ISSN 2515-8260 Volume 09, Issue 04, 2022

Clinicopathological Study of Non Infectious Vesiculobullous lesions of Skin and Mucous Membranes"

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ABSTRACT

INTRODUCTION: The vesiculobullous lesions of the skin are a group of heterogeneous diseases characterized by the formation of vesicles/blister and are associated with variable clinical manifestations and have multiple causes.

The immunobullous disease are mainly a consequence of pathogenic autoantibodies which target those antigens which mainly function to maintain either cell to cell adhesion within the epidermis or adhesion of stratified squamous epithelium to dermis or mesenchyme.

MATERIALS AND METHODS: The study was prospective and observational case series carried out in the Department of Pathology, SBKS MI&RC, Sumandeep Vidyapeeth, Piparia, Vadodara in the time period of January 2019 to July 2020. In the study 30 punch biopsies of patients taken from their cutaneous or mucocutaneus lesions were fixed, processed and stained stained with Hematoxylin and Eosin and examined light microscopy.

RESULT: Total 30 cases as per inclusion criteria were included in present study. Peak incidence is seen in the age group of 40-50 years with a slight female prepondarance. The most common morphological presentation was in the form of blister/vesicle. Pemphigus vulgaris is the most common lesion(47%) encountered followed by Pemphigus Foliaceous in 3 (10%) cases and Bullous Pemphigoid in 3 (10%) cases, Dariers Disease and Hailey Hailey Disease showed 2 (6.6%) cases each, a single case each of Epidermolysis Bullosa Simplex, Dermatitis Herpetiformis, Irritant Contact Dermatitis and Pemphigus Herpetiformis.

CONCLUSIONS: The highest incidence of vesiculobullous disorders is seen in the age age group of 40- 50 years and M:F ratio being 1:1.14. Pemphigus Vulgaris is the most prevalent disorder. On light microscopy, the most common site of blister formation is suprabasal. The diagnosis could be made on the basis of clinical features or histopathological features alone (70%) or their correlation in 90% of the cases.

KEY WORDS: Bullous Pemphigoid, Light microscopy, Pemphigus Foliaceous, Pemphigus Vulgaris, Punch biopsy, Vesiculobullous lesions.

ISSN 2515-8260 Volume 09, Issue 04, 2022

INTRODUCTION

The vesiculobullous lesions of the skin are an uncommon group of heterogeneous diseases characterized by the formation of vesicles/blister and are associated with variable clinical manifestations and can cause significant morbidity and mortality.[1]

There can be various causes leading to these blistering erosions over the body which include inflammatory, infectious, autoimmune, drug induced as well as genetic of which noninfectious or autoimmune have been included in this study.[2] In these disorders, autoantibodies target against those antigens which function to maintain either cell to cell adhesion within the epidermis or adhesion of stratified squamous epithelium to dermis or mesenchyme.[1]

These disorders are usually diagnosed on routine/ conventional histopathology in conjunction with the clinical correlation/presentation; however, confirmation still depends on direct and indirect immunofluorescence.[1]

On reviewing the co relation of the clinical with the histopathological features and with immunofluorescence findings it was observed that clinical features corelated with histopathological diagnosis in 87.1% cases in study conducted by (Damle P et al), 73% with histopathological diagnosis and 60% with immunofluorescence findings in study done by (Viratktamath C et al), 70% with histopathological and 77% immunofluorescence findings in study by (Minz et al and 91.3%) with histopathological and 92.6% with immunofluorescence findings in study by (Mittal et al.)

Thus, the correlation of the histological/morphological features with the clinical features is an effective method for the diagnosis of bullous disorders.

Now considering the value of morphological findings in the diagnosis of vesiculobullous disorders as confirmed by immunofluorescence, the concordance rate was found to be 77.77% and 85.37% in study conducted by (Anupama K et al and Singh K et al), of 94.4% and 96% with final diagnosis in case of pemphigus group of bullous disorders in studies by (Buch et al and Basu K et al) respectively.

In the study conducted by (Viratktamath C et al), it was seen that 18.6% of cases which could not be diagnosed by immunofluorescence were diagnosed by histopathological features. Hence morphological features even without confirmation with immunofluorescence can be considered effective to be effective in diagnosing these disorders.

The present study was undertaken based on the observations of the various studies in the literature, with the aim/objective of studying the correlation between the clinical features and the histological feature in the diagnosis of Vesiculobullous lesions of the Skin.

MATERIALS AND METHODS

The present study was conducted at Dhiraj General Hospital & Shrimati B. K. Shah Medical Institute & Research centre, Sumandeep Vidyapeeth.

This study was a prospective observational analysis carried out after taking approval from the local ethical committee of the institute SVIEC on patients that presented with vesicular or bullous skin/mucosal lesion and whose punch biopsies were taken and received in the histopathology laboratory over a period of one and half years from January 2019 to June 2020.

ISSN 2515-8260 Volume 09, Issue 04, 2022

AIMS

To study the spectrum of vesiculobullous lesions, received at Dhiraj Hospital through punch biopsies and co relate them with clinical findings.

OBJECTIVES

- To describe the Histopathological features of various vesiculobullous lesions of skin.
- To assess various types of vesiculobullous lesions in relation to morphology and it's demographic pattern in this part of our country.
- To do clinicopathological correlation and give diagnosis based on it.

Punch biopsies of total 37 patients with vesiculobullous disease were included in this study.

INCLUSION CRITERIA:

All the biopsies of vesiculobullous lesions received by the Department of Pathology, SBKS MIRC will be included.

EXCLUSION CRITERIA:

- Autolysed specimen
- Inadequate biopsies(<3mm)
- Without clinical history, examination and diagnosis

Out of 37 biopsies received, 7 biopsies were rejected due to the given reasons due to the exclusion criteria mentioned above.

The clinical data of the remaining 30 patients i.e, name, age, sex, signs and symptoms, past history and family history were recorded either in the case report form or by personal communication with the patients or resident doctors.

The biopsies which were received in 10% formalin, fixed for 24 hours then processed in an automated tissue processor, then 4-5 micron thin sections were cut and placed on a slide and lastly stained with routine H&E stains (manual method).

Then, all the slides were examined under light microscope in scanner(4x), low(10x) and high(40x) magnification.

The biopsies were evaluated morphologically and then catogerised into subclasses based on their morphological picture.

Then the histopathological diagnosis was made by correlating morphological features with the clinical data.

RESULTS & ANALYSIS

The present study includes 30 cases of vesiculobullous disorders who presented in Dhiraj hospital and whose biopsies were received in pathology department, Piparia, Waghodiya from December 2018 to May 2020. This is prospective observational type of study.

The total number of skin biopsies received in the histopathology department in that time period was 203 of which vesiculobullous disorders constituted 37 biopsies that is 18.2%.

TABLE 1: Distribution of vesiculobullous disorders

Types of Disorders	No of cases out of 30	Percentage
Bullous Pemphigoid	3	10.00%
Dariers Disease	2	6.67%
Dermatitis Herpetiformis	1	3.33%
Epidermolysis Bullosa Simplex	1	3.33%
Hailey Hailey Disease	2	6.67%
Irritant Contact Dermatitis	1	3.33%
No bulla seen	1	3.33%
Pemphigus	1	3.33%
Pemphigus Foliaceous	3	10.00%
Pemphigus Herpetiformis	1	3.33%
Pemphigus Vulgaris	14	46.67%
Grand Total	**30**	**100.00%**

