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Original Research Article

Clinical, histopathological and immunofluorescent study of vesicobullous lesions of skin

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ABSTRACT

Background: Vesiculobullous diseases have been the focus of intensive investigation in recent years. However, these disorders are still associated with substantial morbidity, considerable mortality and impaired quality of life. Accurate diagnosis of vesiculobullous lesions of skin entails evaluation of clinical, histopathologic and immunofluorescence findings.
Methods: Hospital based prospective study for a period of 24 months from August 2014 to July 2016 in the Department of Pathology at Andhra Medical College, Visakhapatnam, India. Total of 50 patients aged 3-70 years with vesiculobullous lesions of both sexes attending the Department of Dermatology were selected and analysed clinically, histopathological examination and direct immunofluorescence (DIF).
Results: In the present study, majority of patients presented between 51-60 yrs of age (32%) with male to female ratio of 1.08:1 and mean age of 46.02 years. Pemphigus vulgaris constituted the most common vesiculobullous disorder (32%) followed by bullous pemphigoid and pemphigus foliaceous, 18% each. Bullae were located intra epidermally in 68% and sub epidermally in 32% of the patients. DIF was positive in 80% of the cases. Overall clinicopathological correlation was established in 74%. Overall histopathological and direct immunofluorescence correlation was established in 78%. Out of 50 cases, 35 cases (70%) correlated clinically and histo-pathologically with direct immunofluorescence.
Conclusions: In the present study, on histopathological examination alone pemphigus foliaceus and pemphigus vulgaris could be differentiated. Direct immunofluorescence was useful in differentiating epidermolysis bullosa acquisita from bullous pemphigoid which have similar histopathological picture. This study proves that direct immunofluorescence is confirmatory as well as diagnostic for vesiculobullous disorders.

Keywords: Immunofluorescence, Pemphigus, Vesiculobullous

INTRODUCTION

Skin forms not only a protective covering but is a part of immune apparatus of body.[1] Vesiculobullous diseases are heterogeneous and include many diverse disorders.[2] The vesiculobullous reaction pattern is characterized by the presence of vesicles or bullae at any level within the epidermis or at the dermoepidermal junction.[3]

A blister is a fluid-filled cavity formed within or beneath the epidermis. At first glance, the observation of blisters seems to imply that blistering is too general or nonspecific for use in clinical gross evaluation. However, the character of blisters in a given disorder tends to be uniform and to have reproducible characteristics.[4]

Vesiculobullous diseases have been the focus of intensive investigation in recent years. However, these disorders are still associated with substantial morbidity, considerable mortality and impaired quality of life. The evolution and temporal relationship of histologic changes of dermatitides under various therapies are not sufficiently documented to allow optimal or perhaps even accurate diagnostic study.[4] Dermatopathology, as pioneered by Unna, affords a keystone not only for modern dermatology but also for the use of immunofluorescence in studies of skin immunopathology.[5]

The aim was to study and proportionate different types of vesiculobullous lesions in relation to age and sex, to evaluate the correlation between clinical, histopathological and direct immunofluorescence (DIF) patterns and to assess the diagnostic value of DIF.

METHODS

The present study was an hospital based prospective study for a period of 24 months from August 2014 to July 2016 in the Department of Pathology, at Andhra Medical College, Visakhapatnam, India.

Total of 50 patients aged 3-70 years with vesiculobullous lesions of both sexes attending the Department of Dermatology were selected and analysed clinically, histopathological examination and direct immunofluorescence (DIF).

Inclusion criteria

All skin biopsies from the cases with vesiculobullous disorders irrespective of age, sex and associated diseases.

Exclusion criteria

Mechanical, thermal, suction and chemical blisters, metabolic (porphyrias) disorders, drug induced blisters, bullous lesions secondary to infections, and others like irritant contact dermatitis and eczematous dermatitis were excluded from the study as these disorders present with characteristic clinical features and histopathology and DIF are not the main diagnostic methods.

