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RESEARCH ARTICLE

RETROSPECTIVE ANALYSIS OF MORBIDITY PROFILE OF AUTOIMMUNE BULLOUS DISEASES IN A TERTIARY CARE HOSPITAL OF SOUTH TAMILNADU- A ONE YEAR STUDY

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ABSTRACT

Background: Autoimmune bullous diseases are a heterogeneous group of diseases characterized by autoantibodies directed against adhesion proteins. Among these, bullous pemphigoid contributes maximally to the burden followed by pemphigus vulgaris in the global literature while Indian literature substantiates pemphigus vulgaris as the commonest. There is a paucity of data on the prevalence, demographic, regional variation and clinicopathological correlation of various autoimmune bullous diseases from India.We aim to estimate the prevalence and pattern of various autoimmune bullous diseases in patients attending dermatology OPD of Tirunelveli Medical College Hospital and to correlate it with skin biopsy,immunofluorescence study and other investigations. **Materials and Methods**: This is a retrospective clinical study conducted in the Department of Dermatology, Tirunelveli Medical College in 32 diagnosed autoimmune bullous diseases over a period of one year (January to December 2018). **Results:** Of the total 32 diagnosed autoimmune bullous disease patients, 19 (59.3%) were pemphigus and 13 (40.6%) were pemphigoid group of diseases (Bullous pemphigoid). Of the 19 pemphigus patients, 13 (40.6%) were pemphigus vulgaris, 4 (12.5%) were pemphigus foliaceous, 1 (3.1%) was pemphigus vegetans and IgA pemphigus each. Both histopathology and direct immunofluorescence were 100% concordant with the clinical diagnosis. **Conclusion:** Pemphigus vulgaris is the commonest autoimmune bullous disease in India which was confirmed in our study contrasting the world pattern with bullous pemphigoid as the commonest. Larger community-based studies are needed for the epidemiological and clinicoimmunological profile of autoimmune bullous diseases in India which will help in accurate characterisation of autoimmune bullous diseases.

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INTRODUCTION

Autoimmune bullous diseases (AIBD) are a heterogeneous group of diseases characterized by autoantibodies directed against adhesion proteins like desmosomes, hemi desmosomes and various other antigens in skin.[1] The incidence of pemphigus among dermatology outpatient department attendees worldwide and in India ranges from 0.09 to 1.8% and the incidence of bullous pemphigoid worldwide is 2.4 to 21.7% and in India, it's around 0.03% only.[2,3,4]They are classified based on their clinical, histopathological and immunopathological features into epidermal and sub-epidermal blistering diseases. This classification is necessary for diagnosis, treatment, assessment of prognosis and preventing complications because intraepidermal blistering diseases like pemphigus has a poor prognosis and higher mortality rate than subepidermal blistering diseases like bullous pemphigoid.[5] Corticosteroids were the main stay of treatment for bullous diseases previously but at recent times, various steroid sparing drugs like cyclophosphamide, azathioprine and biologicals has brought down the high mortality rates that had been encountered in pre-corticosteroid era with the aim of arresting disease progression. Prior to the advent of corticosteroids there was high mortality (90%) in pemphigus patients because of septicaemia or electrolyte imbalance. Later on, mortality declined with the use of steroids to 30% and with immunosuppressants like cyclophosphamide to 5.9%.[6] In today's scenario the dermatologists face great challenge in management of AIBD as they have a high mortality among dermatological diseases.[7]There is only few studies in the Indian literature giving importance for the prevalence and pattern of AIBD which aids in the appropriate management in order to prevent mortality. Thus, this study was done to analyse the prevalence and pattern of disease in patients with AIBD in our hospital for prevention of mortality and future planning of disease management.