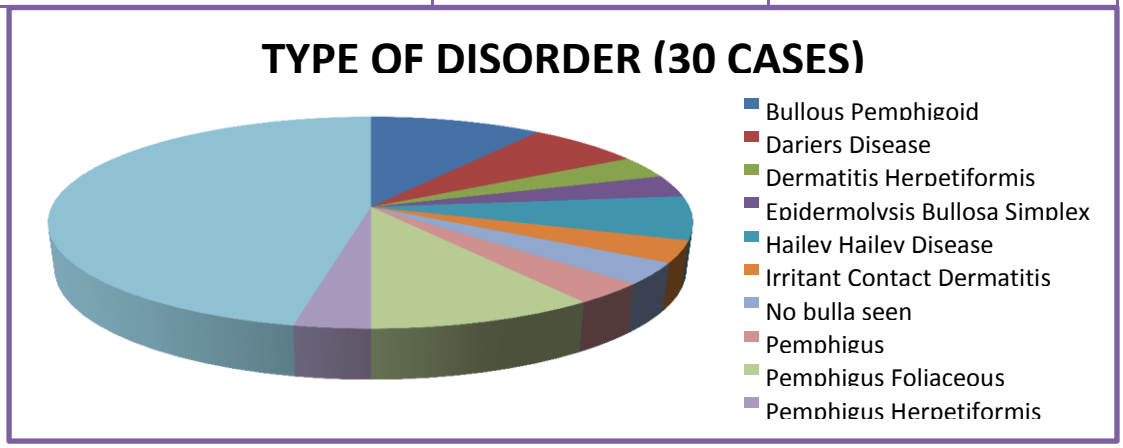
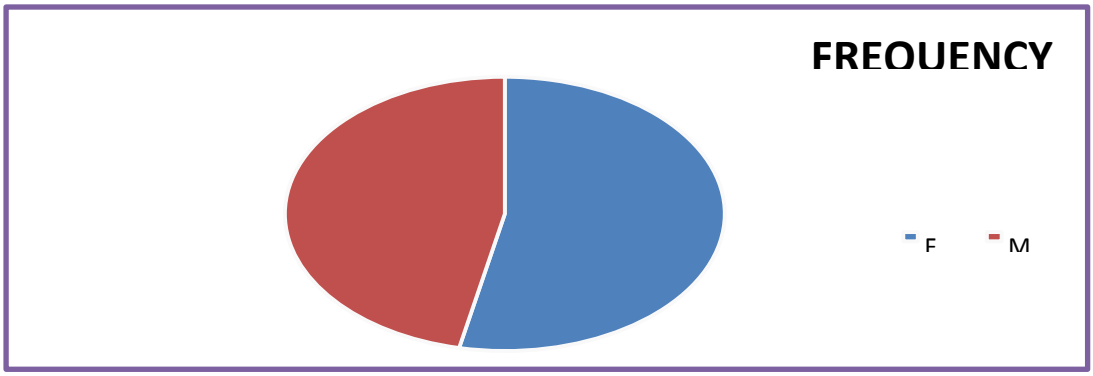


TABLE 2: Sex distribution

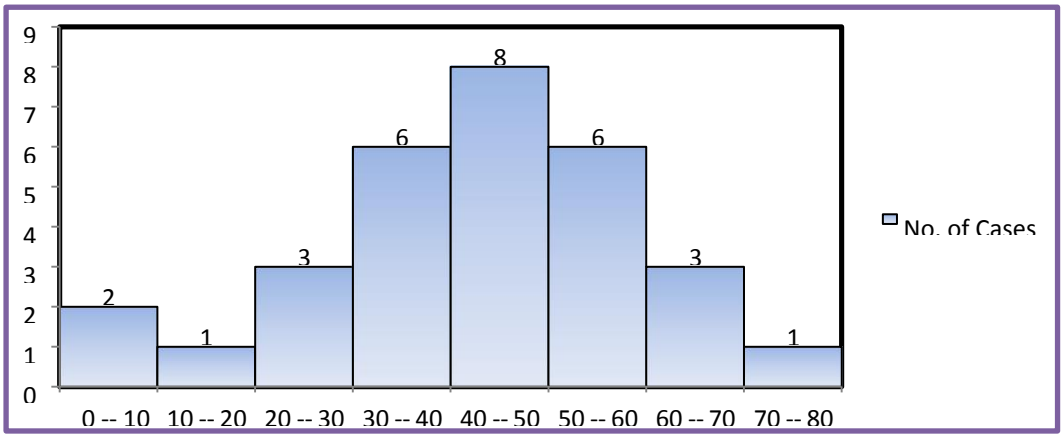
SEX	FREQUENCY	PERCENTAGE
F	16	51.18%
M	14	48.82%
Grand Total	**30**	**100.00%**



The study of 30 cases of vesiculobullous lesions comprised of /included 16 female and 14 males with a sex ratio of M:F:: 1:1.14.

TABLE 3: Age wise distribution of the cases.

Age (yrs.)	No. of Cases	% of Cases
0 -- 10	2	6.67%
10 -- 20	1	3.33%
20 -- 30	3	10.00%
30 -- 40	6	20.00%
40 -- 50	8	26.67%
50 -- 60	6	20.00%
60 -- 70	3	10.00%
70 – 80	1	3.33%
Total	30	100.00%



Age of cases in years

TABLE 4: Age distribution in specific disorders

Disorder	0-9	10-19	20-29	30-39	40-49	50-59	60-69	Grand Total
Bullous pemphigoid (n=3)				1		1	1	3
Darriers disease(n=2)			1	1				2
Dermatitis herpetiformis	1							1

(n=1)								
Epidermolysis Bullosa Simplex (n=1)	1							1
Hailey Hailey Disease(n=2)						2		2
Irritant contact dermatits(n=1)					1			1
Pemphigus herpeiformis(n=1)						1		1
Pemphigus foliaceous(n=3)			1		1		1	3
Pemphigus vulgaris(n=14)		1	1	3	6	1	2	14
Grand Total	**2**	**1**	**3**	**5**	**8**	**4**	**4**	**28**

Pemphigus vulgaris showed the maximum prevalence in the age group of 40-49 years, followed by 30-39 years. The age distribution in case of Pemphigus foliaceous was 1 case each seen in 20-29, 40-49and 60-69 years group respectively. The three cases of Bullous pemphigoid, were seen 1 case each in 30-39, 50-59and 60-69 years age group respectively.

TABLE 5: Symptoms in specific disorders

Disorder	**Prutitus**	**Pain**	**Others**
Bullous pemphigoid (n=3)	2(66.67%)	-	-
Darriers disease(n=2)	1(50%)	-	
Dermatitis herpetiformis (n=1)	1(100%)	1(100%)	Photosensitivity-1 (100%)
Epidermolysis Bullosa Simplex(n=1)	1(100%)	1(100%)	-
Hailey Hailey Disease (n=2)	-	-	-
Irritant contact dermatitis (n=1)	-	-	-
Pemphigus herpetiformis (n=1)	1(100%)	1(100%)	-
Pemphigus foliaceous (n=3)	2(66.67%)	-	Burning sensation-1(33%)
Pemphigus vulgaris (n=14)	8(57.14%)	8(57.14%)	Burning sensation-3(21.4%) Difficulty in swallowing-3 (21.4%) Photosensitivity-1(7.14%)

The main symptoms noticed in **Pemphigus Vulgaris** were pain (57.14%) and pruritus (57.14%), followed by burning sensation (21.4%) and difficulty in swallowing (21.4%) due to involvement of oral mucosa.

In the case of **Pemphigus Foliaceous** also pruritus (66.67%) was the main presenting symptom followed by burning sensation (33.3%).
In **Bullous Pemphigoid** also pruritus (66.67%) was the main presenting symptom.
The lesions in case of both **Dermatitis Herpetiformis and Epidermolysis Bullosa Simplex** were painful as well as pruritic.
In the single case of Irritant Contact Dermatitis as well as the two cases of Hailey Hailey Disease in the study no symptoms were reported.

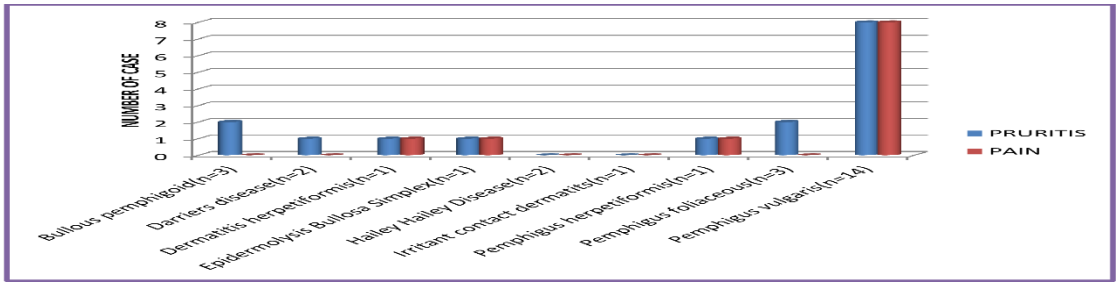


TABLE 6: Presentation of lesions in specific disorders

Disorder	**Primary lesion presentation**	**Erythematous**	**Eroded/Crusted**	**Blister type**		**Nikolsky's sign**
				Tense	**Flaccid**	**Positve**
Bullous pemphigoid (n=3)	Bulla-3(100%)	1(33.3%)	2(66.67%)	2 (66.67%)	1 (33.3%)	-
Darriers disease (n=2)	Papules-2 (100%)	2 (100%)	-	-	-	-
Dermatitis herpetiformis (n=1)	Bulla-1 (100%)	1 (100%)	1 (100%)	-	-	-
Epidermolysis Bullosa Simplex (n=1)	Bulla-1 (100%)	-	-	-	-	-
Hailey Hailey Disease (n=2)	Plaques-1 (50%) Vesicles-1 (50%)	1 (50%)	1 (50%)	-	-	-
Irritant contact dermatits(n=1)	Vesicle-1 (100%)	1 (100%)	-	-	-	-
Pemphigus herpetiformis(n=1)	Papule-1 (100%)	1 (100%)	-	-	-	-
Pemphigus foliaceous(n=3)	Bulla-2 (66.7%) Vesicles-1 (33.3%)	1 (33.3%)	2(66.7%)	-	1(33.3%)	2(66.67%)

Pemphigus vulgaris(n=14)	Bulla-10 (71.4%) Plaques-1 (7.14%) Vesicles-2 (14.28%)	10 (71.4%)	11 (78.57%)	5 (35.71%)	7 (50%)	9 (64.28%)

Presentation in the form of **bulla** was seen in all 3 (100%) cases of bullous pemphigoid, 1(100%) case of dermatitis herpetiformis, 1 (100%) case of epidermolysis bullosa simplex, 2 (66.67%) cases of pemphigus foliaceous and 10 (71.4%) cases of pemphigus vulgaris.

