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Clinico-Pathological Study of Immunobullous Disorders with Special Reference to Immunofluorescence

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ABSTRACT

Background: Autoimmune bullous diseases are group of blistering dermatosis in which pathogenic autoantibodies are directed against various target antigens against adhesion complex molecules in epidermis and dermo-epidermal junction which leads to gradual weakening of intercellular bridges between adjacent keratinocytes and those of with basement membrane and subsequent blister formation. The yearly worldwide incidence of this disease category is about 0.3/100000

Aims:

1.To study the clinical and pathological characteristics of autoimmune bullous diseases.

2. To study direct immunofluorescence characteristics of different subgroups of autoimmune bullous diseases

3. To find out the clinico-pathological correlation of different subgroups of autoimmune bullous diseases.

Materials and Methods: Cross sectional study was done on 35 patients under dermatology department, detailed clinical history, examinations and routine investigations were recorded according to the case record form. Tzanck smear was prepared from blister fluid and stained by Leishman Giemsa stain for cytological examination to screen out presence of acantholytic cells. Histopathology and immunofluorescence study of two biopsies from lesional and perilesional skin were done under the department of pathology.

Results: Clinical, histopathological and direct immunofluorescence concordance varies considerably among the spectrum of diseases. The concordance was 81% in pemphigus vulgaris, 60% in pemphigus foliaceus, 50% in bullous pemphigoid and, 50% in dermatitis herpetiformis. We had two cases of linear IgA bullous disease and only one case of Pemphigoid gestationis. The percentages of concordance in these cases were 100%, for both. Out of 35 cases of autoimmune vesiculobullous diseases clinical, histopathological and immunological correlation was present in 26 cases (74.2%).

Keywords: Immunobullous, Tzanck smear, Direct immunofluorescence

INTRODUCTION

Autoimmune vesiculo bullous disorders represent a heterogenous group of dermatosis with variable manifestations. They have stranious impact on the patient and their family and have severe economic consequences for the family and healthcare service providers. The diseases have been investigated intensively in recent years [1]. The immunological diseases are diversified largely by their wide spectrum of clinical presentation, histopathology and immunoreactants deposition pattern. The immune-bullous diseases are characterized by pathogenic autoantibodies directed at

target antigens whose function is either cell to cell adhesion within the epidermis or adhesion of stratified squamous epithelium to dermis. These target antigens are components of desmosomes or the functional unit of the basement membrane zone known as the adhesion complex [1]. Histopathology and direct immunofluorescence are the most important techniques for investigations of patients with immunobullous diseases. Direct immunofluorescence technique most valuable for aiding the confirmation of diagnosis made by clinical and histopathological examination [2].

METHODS

An institution based observational study of clinical, histopathological and DIF features of autoimmuno vesiculobullous diseases was conducted on patients attending department of dermatology of tertiary care hospital over a period of one and half year. After obtaining institutional ethical committee clearance and written consent, all the patients attending out-patient department of dermatology were screened for presence of vesiculobullous lesions. In patients with vesiculobullous lesions, detailed history and clinical examination was done with particular reference to age, gender, Morphology of lesions, site of involvement and clinical tests such as Nikolsky's sign and Bulla spread sign. The patients with clinical features suggestive of immunobullous disorders were included in the study as these disorders show varied clinical manifestations. Histopathology and DIF in these disorders help in the final diagnosis to validate clinician's suscpicion. In all the patients, punch biopsy from the lesional skin preferably including intact vesicle was performed for histopathological study and another biopsy from perilesional normal looking skin was taken for DIF on same sitting under local anaesthesia. Of the two biopsies, one was sent in mitchel transport media for DIF and the other in 10% neutral buffered formalin for hematoxylin and eosin staining (H and E) and both submitted as properly labelled samples to the department of pathology. Alongside with taking biopsies, smear from blister fluid was made and stained to screen for acantholytic cells.

