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Case Series

A case series of comorbidities seen in bullous pemphigoid

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ABSTRACT

Bullous pemphigoid (BP) is an autoimmune skin blistering disease commonly seen in the elderly which is associated with increased morbidity. The association of BP with comorbidities, especially cardiovascular, neurological, type 2 diabetes mellitus (T2DM) and has been seeing a rising trend in the recent years, not only with the underlying condition but also the drugs associated. A systematic literature review was conducted to identify and analyze the comorbidities prevalent in patients with BP.

Keywords: Bullous pemphigoid, Omalizumab, Comorbidities

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering disorder characterized by Itchy wheals which later turn to fluid filled bullae seen predominantly over the upper extremities, trunk, groin, flexures (Figure 1 A and B). There is formation of subepidermal blisters and erosions on the skin and mucous membranes. While the pathogenesis of BP primarily involves the production of autoantibodies against hemidesmosomes, the clinical course and management of this dermatological condition are further complicated when patients present with an array of comorbid medical conditions.

BP predominantly affects the elderly population, and this demographic group often carries a higher burden of comorbidities such as diabetes mellitus, hypertension, chronic kidney disease, and cardiovascular disease.[1] The presence of these concurrent medical conditions raises questions regarding the impact of comorbidities on the clinical presentation, treatment response, and overall prognosis of BP patients.

Comorbidities can complicate the clinical picture of BP in several ways. First, they may influence the severity and extent of cutaneous and mucosal involvement, making differential diagnosis and disease monitoring more intricate. Second, comorbidities can affect the choice of treatment modalities, drug interactions, and the overall management strategy. Third, they may impact patient outcomes, including the risk of hospitalization, complications, and mortality. We present a case series of BP patients with comorbidities, aiming to elucidate the clinical characteristics, treatment outcomes faced in managing this complex patient population. By examining the intricate association between BP and comorbidities.

This is a retrospective case series study, medical records of patients who confirmed diagnosis of BP was taken, with detailed h/o their comorbidities and past medications for same. We identified all BP patients and admitted to our tertiary clinic over a 1-year period in order to register demography, treatment and comorbidities.

Patients were included if characteristic clinical presentations of BP such as pruritus, bullae, or positive indirect Nikolsky's sign were described or if skin biopsies revealed subepidermal bullae or clusters of eosinophils, and/or if direct immunofluorescence (IF) showed linear deposits of IgG or complement C3 along the basement membrane zone.

Patients who have been visiting in the last one year have been included with their follow up visits.

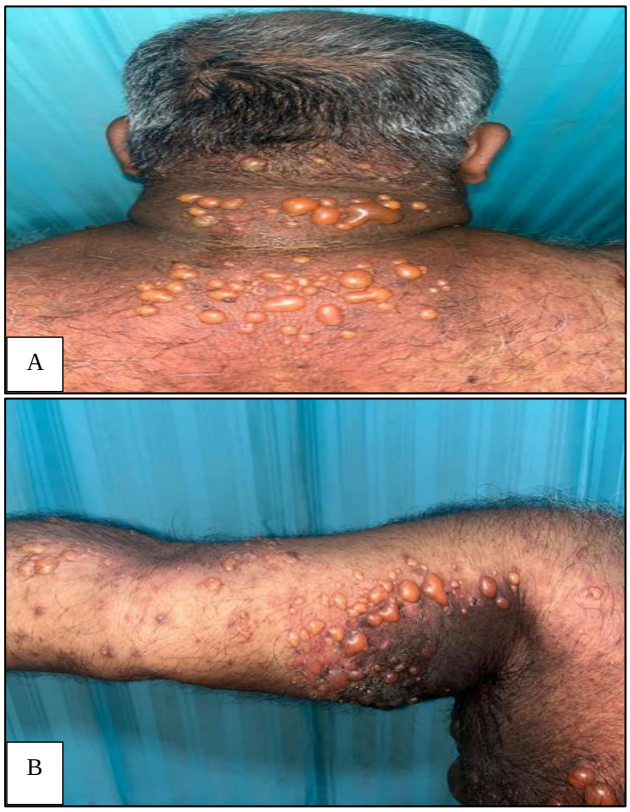

Figure 1 (A and B): Multiple, well defined fluid filled tense bullae seen over the flexural distribution.

CASE SERIES

Out of the 8 patients (Table 1 and Figure 2) with BP 4 patients had hypertension, 5 patients had diabetes mellitus, 5 patients had cardiovascular disease 3 with bronchial asthma, 1 with neurological manifestation and 1 with malignancy (CA Breast). The investigations were done and there was an elevation of serum IgE levels, BP180 antigen, BP230 antigen and eosinophils.