Vesicles were seen in 1 (100%) case of Hailey Hailey disease, 1 (100%) case of irritant contact dermatitis, 1(33.3%) case of pemphigus foliaceous and 2 (14.28%) cases of pemphigus vulgaris

Papules were seen in both the cases of Darrier's disease and 1 case of pemphigus herpetiformis.

Plaques were seen in 1 case of Hailey Hailey disease and 1 case of pemphigus vulgaris.

Erythematous lesions were seen in 10 (71.4%) cases of pemphigus vulgaris, 1 (33.3%) case of pemphigus foliaceous and bullous pemphigoid, 1(50%) case of Hailey Hailey disease, both cases of Darrier's disease and in 1 (100%) case of irritant contact dermatitis, pemphigus and dermatitis herpetiformis.

Erosions or Crustations or both were noted in 11 (78%) cases of pemphigus vulgaris, 2 (66.7%) out of 3 cases of pemphigus foliaceous and bullous pemphigoid, 1 case of Hailey Hailey disease and in dermatitis herpetiformis.

Tense bullae were seen in 2 (66.7%) cases of bullous pemphoid and 5 (35.71%) cases of pemphigus vulgaris Flaccid bulla were seen in 7 (50%) cases of pemphigus vulgaris 1 (33.3%) case of pemphigus foliaceous and bullous pemhigoid

Nikolsky's sign was positive in 9 (64.8%) cases of pemphigus vulgaris and 2 (66.67%) cases of pemphigus foliaceous

TABLE 7: Site wise distribution in specific disorders

FINAL DIAGNOSIS	**Site or part of body involved**							
	Oral mucosa	Scalp	Face	Neck	Upper extremity	Lower Extremity	Trunk	Flexural aspects
Pemphigus Vulgaris	14	8	8	5	9	7	6	1
Pemphigus foliaceous	0	1	1	0	2	3	3	0
Darrier's disease	0	0	1	2	1	0	2	0
Hailey Hailey disease	0	0	0	1	0	0	0	2

Irritant Contact Dermatitis	0	0	1	0	0	0	0	0
Dermatitis Herpetiformis	0	0	0	0	1	1	1	0
Bullous Pemphigoid	0	0	1	0	1	3	2	0
Pemphigus herpetiformis	0	1	0	0	1	1	1	0
Epidermolysis Bullosa Simplex	0	0	0	0	1	1	1	0

The most commonly involved sites in the study included oral mucosa, trunk, lower extremity, upper extremity, scalp, face, and neck.

Mucosal involvement was present in 100% (14/14) cases in Pemphigus Vulgaris.

Table 8&9: Plane of separation in vesiculobullous disorders

Site of Blister Formation	**No. of Cases**	**% of Cases**
Sub epidermal	04	13.3%
Intra epidermal	23	76.6%
Total	27	89.9%

Type of Intra epidermal Blister	**No. of Cases**	**% of Cases**
Suprabasal	13	43.3%
Midepidermal	02	6.67%
Suprabasal+Midepidermal	02	6.67%
Subcorneal	04	13.3%
Subspinous	02	6.67%
Total	23	89.9%

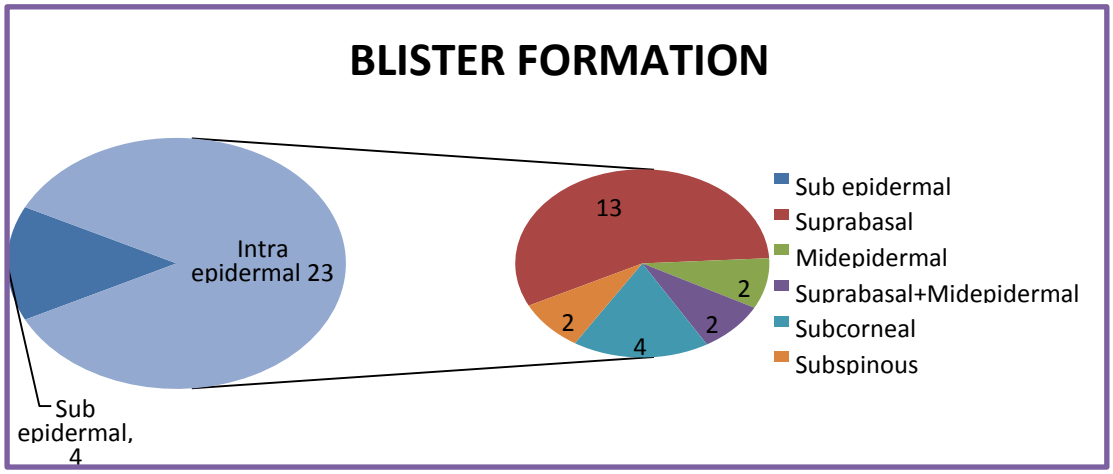


TABLE 10: Plane of Separation in specific disorders

Disorder	Intraepidermal	Subepidermal	No bulla
Bullous pemphigoid (n=3)	-	3 (100%)	-
Darriers disease (n=2)	Suprabasal-1 (50%) Midepidermal-1 (50%)	-	
Dermatitis herpetiformis (n=1)	-	-	1 (100%)
Epidermolysis Bullosa Simplex (n=1)	-	1 (100%)	-
Hailey Hailey Disease(n=2)	Subspinous-2 (100%)	-	-
Irritant contact dermatitis(n=1)	-	-	-
Pemphigus herpetiformis (n=1)	Subcorneal-1 (100%)	-	-
Pemphigus foliaceous (n=3)	Suborneal-3(100%)	-	-
Pemphigus vulgaris (n=14)	Suprabasal-12 (85.7%) Suprabasal with Midepidermal-2 (14.2%)	-	-

The most common plane of cleft formation was **suprabasal** in 43.3% of the total 30 cases, followed by the sub-corneal plane -13.3%. The remaining cases showed cleft formation in Mid-epidermal , Supra-basal +Mid-epidermal and Subspinous locations in equal proportion.

Subepidermal cleft were seen only in the cases of **Bullous pemphigoid and** Epidermolysis Bullosa Simplex.

The solitary case of **Dermatitis herpetiformis** was the only case in the study in which a neither Intra-epidermal nor a Subepidermal cleft was present.

Among the acantholytic disorders, most of the cases of Pemphigus vulgaris demonstrated Suprabasal (14) cleft formation along with 2 cases showing suprabasal+ midepidermal clefting, all the cases pemphigus foliaceous (3) showed subcorneal cleft formation, Darrier's disease showed suprabasal plane of separation in one case and midepidermal in another case whereas Hailey Hailey disease showed subspinous plane of separation in both cases.

TABLE 11: Epidermal changes in specific disorders

DISORDER	**EPIDERMALCHANGES**						
	Row of tomb stone	**Acantholytic cells**	**Spongiosis**	**Dyskeratosis**	**Papillomatosis**	**Parakeratosis**	**Hyperkeratosis**

Pemphigus Vulgaris(n=14)	**12**	**12**	1	1	1	1	2
Pemphigus foliaceous(n=3)	0	0	0	0	0	0	0
Darrier's disease(n=2)	0	1	0	**2**	1	1	1
Hailey Hailey disease(n=2)	0	**2**	0	0	0	1	2
Irritant Contact Dermatitis(n=1)	0	0	**1**	0	0	0	0
Dermatitis Herpetiformis(n=1)	0	0	0	0	0	0	0
Bullous Pemphigoid(n=3)	0	0	0	0	0	0	**1**
Pemphigus herpetiformis(n=1)	0	0	0	0	0	0	0

TABLE 12: Type of inflammatory infiltrate in blister cavity in specific disorders

DISORDER	**Type of inflammatory infiltrate**					
	Neutrophils	Lymphocytes	Eosinophils	Plasma cells	Mixed	Not seen
Pemphigus Vulgaris (n=14)	**9 (64.28%)**	6 (42.8%)	1 (7.14%)	0	1 (7.14%)	4 (28.5%)
Pemphigus foliaceous (n=3)	2(66.7%)	**3(100%)**	0	0	0	0
Darrier's disease (n=2)	0	1(50%)	0	0	0	1 (50%)
Hailey Hailey disease (n=2)	0	1(50%)	0	0	0	1 (50%)
Irritant Contact Dermatitis(n=1)	1 (100%)	1 (100%)	1 (100%)	0	0	0
Dermatitis Herpetiformis (n=1)	1(100%)	0	1(100%)	0	0	0
Bullous Pemphigoid (n=3)	**2(66.7%)**	**2(66.67%)**	**2(66.7%)**	**1(33.3%)**	**1(33.3%)**	**1(33.3%)**
Pemphigus herpetiformis (n=1)	1(100%)	0	1(100%)	0	0	0

TABLE 13: Clinicopathological correlation of vesiculobullous disorders

Consistent with clinical diagnosis	No. of Cases	% of Cases
YES	22	73.3%
NO	8	26.6%
Total	30	100.00%

Out of 30 biopsies studied, histopathological diagnosis in 22 biopsies was consistent with the clinical diagnosis.