RESULTS

The present study was conducted over a period of 18 months from December 2016 to July 2018 in the OPD of Dermatology, Venereology and Leprosy and in the department of Pathology in a tertiary care hospital. In the present study, pemphigus vulgaris (Figure 1,A) constituted the most common vesiculobullous disorder constituting 62.85% (22 out of 35 cases), followed by pemphigus foliaceus constituting 11.4% of the cases. Bullous pemphigoid (Figure 1,B) and dermatitis herpetiformis constituted 11.4% and 5.7% of the cases respectively. Linear IgA disease was found in 5.7% of cases and pemphigoidgestationis constituted 2.9% of total cases as shown in Table 1.

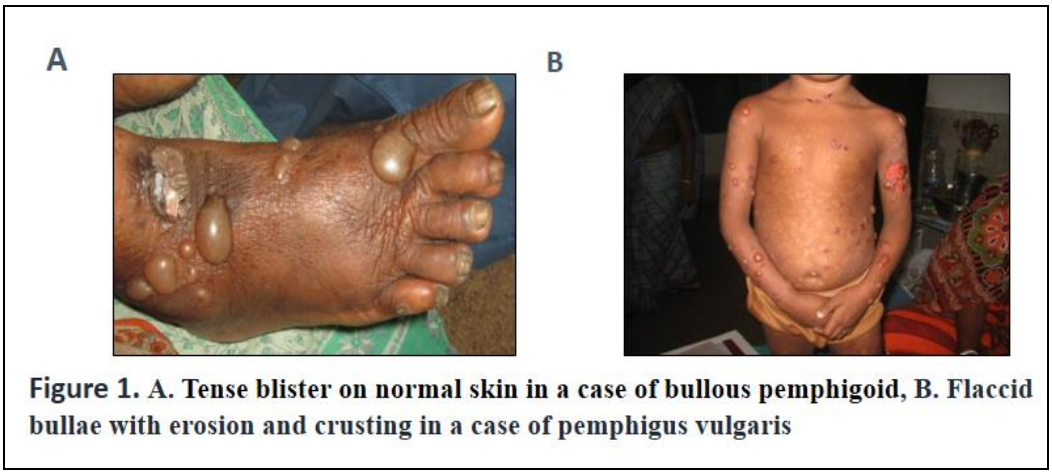


Figure 1. A. Tense blister on normal skin in a case of bullous pemphigoid, B. Flaccid bullae with erosion and crusting in a case of pemphigus vulgaris

TABLE 1: Distribution of Cases

Clinical diagnosis	Number of cases	Percentage
Pemphigus vulgaris(PV)	22	62.85%
Pemphigus foliaceus (PF)	4	11.4%
Bullous pemphgoid (BP)	4	11.4%
Dermatitis herpetiformis (DH)	2	5.7%
Linear IgA disease(LAD)	2	5.7%
Pemphiodgestationis(PG)	1	2.9%
Total	35	100%

The youngest patient was 07 years old and the oldest patient was 69 years old. The maximum numbers of cases were seen in the age group 40-49 years (37.14%) followed by 20-29 years (17.14%) and 50-59years (14.28%). The mean age of the study population was 42.25 years. The age distribution of various cases is shown in [Table 2]

TABLE 2: Distribution of Cases according to age

Age group	0-9 years	10-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	TOTAL
PV		1	3	3	10	4		22
PF		1	1		2			4
BP						1	3	4
DH			1		1			2
LAD	1			1				2
PG				1				1
TOTAL	1	2	6	5	13	5	3	35

PV=PEMPHIGUS VULGARIS, PF=PEMPHIGUS FOLIACEUS, BP=BULLOUS PEMPHIGOID, DH=DERMATITIS HERPETIFORMIS, LAD=LINEAR IGA BULLOUS DISEASE, PG=PEMPHIGOID GESTATIONIS