Steroids were avoided as it would worsen the pre-existing conditions, 3 patients were on a combination of doxycycline with nicotinamide with super potent topical steroids, there was a slow progress in reduction of new blisters.

Three patients were given a combination of MMF with nicotinamide and also doxycycline, the results were time taking, unsatisfactory and non compliant with patients.

Two patients were treated with 150 mg inj omalizumab, two injections were given subcutaneously 15 days apart. They were followed up and had no new blisters for two consecutive follow ups two weeks apart. Omalizumab is a safe steroid sparing biologic used as an off label drug in BP where steroids can worsen the condition.

They were monitored post infusion after the two doses were given and there was a significant improvement with reduced pruritus, no new lesions and also improvement in the preexisting lesions. There was also a reduction of the serum IgE levels, BP 180 antigen levels and platelets and eosinophils were in the normal range.

Table 1: Summary of BP patients with comorbidities and medications

Age (in years)	Sex	Duration of BP	Cardiovascular diseases (±)	Neurological comorbidities (±)	HTN (±)	T2DM (±)	Medications taken
83	Female	3 months	+ (Coronary artery disease)	-	+ (20 years)	+ (20 years)	Prednisolone, doxycycline, niacinamide, vidagliptin, dapagliflozen, telmisartan, hydrochlorothiazide,
67	Female	1 year	+ (Angina)	-	-	-	Prednisolone, doxycyline niacinamide, terbinafine
75	Female	1 year	+ (Coronary artery disease)	+ (Dementia)	+ (35 years)	+ (35 years)	Prednisolone, omalizumab, ecosprin atorvastatin, vildagliptin
50	Female	6 months	-	-	-	+ (6 years)	Prednisolone
57	Female	2 years	-	-	-	-	Prednisolone, omalizumab
53	Male	3 months	-	-	+	+	Doxycycline, metformin
67	Female	4 months	+(stroke +CA breast)				Omalizumab
56	Female	6 months	+	-	+	+	Metformin, dapagliflozin

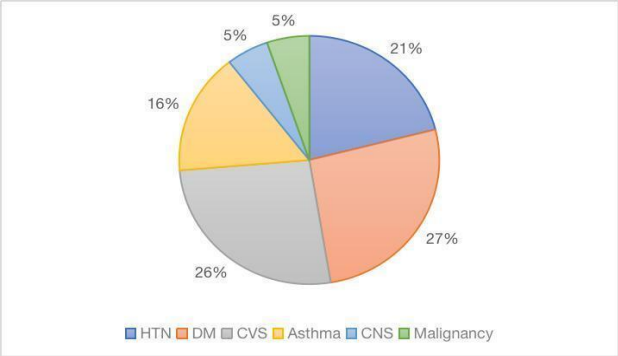

Figure 2: Prevalence of comorbidities.

DISCUSSION

BP is indeed a common autoimmune blistering disease characterized by the production of autoantibodies directed against specific proteins within the skin's basement membrane zone. These proteins are hemidesmosomal proteins known as BPAG1 (BP antigen 1, also called BP230) and BPAG2 (BP antigen 2, also known as BP180 or collagen XVII).

The disease is characterised by intense pruritus and blistering of the skin. Tzanck smears of our patients had no acantholytic cells with a few scattered leucocytes and rules out pemphigus vulgaris (Figure 3). Final diagnosis is confirmed with biopsy of the lesion or IF.

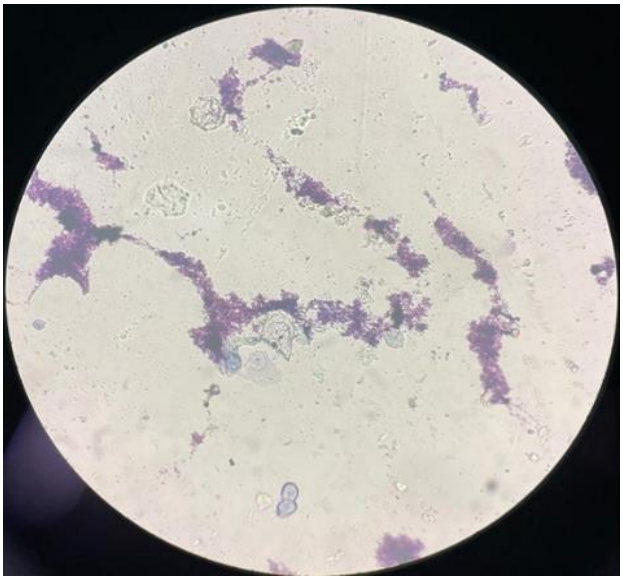

Figure 3: Tzanck smear seen with few leucocytes.