The clinical diagnosis which was deduced on the basis of the symptoms, signs and on the examination of the lesion by the clinician was seen to be **correlating with the the histopathological features of the lesion in 22 that is 73% of cases.**

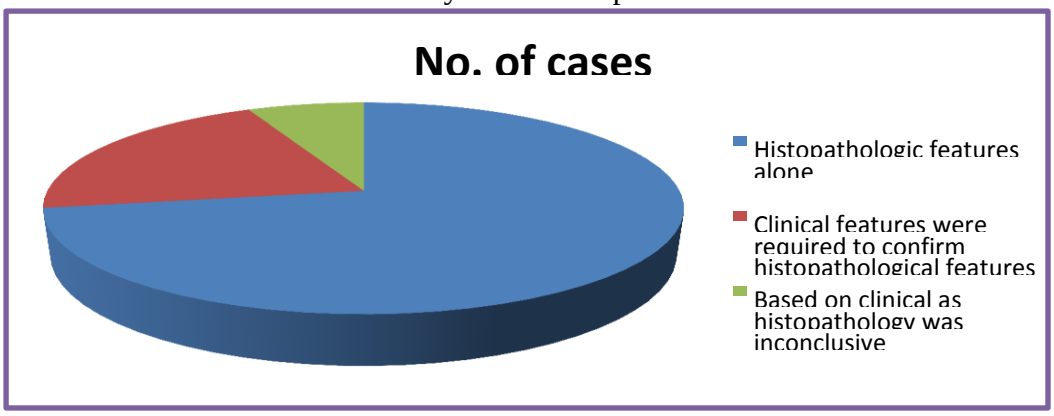
TABLE 14: Accuracy of clinicopathological evaluation in diagnosis of vesiculobullous disorders

Diagnosis was made on	No. of Cases	% of Cases
Histopathologic features alone	21	70%
Clinical features were required to confirm histopathological features	6	20%
Based mainly on clinical as histopathology was inconclusive	2	6.67%

In 70% of the cases the final diagnosis was arrived at independently based on Histopathological features alone; however, when combined with the clinical diagnosis the accuracy rate improved by 20% upto 90%.

In 6.67% cases though the histopathology was inconclusive clinical data was mainly used to diagnose the cases.

In one of the cases included in the study the final diagnosis could not be made because the clinical finding/features were inconclusive and the histopathological features were not characteristic any lesion/nonspecific.



DISCUSSION

The present study includes 30 cases of vesiculobullous disorders who presented clinically with vesicles or bulla formation and were biopsied for histopathological diagnosis. All specimen were subjected to histopathological examination and reported on the basis of their clinical and morphological features.

Singh K et al in the year 2016 published a research article in which he studied 41 biopsy specimen of vesiculobullous disorders **correlated their clinical and histopathological findings to give the diagnosis and used immunofluorescence in those cases where histopathological features were not diagnostic.**

Mittal H et al in the year 2017 published a research article in which he studied 110 biopsy specimen of vesiculobullous disorders which were first evaluated clinically and differential diagnosis were made instead of single diagnosis, then biopsy specimen were collected from two sites one from the lesion or oral mucosa for light microscopy and another from perilesional area or oral mucosa and were subjected to immunofluorescence microscopy**. Thus all the biopsies were studied on the basis of their clinical features, primarily diagnosed based on their histopathological features and confirmed by immunofluorescence.**

Chanabasayya et al in the year 2017 published a research article in which he studied 91 biopsy specimens of **immunobullous disorders.** Medical records of patients with clinically suspicion of immunobullous disorders subjected to two biopsies one from lesional area for light microscopy and one from perilesional areas for immunofluorescence. **Thus, all the biopsies were studied on the basis of their clinical features, diagnosed based on their histopathological features and confirmed by immunofluorescence.**

Deepthi S et al in the year 2015 published an article in which she studied 50 cases which had clinical history of vesiculobullous disorders and which were biopsied and subjected to both light microscopic examination and immunofluorescence microscopy.

Anupama R et al in the year 2018 published an article in which 100 clinically diagnosed cases of non-infectious vesiculobullous disorders were taken and subjected to light microscopy for histopathological diagnosis and to immunofluorescence to know the patterns and to correlate it with histopathological diagnosis.

Recently in this year, Deshpande A et al published a research article in which he studied 42 cases of vesiculobullous disorders which were **diagnosed on the basis of their clinical and histopathological correlation and this diagnosis was later confirmed using immunofluorescence microscopy.**

Various parameters are discussed as below:

1. Age and sex distribution:

Table 15: Comparison age and sex distribution of Vesiculobullous disorders
Age at presentation and sex distribution:

Study	Most common age group (in years)	Sex distribution M:F ratio
Chanabasayya et al (2017) (n=91) [3]	40-70	1.2:1
Singh K et al (2016) (n=41) [4]	40-49	1:1.4
Mittal H et al (2017) (n=110) [5]	41-50	1:1.15
Deepthi S et al (2015) (n=50) [6]	40-49	1:1.5
Present study(n=30)	40-50	1:1.14

As in evident from the above table that the most of the studies have reported a similar peak incidence in the age group of 40-50 years except for Chanabasayya et al (2017) in their study of 91 cases , reported a wider and an extended range of peak age group of 40-70 years, partly overlaping with most other studies.

In the present study, the Male: Female ratio was found to be 1:1.14 with a female preponderance was observed, which is similar to other studies However, in the study of 91 cases conducted by Chanabasayya et al (2017)[15] , their observation was different as it showed male preponderance and a M:F ratio of 1.2:1 which may be because their study was carried in Egyptian population.

2. Distribution according to type of vesiculobullous disorder

Table 16: Comparison of distribution of Vesiculobullous disorders according to type of lesions

STUDY	PV	PF	BP	DD	HHD	ICD	PH	DH	EBS	Others
Chanabasayya et al (2017) (n=91) [3]	18.6%	10.9 %	46.15 %					5.5%		18.7%
Singh K et al (2016) (n=41) [4]	39.02 %	7.32 %	29.27 %		7.32 %	4.8 %				12.1%
Mittal H et al (2017) (n=103) [5]	51.54 %	3.8%	29.12 %		0.97 %			8.7%		5.8%
Deepthi S et al (2015) (n=47) [6]	36.17 %	8.5%	27.6%					4.25 %		23.40 %

Present study (n=30)	46.67 %	10%	10%	6.67 %	6.67 %	3.3 %	3.3 %	3.3%	3.3 %	

PV-Pemphigus vulgaris, PF- Pemphigus Foliaceous, BP- Bullous Pemphigoid DD- Darriers disease HHD- Hailey Hailey disease ICD- irritant contact dermatitis PHPemphigus Herpetiformis, DH- Dermatitis Herpetiformis, EBS- Epidermolysis Bullosa Simplex

In the present study, the maximum number of cases (46.67%) were of Pemphigus Vulgaris which is similar to some studies, whereas in study published by Chanabasayya et al the maximum number of cases (46.15%) were of Bullous Pemphigoid while Pemphigus Vulgaris was the second most common (18.6%) lesion. This discordance may be because the study was conducted on Egyptian population and it included only immunobullous disorders.

Bullous Pemphigoid (10%) was the second most prevalent lesion in our study which is similar to the studies of Deepthi S et al (26%), Mittal H et al (27.3%) and Singh Ket al (29.27%) whereas in study published by Chanabasayya et al it constituted the maximum number of cases (46.15%).

Pemphigus Foliaceous(10%) also shared equal incidence with Bullous Pemphigoid in our study which was not observed in the other studies.

The others studies included lesions like vasculitis, SLE, Lichen Planus Pemphigoids, Pemphigus Vegetans and Pemphigus Erythematosus which are non-infectious and were observed in study conducted by Chanabasayya et al and Singh K which, but were not encountered in our study, whereas in the studies conducted by Deepthi S et al and Mittal H et al included infective causes of vesiculobullous lesions and hence, the data presented in the above table is extracted from these studies after excluding the infectious lesions and others lesions in these studies including other noninfectious lesions and drug induced bullous disorders which were not encountered in our study.