It was noticed that the most predominant lesions were fluid filled lesions (Vesicles/bullae) in all autoimmune vesiculobullous disorders. Erosions/crusting were present in 100% of cases of pemphigus, linear IgA disease and pemphigoid gestationis and 75% patients of bullous pemphigoid and 60% of dermatitis herpetiformis patients. Oral lesions were present in 79.07% of pemphigus patients and 50% patients of bullous pemphigoid. The commonest site of mucosal involvement was oral mucosa, which was involved in 79.07% of the cases of pemphigus vulgaris and 50% of the bullous pemphigoid cases. Out of all, 7 patients (32.56%) with pemphigus vulgaris also had involvement of the genital mucosa in addition to involvement of the oral mucosa. There was no mucosal involvement in pemphigus foliaceus, linear IgA bullous disease and pemphigoid gestationis. The mucosal involvement of various diseases is shown in Table 3.

TABLE 3: Distribution of cases according to mucosal involvement

Mucous membrane	PV	PF	BP	DH	LAD	PG
ORAL	16(79.07%)	0	2 (50%)	0	0	0
CONJUNCTIVAL	1(4.65%)	0	1 (50%)	0	0	0
NASAL	4 (16.28%)	0	1 (50%)	0	0	0
GENITAL	7 (32.56%)	0	1 (50%)	0	0	0

PV=PEMPHIGUS VULGARIS, PF=PEMPHIGUS FOLIACEUS, BP=BULLOUS PEMPHIGOID, DH=DERMATITIS HERPETIFORMIS, LAD=LINEAR IGA BULLOUS DISEASE, PG=PEMPHIGOID GESTATIONIS.

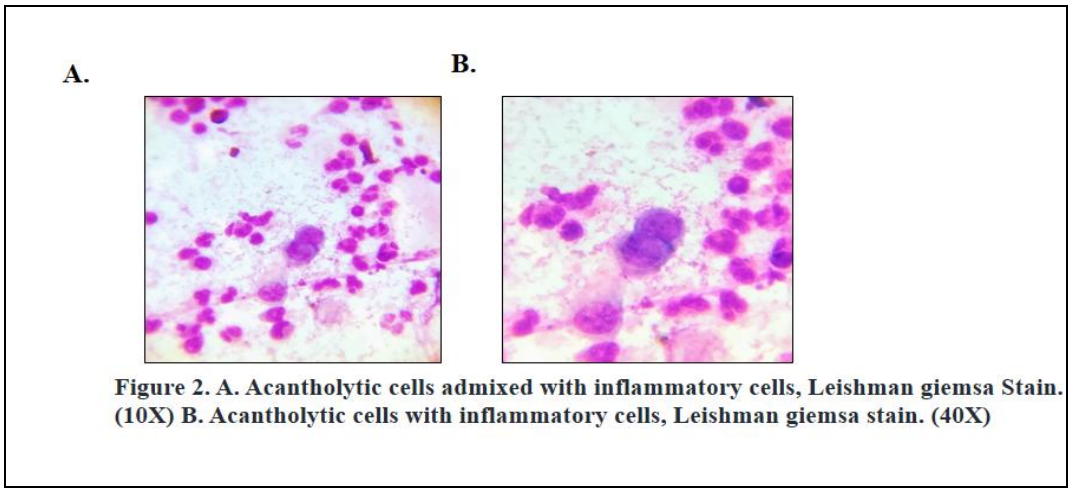


Figure 2. A. Acantholytic cells admixed with inflammatory cells, Leishman giemsa Stain. (10X) B. Acantholytic cells with inflammatory cells, Leishman giemsa stain. (40X)

Acantholytic cells were present on Tzanck smear in all the patients with pemphigus group of disorders. There was also presence of inflammatory cells, predominantly neutrophils in pemphigus vulgaris (53.49%) and pemphigus foliaceous (54.55%) as shown in Figure 2.

Tzanck smear showed absence of acantholytic cells and presence of inflammatory cells in all patients with bullous pemphigoid and linear IgA disease, with predominance of neutrophils (100%) in bullous pemphigoid and predominance of neutrophils (100%) and other cells (100%) in Linear IgA disease.

