Brief Report

Bullous pemphigoid in India: Review of cases registered in an autoimmune bullous disease clinic

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Abstract

Background: Information on bullous pemphigoid in an Indian context is scarce.

Aim: To report clinico-demographic profile, associated comorbidities and prescription pattern of bullous pemphigoid patients in India.

Methods: This was a retrospective study, where past records of all bullous pemphigoid patients diagnosed and treated between November 2013 and October 2019 were accessed and analysed. Patients having a compatible clinical presentation with either histopathological and/or direct immunofluorescence evidence of bullous pemphigoid were included.

Results: There were 96 bullous pemphigoid patients, with a male: female ratio of 1.6:1. The mean age at diagnosis was 62.5 ± 2.2 years, with mean duration of illness 27.5 ± 4.5 months before presentation. Comorbidities were present in 80 (83%) patients, with type 2 diabetes mellitus (38.5%), hypertension (36.4%) and neurological illness (16.7%) being the commonest ones. Clinically, blisters were the predominant presentation in 81 (84.4%) patients. The majority (87.5%) of patients showed a predominant eosinophilic infiltrate on histopathology. Direct immunofluorescence revealed immunoglobulin G deposits with complement C3 in 77 (80.2%) cases. The majority of patients (77.1%) were treated with oral prednisolone, either alone (11.5%) or in combination (65.6%) with other topical and systemic agents. Topical steroids were used in 29.1%, azathioprine in 28%, dapsone in 16.7% and omalizumab in 6.2% of patients.

Limitations: The study is retrospective. Immunofluorescence on salt split skin, direct immunofluorescence serration pattern analysis, and immunoblotting were not performed. Hence, there is a possibility that a few included cases were suffering from other subepidermal autoimmune bullous diseases like epidermolysis bullosa acquisita or anti-p200 pemphigoid.

Conclusion: Bullous pemphigoid patients in this study had a younger age of onset and showed male preponderance. Comorbidities like type 2 diabetes, hypertension and neurological disorders were frequent. Cutaneous blisters were the most frequent clinical presentation. Systemic corticosteroids comprised the mainstay of therapy.

Key words: Bullous pemphigoid, India, demography, clinical features, comorbidities

Plain Language Summary

Bullous pemphigoid is an autoimmune disease of the skin where tense blisters appear on itchy red skin or it can present only as itchy red erythematous skin which resembles wheal. This disease is considered rare in India. In this report, our findings in 96 patients who were seen over a six year period in a prominent research institute in north India are described. We found that the patients are younger by at least two decades than their western counterparts. Comorbidities like type 2 diabetes, high blood pressure and disorders of the nervous system were frequent. Blisters on the skin were the most frequent clinical presentation. The majority of the patients were treated with oral corticosteroids.

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Introduction

Bullous pemphigoid is the commonest autoimmune subepidermal blistering disorder in Europe and the United States of America. It is predominantly seen in the elderly population.[1] The reported literature on bullous pemphigoid in the Indian population is sparse. The reported global incidence ranges between 2.4 and 21.7 new cases per million population per year, with many studies suggesting a rising incidence in the past two decades.[2-4] Proposed reasons for this reported increase are better life expectancy, early diagnosis and better awareness, rising incidence of predisposing factors (e.g., neurological and malignant disorders) and drugs like dipeptidyl peptidase-4 (DPP-4) inhibitors, also called gliptins.[2] A subset of patients tend to develop a variant of the disease, called non-bullous pemphigoid. Instead of developing typical bullous lesions, they present with pruritus, urticarial lesions, excoriations or papulo-nodules. The present study was carried out owing to scarcity of data on bullous pemphigoid from India.

Patients and methods

A retrospective chart review was performed on the patients registered at the autoimmune bullous disease clinic of the Postgraduate Institute of Medical Education & Research, Chandigarh. Institute Ethics Committee (Intramural) approval was obtained retrospectively. Patient record files and treatment records of all bullous pemphigoid patients diagnosed and treated between November 2013 and October 2019 were accessed and analysed. Only those patients were included who had a compatible clinical presentation with histopathological evidence on light microscopy (subepidermal split/bullae with inflammatory infiltrate, eosinophils with/without neutrophilic infiltrate in the upper dermis) and/or positive direct immunofluorescence findings (linear immunoglobulin G deposits with/without C3 and IgM).[5] Non-bullous pemphigoid was diagnosed based on direct immunofluorescence findings. Clinical exclusion of mucous membrane pemphigoid and epidermolysis bullosa was important and they were excluded by the absence of conjunctival/oral mucosal/nasal or other mucosal scarring or scarring on the skin as an aftermath of healed erosions, predominantly on the pressure points. Patients with incomplete data entered on the records or where the diagnosis of bullous pemphigoid was not reasonably certain based on clinical, histopathologic and direct immunofluorescence scheme as outlined above were excluded from the study. Irrespective of the time of registration to the clinic, patients were contacted over telephone between May 1 and June 30, 2020 and were asked about any newly diagnosed comorbidity after registering to our clinic. To identify any undetected comorbidity, a telephonic interview was performed after taking verbal informed consent and study participants were asked for information with reference to any recent-onset weight loss suggestive of malignancy or features suggestive of stroke[6] or Parkinson's disease.[7] Medical records and investigations performed subsequently corresponding to comorbidities were duly accessed and noted during telephonic interviews, where ever possible. Descriptive statistics were used to analyse and interpret the data.