3. Plane of separation

Table 17: Comparison of distribution of Vesiculobullous disorders according to plane of separation

Site of cleft formation	**Mittal H et al (2017) (n=103) [5]**	**Deepthi S et al (2015) (n=47) [6]**	**Deshpande A et al (2020) (n=42) [7]**	**Anupama R (2018) (n=100) [8]**	**Present study (n=30)**
Suprabasal	30.09%	31.9%	23.8%	48%	46.67%
Midepidermal/ Intraepidermal	20.38%	10.6%		9%	20.1%
Subcorneal	4.85%	8.5%	19.04%	14%	13.3%
Subepidermal	37.86%	36.17%	57.1%	29%	13.3%
No bulla	6.79%	4.2%			

The most common site of cleft formation was suprabasal as Pemphigus Vulgaris constituted the most common lesion in our study and this finding is similar to study conducted by Anupama R et al as Pemphigus Vulgaris was the most common lesion in that study too.

In other studies, like Mittal H et al, though Pemphigus Vulgaris was the most common lesion encountered but the major site of cleft formation was sub-epidermal because the total of cases of Bullous Pemphigoid and Dermatitis Herpetiformis exceeded the total number of cases of Pemphigus Vulgaris.

Similarly, in the study conducted by Deepthi S et al and Deshpande A et al basement membrane disorders like Bullous Pemphigoid, Epidermolysis Bullosa Acquisita, Erythema Multiforme, Dermatitis Herpetiformis and Bullous Drug Eruption were far more common than Pemphigus Vulgaris,so subepidermal plane of cleft formation was most commonly seen.

4. CONCORDANCE OF CLINICAL DIAGNOSIS WITH HISTOPATHOLOGICAL DIAGNOSIS

Table 18: Comparison of concordance of clinical diagnosis with histopathological diagnosis

STUDY	**PERCENTAGE OF CASES SHOWING CONCORDANCE**
Mittal H et al (2017) (n=110) [5]	91.3%
Chanabasayya et al (2017) (n=91) [3]	70%
Present study (n=30)	73%

The concordance of clinical diagnosis with histopathological diagnosis in our study was similar to Chanabassya et at which is about 73% where Mittal H et al showed very high concordance rate (91%). In both the above studies, immunofluorescence was used to confirm the diagnosis and the concordance rate of clinical diagnosis with immunofluorescence was found to be 92.6% and 77% which is almost similar to clinic-histopathological concordance rate. Hence clinic-histopathological correlation can be considered as an effective way for arriving at a final diagnosis in vesiculobullous disorders.

5. UTILITY OF HISTOPATHOLOGICAL FEATURES IN FINAL DIAGNOSIS

Table 19: Comparison Utility of histopathological features in final diagnosis

STUDY	**PERCENTAGE OF CASES SHOWING CONCORDANCE**
Anupama R et al (2018) (n=100) [7]	77.7%
Singh K et al (2016) (n=41) [4]	85.37%

Present study (n=30)	70%

In our study the diagnosis could be made based on morphological features alone in about 70% of cases which is lower than that observed in studies conducted by Anupama R et al and Singh K et al. But in both these studies the histopathological diagnosis was confirmed by by immunofluorescence and yet histopathological diagnosis proved to be diagnostic in more than 70% of cases in both the studies. Hence it can be derived that histopathological features alone can be very effective in diagnosing vesiculobullous disorders.

Viratktamath C et al, In the study conducted by them have reported that in 18.6% of cases in which diagnosis could not be made by immunofluorescence, were diagnosed by histopathological features. Hence morphological features even without confirmation with immunofluorescence can be considered to be effective in diagnosing the vesiculobullous disorders.

CONCLUSION

The following conclusions can be drawn on the basis of the results of this study:

1. Pemphigus Vulgaris is the most common vesiculobullous disorder among the non infectious vesiculobullous disorders of skin and mucosa.
2. The highest incidence was seen in the age group of 40-50 years
3. The sex ratio of 1:1.14. showed a slight female preponderance.
4. The most common form of clinical presentation in vesiculobullous disorder is blister/vesicle formation, followed by plaques or papules and they were accompanied by pruritus as the main symptom in most cases.
5. Nikolsky's sign was positive in 64% of cases of pemphigus vulgaris and 66% cases of pemphigus foliaceous.
6. Oral mucosal involvement was seen exclusively and in all the cases of pemphigus vulgaris, but not in any other disorder.
7. On histopathological examination, in majority of the case cleft formation was observed to be intraepidermal most frequently suprabasal, as in the Pemphigus Vulgaris the most frequently encountered lesion in the study. All the cases of bullous pemphigoid showed subepidermal cleft formation.
8. The histopathological features of suprabasal cleft with row of tomb stone appearance containing acantholytic cells and neutrophilic inflammatory infiltrate was seen in majority of the cases of Pemphigus Vulgaris were useful in arriving at a diagnosis.
9. The histological finding of Subepidermal cleft formation and inflammatory infiltrate consisting of eosinophils and neutrophils were helpful in the diagnosis of Bullous Pemphigoid
10. A positive family history, involvement of flexural aspects of body and the histopathological features of dilapidated brick wall appearance, sub-spinous plane of separation and acantholytic cells seen in both the cases of Hailey Hailey disease were useful in making the diagnosis of Hailey Hailey disease.

11. The presence of Dyskeratosis in the epidermis on histopathology was useful in both the cases to make a diagnosis of Darrier's disease.

12. The histopathological features of disease were consistent with the clinical diagnosis in majority (73%) of cases.
13. In 6.67% cases although the histopathology was inconclusive, the clinical data/features were useful/helpful in arriving at a diagnose in these cases.
14. The final diagnosis was arrived at on morphological features alone in 70% of cases and in conjunction with the clinical features in additional 20% cases, thus upto 90% cases could be diagnosed with clinic-histopathological correlation.
15. Only in 10% of cases, where the clinical finding and histopathological features were both inconclusive, direct immunofluorescence could be useful, in making the final diagnosis

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FIGURES

BULLOUS PEMPHIGOID

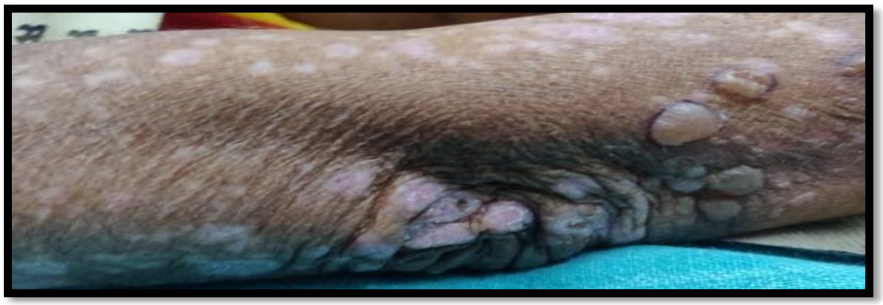

FIGURE 1: Clinical image of bullous pemphigoid showing intact blisters (BP)

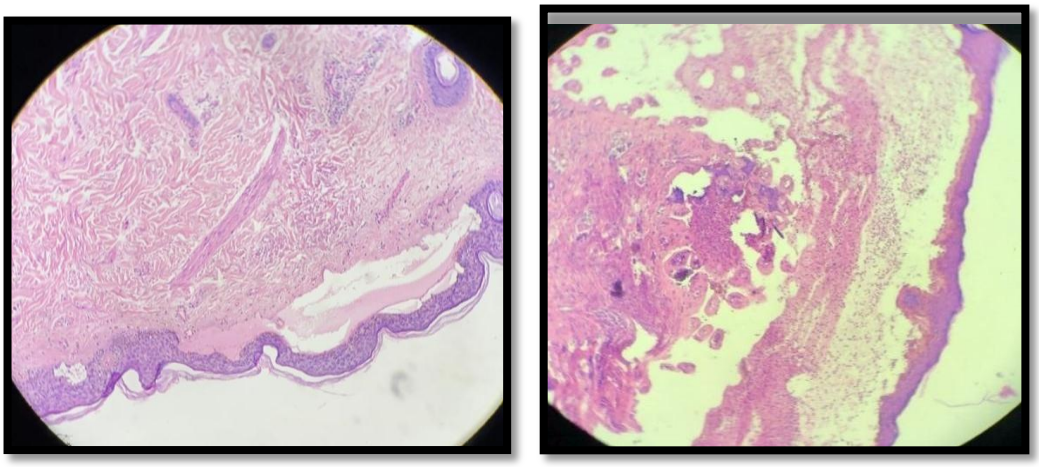

FIGURE 2 :(4X) : Histopathological image showing subepidermal clefting with edema fluid in blister cavity and **FIGURE 3 (10X) :** Histopathological image showing subepidermal bulla with inflammatory infiltrate (BP)