Histopathology showed presence of subcorneal blisters with acantholytic cells and few inflammatory cells in the epidermis in all patients with pemphigus foliaceus. Suprabasal cleft with acantholytic cells were present in all patients and inflammatory cells in the epidermis were present in patients with pemphigus vulgaris. Row of tombstone appearance was seen in majority of the cases of pemphigus vulgaris (58.14%) as shown in Figure 3.A, B. In epidermal changes, acantholysis was present in 90.07% of pemphigus vulgaris cases and in 100% of cases of pemphigus foliaceus. Other changes like villi were present in 41.86% and hyperkeratosis in 27.43% of cases of pemphigus vulgaris. Subepidermal cleft, and eosinophils in the epidermis were present in all bullous pemphigoid patients as shown in Figure 3C.

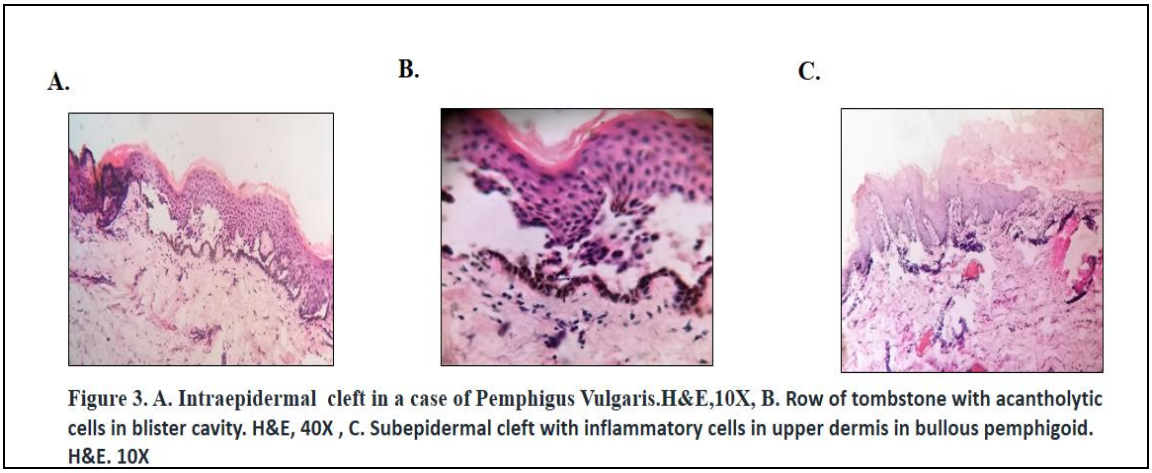


Figure 3. A. Intraepidermal cleft in a case of Pemphigus Vulgaris.H&E,10X, B. Row of tombstone with acantholytic cells in blister cavity. H&E, 40X , C. Subepidermal cleft with inflammatory cells in upper dermis in bullous pemphigoid. H&E. 10X

Subepidermal cleft and inflammatory cells in the epidermis was present in all patients with linear IgA disease. The epidermal changes of various diseases is shown in Table 4.

TABLE 4: Distribution of cases according to epidermal change

FINAL DIAGNOSIS	ROW OF TOMBSTONE	VILLI	HYPERKERATOSIS	DYSKERATOSIS	ACANTHOSIS	ACANTHOLYSIS
PV	13 (58.14%)	9(41.86%)	6 (27.43%)	0	3 (13.95%)	19 (90.07%)
PF	0	1(18.18%)	0	1 (18.18%)	1 (18.18%)	5 (100%)
BP	0	0	0	0	0	0
DH	0	0	0	0	0	0
LAD	0	0	0	0	0	0
PG	0	0	0	0	0	0

PV=PEMPHIGUS VULGARIS, PF=PEMPHIGUS FOLIACEUS, BP=BULLOUS PEMPHIGOID, DH=DERMATITIS HERPETIFORMIS, LAD=LINEAR IGA BULLOUS DISEASE, PG=PEMPHIGOID GESTATIONIS

