International Journal of Research in Dermatology
Ramalingam R et al. Int J Res Dermatol. 2019 Aug;5(3):486-492
http://www.ijord.com

DOI: http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20193121

Original Research Article

A retrospective study on clinical and demographic features of autoimmune vesiculobullous disorders from a rural tertiary care institute in Tamil Nadu

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Received: 01 June 2019
Revised: 02 July 2019
Accepted: 03 July 2019

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ABSTRACT

Background: Autoimmune vesiculobullous disorders are a heterogenous group of skin diseases in which autoantibodies are directed against cell adhesion molecules which are essential for the integrity of skin and oral mucosa. They are clinically characterized by the presence of vesicles, bullae or erosions over the skin and/ or mucosa depending on the antibodies involved. They are divided into intraepidermal and subepidermal based on the location of the bulla. Among intraepidermal bullous disorders, pemphigus vulgaris (PV) is most common. Bullous pemphigoid (BP) is the most common among the subepidermal bullous disorders. Although they occur worldwide, the incidence shows geographical variation. A retrospective study was carried out with the objective to analyse the clinical and demographic profile of patients with autoimmune vesiculobullous disorders among patients attending a tertiary care teaching hospital in a rural setup.
Methods: A total of 137 case sheets were audited from the Medical Records Department of our institute. Details were collected and tabulated, compiled and analysed.
Results: Out of the 137 cases studied, intraepidermal autoimmune vesiculobullous disorders accounted for 63.4% of cases, and subepidermal autoimmune vesiculobullous disorders accounted for 36.6% of cases. Out of the 137 cases, 74 patients (54%) were females, and 63 patients (46%) were males. Majority of the patients were in the age group of 51-60 years (29.9%), followed by 41-50 years (24.1%) and 61-70 years (17.5%).
Conclusions: Pemphigus vulgaris was the most common among the intraepidermal autoimmune vesiculobullous disorders, and bullous pemphigoid was the most common among the subepidermal autoimmune vesiculobullous disorders.

Keywords: Pemphigus vulgaris, Bullous pemphigoid intraepidermal, Subepidermal

INTRODUCTION

The epidermis is a highly dynamic structure held together by adhesion molecules which have an important role in cell-cell and cell-matrix adhesion. Adhesion molecules are transmembrane proteins, the extracellular domains of which are homophilic, and the intracellular portions are linked to the cytoskeleton of the cells. There are four

major families of adhesion molecules- viz cadherins, integrins, selectins, immunoglobulin family, which are localized to two specialized intercellular junctions known as desmosomes and adherens junctions.[1]

Autoimmune vesiculobullous disorders are a heterogenous group of skin diseases in which autoantibodies are directed against cell adhesion molecules which are essential for the integrity of skin and oral mucosa. They are clinically characterized by the presence of vesicles, bullae or erosions over the skin and/ or mucosa depending on the antibodies involved. There are various mechanisms which are involved in formation of blisters such as acantholysis, spongiosis, reticular degeneration, cytolysis and basement membrane zone disruption or destruction.[2] They are classified into various groups based on clinical, histomorphological and immunological criteria. They are divided into intraepidermal and subepidermal based on the location of the bulla. Among intraepidermal bullous disorders, pemphigus vulgaris (PV) is most common.[3] Bullous pemphigoid (BP) is the most common among the subepidermal bullous disorders.[4] Although they occur worldwide, the incidence shows geographical variation. Epidemiological data from India are lacking. Pemphigus vulgaris is more commonly encountered than bullous pemphigoid in India.[5]

Diagnosis of autoimmune vesiculobullous disorders is based on the clinical and histopathological features, and confirmation is by direct immunofluorescence. However, among patients who are not able to meet out the diagnostic cost, it is largely relied on the clinical and histopathological diagnosis. A retrospective study was carried out with the objective to analyse the clinical and demographic profile of patients with autoimmune vesiculobullous disorders among patients attending a tertiary care teaching hospital in a rural setup.

METHODS

The study was presented before Institutional Research Board and Institutional Ethical committee and cleared.

Study centre: Department of Dermatology, Venereology and Leprology, Trichy SRM Medical College Hospital and Research Centre, Irungalur, Trichy.

Study design: Retrospective study.

Study type: Observational type.

Study period: January 2009-December 2018.

Inclusion criteria: All autoimmune vesiculobullous disorders with concordant clinical and histopathological diagnosis.