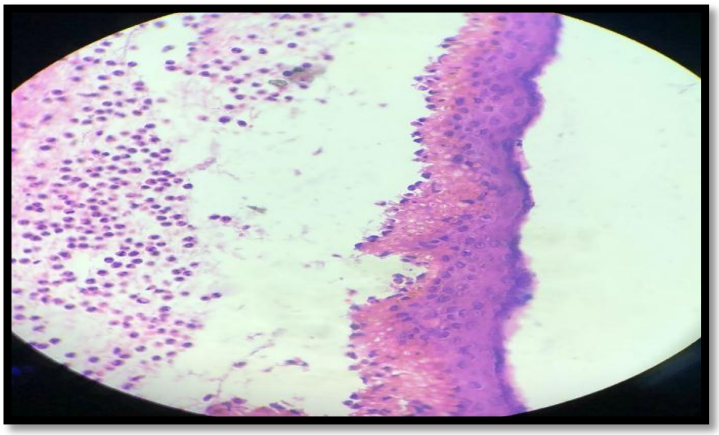

FIGURE 4(40X) : Histopathological image showing subepidermal bulla with mixed inflammatory infiltrate in the form of neutrophils and eosinophils (BP)

DARRIER'S DISEASE

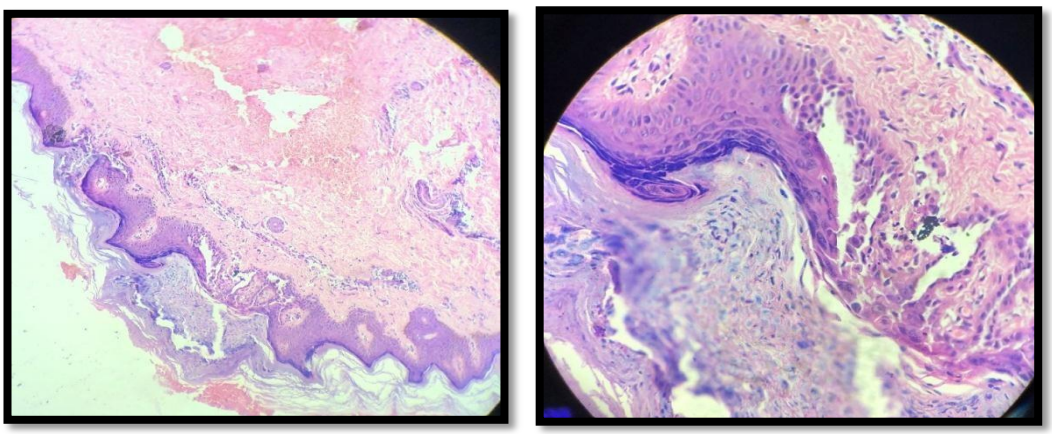

FIGURE 5 (4X&10X) : Histopathological Image Showing Suprabasal Clefting With Acantholytic Cells In Blister Cavity (DD)

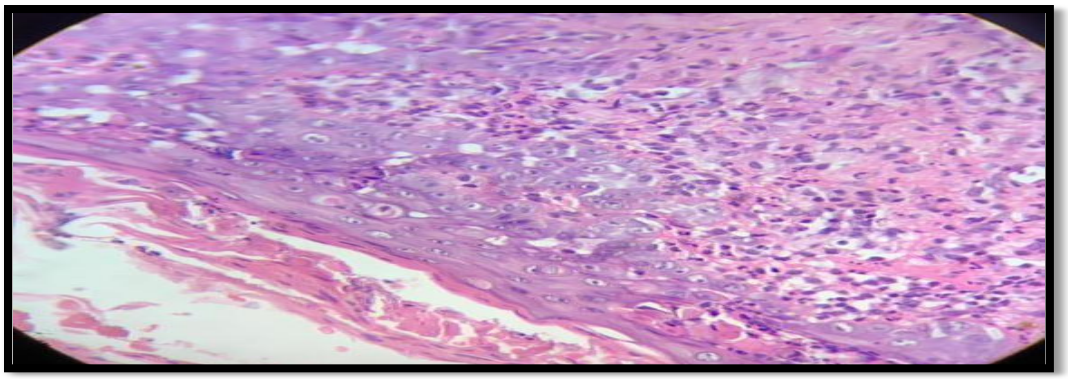

FIGURE 6 (40X): Histopathological image showing dyskeratotic cells within the epidermis (DD)

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HAILEY- HAILEY DISEASE

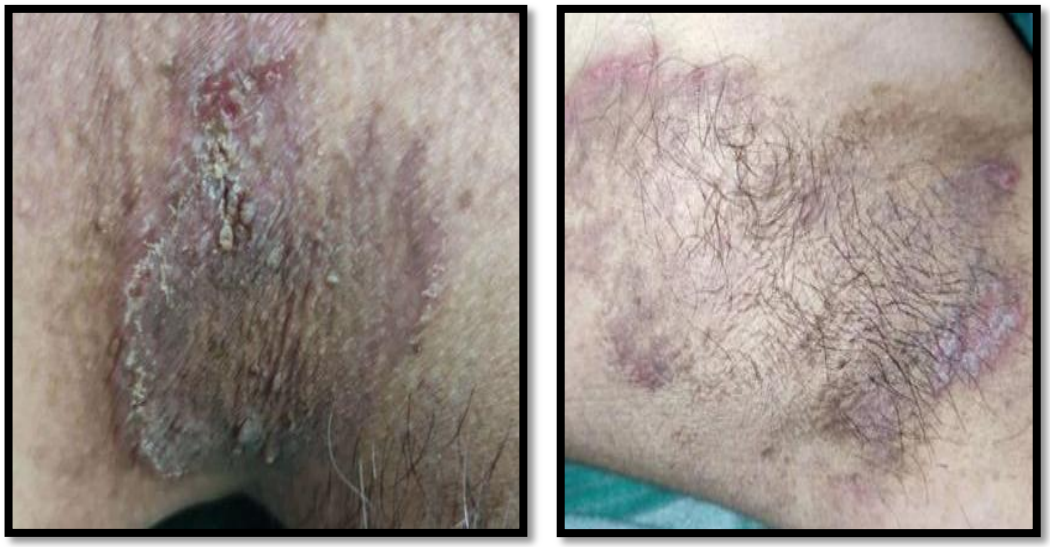

FIGURE 7: Clinical image showing plaques on flexural aspect of body (HHD)

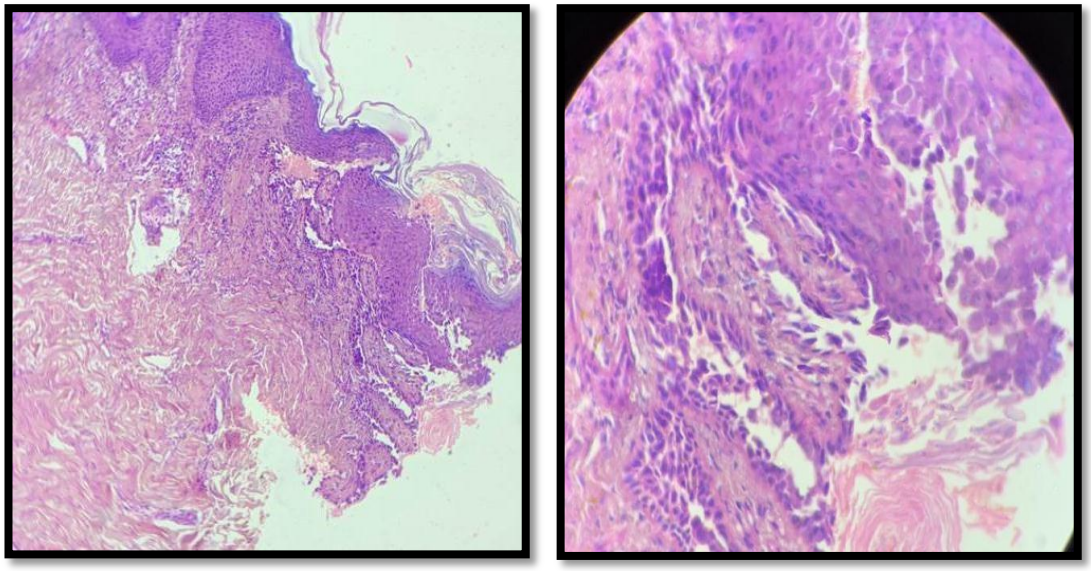

FIGURE 8&9 (4X&10X) : Histopathological images showing dilapidated brick wall appearance with suprabasal clefting and acantholytic cells (HHD)

