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Histopathological Spectrum of Vesiculobullous Lesions of Skin: A Hospital Based Cross Sectional Study

KEYWORDS: VBL= vesiculobullous lesion, Histopathological spectrum, Pemphigus, Pemphigoid

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ABSTRACT *Aim: A few people in North India have attempted a detailed histopathological examination of VBL. Present study was aimed to broaden the wide histopathological spectrum of VBL and be cognizant of various differential diagnoses.*
Settings and design: A cross-sectional, hospital based study was undertaken in the Department of Pathology, S.N. Medical College Agra during the study period of 18 months.
Material and methods: A total of 45 skin biopsies clinically labeled as VBL were subjected to routine histoprocessing.
Results: Clinically labeled VBL constituted 18.36% of the total skin biopsies. Pemphigus vulgaris was most common (37.79%). Other VBL included Pemphigus Foliaceous (11.11%), Bullous Pemphigoid and Non-specific Spongiotic Dermatitis (8.89% each). Dermatitis herpetiformis and Dariers disease comprised 4.44%. Less common entities included Bullous SLE, Bullous drug eruption, Epidermolysis bullosa.
Conclusion: The dermato-pathologist plays a crucial role in the diagnosis, classification, prognostication and treatment of the individual patient with VBL.

INTRODUCTION

VBLs are associated with IgG or IgA autoantibodies against intercellular junction adhesion molecules- desmosomes and hemidesmosomes leading to clinical presentation of blisters or erosions.

The VBL are divided in two broad categories; first category of intra-epidermal blistering referred to as pemphigus group and the second applies to group of sub epidermal blistering, and in situ deposition of autoantibodies at the dermal–epidermal junction. It includes BP,MMP, DH, EBA, EBS, BSLE etc. [1]

Immunofluorescence techniques supplement histopathology but, are available only at tertiary care centres in developing country like India and has numerous pitfalls and difficulties[2].

The task of the dermatopathologist is to describe precisely these light microscopic findings, mention differential diagnoses and to recommend how these can be confirmed or excluded by immunoserological studies[3].

Present study was undertaken to study the histopathological changes of the various blistering disorders and further broaden the understanding of their wide spectrum and be cognizant of the various differential diagnosis on histology.

MATERIALS AND METHODS

This cross-sectional, hospital based study included 45 skin biopsies clinically labelled as vesiculobullous lesions (VBL) received in the Department of Pathology, S.N. Medical College Agra during the study period March 2014-August 2015. After routine tissue processing and staining with H&E, the biopsy were scrutinized under light microscope.

RESULTS

A total of 245-skin biopsy was received during study period of 18 months out of which 45 were clinically labeled as VBL (18.36%).

VBL was twice as common in males compared to females (68.8% and 31.2% respectively). PV was 2.4 times frequent in males in comparison with females.

The maximum number of cases (60%) belonged to age group 21-60 years. The youngest patient was 7 years old and oldest being 80 years of age.

The study showed that 39 cases (86.67%) presented with bulla/cleft on histology while from the remaining 13.33%, two cases (4.44%) were unremarkable histopathologically and 4 cases (8.89%) fell beneath category of spongiotic dermatitis.

The pemphigus group of disorder formed the major proportion. (23 cases, i.e. 51.10% of total). Pemphigus vulgaris (PV) was the most common bullous lesion with 17 cases (37.77%). Pemphigus foliaceus (PF) contributed 5 cases (11.11%), Bullous pemphigoid (BP) and Non-specific spongiotic dermatitis (NSSD) constituted 4 cases (8.89%) each. Dermatitis herpetiformis (DH) and Dariers disease (DD) comprised 2 cases (4.44%) respectively. Other less common entities included Bullous drug eruption (BDE) with 3 case (6.68%) and rest entities contributed 1 case each (2.22% respectively). **(TABLE 1)**

The level of split in all histologically confirmed cases of PV (n=17) was suprabasal (100%) while in case of PF it was at subcorneal plane. In the remaining cases including BP, the bulla was in sub-epidermal location. Epidermal cleft was observed in Darier's disease. **(TABLE 2)**

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The primary mechanism of bulla formation seen was acantholysis in 100% cases of PV and PF. Basement membrane disruption was the most common mechanism of bulla formation for subepidermal vesiculobullous dermatoses. Keratinocytes degeneration & Cytolysis was chief mechanism in Epidermolysis Bullosa Simplex (EBS). In BSLE, the hydropic basal layer degeneration was seen along with basement membrane disruption.