MATERIALS AND METHODS

This is a retrospective clinical study that was conducted in the Department of Dermatology, Tirunelveli Medical College over a period of one year (January 2019- December 2019) after obtaining institutional ethical committee clearance of Tirunelveli Medical College. Medical records of all patients with diagnosed immunobullous disorders who attended the Outpatient and Inpatient Department of Dermatology were taken from autoimmune bullous clinic register. Nonimmune-mediated vesiculobullous lesions secondary to mechanical injury, infections, eczemas, and burns (chemical or thermal) were excluded from the study. From these medical records, demographic data of patients, provisional clinical diagnosis, histopathological and Direct Immunofluorescence (DIF) findings were collected. For histopathological examination, an unruptured early vesicle or bulla was taken and sent in 10% formalin and for DIF, a perilesional skin biopsy was taken and the specimen was sent in normal saline. Histopathological diagnosis was made on the basis of the level of split, nature of inflammatory infiltrate, altered keratinocytes and dyskeratotic cells, and pattern of arrangement of epidermal keratinocytes (e.g. row of tombstone). The DIF result was based on the site (intercellular, along basement membrane zone (BMZ) or dermal papillae), type of antibody (IgG, IgM, IgA, or C3), pattern (granular or linear) and intensity of deposition of immune reactants. On the basis of these features, the vesiculobullous diseases were divided into intraepidermal or subepidermal blistering disorders. They were further classified into subcorneal[pemphigus foliaceus (PF), pemphigus erythematosus (PE)], suprabasal [(pemphigus vulgaris (PV), pemphigus vegetans]and subepidermal [(bullous pemphigoid (BP), dermatitis herpetiformis (DH)] blistering disorders. Thorough investigations like complete blood count, peripheral smear, renal and liver function test, chest X-ray, ECG, HBsAg and other relevant investigations on case-to-case basis were done before starting any immunosuppressants. Various immunosuppressants like corticosteroids, cyclophosphamide, azathioprine and biologicals like rituximab were used for the treatment of these patients.

RESULTS

Of the total 32 clinically and diagnostically proved AIBD patients, 19 (59.3%) were pemphigus and 13 (40.6%) were pemphigoid group of diseases. Among pemphigus group, 13 (40.6%) were pemphigus vulgaris (Figure 1), 4 (12.5%) were pemphigus foliaceous, 1 (3.1%) was pemphigus vegetans (Figure 2) and IgA pemphigus each. Among pemphigoid group, bullous pemphigoid (figure 3) was the only disease encountered in 13 cases (40.6%). There were no cases of paraneoplastic pemphigus and any other atypical presentation of AIBD. The most common age group affected was 41 to 50 years (25%) overall. PV and BP were seen in a wide range of age groups from 11 to 80 years with PV more common between 21 and 30 years of age (4 cases,12.5%) while BP more common between 61 and 70 years of age (3 cases, 9.3%). PF was common among the age group of 41 to 50 years (2 cases,6.3%). PF also affected a child of 8 years, being the youngest age in our study. One case (3.1%)of Pemphigus vegetans and IgA pemphigus was seen in the age group of 41 to 50 years and 11 to 20 years of age respectively. There was a female preponderance in the ratio of 1.9: 1 (21 females and 11 males). PV was more common among females accounting to