Diagnosis was confirmed by biopsy with a characteristic sub-epidermal split (Figure 4A and B). In this retrospective study of case series of patients admitted with BP of moderate to severe disease, 4 out of the 6 patients had DM, 3 pts had hypertension, 3 patients had cardiovascular disease, one had asthma and one had CNS manifestations.

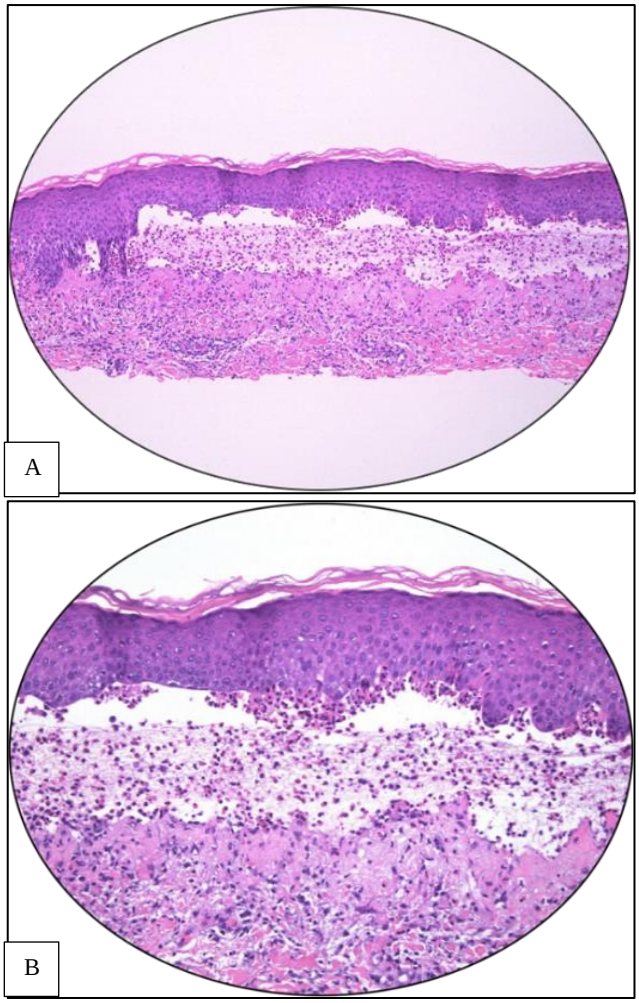

Figure 4 (A and B): (10x): Subepidermal separation with normal stratum corneum epidermis showing mild acanthosis. (20x) subepidermal split with fluid showing an aggregate of eosinophils and neutrophils.

BP and central nervous system

Molecular link between BP and neurodegenerative diseases is hypothesized to be autoantibodies against antigens BP180 and BP230 expressed in neurons as well as the basement membrane of human skin, however these have only been hypotheses and yet to be confirmed.[3,6]

Whether BP precedes neurological diseases or vice versa is unknown and fosters an ongoing discussion. Gambichler et al found in their database of inpatients with BP a significantly increased frequency of neurological diseases.[9] The reference to studying brain tissue from mammals treated with serum from BP patients with elevated BP180 autoantibodies suggests an investigation into the potential neuroinflammatory effects of these autoantibodies.

BP and endocrine disease

There is some association between BP and endocrine diseases, particularly diabetes.[7] Several studies have

shown an increased risk of BP in individuals with diabetes. The exact reason for this association is not entirely clear, but it is believed that chronic inflammation and immune system dysregulation in diabetes may play a role in triggering or exacerbating BP. In our study 5 patients with T2DM have an increase in BP 180 and normal level of 230 antigen.

There has been a study showing that BP due to drugs like DPP-4 inhibitors has shown an increase in incidence of BP.[7]

BP and cardiovascular disease

BP is more common in the elderly, and age itself is a risk factor for cardiovascular disease. The exact association between cardiovascular disease and BP is not clear but has been linked to factors like Chronic inflammation. BP is an inflammatory condition, and chronic inflammation can lead to the development of cardiovascular disease, promoting atherosclerosis, a condition in which fatty deposits accumulate in the arteries.

BP and malignancy

Studies have shown the link between autoimmune bullous diseases is high especially in the elderly rendering an inclination towards hematological malignancies, lung and GI malignancy. One such theory is that antibodies directed against tumour-specific antigens may cross-react with antigens in the basement membrane zone, leading to the formation of blisters.[10]

However, our patient has been diagnosed with CA breast happens to be an incidental finding, although the association has been rare.