Spongiosis was present in 100% cases of NSSD, Paraneoplastic pemphigus (PP) and in 52.94% of PV.

The content in the bulla was mixed inflammatory cells in more than 60% of VBL. Predominant eosinophilic infiltration was the principal composition in two thirds of pemphigoid group of dermatoses and one third of the pemphigus group. Approximately half of the case of BP had eosinophilic infiltration of dermis as in MMP. **(TABLE 3)**

Row of tombstone was seen exclusively in 82.4% of PV. Dyskeratosis was invariably evident in PP and in 60% cases of PF. Additionally, parakeratosis was a prompt histopathological feature in PP, over half of the cases of PV and in 40% cases of PF.

Intraepidermal Abscess and Basal layer vacuolization was the attendant feature in PP.

Hair shaft/sebaceous gland in bulla cavity was seen in 5.88% cases of PV only. Papillary edema was seen in 100% of pemphigus, pemphigoid group and DH. Acantholysis in adnexa was recorded in 29.41% of PV. Perivascular inflammation was seen in 13 cases (76.47%) of PV and 2 cases of DH.

Moreover, leukocytoclasis was conferred in 23.53% of pemphigus group and both cases of DH.

In both the cases of DH papillary microabscess is seen.

In all 3 cases of BDE, a predominant eosinophilic infiltrate in papillary dermis was evident.

Both cases of Darier's disease showed corps Ronds and Grains and eosinophilic spongiosis.

In the current study, 2 cases were sent as biopsy from a bulla and found to be completely unremarkable on histopathological examination and comprised 4.44% of the total cases.

DISCUSSION

The histopathological spectrum of vesiculobullous disorders is substantial. This cross-sectional study was undertaken to assess the spectrum in a hospital-based set up. In the present study, 18.36% of skin biopsy were clinically labeled as VBL nearly in consensus with Pavithra P et al,[4] (20.59%) but in contrast to Leena JB et al[5] (6.1%). This was probably due to higher number of patients (648) in study by Leena JB et al.

The clinical and histopathological correlation in our study was 86.67% in consensus with Pavithra P et al (90.41%) but dissimilar to Thejasvi KM et al[6](64.2%). This might be due to inappropriate site of selection of biopsy or sloughing of the epidermis/roof of blister due to fragility.

In study by Leena JB et al pemphigus group was the eminent (55.0%) dermatoses in concordance with our work (51.10%). PV was the most common VBL (37.79%), almost similar to Pavithra P et al et al (40.0%) and PF was second most common which was in discordance with Deepthi SP[7] where BP was second most common. The difference may be due to ascertainment bias, misclassification, or true rise in incidence of BP.

A male preponderance was seen in this study (M: F = 2.2:1) in accordance with Leena JB et al (1.35:1) and Thejasvi et al (1.49:1). In contrast, Arundhati et al[8] (1:1.27) reported a definite female predominance probably due to more number of female attendances at their OPD.

In the present study, maximum patients (60.00%) of VBLs belonged to 21-60 years age in consensus with Arundhati et al.

PEMPHIGUS GROUP

PV was the most common in this group followed by PF (73.9% and 21.70% of total pemphigus group respectively) similar to most of the studies; Arya et al[9] (61.4% and 35.7%), Arundhati et al (52.94% and 8.82%). In contrast Shafi[10] et al reported PF as cardinal type. This heterogeneity was probably due to differences in ethnicity and geographic distribution of the study population.

The mean age of presentation of PV in the current study was 35.80 ± 17.60 years almost same as Nanda et al[11] (mean = 36.50 ± 11.36 years) and a decade less than Chan PT et al[12] (57.0 ± 14.0 years).

Arya et al (1.4:1) and Leena JB et al (1.35:1) found male predominance in PV similar to our study (M: F = 2.4:1). On the contrary, females were predominant in study by Shafi et al (1:4.6).