Results

Demographic data

A total of 96 bullous pemphigoid patients were included in the study, with a male: female ratio of 1.6:1. There were 1,285 patients registered in the autoimmune bullous disease clinic, thus bullous pemphigoid constituted 7.5% of autoimmune bullous diseases in our centre. The mean age at diagnosis was 62.5 ± 2.25 years, with the youngest patient being 6 years old and the oldest 87 years. The mean duration of illness was 27.5 ± 4.5 months before patients presented to our centre. Demographic and clinical details are summarized in Table 1.

Comorbidities were assessed and recorded at the time of initial presentation in all patients [Table 2]. At the time of presentation, 80 (83%) patients had comorbidities. History of neurological disease was present in 16 patients (15 patients had a history of stroke, one had epilepsy) and six patients had a history of underlying malignancy, with carcinoma prostate seen in two male patients. Thirteen (13.5%) patients gave a history of gliptin use within the preceding six months of the onset of symptoms and nine (9.3%) had history of smoking. Follow-up using telephone calls was performed in 51 patients with the remaining patients either being inaccessible or not consenting to share details over telephone. Of the 51 patients contacted, five (9.8%) had a stroke and/or transient ischemic attack, three (5.8%) had new-onset hypertension and two (3.9%) had hypothyroidism diagnosed after the initial visit to the autoimmune bullous disease clinic. It was found that 7/51 (13.7%) patients had died, the cause of death being stroke in three patients, underlying malignancy in two patients, acute liver failure in one and myocardial infarction in one.

Clinical and biopsy findings

Bullous lesions were the presenting feature in 81 (84.4%) patients, with the remainder (15.6%) presenting with non-bullous lesions like eczematous plaques, urticarial plaques and papules and localized erythema. Among patients presenting with bullous lesions, most lesions were in the form of tense blisters and/or vesicles, with ten (10.4%) patients presenting with erosions. Mucosal involvement was present in 26 (27%) patients, nail involvement was seen in 32 (33.3%) and scalp involvement in 27 (28%) patients. The majority of patients (63.6%) had total body surface area involvement of <10%. The most common pattern of nail involvement was longitudinal ridging, followed by Beau's lines and onycholysis.

Histopathological examination of biopsy samples revealed an inflammatory infiltrate with subepidermal cleft/bullae in all patients clinically presenting with blisters. Among patients with non-bullous pemphigoid, the histological findings included dermal oedema and perivascular inflammatory infiltrate. While predominant eosinophilic infiltrate in the

Table 1: Demographic and clinical characteristics of bullous pemphigoid patients included in the study

Demographic characteristics	Number of patients, *n* (%)
Sex	
Males	59 (61.5%)
Females	37 (38.5%)
Mean age (in years)	62.5 ± 2.25 (Range: 6–87)
Mean duration of illness (in months)	27.5 ± 4.5
Clinical characteristics	
BSA involved at presentation	
<10%	61 (63.6%)
10–20%	12 (12.5%)
20–40%	20 (20.8%)
>40%	3 (3.1%)
Clinical features	
A. Cutaneous blisters and erosions	81 (84.4%)
Vesicles and bullae	71 (73.9%)
Erosive disease	10 (10.4%)
B. Non-bullous lesions	15 (15.6%)
Urticarial papules and plaques	6 (6.2%)
Eczematous plaques	6 (6.2%)
Localized erythema	3 (3.1%)
C. Mucosal involvement	26 (27.1%)
D. Scalp involvement	27 (28.1%)
E. Nail involvement	32 (33.3%)
Longitudinal ridging	11
Beau's lines	7
Onycholysis	5
Onychomadesis	3
Others (e.g., paronychia)	6
Biopsy findings	
Light microscopy findings	
Predominant eosinophilic infiltrate	84 (87.5%)
Non-specific mononuclear cell infiltrate without eosinophils	10 (10.4%)
Non-inflammatory; only dermal edema	2 (2.1%)
Direct immunofluorescence findings	
IgG and C3 without other antibodies	74 (77.1%)
IgG and C3 with IgM, IgA	3 (3.1%)
Only C3	9 (9.4%)
IgG without C3	5 (5.2%)
IgM with C3	2 (2.1%)
Negative direct immunofluorescence	3 (3.1%)