Case sheets were audited from the Medical Records Department of our institute. A total of 137 cases with concordant clinical and histopathological diagnosis of autoimmune vesiculobullous disorders were seen in this setup over a period of 10 years from 2009 to 2018. Details regarding the patients' age, gender, duration of the disease (at the time of consultation), site of involvement- scalp, face, trunk, upper limbs, lower limbs, oral mucosa, genital mucosa, palms and soles, associated nail changes, Tzanck smear, skin biopsy findings were collected and tabulated. Chi square test was done to find out the correlation between variables.

Exclusion criteria

Exclusion criteria were vesiculobullous disorders other than autoimmune origin; histopathologically discordant cases were excluded from the study.

RESULTS

In this study, the data was analysed for the clinical and demographic profile of 137 patients with autoimmune vesiculobullous disorders. Out of the 137 cases studied, intraepidermal autoimmune vesiculobullous disorders accounted for 63.4% of cases, and subepidermal autoimmune vesiculobullous disorders accounted for 36.6% of cases. Out of the 137 cases, 74 patients (54%) were females, and 63 patients (46%) were males (Figure 1). Overall, there was female preponderance in our study with a male to female ratio of 1:1.2. But males outnumbered the females in pemphigus group of bullous disorders like pemphigus vulgaris, pemphigus vegetans, pemphigus erythematosus, localized pemphigus, linear IgA pemphigus and oral pemphigus. Female preponderance was seen in all the other bullous dermatosis like bullous pemphigoid, dermatitis herpetiformis, linear IgA bullous dermatosis, epidermolysis bullosa acquisita and pemphigus foliaceous.

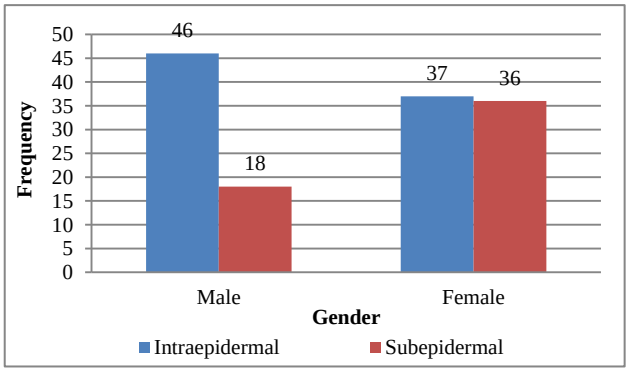

Figure 1: Gender wise autoimmune vesiculobullous disorders.

In this study, the age of the patients ranged from 2 years (a female child with chronic bullous dermatosis of childhood) to 89 years (a male with bullous pemphigoid). Majority of the patients were in the age group of 51-60 years (29.9%), followed by 41-50 years (24.1%) and 61-

70 years (17.5%). Only two patients were less than 10 years of age, and had chronic bullous dermatosis of childhood. Three patients were above 80 years of age, and they had bullous pemphigoid. None of the patients with pemphigus group of disorders were less than 20 years of age. None of our patients with bullous pemphigoid were less than 30 years of age (Table 1).

Table 1: Age distribution of patients with autoimmune vesiculobullous disorders.

Clinical diagnosis	Age group (n=137)									
	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	Total
Pemphigus vulgaris	0 (0)*	0 (0)	6 (4.3)	9 (6.5)	18 (13.1)	24 (17.5)	5 (3.6)	1 (0.7)	0 (0)	63
Pemphigus vegetans	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.4)	2 (1.4)	0 (0)	1 (0.7)	0 (0)	5 (3.6)
Pemphigus foliaceous	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.7)	1 (0.7)	0 (0)	0 (0)	3 (2.1)
Pemphigus erythematosus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)	1 (0.7)	0 (0)	0 (0)	5 (3.6)
IgA pemphigus	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Oral pemphigus	0 (0)	0 (0)	0 (0)	2 (1.4)	2 (1.4)	0 (0)	1 (0.7)	0 (0)	0 (0)	5 (3.6)
Localized pemphigus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7))	0 (0)	0 (0)	0 (0)	1 (0.7)
Bullous pemphigoid	0 (0)	0 (0)	0 (0)	3 (2.1)	6 (4.3)	8 (5.8)	15 (10.9)	5 (3.6)	3 (2.1)	40 (29.1)
Dermatitis herpetiformis	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)	1 (0.7)	1 (0.7)	2 (1.4)	0 (0)	8 (5.8)
Linear IgA bullous dermatosis	0 (0)	0 (0)	0 (0)	3 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)
Chronic bullous dermatosis of childhood	2 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.4)
Epidermolysis bullosa acquisita	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Total	2 (1.4)	0 (0)	7 (5.1)	18 (13.1)	33 (24.1)	41 (29.9)	24 (17.5)	9 (6.5)	3 (2.1)	137

*Parenthesis denotes percentage.