Procedure

All patients were subjected to a detailed history taking and clinical examination. Their particulars regarding age, gender, occupation, personal and family history, presenting complaints, duration, general condition and findings on clinical examination were recorded in the proforma. Routine hematological and biochemical investigations were done, and reports recorded. Two 4 mm punch biopsies were done in all cases, one from the vesicle (fixed in 10% buffered formalin for histopathological examination) and another from the perilesional area (sent in Michel's transport medium for DIF testing). Specimens collected in 10% formalin were grossed with detailed examination according to standard protocol and bits were given. Tissue was subjected to routine processing and sections were stained with haematoxylin and eosin. The histopathological sections were diagnosed and correlated with their clinical and immunofluorescence findings.

RESULTS

The present study was a hospital based prospective study conducted over a period of 24 months from August 2014 to July 2016 in the Department of Pathology, at Andhra Medical College, Visakhapatnam, India.

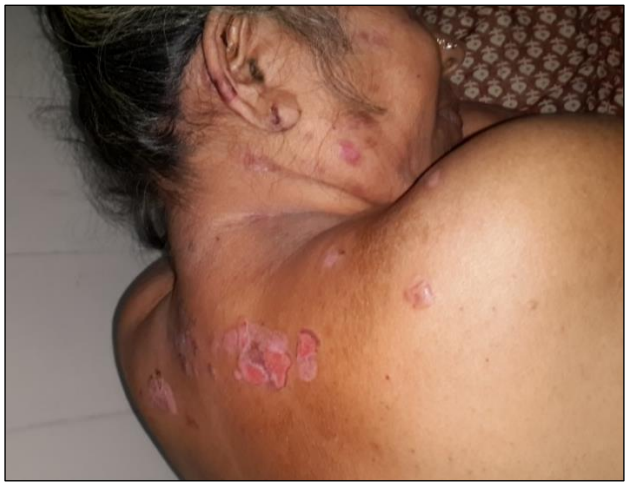

Figure 1: Clinical photograph of 50 years old female with pemphigus vulgaris lesions.

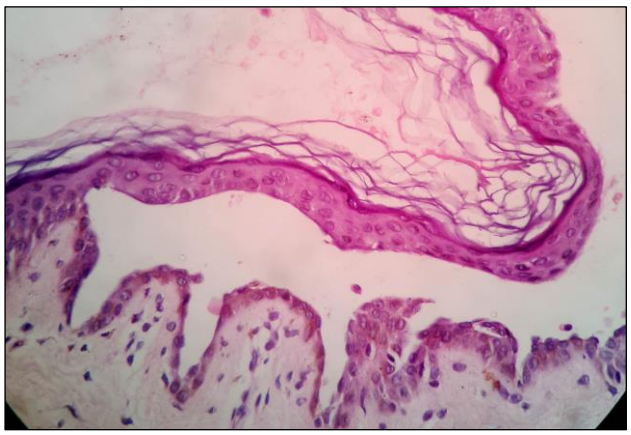

Figure 2: Photomicrograph of case of pemphigus vulgaris with suprabasal clefting and row of tombstone appearance. H&E stain (400x).

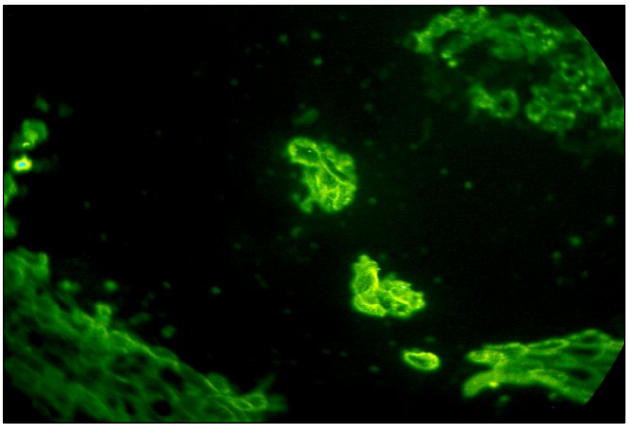

Figure 3: Direct immunofluorescence of pemphigus vulgaris acantholytic cells.