BSA: Body Surface Area; IgG: Immunoglobulin G; C3: Complement 3

Table 2: Comorbidities of bullous pemphigoid

Comorbidities at presentation	
None	16 (16.7%)
Present	80 (83.3%)
Distribution of comorbidities	
Type 2 diabetes	37
Hypertension	35
Both diabetes and hypertension	24
Neurological disease	16
Stroke	15
Epilepsy	1
Coronary artery disease	11
Thyroid disease	8
Hypothyroidism	7
Hyperthyroidism	1
Malignancy	6
Carcinoma prostate	2
Carcinoma breast	1
Squamous cell carcinoma of the tongue	1
High-grade serous ovarian carcinoma	1
Carcinoma cervix	1
Respiratory disease	7
Bronchial asthma	4
Chronic obstructive pulmonary disease	3
Others	5
Cataract	3
Ankylosing spondylitis	1
Psoriasis	1
Psychiatric illness	0
Drugs: History of gliptin use	13 (13.5%)
Comorbidities on telephonic follow-up	
Total patients accessed	51 (53.1%)
No new comorbidities	32
New comorbidities detected	19
Neurological disease	5
Stroke	4
Transient ischemic attack	1
Hypertension	3
Diabetes mellitus	1
Cardiac disease (congestive failure)	1
Hypothyroidism	2
Rheumatoid arthritis	1
Hepatocellular carcinoma	1
Renal failure	1
Cholelithiasis	1
Asymptomatic transaminitis	1
Alcoholic liver disease	1
Patients expired	7 (13.7%)
Stroke	3
Underlying malignancy	2
Acute liver failure	1
Myocardial infarction	1

dermis was present in 84/96 (87.5% patients, 10 (10.4%) patients showed a mononuclear inflammatory infiltrate without eosinophils and two (2.1%) patients had non-inflammatory histology, comprising only mild dermal edema. Direct immunofluorescence revealed immunoglobulin G deposits along with C3 in 77 cases. Isolated C3 deposits were present in nine (9.4%) cases, while three (3.1%) patients had a negative direct immunofluorescence study [Table 1].

Treatment administered

Details of treatment modalities given are presented in Table 3. Oral prednisolone comprised the mainstay of therapy; 74 patients (77.1%) were managed with prednisolone as a first-line agent. While only 11 patients received oral prednisolone as monotherapy, the majority received it as a part of a combination regimen with other agents, as summarised in Table 2. Of 23% patients not receiving oral

Table 3: Treatment modalities used in bullous pemphigoid patients

Treatment modality	Number of patients
Oral corticosteroids (e.g. prednisolone)	74 (77.1%)
As monotherapy	11 (11.5%)
As combination regimen	
With other non-steroidal immunosuppressants	39 (40.6%)
With topical steroids	11 (11.5%)
With monoclonal antibodies	7 (7.3%)
With antibiotics	6 (6.2%)
Topical steroids	28 (29.2%)
As monotherapy	9 (9.4%)
As combination regimen with oral steroids/ other immunosuppressants	19 (19.7%)
Non-steroidal immunosuppressants[¶]	
Azathioprine	27 (28.1%)
Dapsone	16 (16.7%)
Mycophenolate mofetil	3 (3.1%)
Cyclophosphamide	2 (2.1%)
Methotrexate	1 (1%)
Monoclonal antibodies	
Omalizumab	6[§] (6.2%)
Rituximab	2 (2.1%)

[¶]All non-steroidal immunosuppressants were used in combination with either oral or topical corticosteroids

[§]One patient received monotherapy with omalizumab

prednisolone, most received topical corticosteroids alone (9.38%) or in combination with other agents, including cyclophosphamide, dapsone, azathioprine, doxycycline, mycophenolate mofetil and omalizumab. Another 6% received neither topical nor oral steroids and were managed with other immunomodulators/immunosuppressants as mentioned above, singly or in combination.

Discussion

Bullous pemphigoid is considered to be the most common autoimmune blistering disease worldwide and a study from Malaysia suggested Indian ethnicity to be particularly prone to developing bullous pemphigoid.[8] Still, adequate information related to clinico-demographic patterns of disease in Indians is inexplicably lacking. This study revealed data on expected patterns with interesting differences in some aspects.