The dermis showed inflammatory cell infiltrate in all the subtypes of autoimmune vesiculobullous disorders. Pemphigus vulgaris and pemphigus foliaceus showed predominance of neutrophils in 27.91% and 36.37% respectively. Linear IgA disease also showed predominance of neutrophils. A characteristic papillary micro abscess was present in 50% cases of dermatitis

herpetiformis. Predominantly eosinophilic infiltrate was present in 50% cases of bullous pemphigoid and in 100% cases of Pemphigoid gestationis. The dermal changes of various disease are shown in Table 5.

TABLE 5: Distribution of cases according to dermal changes

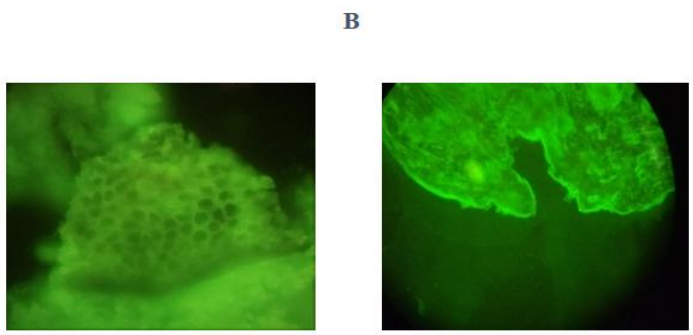
name of cases	Papillary edema	Papillary micro-abscess	Predominantly eosinophil	Predominantly neutrophil
PV	0	0	0	6 (27.91%)
PF	0	0	0	2 (36.37%)
BP	1 (25%)	0	2 (50%)	1 (25%)
DH	1 (50%)	1 (50%)	1 (50%)	1 (50%)
LAD	1 (50%)	0	0	2 (100%)
PG	0	0	1 (100%)	0

PV=PEMPHIGUS VULGARIS, PF=PEMPHIGUS FOLIACEUS, BP=BULLOUS PEMPHIGOID, DH=DERMATITIS HERPETIFORMIS, LAD=LINEAR IGA BULLOUS DISEASE, PG=PEMPHIGOID GESTATIONIS.

TABLE 6: DIF pattern of deposition of various antibodies.

		PV	PF	BP	DH	LAD	PG
IgG	Intercellular space(ICS)	17	3				
Deposition	Basement membrane zone(BMZ)			2	1		
IgA	ICS		1				
Deposition	BMZ			1	1	1	1
IgM	ICS	1					
Deposition	BMZ						
C3	ICS	9	3				
Deposition	BMZ			1		1	
Fibrinogen	ICS						
Deposition	BMZ			1			1

PV=PEMPHIGUS VULGARIS, PF=PEMPHIGUS FOLIACEUS, BP=BULLOUS PEMPHIGOID, DH=DERMATITIS HERPETIFORMIS, LAD=LINEAR IGA BULLOUS DISEASE, PG=PEMPHIGOID GESTATIONIS.



Figuire 4. A. Fishnet pattern of intercellular deposition of IgG in a case of Pemphigus Vulgaris, Direct Immunofluorescence, B. Linear pattern of deposition of C3 at Basement Membrane Zone in bullous pemphigoid, Direct Immnofluorescence

The type and pattern of autoantibodies deposition in the various types vesicobullous diseases is shown in Table 6. The wonderful fishnet pattern of IgG deposition in intercellular spaces and linear pattern of C3 deposition in subepidermal space in pemphigus vulgaris and bullous pemphigoid respectively is specifically shown in Figure 4A & 4B.

