis of 138 BP patients of whom 98 (71.0%) were administered methotrexate, 61 continued methotrexate as monotherapy (group 1) while 37 were administered prednisone in addition to methotrexate (group 2). After 24 months, remission rate was 43% in group 1 and 35% in group 2. The authors concluded that methotrexate was the most effective treatment with only few adverse effects and a tendency toward better survival rate in patients with moderate to severe disease.[35] The overall response rate to dapsone, when given either alone or in combination with corticosteroids or immunosuppressive agents, is about 81% in BP.[35] A randomized, open-labeled trial comparing the combination of 500 mg of nicotinamide 3 times daily and 500 mg of tetracycline 4 times daily with prednisone therapy alone found comparable response rate. At 10 months of follow-up, of 3 cases who followed up in prednisolone group, 2 had multiple recurrence, while in nicotinamide + tetracycline group, all 5 cases who followed-up were in remission and remained disease free during medication tapering.[36]

Up to 24% of patients with BP do not respond to conventional therapy. Other drugs for treating BP include biologicals (anti-TNF drugs,[37] rituximab), IVIg and plasma exchange.

Roujeau *et al*.[38] compared prednisolone with prednisolone and plasma exchange, and found that disease control was achieved with less than half the total prednisolone dose in the plasma exchange group; control was achieved with mean prednisolone daily dose of 0.52 ± 0.28 mg/kg in the plasma exchange treated group versus 0.97 ± 0.33 mg/kg in the prednisolone only treated group.

IVIg appears to be an effective alternative in treating patients with severe BP whose disease is nonresponsive to conventional therapy or who are at risk of experiencing serious or potentially fatal side effects from conventional immunosuppressive therapy. IVIg may be particularly useful if treatment is begun early.[39] A dose of 1–2 g/kg is recommended, usually delivered as a 5-consecutive-day cycle of 0.4 g/kg/day, although a 3-day cycle may be used. The initial frequency is generally 1 cycle every 3–4 weeks. High-dose IVIg is tapered maintaining the same dose but increasing the time interval between infusions.[40]

Among all the treatment modalities in India, the most commonly used is steroids, either oral or in the form of pulse therapy. Non-steroidal immunosuppressive drugs are added as adjuvants to increase the efficacy and to have a steroid sparing effect.

In a recent Cochrane review, 10 randomized controlled trials (with a total of 1049 participants) were included. All studies involved different comparisons; none had a placebo group. In one trial, plasma exchange plus prednisone (0.3 mg/kg) gave significantly better disease control at 1 month than prednisone alone (1.0 mg/kg), while another trial showed no difference in disease control at 6 months. No differences in disease control were seen for different doses or formulations of prednisolone, for azathioprine plus prednisone compared with prednisone alone (one trial), for prednisolone plus azathioprine compared with prednisolone plus plasma exchange (one trial), for prednisolone plus MMF or azathioprine (one trial), and for tetracycline plus nicotinamide compared with prednisolone (one trial). There were no significant differences in healing in a comparison of a standard regimen of topical steroids (clobetasol) with a milder regimen in one trial. In a trial, clobetasol showed significantly more disease control than oral prednisolone in people with extensive and moderate disease, with significantly reduced mortality and adverse events.[41]

PROGNOSIS

BP, even without therapy, is often a self-limiting disease, but it may last from several months to many years. About one-half of the treated patients attain remission within 2.5–6 years; however, in individual patients, the disease may continue for 10 years or more. Clinical remission with reversion of DIF and IIF to negative has been noted in patients, even in those with severe generalized disease.

Bernard *et al*.[42] studied the prognostic factors for relapse in the first year after cessation of therapy and concluded that high-titer anti-BP180 ELISA score and, to a lesser degree, a positive DIF finding are good indicators of further relapse of BP. At least one of these tests should be performed before therapy is discontinued.

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