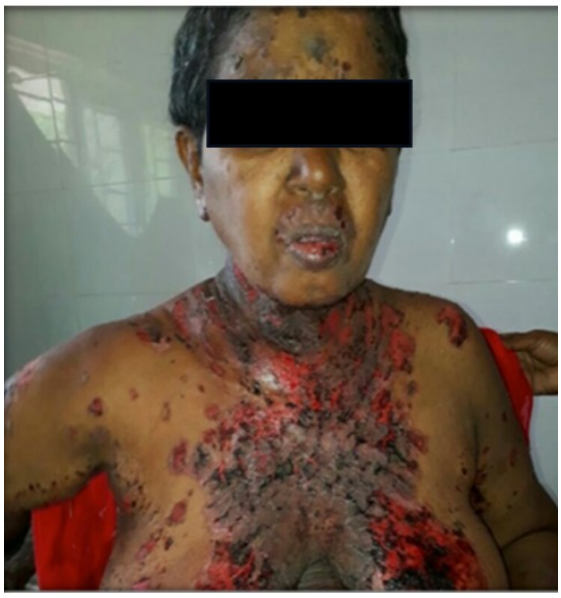

Figure 1. Flaccid bulla and erosions over the trunk in Pemphigus vulgaris

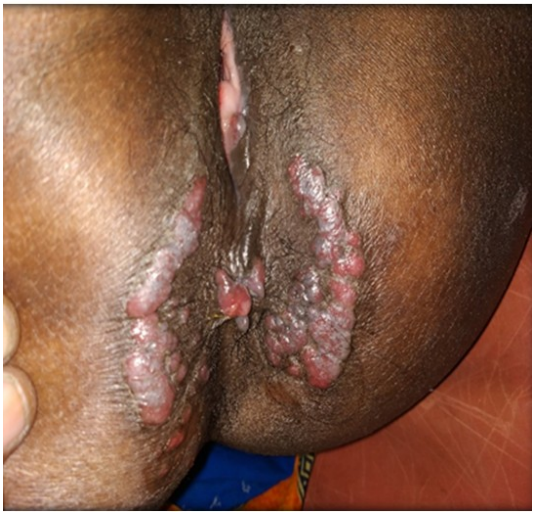

Figure 2. Vegetative plaques over perianal region in Pemphigus vegetans

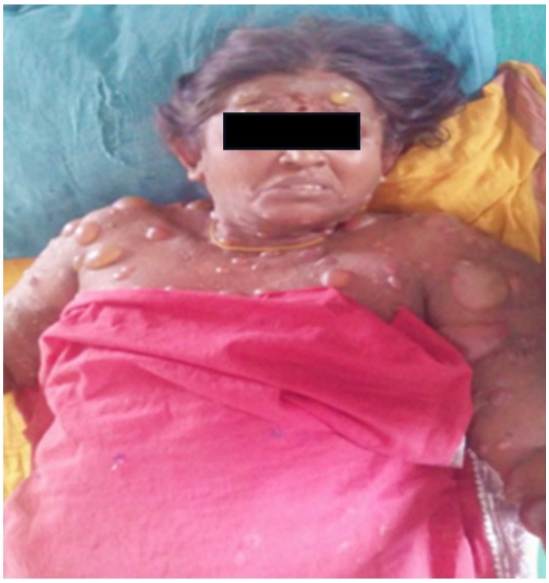

Figure 3. Multiple tense bulla all over trunk and face in Bullous pemphigoid

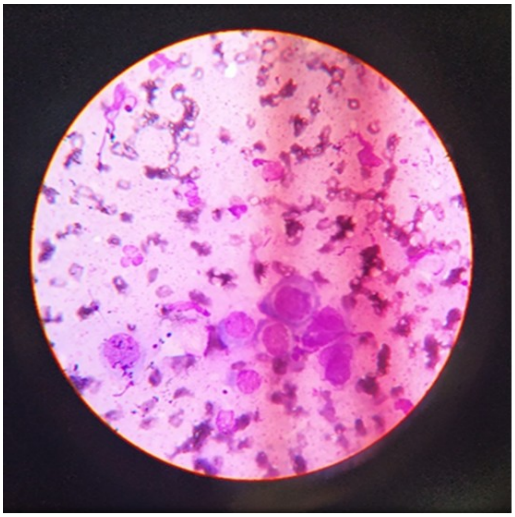

Figure 4. Tzanck smear- Acantholytic cells seen in Pemphigus vulgaris

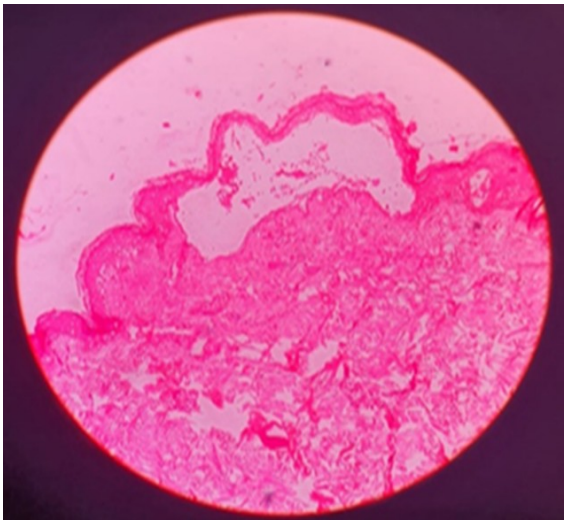

Figure 5. H & E 10x showing intraepidermal bulla in Pemphigus vulgaris

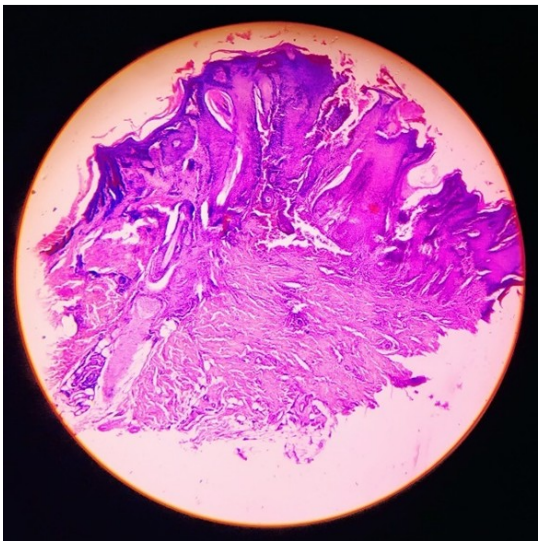

Figure 6. H & E 10x showing suprabasal bulla with eosinophilic microabscesses in Pemphigus vegetans

10 cases (31.3%) and BP had almost equal gender involvement with slight male preponderance accounting to 7 cases (21.9%). PF was more common in females 3(9.4%) while pemphigus

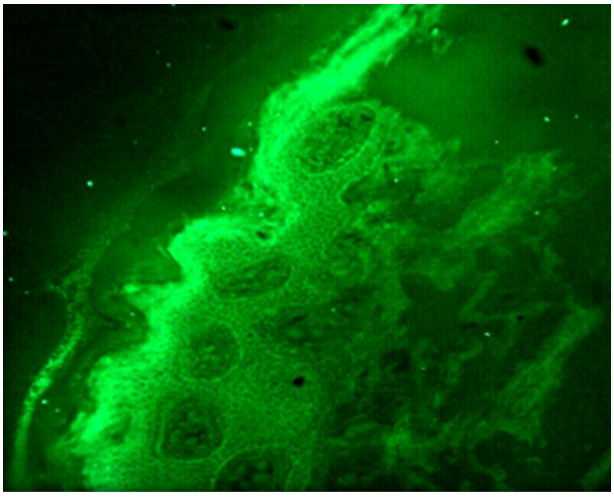

Figure 7. Direct immunofluorescence study showing intercellular deposits of IgG & IgM in the intraedpidermal space in Pemphigus Vegetans

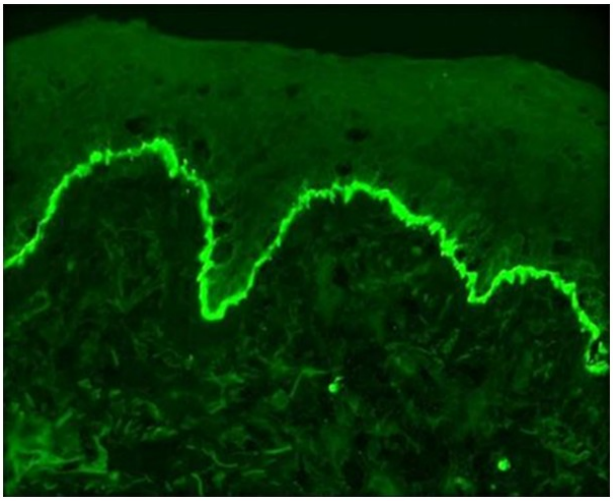

Figure 8. Direct immunofluorescence study showing linear IgG & C3 deposits in basement membrane zone in Bullous pemphigoid