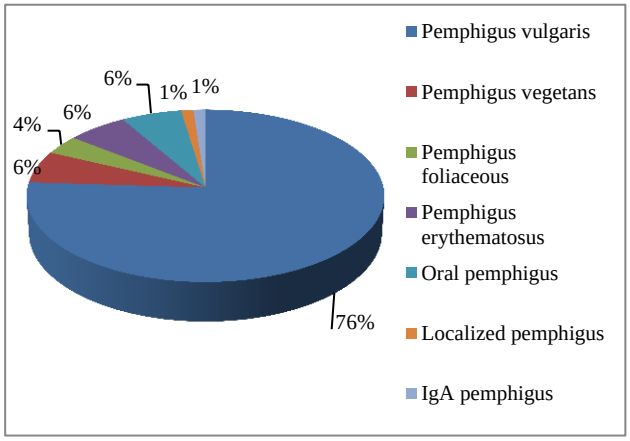

Figure 2: Pattern of intraepidermal vesiculobullous disorders.

Out of the 83 patients of pemphigus group, 63 patients had pemphigus vulgaris (76%), 5 patients had pemphigus vegetans (6%), 5 patients had pemphigus erythematosus (6%), 3 patients had pemphigus foliaceous (3.6%), 5 patients had oral pemphigus (6%), one each had IgA pemphigus and localized pemphigus (1.2%) (Figure 2). Among the 63 patients with pemphigus vulgaris subtype, the commonest age group affected was 51-60 years (24 patients, 38%), followed by 41-50 years (18 patients, 28.5%), 31-40 years (9 patients, 14.2%), 21-30 years (6 patients, 9.5%), 61-70 years (5 patients, 7.9%), 71-80 years (1 patient, 1.5%). Among the patients with pemphigus vegetans, two patients each were in the age group of 41-50 years and 51-60 years of age group, and one patient was in the age group of 71-80 years. In our study, four out of five patients with pemphigus erythematosus were in the age group of 51-60 years (Table 1). Tzanck smear was consistent in all 83 patients of pemphigus (all types) with predominant acantholytic cells.

In patients with pemphigus vulgaris, oral lesions were seen in 100% of patients. Oral pemphigus was seen in five patients, whereas skin and mucosal lesions were seen in rest of the patients. Itching and burning sensation of the eroded skin were the common symptoms. Flaccid

vesicles, bullae, erosions and crusting were the most common clinical findings observed. Skin lesions were mainly seen over the scalp (62/63 patients- 98%), followed by face (49/63 patients- 77%), trunk (50/63 patients-79.3%), upper limbs (61/63 patients- 96.8%), lower limbs (42/63 patients- 66%), palms and soles (12/63 patients- 19%), genitalia (19/63 patients- 30%). 29 out of 63 patients (46%) with pemphigus vulgaris had nail changes—paronychia, nail dystrophy. Oral candidiasis was present in almost 70% of individuals with oral involvement.

Scalp involvement was seen in all the three (100%) patients with pemphigus foliaceous, all the five patients with pemphigus erythematosus. One patient had localized pemphigus- lesions limited only to the neck and clavicular region- diagnosis was confirmed by Tzanck smear, histopathology and direct immunoflourescence. One patient had IgA pemphigus, diagnosis of which was confirmed by DIF. One patient with pemphigus vulgaris had deep vein thrombosis of the lowerlimb. Three patients with pemphigus vulgaris died because of sepsis.

Out of the 5 patients with pemphigus vegetans, 2 patients had vegetative plaques in the axillae, groin, perianal region at the time of presentation itself without any vesiculobullous lesions. Rest of the 3 patients, had flaccid vesicles, bullae, and erosions which later evolved into vegetative plaques in the course of the disease. Two out of three patients with pemphigus foliaceous and three out of five patients with pemphigus erythematosus presented with exfoliative dermatitis. All the five patients with pemphigus erythematosus had ANA positivity. None of the patients in our study had drug history prior to the onset of pemphigus or any associated malignancies.