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PEMPHIGUS VULGARIS

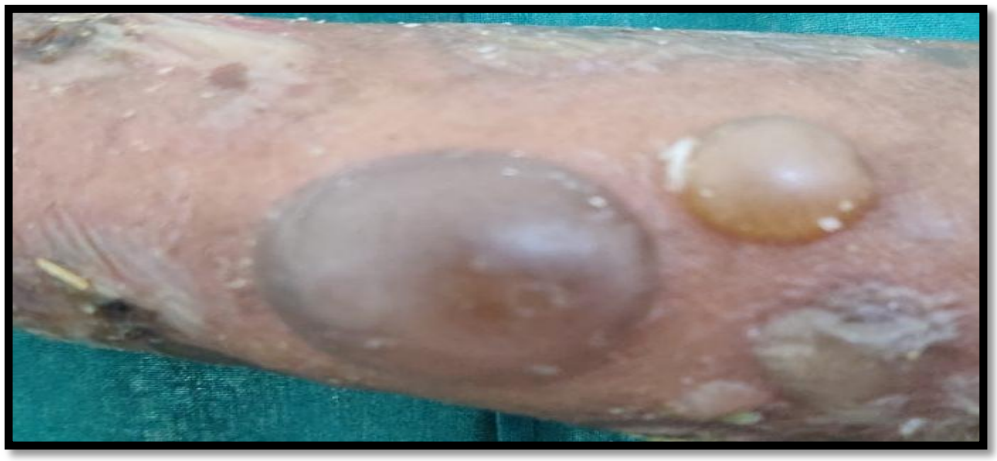
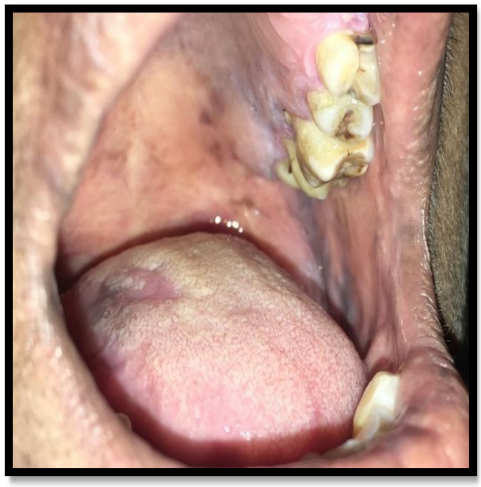


FIGURE 10: Clinical image showing intact bulla on the arm of patient (PV)



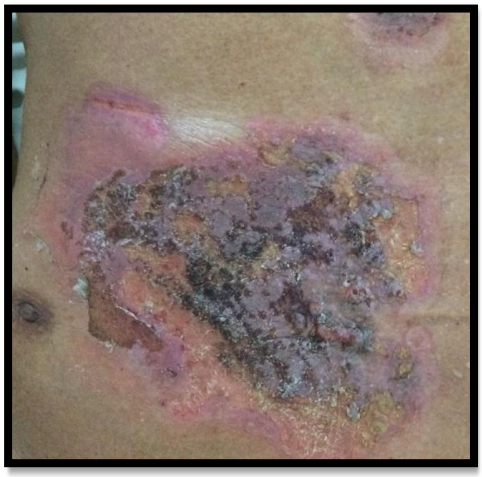


FIGURE 11: Clinical image showing involvemnt of oral mucosa (PV)

FIGURE 12: Clinical image showing involvement of erythematous eroded lesion on chest (PV)

FIGURE 13: Clinical image showing erythematous eroded and crusted lesions on back in patient who was diagnosed as having pemphigus vulgaris with cavernous hemangioma (PV)

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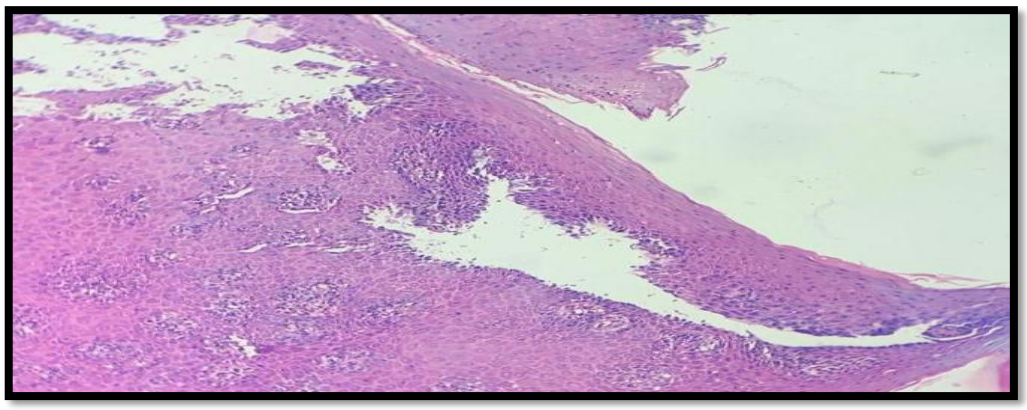


FIGURE 14 (10x): Histopathological image showing involvemnt of complete suprabasal clefting (PV)

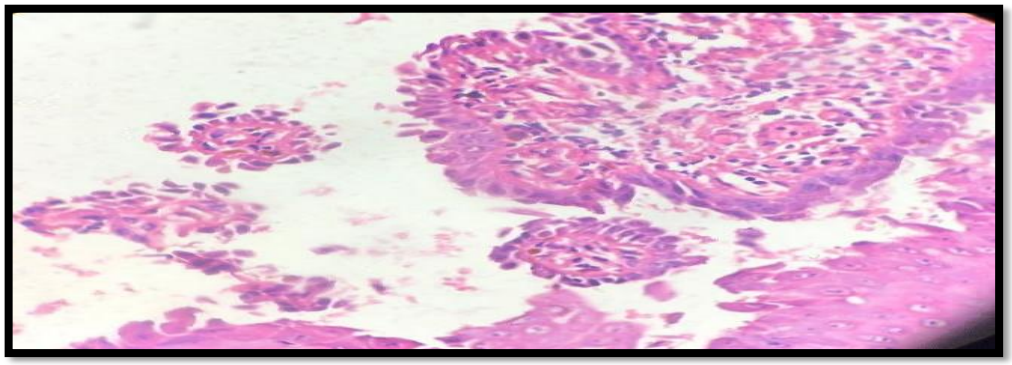


FIGURE 15 (40x): Histopathological image showing involvemnt of dispersed acantholytic cells with suprabasal clefting (PV)

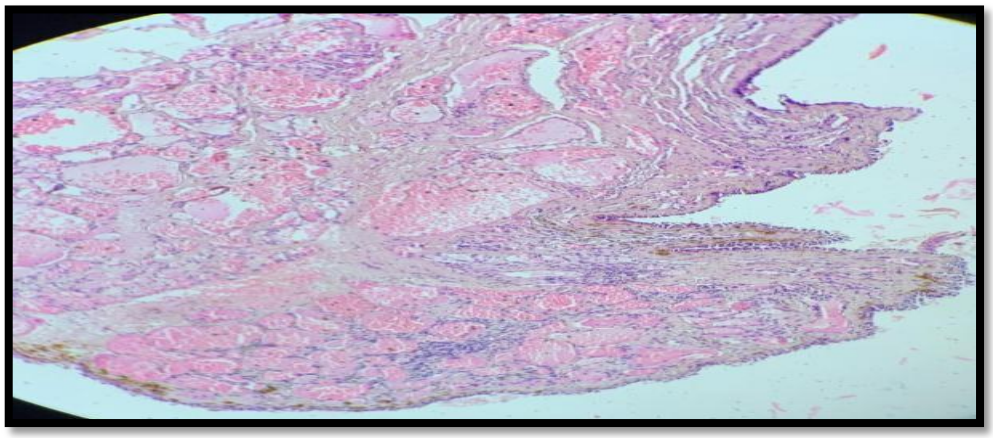


FIGURE 16 (40x): Histopathological image showing row of tonb stone appearance in an eroded lesion with cavernous hemangioma (PV)

PEMPHIGUS FOLIACEOUS

FIGURE 17: Clinical image showing eroded and crusted lesions on the back of patient (PF)