Table 1. Clinical Pattern And Sex-Wise Distribution Of Autoimmune Bullous Diseases

CLINICAL PATTERN	MALE n(%)	FEMALE n(%)	TOTAL NO. OF CASES (n=32)
Pemphigus vulgaris	3(9.4%)	10(31.3%)	13(40.6%)
Bullous pemphigoid	7(21.9%)	6(18.7%)	13(40.6%)
Pemphigus foliaceous	1(3.1%)	3(9.4%)	4(12.5%)
Pemphigus vegetans	-	1(3.1%)	1(3.1%)
IgA pemphigus	-	1(3.1%)	1(3.1%)
TOTAL	11(34.4%)	21(65.6%)	32(100%)

vegetans and IgA pemphigus were seen in only one female1(3.1%) each. (Table 1 & 2). All cases of PV showed classical picture of flaccid vesicles, bullae and erosions over various parts of the body with oral mucosal involvement. All 13 cases of BP showed tense vesicles and bulla and associated oral mucosal involvement was seen only in 4 patients (30.8%). Itching was seen in 9 (69%) out of 13 cases of BP. Four cases of pemphigus foliaceous showed flaccid vesicles and crusted plaques over the seborrhoeic areas with no mucosal involvement. One case of pemphigus vegetans showed vegetating plaques over the perianal region associated with oral mucosal involvement. And finally, one case of IgA pemphigus showed multiple small flaccid vesicles over the trunk with oral mucosal involvement. Pemphigus Area and