We found a male preponderance in our bullous pemphigoid patients, with a male: female ratio of 1.6:1. This is in contrast to most published studies which show either a higher incidence in females,[3,4,9] or an equal incidence across both genders.[10] Likewise, the mean age at diagnosis in our study (62.5 years) was younger compared to western studies where most cases are reported above 70 years of age, with the median age reported between 64 and 82.6 years.[11] An earlier study by the authors also reported a relatively younger age at diagnosis (59 years).[5] The mean duration of illness was 27.5 ± 4.5 months before patients presented to our centre. This apparent long duration before the presentation was multifactorial; in part attributable to ours being a tertiary care centre and patients reporting late to us, late referrals, socio-cultural reasons related to a lack of adequate information and a general tendency to neglect skin-related diseases in the elderly.

Comorbidities were present in more than 80% of bullous pemphigoid patients at initial presentation, with type 2 diabetes and hypertension observed most commonly. As opposed to the reported frequent association with neuropsychiatric disorders (22–46%),[12] only 8.3% of our patients had neurological involvement, mostly strokes. However, an additional 9.8% of patients reported new-onset stroke and/or TIA when follow-up was done via a telephone call. There were no patients in our study with multiple sclerosis, parkinsonism, schizophrenia or dementia.

Gliptin use for type 2 diabetes within the preceding six months of disease onset was reported by 13 (13.5%) patients. Up to three times greater risk of developing bullous pemphigoid has been reported with the use of gliptins in diabetes patients.[13] Gliptin usage was stopped in all such patients and alternative drugs for diabetes were started. Seven such patients reported a reduction in new lesions when topical corticosteroid therapy was accompanied by withdrawal of gliptins.

Similar to previously reported studies, cutaneous blisters and bullae were the most frequent clinical presentation in our study. Non-bullous lesions were in the form of urticarial papules and plaques, eczematoid plaques and localised erythema. Mucosal involvement in bullous pemphigoid is variable. Mucosal involvement of 27% was observed in our study which is similar to that reported by a cohort study over 14 years in Poland.[14] Nail involvement in bullous pemphigoid is considered to be rare,[15] but 33% of our patients showed nail changes at the time of registration to the clinic. These were in the form of longitudinal ridging, followed by Beau's lines and onychomadesis. One study from India has previously reported nail changes in five out of seven bullous pemphigoid patients.[16]

Subepidermal split/bullae were present in all patients with blistering lesions. The most common light microscopic finding was dermal infiltration with predominant eosinophils in 87.5% of patients, while about 80% of patients showed linear deposits of immunoglobulin G with C3 complement on direct immunofluorescence. These findings are similar to earlier reports, including a recent study from Singapore.[17] Of note, C3 deposits alone were found in 9.4% of patients, deposits of immunoglobulin G alone were present in 5% of patients and 3.1% of patients had negative direct immunofluorescence.

Due to its autoimmune pathogenesis, immunosuppression remains the cornerstone of management for bullous pemphigoid. Only 29% of patients in our study reported topical steroid use, despite the majority having body surface area involvement of <20%. This reflects the fact that despite literature mentioning topical steroids providing acceptable disease control in mild localised diseases, systemic corticosteroids are often used extensively in bullous pemphigoid. Additionally, the application of topical corticosteroids over erosions and extensive areas of the skin are considered to be messy and cumbersome by most of the patients.

While azathioprine was used in combination with low-dose steroids in 28% of patients, dapsone was used in 16.7% of cases. Sticherling *et al*. [18] have reported both dapsone and azathioprine to have useful adjuvant effects in bullous pemphigoid when used with oral methylprednisolone. Other immunosuppressants and rituximab were infrequently used.

Limitations

The study is retrospective. Immunofluorescence on salt split skin, direct immunofluorescence serration pattern analysis, and immunoblotting were not performed. Hence, there is a possibility that a few included cases were suffering from other autoimmune sub-epidermal bullous diseases like epidermolysis bullosa acquisita or anti-p200 pemphigoid.

Conclusion

Despite the mentioned limitations, this study is important because it is possibly the first study from India reporting a large number of bullous pemphigoid patients. This study summarises the demographic, clinical and treatment patterns in bullous pemphigoid over a six year period. Bullous pemphigoid showed a tendency to afflict a younger age and showed male preponderance in an Indian setting. Bullous lesions were the most frequent clinical presentation, with more frequent mucosal and nail involvement compared to previously reported literature. Systemic corticosteroids comprised the mainstay of therapy in 3/4 patients despite most patients having body surface area involvement of less than 20%. Azathioprine, dapsone and more recently, omalizumab were used successfully as adjuvant therapies with corticosteroids.

Declaration of patient consent

Patient consent not required as patients' identity is not disclosed or compromised.

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Nil.

Conflict of interest

There are no conflicts of interest.

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