In PF, current study showed female predominance (M: F = 1:1.5) similar to Deepti SP et al (1:3).

In the current study, a suprabasal bulla was seen in 100% of PV approaching Arundhati et al (96.2%). In PF, 100% case showed subcorneal bulla kindred with Deepti SP et al. Inversely, Arundhati et al found no bulla in 3.8%. Arya et al reported subcorneal bulla in 60% of PF and midepidermal bulla in 24%. It was plausibly due to the fragile blister, which undergoes multiple cycles of regeneration and degeneration shifting the level of bulla in epidermis.

A inflammatory infiltrate in the bulla cavity was seen in 100% cases comparable with Deepti SP et al (94.0%). The nature was mixed type (comprising neutrophils, eosinophils, lymphocytes and histiocytes) primarily (64.7% in the current study) akin to Thejasvi KM et al. In contrast, Deepti SP et al differed with PNI being most common (58.8%). It may be due to different stage of lesion in which biopsy was taken.

The predominant infiltrate in bulla of PF was mixed (60.0%) which was slightly more than Arya et al (53.5%).

Leena JB et al observed hair shaft in bulla cavity as in our study. This was probably an artifact caused by damage to the fragile adnexa during tissue processing and the squeezing effect of the microtome knife. Some consider it to be a natural phenomenon.

Acantholysis was the major mechanism of bulla formation (100% cases) in PV comparable to Thejasvi et al, Arya et al. Acantholysis of adnexa was present in 29.41% of PV

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which was more than Leena JB et al (22.2%) and less than Arya et al (46.5%) which was probably due to biopsy taken from a more chronic lesion. In PF, acantholysis was predominant mechanism (80%) in consensus with Arundhati S et al (75%).

Row of tombstones was seen in 82.4% of PV in consensus with Deepti SP et al (70.5%) and dissimilar to Arya et al. (41.8%). This was probably due to all biopsy taken from established blisters in our case. Hyperkeratosis was present in 11.77% case in accordance with Arundhati S et al (7.7%).

In PF, dyskeratosis was present in 60% cases, which was more than Arundhati S et al (25%) and less than Deepti SP et al (100%). This might be due to previous corticosteroid therapy induced change.

In the present study, both PV and PF showed perivascular inflammation in unison with Leena JB et al (100%).

BULLOUS PEMPHIGOID

BP contributed 8.89% of total VBL; which was close to findings of Arundhati et al (11.76%). Around 75% of cases were in age group 40 and above in accordance with Chan P.T. et al .

M: F ratio in BP in our study was 1:1, which was in accordance with Deepti SP et al (1:1.1) but dissimilar to Langan et al[13] (1:2.02) showing female predominance. The variation for this might be that all studies including ours were hospital based, with excellent validity but may be less representative of the disease in the population.

A sub-epidermal bulla in BP was reported by Chan P.T. et al; but Arudhati et al reported sub-epidermal bulla in less than 80% which may be due to older stage of lesion in their study associated with epithelial migration and regeneration. The predominant content of the bulla was eosinophil (75% in our study) similar to Deepti SP et al.

DERMATITIS HERPETIFORMIS

In study by Deepti SP et al, DH constituted 4.0% in accordance with our study(4.44%). Subepidermal bulla and neutrophilic infiltrate and papillary microabsesses were seen in 100% cases in consensus with Bonciolini et al.[14]

NON-SPECIFIC SPONGIOTIC DERMATITS

About 8.89% of all VBL fell in the category of NSSD nearly same as Deepti SP et al (8.0%). These cases were histologically ambiguous and could not be rendered a precise diagnosis as no bulla was seen in any of the cases in consensus with Arundhati et al. This may be due to non-representative biopsy or treatment induced modification in morphology.

OTHER DERMATOSES:

BDE : Absence of dyskeratotic keratinocytes and presence of subepidermal bulla, predominant eosinophilic infiltrate in papillary dermis, perivascular infiltration and pigment incontinence in present study also showed coherence with Deepti SP et al.

DD : Puri N et al[15] in her study of 30 cases of DD reported presence of suprabasal cleft with acantholysis, hyperkeratosis, dyskeratosis and Corps Ronds and Grains similar to present study.