Table 2. Age Wise Distribution Of Autoimmune Bullous Diseases

CLINICAL PATTERN	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	TOTAL
Pemphigus vulgaris	-	-	4(12.5%)	1(3.1%)	3(9.3%)	2(6.3%)	2(6.3%)	1(3.1%)	**13(40.6%)**
Bullous pemphigoid	-	1(3.1%)	2(6.3%)	1(3.1%)	2(6.3%)	2(6.3%)	3(9.3%)	2(6.3%)	**13(40.6%)**
Pemphigus foliaceous	1(3.1%)	-	-	-	2(6.3%)	1(3.1%)	-	-	**4(12.5%)**
Pemphigus vegetans	-	-	-	-	1(3.1%)	-	-	-	**1(3.1%)**
IgA pemphigus	-	1(3.1%)	-	-	-	-	-	-	**1(3.1%)**
TOTAL	**1(3.1%)**	**2(6.3%)**	**6(18.75%)**	**2(6.3%)**	**8(25%)**	**5(15.6%)**	**5(15.6%)**	**3(9.3%)**	**32(100%)**

Table 3. Mucosal Involvement and Investigations

CLINICAL PATTERN	ORAL MUCOSA INVOLVEMENT	TZANCK SMEAR	HPE	DIF	TOTAL NO.OF CASES (n=32)
Pemphigus vulgaris (n=13)	13	12	13	13	13(40.6%)
Bullous pemphigoid (n=13)	4	-	13	13	13(40.6%)
Pemphigus foliaceous (n=4)	-	3	4	4	4(12.5%)
Pemphigus vegetans (n=1)	1	1	1	1	1(3.1%)
IgA pemphigus (n=1)	1	-	1	1	1(3.1%)
TOTAL	19(59%)	16(50%)	32(100%)	32(100%)	32(100%)

Activity Score ranged from 11to 38.6 and mucosa score ranged from 0 to 4. Bed side laboratory test like Tzanck test was taken for all AIBD patients as a routine procedure. Twelve (92.3%) out of 13 cases of PV, 3 (75%) out of 4 cases of PF andone case (100%) of pemphigus vegetans showed acantholytic cells**.** (Figure 4) One case (7.7%) of BP showed eosinophils in Tzanck smear and remaining other cases showed mixed inflammatory cells. Histopathology of all cases of PV showed suprabasal bulla in all 13 cases (100%) (Figure 5) and all 13 cases of BP showed subepidermal bulla (100%) with eosinophils in bulla cavity in 4 cases (30.8%). All 4 cases (100%) of pemphigus foliaceous showed subcorneal bulla with few acantholytic cells and neutrophils. One case of pemphigus vegetans showed suprabasal bulla with eosinophilic micro abscesses (Figure 6) and one case of IgA pemphigus showed intraepidermal bulla. All these were 100% concordant with the clinical diagnosis. Direct immunofluorescence findings of pemphigus vulgaris showed both IgG and C3 deposition in intercellular substance in 10 cases (77%)and only IgG deposition in remaining 3 cases (23%).DIF results of bullous pemphigoid showed linear deposition of both IgG and C3 at the BMZ in 8 cases (61.5%) (figure 8) and only C3 deposition in remaining 5 cases (38.5%). In pemphigus foliaceous, DIF showed deposition of both IgG and C3 in all four cases. One case of pemphigus vegetans showed IgG, IgM and C3 deposition in intercellular epidermis (figure 7) and a single case of IgA pemphigus showed only IgA deposition in the intercellular epidermis. This showed 100% concordance with the clinical and histopathological diagnosis. (Table 3)