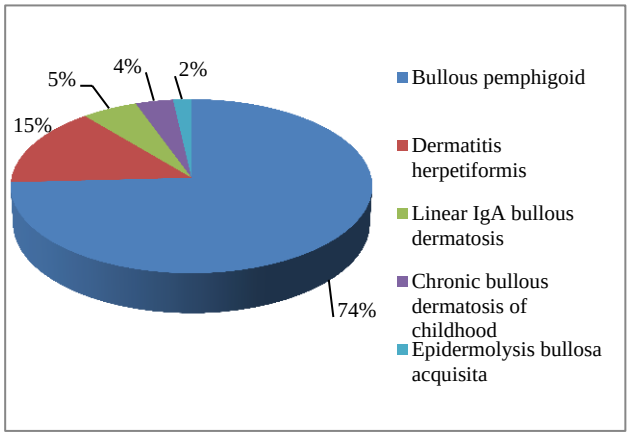

Figure 3: Pattern of subepidermal autoimmune vesiculobullous disorders.

Bullous pemphigoid (40/54, 74%) was the most common among the pemphigoid group of autoimmune bullous disease (Figure 3). Out of the 54 patients with subepidermal autoimmune vesiculobullous disorders, bullous pemphigoid was common in the age group of 61-70 years (15/40 patients, 37.5%). Eight patients (20%) were in the age group of 51-60 years, 6 patients (15%) were in the age group of 41-50 years, 5 patients (12.5%) were in the age group of 71-80 years, three (7.5%) patients each were in the age group of 31-40 years and 81-90 years. None of the patients with bullous pemphigoid were below 30 years of age. In the dermatitis herpetiformis group, the common age group affected was between 41-50 years (4/8 patients, 50%). In our study, we had two children with chronic bullous dermatosis of childhood with age less than 10 years (Table 1). We had only one patient with localized bullous pemphigoid with lesions localized to the pretibial region. Females outnumbered the males in all subepidermal bullous disorders.

Severe pruritus was present in all the patients with bullous pemphigoid group. Tense vesicles and bullae over urticarial wheals were the classical lesions in all the patients. Two patients with bullous pemphigoid had skin lesions with string of pearls appearance. The incidence of oral mucosal involvement in patients with bullous pemphigoid was 21/39 patients (53%) in our study. Lesions were predominantly seen over the trunk, and extremities in bullous pemphigoid patients. Only one patient with bullous pemphigoid had lesions over the scalp. None of the patients with other subepidermal bullous disorders had lesions over the scalp.

In our study, we had two children (one male- 7 years and one female- 2 years) with chronic bullous dermatosis of childhood with age less than 10 years. Both the children had intensely itchy vesiculobullous lesions with characteristic string of pearls appearance. Lesions were predominantly seen over the trunk, upper limbs, lower limbs, palms and soles. Oral mucosa was not involved in both the patients. Genital mucosal involvement was seen in the female child with CBDC.

In the present study, we had one female patient with epidermolysis bullosa acquisita with tense vesicles and haemorrhagic bullae over the extremities. Lesions healed with scarring and milia formation in that patient. There were no mucosal lesions. We had 8 patients with dermatitis herpetiformis who presented with intense pruritus over the trunk especially over the back. The lesions were predominantly excoriation marks without any mucosal lesions.

Two patients with bullous pemphigoid had associated cutaneous myiasis, and one patient had oral myiasis. None of the patients with bullous pemphigoid had oral candidiasis. 14 out of 40 patients with bullous pemphigoid showed eosinophils in the smear. None of the patients had associated internal malignancy in subepidermal group.

DISCUSSION

Autoimmune vesiculobullous disorders are characterized by antibody mediated bullous eruption affecting skin and

or mucosa. It includes intraepidermal disorders like pemphigus vulgaris (PV) and pemphigus foliaceus (PF) and subepidermal disorders like bullous pemphigoid (BP), cicatricial pemhigoid (CP), linear IgA disease (LAD), dermatitis herpetiformis, pemphigoid gestations, lichen planus pemphigoides (LPP), epidermolysis bullosa acquisita and bullous systemic lupus erythematosus by Huilgol et al.[6] Light microscopy is a simple method for diagnosis of immunobullous disorders and should be correlated with clinical findings. But to make a definitive diagnosis, immunofluorescence technique is required and it is considered as the gold standard. According to Chhabra et al.[7] Direct immunofluorescence (DIF) is done using perilesional skin or mucosa as substrate whereas indirect immunofluorescence (IIF) is done using patient's serum.[7]