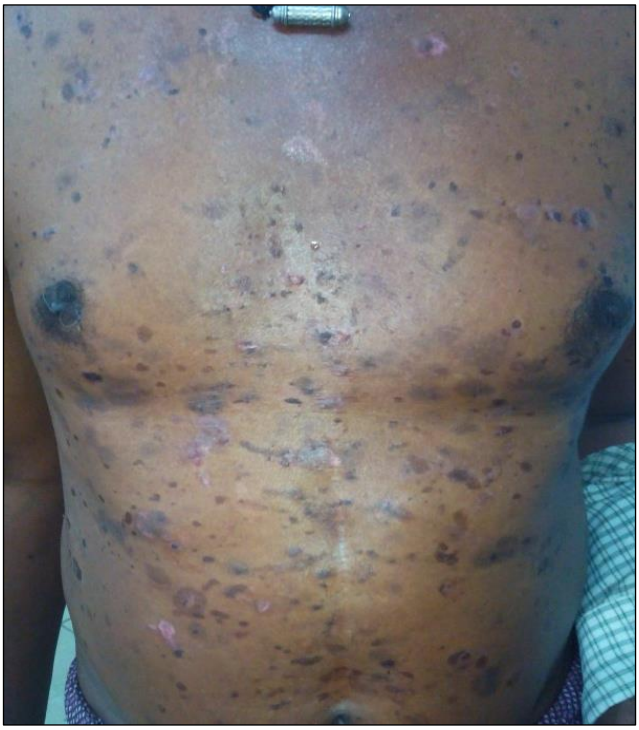

Figure 4: Clinical photograph of 45-year-old male with pemphigus foliaceus.

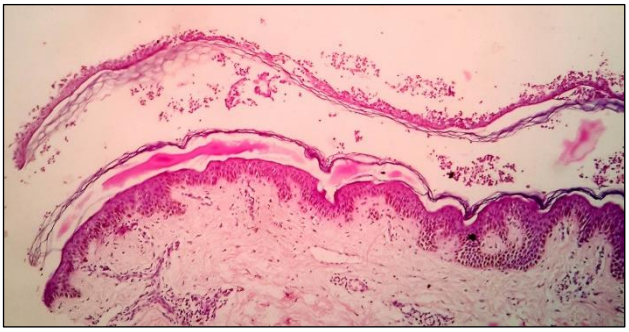

Figure 5: Photomicrograph of pemphigus foliaceus subcorneal bullae with acantholytic cells. H&E stain (100x).

In the present study, out of 50 cases studied, 52% (26 cases) showed male preponderance with mean age of 43.11 years (4-70 years), and female cases were 48% (24 cases) with mean age of 49.16 years (20-70 years).

Majority of patients presented between 51-60 yrs of age (32%) with slight male prepondarance of 1.08:1 and mean age of 46.02 years. Youngest patient in the study was 4 years old and the oldest being 70 years.

In the present study, pemphigus vulgaris constituted the most common vesiculobullous disorders constituting 32% (16 out of 50 cases) (Figure 1, 2 and 3), followed by Bullous pemphigoid and Pemphigus foliaceous (Figure 4 and 5), 18% each (9 out of 50 cases).

Out of the remaining vesiculobullous diseases, Darier's disease constituted 10% (5 out of 50 cases), Hailey Hailey disease 6% (3 out of 50 cases), dermatitis herpetiformis and epidermolysis bullosa acquisita- 4% each (2 out of 50 cases). Least common were chronic bullous disorder of childhood (CBDC), bullous erythema multiforme, lichen planus pemphigoides and ichthyosiform erythroderma which constituted 2% each (1 out of 50 cases) (Table 1).

Table 1: Distribution of cases (n=50).

Type	Frequency	%
Pemphigus vulgaris	16	32
Pemphigus foliaceous	9	18
Bullous pemphigoid	9	18
Darier's disease	5	10
Hailey hailey disease	3	6
Dermatitis herpetiformis	2	4
CBDC	1	2
Epidermolysis bullosa acquisita	2	4
Bullous erythema multiforme	1	2
Lichen planus pemphigoides	1	2
Ichthyosiform erythroderma	1	2
Total	50	100

In present study, pemphigus vulgaris presented most commonly in age group of 31-40 years (31.25%) followed by 51-60 (25%) years age group. Bullous pemphigoid presented commonly in the age group of 61-70 years (55.55%) (Figure 6 and 7), pemphigus foliaceus were common at age group of 51-60 years (44.44%).