DISCUSSION

Immunobullous disorders are characterized by autoantibody-mediated vesicles and bullae affecting the skin and or mucosa. These autoantibodies cause stearic hindrance with the desmosomal attachment proteins causing pemphigus (intraepidermal) and with adhesion proteins in BMZ causing pemphigoid (subepidermal). Although various dermatological diseases present clinically with vesiculobullous lesions, their etiology, pathogenesis, severity and course differ. Therefore, accurate diagnosis of these diseases is essential for appropriate management to minimize the morbidity and mortality. Total number of new cases over a period of one year (Jan –Dec 2019) in our OPD was 20,683. The incidence of AIBD overall during the study period was around 0.15%. Incidence of pemphigus in our study was 0.09% which is similar to the incidence of pemphigus overall and in India ranging from 0.09 to 1.8%. [2] Overall, the incidence of bullous pemphigoid worldwide ranges from 2.4 to 21.7% and in India, it's around 0.03% and in our study, the incidence is 0.06% which is comparatively the same.[3,4] Thus, PV is the most common AIBD encountered in various parts of India which is in contrast to the other parts of the world where BP is the commonest. The overall most common age group affected was 41 to 50 years, whereas PV was most common among 21 to 30 years and BP was most common among 61 to 70. This is in contrast to other parts of the world where pemphigus occurs much later, around 40 to 60 years.[8] But in India, pemphigus appears to occur at younger ages less than 40 years as said by Kanwar et al. [2] BP usually affects seventh to eighth decade as given in the literature and it is the same in our study, but there is a wide range of involvement from 11 to 80 years with younger age groups also been affected in our study. [8] The youngest age group reported in our study was 8 years and it was seen in a case of pemphigus foliaceous. Pemphigus is rare and uncommon in young children yet, few studies have been reported with younger ages of 5 and 7 years of age by Ambady et al and Singh et al respectively. [9,10]

Females outnumbered males in the ratio of 1.9: 1 (21 femalesand 11 males). This is similar to a study done by Malhotra et al.[7] Usually a slight female preponderance was noted in many other studies done in India ranging from 1.54:1 to 2:1 and it is because of presence of two X chromosome which has a tendency to develop autoimmunity. [11] Out of the total 32 patients, 19 (59.3%) were pemphigus and 13 (40.6%) were pemphigoid group of diseases. This is in par with the studies done in various parts of India with pemphigus as the commonest. [7,12] This is in contrast to the studies done in western countries showing BP as the most common AIBD encountered and this may be due to racial variations.(5) Among pemphigus group, 13 (40.6%) were pemphigus vulgaris, 4 (12.5%) were pemphigus foliaceous, 1 (3.1%) was pemphigus vegetans and IgA pemphigus each.Pemphigus vegetans is very rare among pemphigus group of diseases accounting for 1-2% in the literature and we had such one rare case in our study. Among pemphigoid group, 13 (40.6%) cases had bullous pemphigoid with no other presentation of subepidermal bullous diseases in our study.Among AIBD, bullous pemphigoid contributes maximally to the burden followed by pemphigus vulgaris in the global literature. The

mortality rate of pemphigus has also been reported three times more than pemphigoid in the worldwide literature.[5]