CONCLUSION

The histopathological spectrum of these bullous disorders is substantial as aforethought. Furthermore, the prognosis of individual bullous diseases is significantly different. Pemphigus vulgaris is potentially fatal while Bullous pemphigoid is self-limiting but with considerable morbidity. All these can be dexterously discriminated by a simple first line investigation such as histopathology.

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TABLES

TABLE 1 (DISTIBUTION OF VESICULOBULLOUS DISORDER)

Name of Skin Lesion	No. of Cases	% of total cases(=45)
Pemphigus Vulgaris	17	37.79
Pemphigus Foliaceous	5	11.11
Bullous Pemphigoid	4	8.89
DH	2	4.44
Darier's Disease	2	4.44
MMP	1	2.22
BDE	3	6.68
BSLE	1	2.22
EBA	1	2.22
EBS	1	2.22
Sweet syndrome bulla	1	2.22
Paraneoplastic Pemphigus	1	2.22
Non-specific Spongiotic Dermatitis	4	8.89
Histologically Unremarkable	2	4.44
Total	45	100

Table 2: EPIDERMAL CHANGES IN VARIOUS VESICULOBULLOUS DERMATOSES

	Row of tombstone	Acantholysis	Dyskeratosis	Parakeratosis	Basal layer Vacuolization	Spongiosis	Corps Ronds	Hair shaft in bulla cavity
PV	14(82.4%)	17(100%)	0	9(52.94%)	0	2(11.77%)	-	1(5.88%)
PF	-	4(80%)	-	2(40%)	-	1(20%)	-	-
BP	-	-	-	1(25%)	-	3(75%)	-	-
DH	-	-	-	-	1(50%)	-	-	-
DD	-	2(100%)	2(100%)	1(50%)	-	2(100%)	2(100%)	-
MMP	-	-	-	1(50%)	-	1(100%)	-	-
BDE	-	-	-	3(100%)	-	1(33.3%)	-	-
BSLE	-	-	-	-	+(100%)	+(100%)	-	-
EBA	-	-	-	+(100%)	-	+	-	-
EBS	-	-	-	-	+(100%)	+	-	-
SSB	-	-	-	+(100%)	-	-	-	-
PP	-	1(100%)	1(100%)	1(100%)	1(100%)	-	-	-
NSSD	-	-		4(100%)	1(25%)	4(100%)	-	-

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Table 3: DERMAL CHANGES VARIOUS VESICULOBULLOUS DERMATOSES

	Papillary edema	PM*	Festooning	Pigment Incontinence	PVI**	PAI***	Leukocytoclasis	PNI@	PEI$	MII#
PV	17(100%)	2(11.77%)	-	3(17.65%)	13(76.47%)	4(23.53%)	4(23.53%)	4(23.53%)	2(11.77%)	11
PF	5(100%)	1(20%)	-	1(20%)	1(20%)	-		1(20%)	1(20%)	3
BP	4(100%)	1(25%)	41(100%)	-	-	-	1(25%)	-	2(50%)	2(50%)
DH	2(100%)	2(100%)	-	-	2(100%)	-	2(100%)	2(100%)	-	-
DD	1(50%)	1(50%)	1(50%)	-		-	-	-	-	1(50%)
MMP	100%	-	1(100%)	-	100%	-	-	-	100%	-
BDE	3(100%)	-	-	3(100%)	3(100%)	-	-	-	3(100%)	-
BSLE	+(100%)	+(100%)	-	+(100%)	+(100%)	+(100%)	+(100%)	+(100%)	-	-
EBA	+(100%)	+(100%)	1(100%)	-	-	-	-	+(100%)	-	-
EBS	+(100%)	-	1(100%)	-	-	-	-	-	-	-
SSB	+(100%)	+(100%)	-	-	+(100%)	+(100%)	+(100%)	+(100%)	-	-
PP	1(100%)	-	-	1(100%)	1(100%)	-	-	-	-	-
NSSD	4(100%)	1(25%)	-	3	4(100%)	-	-	1(100%)	-	-

*Papillary microabscess, **perivascular inflammation, ***Periadnexal inflammation, @Predominant neutrophilic infiltrate, $Predominant eosinophilic infiltrate, #Mixed inflammatory infiltrate

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