In our study the average concordance between clinical and histo-pathological diagnosis was 74.2% and discordance was 28.57% (Supplementary Table 3). Whereas, out of 26 cases of clinically diagnosed pemphigus, 23 were histo-pathologically confirmed so that concordance in intraepidermal bullous diseases is 88.46%. Whereas, In case of sub epidermal bullous disease (like bullous pemphigoid, dermatitis herpitiformis, linear IgA disease and pemphigoidgestationalis), chances of discordance is gradually increased. The concordance was highest in pemphigous vulgaris may be due to more number of cases. The respective concordance data between clinical diagnosis

with histopathological diagnosis, clinical diagnosis with direct immunofluorescence findings and histopathological diagnosis with direct immunofluorescence findings is nicely depicted in supplementary tables and figures. (Supplementary Table 1-2, Figure 1-2)

Table 1: Concordance between clinical diagnosis and histopathological findings

Histopathological Findings		
Clinical diagnosis	**Correct**	**Incorrect**
Intra Epidermal Bullous Disease (PV+PF)	23	3
Sub-epidermal Bullous Disease (BP+PH+LAD+PG)	2	7
	p= 0.0005 (significant, < .05)	

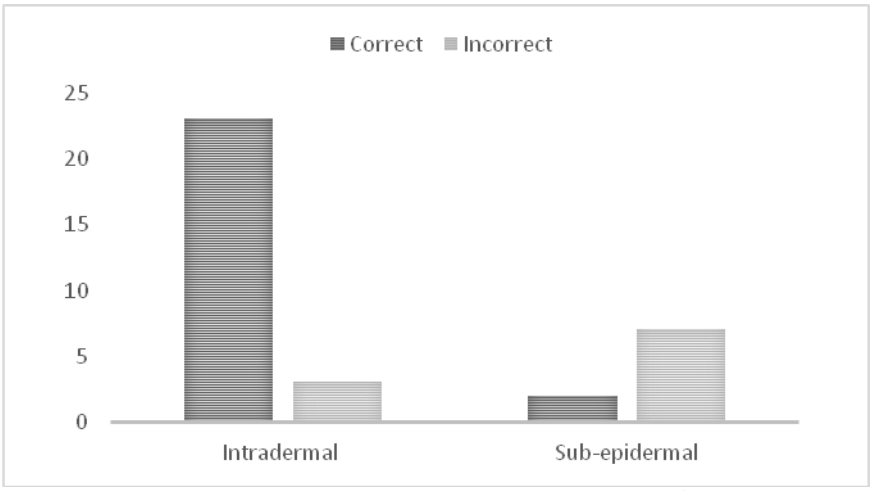


Figure 1: Concordance between clinical diagnosis and histopathological findings

Table 2:Concordance between clinical diagnosis and DIF findings

DIF Findings		
Clinical diagnosis	**Correct**	**Incorrect**
Intra Epidermal Bullous Disease (PV+PF)	24	2
Sub-epidermal Bullous Disease (BP+PH+LAD+PG)	2	7
p= 0.0002 (significant, < .05)		