PV (40.6%) is clinically characterized by flaccid bullae and erosions showing no tendency of healing involving trunk regions more commonly and predominant oral involvement. All 13 cases of PV had the similar classical picture with 100% oral involvement. Around 92.3% of PV cases showed acantholytic cells in Tzanck smear proving its high sensitivity. Histopathological finding was suprabasal split and acantholysis in all cases (100%) and DIF showed IgG and C3 deposition in the intercellular space in nearly 77% of cases and IgG alone in 23% of cases. [7] Pemphigus foliaceous (12.5%) showed flaccid vesicles and crusted plaques over the seborrhoeic areas with no mucosal involvement.Among these, 75% of cases showed acantholytic cells in Tzanck smear. All 4 cases (100%) of pemphigus foliaceous showed subcorneal bulla with few acantholytic cells and neutrophils and DIF showed deposition of both IgG and C3 deposition in the intercellular epidermis.
One rare case of pemphigus vegetans (3.1%) showed vegetating plaques over the perianal region associated with oral mucosal involvement and acantholytic cells were seen in Tzanck smear.Histopathology showed suprabasal bulla with eosinophilic micro abscesses and intercellular IgG, IgM and C3 deposition seen in DIF. Pemphigus vegetans is a rare case accounting for 1-2% of all pemphigus cases with rarest involvement of genital region in our study.[13] A single case (3.1%) of IgA pemphigus showed multiple small flaccid vesicles with classical hypopyon sign over the trunk, axilla and upper limbs associated with oral mucosal involvement. Histopathology, it showed intraepidermal bulla and intercellular IgA deposition predominantly in the subcorneal region in DIF suggesting subcorneal pustular dermatoses type of IgA pemphigus. Pemphigus Area and Activity Score (PAAS) was calculated in all pemphigus cases and it ranged from 11to 38.6 and mucosa score ranged from 0 to 4. There was no mortality encountered in our study. Patients with less PAAS score had good prognosis with faster remission and some with high PAAS score had poor prognosis with slow remission and more recurrences. [14] BP (40.6%) is commonly seen in the elderly with tense bullae on the trunk and extremities with predominant itching in around 69% and oral mucosal involvement in 30.8% of cases. The mucosal involvement was nearly the same as in the study done by Dipankar et al in Chandigarh. [15] One case (7.7%) of BP showed eosinophils in Tzanck smear and remaining other cases showed mixed inflammatory cells. Histopathology showed sub epidermal bulla (100%) with predominant eosinophilic infiltrate in 30.8% cases and DIF showed linear deposition of both IgG and C3 at the BMZ in 61.5% cases and only C3 deposition in 38.5% of cases. Thus, C3 involvement is 100% as given in the texts. [8] Thus, histopathology and DIF are absolutely 100% concordant with our clinical diagnosis. No discordance between the diagnosis reported in our study. This is in contrast to the study done by Chanabassaya et al at Karnataka which showed 26% and 40% discordance in histopathology and DIF respectively. [16] Similar results as in our study was seen in a Belagavi study done by Malhotra et al which showed 100% concordance with clinical, histopathological and DIF findings. [7] Clinically, all patients with autoimmune bullous disorders may not present with classical morphology and distribution of the lesions as observed in various studies conducted in India. They may differ due to the genetic, geographic and ethnic variations. Histopathology is a simple method for the diagnosis of autoimmune bullous disorders that is necessary to be correlated with clinical findings. However, DIF is considered as the gold standard as it makes a definitive diagnosis.After confirmation of diagnosis, patients are treated with immunosuppressants like corticosteroids for the initial control of disease and maintained with steroid sparing agents like cyclophosphamide, azathioprine, methotrexate, etc. Biologicals like Rituximab have a dynamic role in current scenario for refractory cases and in long-term remission of the disease.

CONCLUSION

This retrospective analysis highlights the significant morbidity associated with autoimmune bullous diseases, underlining their chronic, relapsing nature and the impact on patient quality of life. The study emphasizes the need for early diagnosis, standardized treatment protocols and integrated multidisciplinary care. Larger community-based studies are needed for the epidemiological and clinico-immunological profile of individual autoimmune bullous diseases in Indian patients which will help in accurate characterisation of autoimmune bullous diseases.

LIMITATIONS: We could not perform immunoblotting and direct immunofluorescence using salt split technique due to unavailability of the facilities.

CONFLICT OF INTEREST: There is no conflict of interest in our study

FUNDING STATEMENT: There is no funding source for our study

KEY POINTS:

- The common AIBD encountered in our study is Pemphigus Vulgaris which is in par with other Indian studies, but in contrast with global studies where Bullous Pemphigoid is the commonest one, and it may be due to racial variations across the world.
- There are numerous vesicobullous disorders in dermatology and so accurate diagnosis of AIBD is essential for appropriate management to minimize the morbidity and mortality.
- Primary care physicians should be trained to recognize early signs of AIBD and prompt referral to specialized centres can reduce disease burden and complications.Strengthening primary and tertiary care linkages is also crucial for better disease outcomes.

GLOSSARY OF ABBREVIATIONS:

AIBD: Autoimmune bullous diseases
DIF: Direct Immunofluorescence
BMZ: Basement membrane zone
PF: Pemphigus foliaceus
PE: Pemphigus erythematosus
PV: Pemphigus vulgaris
BP: Bullous pemphigoid
DH: Dermatitis herpetiformis
PAAS: Pemphigus Area and Activity Score

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