Mean age of onset of pemphigus vulgaris and foliaceus was 47.63 years and 47.11 years respectively. Mean age of onset of bullous pemphigoid was 57.89 years. One case of chronic bullous disorder of childhood presented at 9 years of age.

In the present study, bullous pemphigoid, Darier's disease, Hailey hailey disease, Epidermolysis bullosa acquisita showed predominantly male preponderance (66.67%, 60%, 66.67%, 100% respectively). Dermatitis

herpetiformis (Figure 8), Pemphigus foliaceous showed female predominance (100%, 77.73% respectively).

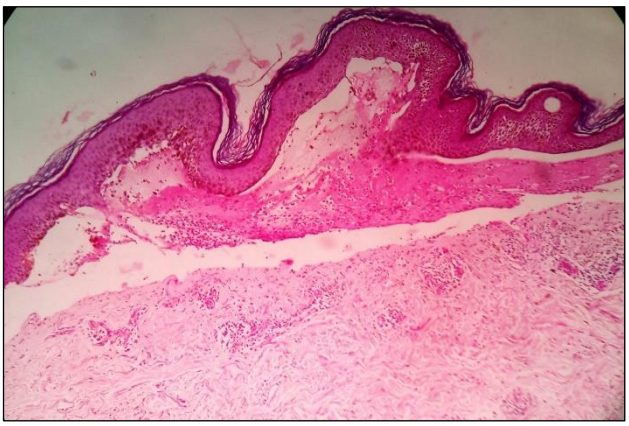

Figure 6: Photomicrograph of bullous pemphigoid subepidermal bulla. H&E stain (100x).

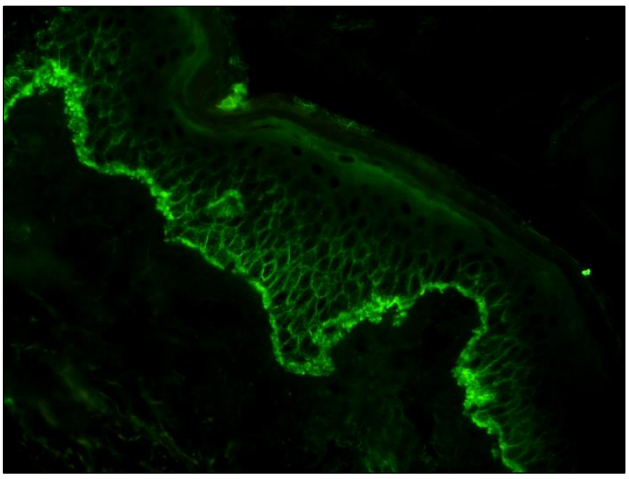

Figure 7: Bullous pemphigoid-DIF linear deposits of IgG along the BMZ.

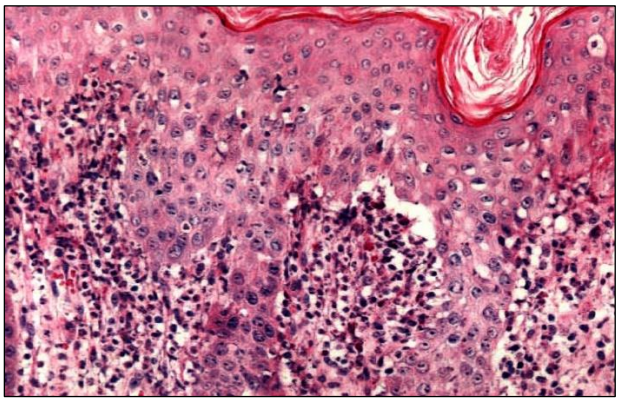

Figure 8: Photomicrograph of dermatitis herpetiformis subepidermal bulla with neutrophila accumulates at the tips of dermal papillae. H&E 100x.

In this study, it was noticed that 38 cases (76%) presented with blisters. Pemphigus vulgaris showed blisters in 93.75% of cases, bullous pemphigoid showed blisters in 88.89% of cases. Darier's disease and Hailey hailey disease (figure 9) less commonly presented with blisters.