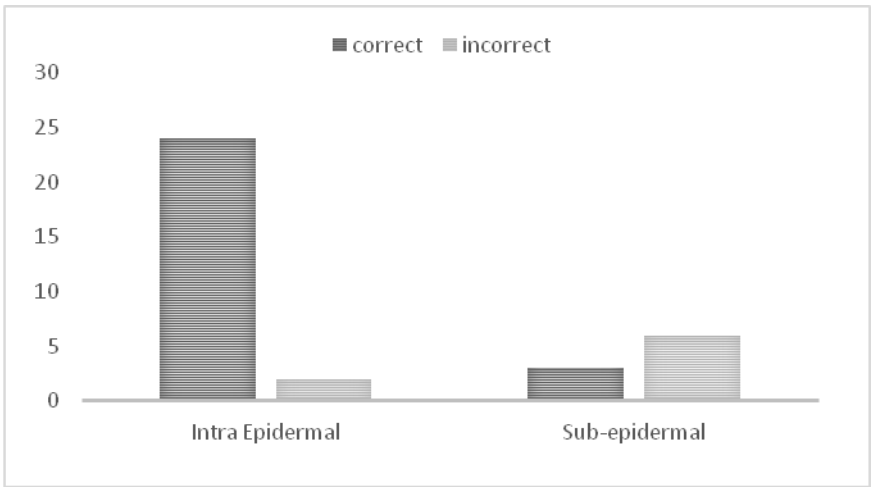


Figure 2:Concordance between clinical diagnosis and DIF findings

Table 3: Correlation between HPE and DIF

			DIF finding wrtHPE		**Total**
			CORRECT	**INCORRECT**	
HPE finding wrt CLINICAL	CORRECT	Count	26	3	29
		% within hpe finding wrt clinical	89.6%	10.4%	100.0%
	INCORRECT	Count	0	6	6
		% within hpe finding wrt clinical	0.0%	100.0%	100.0%
Total		Count	26	9	35
		% within hpe finding wrt clinical	74.2%	25.8%	100.0%

*Comment: The agreement between histo-pathological examination and direct immunofluorescence was more than 85% and this was found to be significant i.e. (p = 0.0001, *significant)*
NOTE: All the statistical calculation has been done by using "SPSS" – chi square analysis tool.

DISCUSSION

Regarding the distribution of vesiculobullous diseases, Pemphigus vulgaris was the most common vesiculobullous disorder constituting 62.85% (22 out of 35 cases) followed by pemphigus foliaceus constituting 11.4% (4 out of 35 cases) of the total cases. Bullous pemphigoid constituted 11.4% of the cases. The pattern of frequency of different types of autoimmune vesiculobullous disorders correlates closely to Arya et al study [3]. The incidence of Linear IgA disease was 5.7% in our study which correlates closely with study by Kanwar AJ et al [4]. Dermatitis herpetiformis was present in 5.7% of cases. Also there was a case of pemphigoidgestationis like in study of Solanki A et al [5]. The mean age of onset for pemphigus vulgaris was 42.25 years and M: F ratio was 1:1.5 in the present study which is almost similar to the results of Javidi Z et al study [6]. Females had a slightly higher incidence of pemphigus vulgaris and pemphigus foliaceous compared to males in the present study. All of these studies Abobaker et al [7], Javidi Z et al [6], Micali G et al [8] and Deepti SP et al [9] also show similar results. The age of the patients ranged from 7 to 69 years. 24 (68.57%) cases were in the age group 21-60 years, which is in agreement with the studies done by Handa F et al [10] and Arya S et al [3]. Oral mucosa was the most common site of mucosal involvement in pemphigus vulgaris in the present study (16 out of 22 cases) which is similar to Micali G et al [8] study. Tzanck smear observations showed acantholytic cells in 100% of the cases. This is in concordance with various studies conducted by MM Huda et al [11], Leena JB et al [12] and Kambil SM et al [13]. The main inflammatory infiltrate comprising of neutrophils was seen in 53.49% cases in the present study as compared to 58.8% cases in Deepti SP et al [9]. The main histopathological features observed in cases of pemphigus vulgaris showed acantholysis in 90.07% cases which closely relates to the finding in Arya SR et al [3] and ArundhatiS et al [14] study and suprabasal bulla was present in 74.42% which was less than above of the studies. "Row of tombstone" appearance of basal cells is another histological feature favouring the diagnosis of pemphigus vulgaris which is present in 58.14% of the cases in the present study which is slightly higher as compared to studies by Arya SR et al [3] (41.8%), Leena JB et al [12] (36.34%) and ArundhatiS et al [14] (41.8%) but Deepti SP et al[9] showed this in 70.5% cases higher than the present study. Pemphigus foliaceus constituted 14.3% of the total cases which correlates closely with the findings of the study by Fernandez J et al [15]. The salient histopathological features of pemphigus foliaceous observed in our study were acantholysis (100%) and subcorneal bulla (81.82%), identical to that observed by Arundhatiet al [14]. Bullous pemphigoid constituted only 11.4% of the total cases of autoimmune vesiculobullous disorders, which is almost similar to the finding of study by Arundhati S et al [14]. The mean age of onset among the adult patients of bullous pemphigoid was 62.5 years in the present study which is similar to study by Nanda A et al [16]. There was a female predominance in the present study with a male to female ratio (M: F) of 1: 1.5, which is again similar to the observations made in studies Nanda et al [16], Bernard P et al [17], Wong SN et al [18], Arundhati SP et al [14] and Deepti et al [9]. Involvement of oral mucosa was seen in 50% of the cases in the present study, which is higher than that reported by Deepti et al[9]and Budimir J et al [19]. Histopathological examination revealed subepidermal bulla in all the cases in the present study. Predominant eosinophilic infiltration (50%) in the dermis was more common than predominant neutrophilic infiltration (25%) in the present study which correlates with the studies done by Nishioka et al [20], Arundhati et al [14] and Deepti SP et al [9]. Papillary edema was present in 15.15% cases in the present study which is less as compared to 29.41% observed in ArundhatiS et al [14] and more than 7.8%