Treatment of BP

Treatment typically involves the use of corticosteroids and immunosuppressive drugs in addition to topical steroids, that may have cardiovascular side effects. For example, long-term use of corticosteroids can lead to high blood pressure, weight gain, and increased risk of heart disease

The treatment of BP depends upon severity of disease.

Doxycycline in combination with steroids and nicotinamide gives very effective anti-inflammatory response and safer as stated by William et al which was also given to our patients keeping in mind long term efficacy.[11]

Steroid is the mainstay in treatment of BP, however patients with co morbid conditions need to be treated with steroid sparing drugs. In order to minimize the daily as well as the cumulative dose of steroids.

Sticherling et al found that dapsone appeared to have a moderately higher corticosteroid-sparing potential than azathioprine.[4]

Azathioprine is a steroid sparing agent used against BP. The effect and side effects of Azathioprine in the treatment of BP was compared to mycophenolate mofetil (MMF), both in combination with oral prednisolone, showing equal efficacy.[4]

MMF while being very effective as a treatment modality however places a huge financial burden on the patients which can result in inadequate treatment, while the liver toxicity is much lower compared to azathioprine.

In few cases with comorbid patients or no compliance to standard treatments, alternative therapies may be considered, and omalizumab is one such drug which can give complete remission.[8]

Omalizumab's immuno-modulatory effects might help in controlling the autoimmune response seen in BP.[8] Two of our patients have been treated with 150 mg subcutaneous omalizumab (2 sessions) and has shown significant improvement with reduced pruritus and no new lesions on the next two follow ups (Figure 5 A and B).

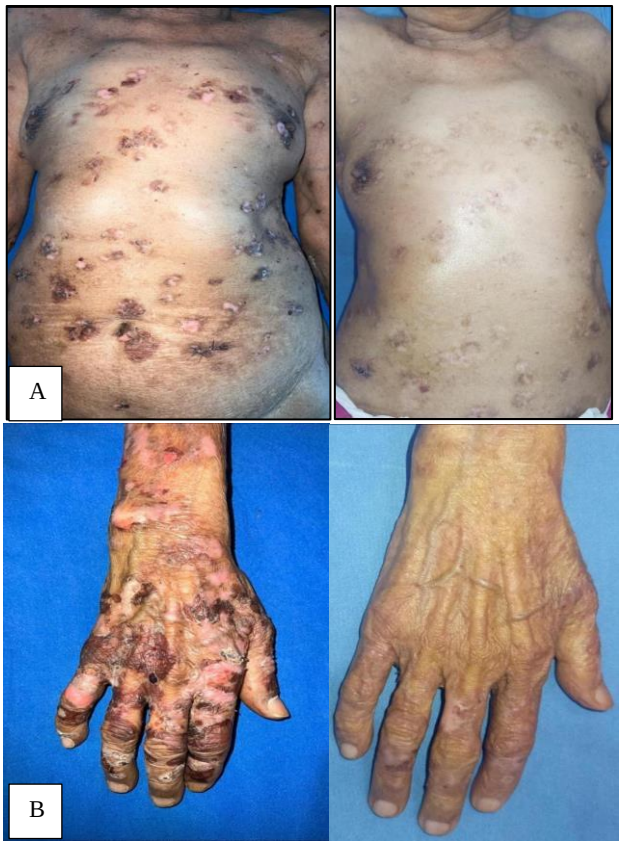

Figure 5 (A and B): Before and after treatment with omalizumab.

Dupilumab has been one such biologic which has been proven to be effective in recalcitrant cases which also helps significantly with pruritus.[5,8] The patient can be started on 300 mg subcutaneous dose, 600 mg in total is given as monotherapy.

CONCLUSION

Our case series provides valuable insights into the complex relationship between BP comorbidities, and treatment in an elderly population. The development of comorbidities like hypertension and diabetes in BP patients highlights the challenges in managing both the autoimmune condition and the associated health issues. This can lead to a higher risk of poor prognosis, especially when medications such as DPP-4 inhibitors, statins, and beta-blockers, known to be potential triggers for BP, are used long-term. Our observations emphasize the importance of early detection and comprehensive management of comorbidities, which could improve the quality of life and overall health outcomes for BP patients. The successful use of omalizumab in patients, with improvements in key markers like serum IgE and BP180 antigen levels, provides support for its potential as an effective treatment option in elderly patients. This is especially relevant when traditional therapies like corticosteroids are contraindicated or pose too much risk due to the patient's age and comorbid status.

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