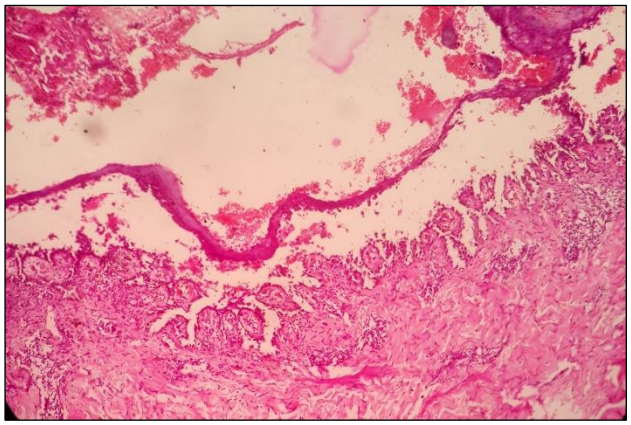

Figure 9: Photomicrograph of Hailey hailey disease dilapidated brick wall appearance. H&E 100x.

In 13 out of 16 cases (81.25%) of pemphigus vulgaris burning sensation was the chief complaint followed by itching (25%) and pain (18.75%). Itching was the most common symptom in bullous pemphigoid and was seen in 7 out of 9 cases (77.78%).

In the present study, pemphigus vulgaris had predominantly flaccid blisters in 93.75% and bullous pemphigoid showed majority of cases with predominant tense blisters in 88.89% and it was statistically significant. Nikolsky sign was present in 26 out of 50 cases (52%) and most common in pemphigus vulgaris and pemphigus foliaceous with 87.5% and 66.67% respectively and it was statistically significant. Bulla spread sign was negative in 72% of cases.

Oral mucosa involvement was present in 42% (21 out of 50 cases) and was predominantly seen in 75% of cases of pemphigus vulgaris.

In the present study, bullae were located predominantly intra epidermally in 68% and sub epidermally in 32% of the patients. 87.5% of pemphigus vulgaris cases and 100% of both Darier's disease and Hailey hailey disease showed suprabasal separation. 100% of cases of bullous pemphigoid, dermatitis herpetiformis, chronic bullous disorder of childhood (CBDC), epidermolysis bullosa acquisita, bullous erythema multiforme and lichen planus pemphigoides (Figure 10) showed subepidermal blisters.

Tomb stone appearance (75%) was noted only in pemphigus vulgaris. Hyperkeratosis was seen in 31.25% of pemphigus vulgaris, 20% of Darier's disease, 100% Hailey hailey disease. Acanthosis was noted in 88.89% of pemphigus foliaceous, 100% in Hailey hailey disease. Dyskeratosis was noted in 88.89% of pemphigus foliaceous, 66.67% of Hailey hailey disease. Acanthocytes was predominantly seen in pemphigus

foliaceous (100%), Hailey hailey disease (100%) and pemphigus vulgaris (93.75%).

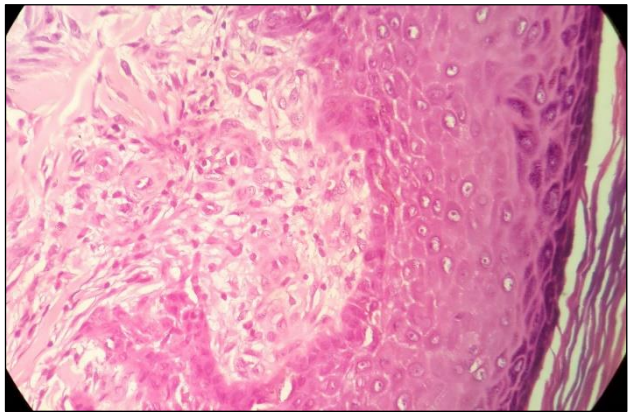

Figure 10: Photomicrograph of Lichen planus pemphigoides. H&E stain 400x.

Out of 50 cases of vesiculobullous disorders, direct immunofluorescence was positive in 80% (40 cases). Darier's disease, Hailey hailey disease and bullous Ichthyosi form Erythroderma were negative on direct immunofluorescence consistent with the histopathological diagnosis. One case of chronic bullous disorder of childhood (CBDC) clinically and histopathologically diagnosed as chronic bullous disorder of childhood (CBDC) was negative on direct immunofluorescence.