In the current study, pemphigus vulgaris (45.9%) constituted the most common vesiculobullous disorder followed by bullous pemphigoid (29.1%) as in other studies by Fatma et al, Nanda et al and Deepti et al.[2,8,9] The proportion of cases with pemphigus vulgaris and bullous pemphigoid were almost similar to that observed by Nanda et al, but higher than that observed in the study by Fatma et al, and Deepti et al.[2,8,9] Pemphigus foliaceous was seen in only 3.6% of patients in our study which is in contrast to other studies like Fatma et al and Deepti et al.[2,9] Overall, there was female preponderance in our study with a male to female ratio of 1:1.2, which is in par with other studies like Fatma et al and Deepti et al.[2,9] In our study, most common age group affected was between 51 to 60 years of age, which is in approximately par with study by Fatma et al.[2]

Pemphigus is an intraepithelial immunobullous disease of the mucocutaneous system. Among the intraepidermal autoimmune vesiculobullous disorders, pemphigus vulgaris (76%) is the most common followed by pemphigus vegetans (6%), and pemphigus erythematosus (6%). Pemphigus vulgaris constitutes about 76% of cases (63/83 patients), which is higher than that of Arya, but lower than that found by Nanda et al and Mahajan et al.[8,10,11] It affects all races and both sexes particularly in their middle ages, but in our study, we had majority of patients in the age group of 51-60 years, which is in contrast with that of Mahajan et al, where half of the patients were in the 4th decade.[11] The sex ratio was almost equal in a large Indian series by Pasricha et al.[5] In our study, there was a slight male preponderance (1.33:1), which is in accordance with the study by Arya (1.4:1) which is in contrast to the study by Mahajan et al.[10,11] where there was a female preponderance (1.16:1). In our study, we did not have any patients with age less than 20 years in pemphigus group, which is not in par with Mahajan et al, where (12.9%) patients were of less than 18 years of age.[11]

Pemphigus foliaceous accounted for only 3.6% of cases in our study, whereas it was the second common among the pemphigus group of disorders in the study by Arya, Mahajan et al, which is not in accordance with our study.[10,11] In our study, we had 6% patients with pemphigus vegetans, which is higher than that observed by Arya, Mahajan et al.[10,11] Majority of the cases were seen in the age group of 51-60 years, with a slight male predominance of 1.33:1, which is in contrast to other studies where there was a female preponderance like in Nanda et al, Arya et al, Mahajan et al.[8,10,11] Flaccid bullae were present in 100% cases. Pruritus was complained of in 25% cases, though it was more common in pemphigus vegetans and vulgaris. Skin and mucosal lesions were seen in all patients of pemphigus vulgaris, whereas the percentage of oral involvement was 52.5% of cases in our study in contrast to 63.63% by Mahajan et al.[11] Exclusive oral mucosal involvement was present in 5/83 patients (6.02%) with intraepidermal disorders, which is almost similar to the observation by Mahajan et al (6.81%).[11] In our study, two out of three patients with pemphigus foliaceous presented with exfoliative dermatitis, whereas one patient of PF presented with exfoliative dermatitis in the study by Mahajan et al.[11] None of our patients with pemphigus foliaceous had mucosal lesions, but Mahajan et al observed 25% of patients with PF having mucosal involvement.[11] According to Taghipour et al, Pemphigus may be associated with thymoma, myasthenia gravis, lupus erythematosus, bullous pemphigoid and neoplasia (paraneoplastic pemphigus).[3] In our study, pemphigus vulgaris is characterised by an increased thrombotic risk as highlighted by the Oxford record linkage study by Ramagopalan et al.[12] Marzano et al, in their study found that coagulation activation in pemphigus is not enhanced as in bullous pemphigoid.13 In our patients, presence of hypertension, diabetes mellitus, deep vein thrombosis, extensive dermatophytosis were seen in patients with pemphigus.