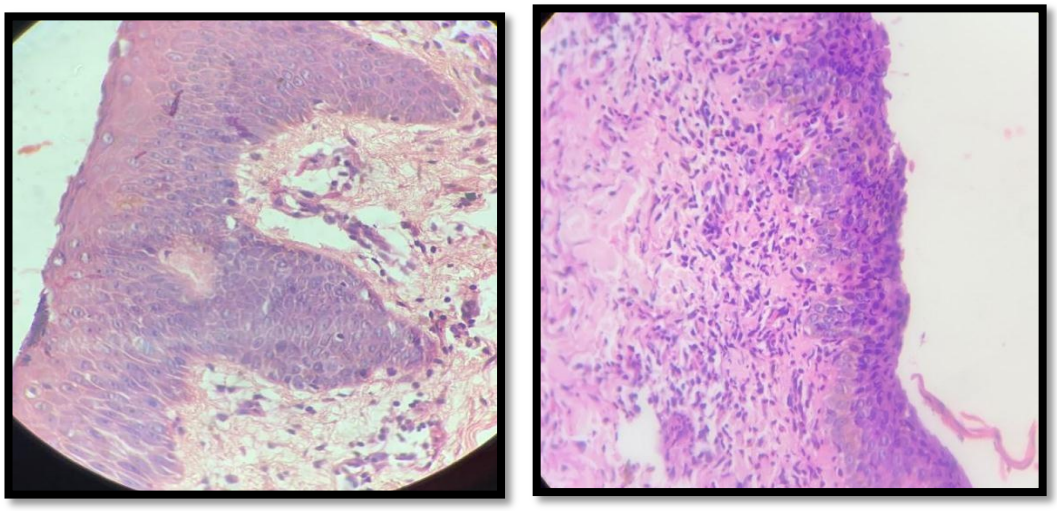
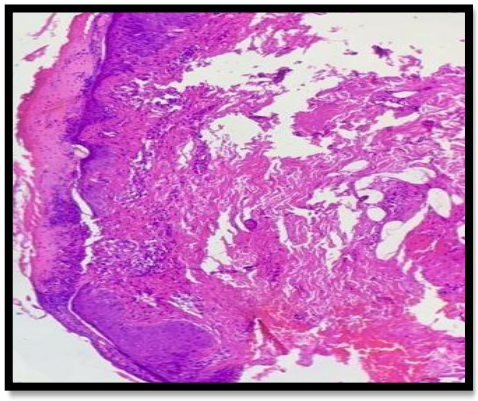


FIGURE 18 (40X): Histopathological image showing subcorneal clefting in biopsies from eroded lesions (PF)

PEMPHIGUS HERPETIFORMIS



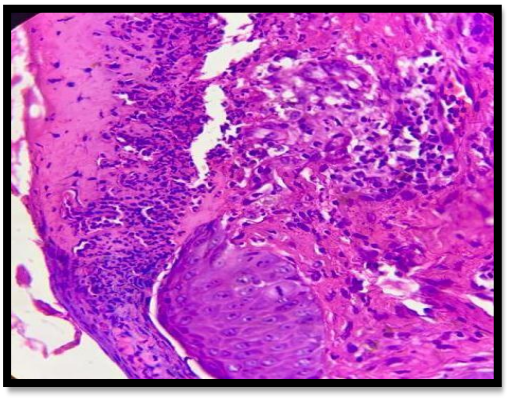


FIGURE 19 (10X): Histopathological image showing subcorneal clefting (PH)

FIGURE 20 (10X): Histopathological image showing subcorneal clefting with mixed inflammatory infiltrate of neutrophils and eosinophils (PH)

DERMATITIS HERPETIFORMIS

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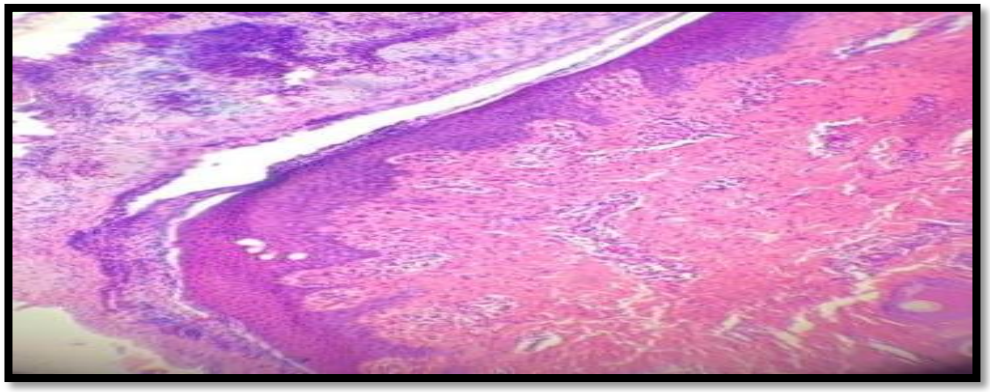

FIGURE 21 (10X): Histopathological image showing no cleft formation (DH)

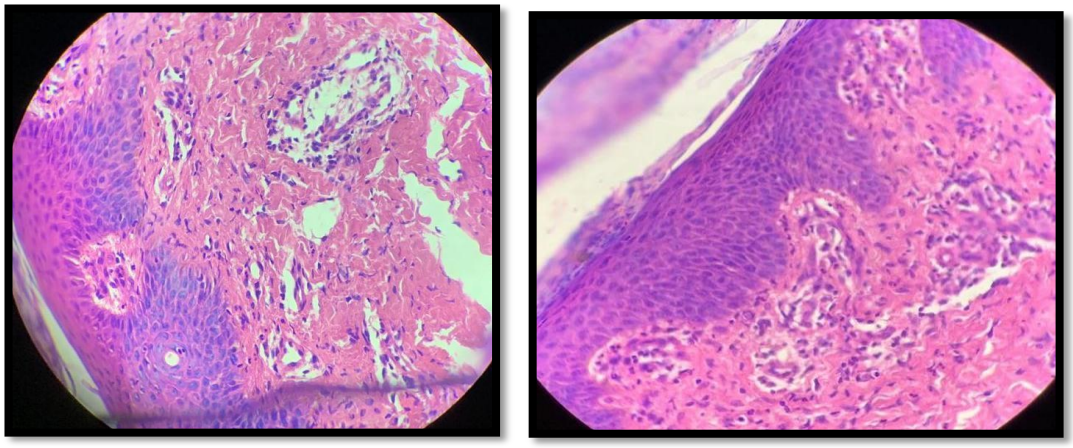

FIGURE 22&23 (40X): Histopathological image showing formation of papillary microabcesses by neutrophils and eosinophils (DH)

IRRITANT CONTACT DERMATITIS

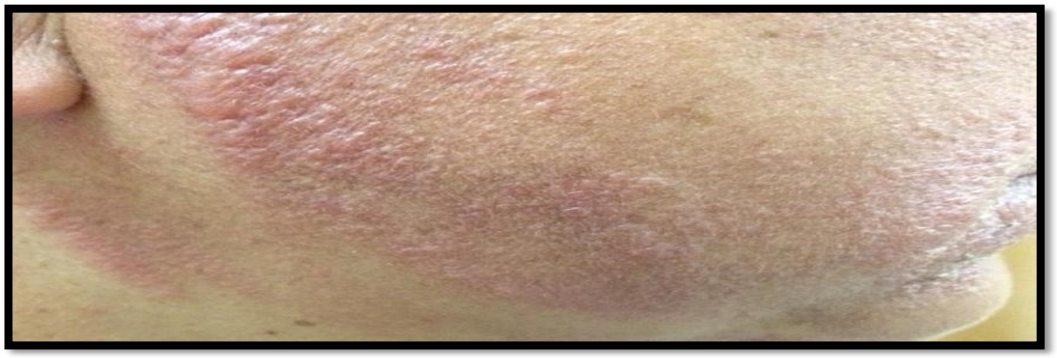

FIGURE 24: Clinical image showing vesicles on right side of cheek following topical application of some medicine (ICD)

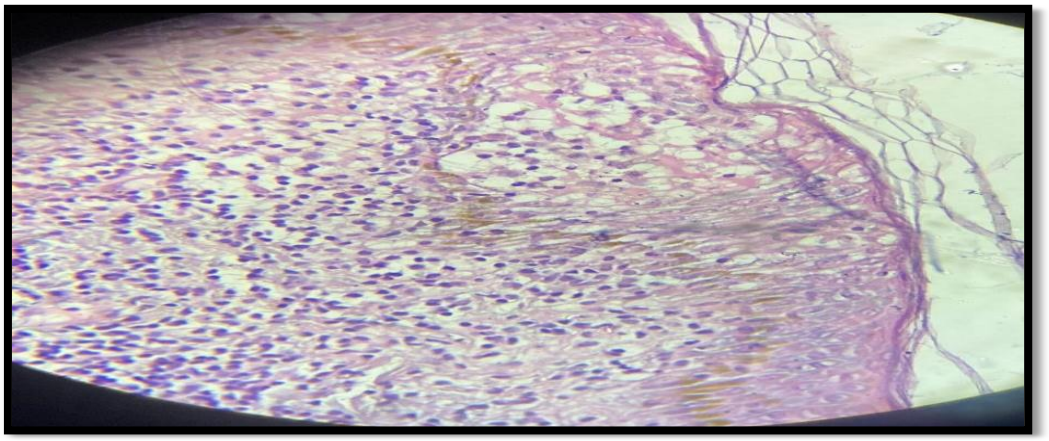

FIGURE 25 (40x): Histopathological image showing intraepidermal spongiosis infiltrated by inflammatory cells (ICD)