On direct immunofluorescence examination, intercellular deposition of IgG and C3 in a fishnet pattern were seen in all cases of pemphigus vulgaris. All the cases of pemphigus foliaceus also showed intercellular deposition of IgG and C3 in the upper epidermis. All cases of bullous pemphigoid showed linear deposition of IgG and C3 along the basement membrane. One case of bullous pemphigoid showed IgA deposition along the basement membrane in addition to IgG and C3.

One case of lichen planus pemphigoides showed IgGand C3 deposition along the basement membrane. Out of two cases of dermatitis herpetiformis, only one case showed granular IgA deposition at the BMZ consistent with the diagnosis, but another case showed linear deposition of IgA discordant with the diagnosis (Table 2).

Overall clinicopathological correlation was established in total 37 cases out of 50 cases (74%). Out of 18 clinically diagnosed cases of pemphigus vulgaris, 14 were proved to be pemphigus vulgaris, 3 as pemphigus foliaceous and one as bullous pemphigoid histopathologically. Hence, clinicopathological correlation was established in 14 cases (77.78%) and it was statistically significant. Out of 8, clinically diagnosed cases of bullous pemphigoid 5 were proved to be bullous pemphigoid histopathologically. So, clinicopathological correlation was seen in 62.5% of cases.

Table 2: Findings of direct immunofluorescence.

Antibody	Deposition	Type	No. of cases
IgG	ICS	PV	16
		PF	9
	BMZ	BP	9
		EBA	2
		LPP	1
IgM	BMZ	BEM	1
IgA	BMZ	BP	1
		DH	1
C3	ICS	PV	16
		PF	9
	BMZ	BP	9
		EBA	2
		BEM	1
		LPP	1
Negative		DD	5
		HH	3
		CBDC	1
		IE	1

ICS=intercellular, BMZ=basement membrane zone.

Table 3: Clinicopathological correlation and deferred cases (n=50).

Clinical diagnosis	No. of cases	Correlated with HPE	Not correlated with HPE
Pemphigus vulgaris	18	14	4 (PF-3, BP-1)
Pemphigus foliaceous	4	4	-
Pemphigus vegetans	1	-	1 (PV)
Pemphigus erythematosis	1	-	1 (PF)
Paraneoplastic pemphigus	1	-	1 (PV)
Bullous pemphigoid	8	5	3 (PF-1,BEM-1,LPP-1)
Darier's disease	5	5	-
Hailey hailey disease	3	3	-
Dermatitis herpetiformis	5	2	3 (BP-3)
CBDC	1	1	-
Epidermolysis bullosa acquisita	2	2	-
Bullous erythema multiforme	1	1	-
Ichthyosiform erythroderma	1	1	-
Total	50 (100%)	37 (74%)	13

One case each of pemphigus vegetans and paraneoplastic pemphigus diagnosed clinically were proved to be pemphigus vulgaris histopathologically. Out of 5 clinically diagnosed cases of dermatitis herpetiformis, only 2 were proved to be DH, other 3 were diagnosed as bullous pemphigoid.

In the present study, total clinicopathological correlation was observed in Hailey hailey disease, Darier's disease, CBDC and Ichthyosi form erythroderma and it was statistically significant (Table 3).

Overall histopathological and DIF correlation was established in total 39 cases out of 50 cases (78%). There was total direct immunofluorescence and histopathological correlation in pemphigus vulgaris, pemphigus foliaceus and bullous pemphigoid and it was statistically significant. Out of two histopathologically diagnosed cases of dermatitis herpetiformis, one was proved to be dermatitis herpetiformis by DIF and one as linear IgA disease.

One case histopathologically diagnosed as CBDC was negative on direct immunofluorescence (Table 4). Out of 50 cases, 35 cases-(70%) correlated clinically and histopathologically with DIF.

Table 4: Histopathological and direct immunofluorescence correlation and deferred cases (n=50).