observed in Deepti SP et al [9]. There were 2 cases of dermatitis herpetiformis which constituted 5.7% of total cases in our study. These were from age group 20- 50 years of with female preponderance with M:F ratio 1:4 which was different from earlier studies. Subepidermal bulla were present all the cases showing papillary microabscesses and neutrophilic and eosinophilic infiltrates as in Deepti SP et al [9] and BanuLebi et al [21]. The total clinicohistopathological concordance in our study was 82.9% which was near to Solanki et al [5] (85%). It was more than ArundhatiS et al [14] 68.85% and less than Kambil et al [13] (88.88%). The concordance in Pemphigus vulgaris was 85.7% which comparable to Solanki et al [5]. The concordance of Bullous pemphigoid was also similar to Solanki et al [5]. The concordance was lowest in Dermatitis herpetiformis 50% which is near to Solanki et al [5]. Total clinicohistopathological correlation was 74.2% as compared to 60% in case Solanki et al [5]. The tabular comparison for the above is mentioned in displayed in [Table 7]

TABLE 7 : Comparison of results between various studies

No	Studies	Year	PV	PF	BP	DH	LAD	PG
1	Arundhati S et al	2013	72.22%	66.6%		0%		100%
2	Kambil SM et al	2014	100%	_	100%	_	66.6%	_
3	Solanki A et al	2015	100%	100%	75%	50%		100%
4	Present study	2018	85.7%	80%	75%	60%	100%	100%

PV=PEMPHIGUS VULGARIS, PF=PEMPHIGUS FOLIACEUS, BP=BULLOUS PEMPHIGOID, DH=DERMATITIS HERPETIFORMIS, LAD=LINEAR IGA BULLOUS DISEASE, PG=PEMPHIGOID GESTATIONIS.

Limitations

The number of patients was less and salt split technique for DIF and indirect immunofluorescence were not used.

CONCLUSION

Pemphigus vulgaris constituted the most common subtype of autoimmune vesiculobullous disorder in this study, followed by pemphigus foliaceus. Pemphigus group of diseases were most common in the 5th decade while bullous pemphigoid was most common in the 6 decade. Histopathological examination showed features typical of each subtype of autoimmune vesiculobullous disorder. Clinical examination is the initial step in making a diagnosis of autoimmune vesiculobullous disorders. Next step are various bed side tests Nikolsky's sign, Bulla spread sign and cytology test like Tzanck smear. Histopathological features were conclusive in diagnosis of most of autoimmune vesiculobullous disorders. The subtle light microscopic features apart from classical diagnostic features help in diagnosis of difficult cases. Direct immunofluorescence microscopic study was done in few cases but it is required in diagnosis of Linear IgA bullous Disease and Dermatitis Herpetiformis. However, it is not a substitute for histopathology, but rather complementary to it.

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Conflict of Interest- Authors have no conflict of interest

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