Little is known about the epidemiology of BP. Previous studies have reported incidence between 0.2 and 3 per 100,000 person years. In UK, a regional study by Langan et al estimated an incidence of 1.4 per 100,000 person years.[14] Epidemiological data from India are lacking. According to Khandpur et al pemphigus vulgaris is more commonly encountered than BP in India and it primarily affects elderly individuals in the fifth to seventh decade of life, with average age of onset being 65 years.[15] These lesions are most common in the lower abdomen, inner or anterior thighs and flexor forearms, although they may occur anywhere, significant pruritus is frequently present. In our study, pemphigus vulgaris (63/137 patients- 45.98%) was more common than bullous pemphigoid (40/137 patients- 29.1), which was similar to the results in a study by Nanda et al.[8] Among the subepidermal autoimmune vesiculobullous disorders, bullous pemphigoid was the most common type (74.07%) in our study which is in par with study by De et al in India, and other studies from Kuwait and Singapore, though there was a variation in the percentage of cases by Wong et al.[8,16,17] Majority of our patients were in the age group of 61-70 years, whereas it was 59 years, 65.97 years and 58.4 years in the study by De et al, Nanda et al and Wong

et al respectively.[8,16,17] In our study, we observed a female preponderance (male to female ratio 1:2), which is in accordance with other studies by De and Nanda et al, except in CBDC, there was equal gender predisposition.[8,16] Majority of our patients (70%) had mild disease unlike moderate to severe disease reported in 96% of cases from Kuwait study by Nanda et al.[8] The incidence of oral mucosal involvement in patients with bullous pemphigoid was 21/40 patients (52.5%) in our study which is higher than that noted in other studies by i.e. De et al- 40%, Nanda et al- 37%.[8,16] So far in the literature myiasis has not been reported in association with bullous pemphigoid, though it has been reported in pemphigus patients by Vinay et al, but in our study, we had two patients of bullous pemphigoid with associated myiasis- one with oral and one with cutaneous myiasis.[18] The percentage of dermatitis herpetiformis (14%) was found to be lower than that observed by De et al (28%).[16] But in the studies reported from Kuwait and Singapore, there were no cases of DH. The percentage of EBA patients in our study was almost similar to that observed by De et al (1.8 vs. 2%), which is in contrast with other studies at Singapore and Kuwait.[16] We have not seen any patients with mucous membrane pemphigoid, lichen planus pemphigoides, pyoderma gangrenosum or bullous SLE in our study, but in the study from PGI Chandigarh, De et al observed 12% cases of MMP, 6% cases with LPP.[16] The percentage of CBDC/LABD cases in our study was 8% which is almost similar to that of De et al (10%), higher than that observed in Singapore study by Wong et al (3%).[16,17] Pyoderma gangrenosum accounted for a significant percentage in the study by Nanda et al (35%) in contrast to other studies.[8]

Localized bullous pemphigoid 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 in study by Khandpur et al.[15] We had one patient with bullous pemphigoid localized to pretibial region, without prior history of any trauma to that site.

CONCLUSION

Intraepidermal autoimmune vesiculobullous disorders accounted for 63.4% of cases, and subepidermal autoimmune vesiculobullous disorders accounted for 36.6% of cases. Overall, there was female preponderance in our study. Pemphigus vulgaris is the most common autoimmune vesiculobullous disorder in our study and is more common in males. It is more commonly seen in 51-60 years of age group. None of our patients in the pemphigus group were in the extreme age group- less than 20 years and more than 80 years. Skin and mucosal lesions were seen in all patients. 46% of patients with pemphigus vulgaris had nail changes. Oral pemphigus was observed in 6% of cases. One patient with pemphigus vulgaris had deep vein thrombosis and one patient associated with extensive dermatophytosis. Bullous pemphigoid was the second most common bullous dermatosis. Females are found to be more commonly affected than males in bullous pemphigoid group. Oral mucosal lesions were seen in 52.5% of cases in our study. None of the patients with other subepidermal bullous disorders had lesions over the scalp. One patient with bullous pemphigoid had associated cutaneous myiasis, and one patient had oral myiasis. The clinical and demographic pattern of autoimmune vesiculobullous dermatosis varies in different populations studied.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge M. Ismail, Research Co-ordinator Trichy SRM Medical College Hospital and Research Centre, Irungalur, Trichy, Tamil Nadu for his contribution towards manuscript preparation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ramalingam R, Ganapathy VKA, Chandrasekar SR, Narasiman B, Gounder DS. A retrospective study on clinical and demographic features of autoimmune vesiculobullous disorders from a rural tertiary care institute in Tamil Nadu. Int J Res Dermatol 2019;5:486-92.