HPE diagnosis	No. of cases	Correlated with DIF	Not correlated with DIF
Pemphigus vulgaris	16	16	-
Pemphigus foliaceous	9	9	-
Bullous pemphigoid	9	9	-
Darier's disease	5	-	5 (-ve)
Hailey hailey disease	3	-	3 (-ve)
Dermatitis herpetiformis	2	1	1 (Linear IgA)
CBDC	1	-	1 (-ve)
Epidermolysis bullosa acquisita	2	2	-
Bullous erythema multiforme	1	1	-
Lichen planus pemphigoides	1	1	-
Ichthyosiform erythroderma	1	-	1 (-ve)
Total	50 (100%)	39 (78%)	11

DISCUSSION

Diagnosis of vesiculobullous lesions are often challenging on histopathology examination. Recent advances in investigative dermatopathology have generated new horizons.[6] Over the last two decades, pronounced advances have been made in understanding the clinical behaviour and molecular nature of autoimmune diseases.

Immunological disorders are classified largely by the clinical and immunofluorescence pattern. Even after the advent of systemic corticosteroids some of them may prove fatal. It is therefore necessary to diagnose and treat the condition early.[7] Early lesions should always be biopsied to ensure that a histopathological diagnosis can be made. Once regeneration of the epidermis commences or secondary changes such as infection or ulceration occur, accurate diagnosis of a vesiculobullous lesion may not always be possible.[3]

In the present study, pemphigus vulgaris constituted the most common vesiculobullous disorder constituting 32% which was similar to results compared to 34% in Deepthi SP et al, and 40.6% in Ahmed K et al, study (Table 5).[7,8]

Table 5: Overall comparison with other studies.

Features	Present study	Ahmed K et al[7]	Deepthi SP et al[8]	Anchal J et al[12]
No. of cases	50	59	50	53
M:F ratio	1.08:1	0.73:1	0.66:1	0.76:1
PV %	32%	40.6%	34%	31.6%
DIF positivity	80%	93.2%	70%	75%
% Clinical /HPE/DIF correlation	70%	69.4%	70%	84.9%

The age group of the patients ranged from 4 to 70 years in the present study. Most patients were in the age group of 41-60 years which is similar Tokambi et al study.[9]

The present study showed male preponderance (52%-26 cases) with male to female ratio of 1.08:1 which was similar to Kanwar AJ et al, study.[10]

In the present study, the commonest presenting clinical features were bullous and vesicopustular lesions (76%) with burning (26 cases-52%) and/or itching (25 cases-50%) symptoms, in variable proportions in different lesions. This was similar to results seen in Vora D et al, study.[11]

In this study, maximum number of patients presented with flaccid bullae accounting for 46% (mostly pemphigus vulgaris) compared to 43.5% of cases in Ahmed K et al, study.[7] There was 22% present with tense

bullae with hemorrhagic fluid, which is seen in subepidermal blistering disorders.

In the present study, Mucosal involvement was lesser (42%) compared to Ahmed K et al, (57.6%) and Deepthi SP et al, (58%) studies and the lesions were mostly distributed in the oral, buccal, palatal, gingival, conjunctiva, and genital mucosa.[7,8]

In the present study, on histopathology, bullae were located predominantly intraepidermally in 68% and sub epidermally in 32% of the patients which was similar to Ahmed K et al, study which was intra epidermally in 54.2% and sub epidermally in 30.5%.[7]

Acanthocytes was predominantly seen in pemphigus foliaceous (100%), Hailey hailey disease (100%) and pemphigus vulgaris (93.75%).

Row of tomb stone appearance (75%) was noted only in pemphigus vulgaris. Hyperkeratosis was seen in 31.25% of pemphigus vulgaris, 20% of Darier's disease, 100% Hailey- hailey disease. Acanthosis was noted in 88.89% of pemphigus foliaceous, 100% in Hailey-hailey disease. Dyskeratosis was noted in 88.89% of pemphigus foliaceous, 66.67% of Hailey-hailey disease.

In the present study, out of 50 cases 29 cases (58%) showed acantholytic cells which was similar to that of Ahmed K et al, study which showed (54.2%) acantholytic cells.

The differentiation between the entities is important for both treatment modalities and prognosis. Present study validates that DIF is requisite for accurate diagnosis of autoimmune bullous disorders of the skin. Direct immunofluorescence was positive in 80% of the cases which was similar to Deepthi SP et al, (70%) and Jindal A et al, (75%) but lower compared to Ahmed K et al, study (93.2%).[7,8,12]

Out of 18 cases, clinically suspected as pemphigus vulgaris, histopathological examination was found to be consistent with the clinical diagnosis in 14 cases. Hence, clinicopathological correlation was established in 14 cases (77.78%).

Direct immunofluorescence was done in all 16 cases of histopathologically diagnosed as pemphigus vulgaris and all 16 (100%) cases were positive. This was similar results compared to Kaur JS et al, study which showed 100 % positive DIF.[13]

Three cases, clinically suspected as pemphigus vulgaris, after histopathology and DIF examination features turned out to be of pemphigus foliaceous.

Out of 8 clinically diagnosed cases of bullous pemphigoid, only 5 were proved to be bullous pemphigoid on histopathological examination, the other 3 were diagnosed as one case of pemphigus foliaceous, bullous erythema multiforme and one case of lichen planus pemphigoides respectively. So, clinic-pathological correlation was seen in 62.5% of cases. DIF was confirmatory in these 3 cases. Lichen planus pemphigoides showed IgGand C3 deposition along the basement membrane and bullous erythema multiforme showed granular IgM and C3 deposits along basement membrane zone.

Out of 5 clinically diagnosed cases of dermatitis herpetiformis, only 2 were proved to be DH on histopathological examination, other 3 were diagnosed as bullous pemphigoid. Out of these two cases, on DIF only one case showed granular IgA deposition at the BMZ consistent with the diagnosis, but another case showed linear deposition of IgA discordant with the diagnosis. Granular deposition of IgA and C3 in the papillary dermis and along the BMZ is diagnostic if DH deposition of IgG or IgM or both is less frequent and less intense.[14]

One case clinically and histopathologically diagnosed as CBDC was negative on direct immunofluorescence.

Two cases with clinical differential diagnosis of EBA or DH, histopathology was in favor of bullous pemphigoid or EBA. In DIF examination, antibody deposition was seen in the floor of blister cavity, favoring the diagnosis of epidermolysis bullosa acquisita.

Accurate diagnosis of vesiculobullous lesions of skin entails evaluation of clinical, histopathologic and immunofluorescence findings. According to Anchal J et al, study in 88.6% of cases, clinical diagnosis was consistent with histopathology diagnosis and in 75.5% of cases, DIF findings were consistent with histopathology diagnosis.[12]

In the present study, clinicopathological correlation was established in total 37 cases out of 50 cases (74%) which was similar to Thejasvi et al, study.[15] Histopathological and DIF correlation was established in total 39 cases out of 50 cases (78%) which was similar to Anchal J et al, study.[12]

Discordance between clinical, histopathological and DIF diagnosis was noted. Analysis of our study showed that out of 50 cases, 35 cases (70%) correlated clinically and histopathologically with DIF. Clinicopathological and DIF correlation was similar to 69.4% in Ahmed K et al, and 70% in Deepthi SP et al, studies but lower compared to 84.9% in Anchal J et al study.[7,8,12] Cases of limited number in our studies were CBDC, bullous erythema multiforme and lichen planus pemphigoides.

CONCLUSION

In the present study, pemphigus vulgaris constituted the most common vesiculobullous disorders constituting 32% followed by bullous pemphigoid and pemphigus

foliaceous, 18% each. In the present study, on histopathological examination alone pemphigus foliaceus and pemphigus vulgaris could be differentiated. Direct immunofloresence was useful in differentiating epidermolysis bullosa acquisita from bullous pemphigoid which have the same histopathological picture.

Overall clinicopathological correlation was established in 74%. Overall histopathological and direct immunofluorescence correlation was established in 78%. Out of 50 cases, 35 cases (70%) correlated clinically and histopathologically with direct immunofluorescence. This study proves that direct immunofluorescence is confirmatory as well as diagnostic for vesiculobullous disorders. However, larger studies with proper selection of cases and judicious use are necessary to optimize its utility.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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