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Original Article

Histopathological Study of Vesiculobullous lesions of skin

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ABSTRACT

Histopathology of skin biopsies is a useful technique in the investigation of various skin diseases, out of which vesiculobullous lesions from one of the predominant groups. Vesicles [blisters less than 0.5 cm in diameter] and bullae [blisters greater than 0.5 cm in diameter] occur in a number of skin conditions[1]. These blistering disorders are the most visually dramatic of skin disease. Each entity in this group has distinct clinical features and these lesions share a number of histologic features, but only to some extent have common pathogenic mechanisms.The present study showed a prevalence of 74 cases [21% of the total skin biopsies] of Vesiculobullous lesions among the 354 skin biopsies received in the department of pathology over a period of 1 year The age of onset varied from 3 years to 65 years. But the types of lesions varied between the various age groups. The commonest lesion overall was bullous pemphigoid followed by Pemphigus vulgaris.In the present study of 74 cases, clinical diagnosis correlated with the histological diagnosis in 64.2% of the cases and in 25.6% of the cases, the diagnosis was done only on histology, where as in 9.4% of the cases it was difficult to offer a conclusive histological diagnosis. This establishes that along with clinical correlation, histo-morphological study forms one of the most useful tool in the diagnosis of Vesiculobullous skin disorders.

Introduction

Histopathology of skin biopsies is a useful technique in the investigation of various skin diseases, out of which vesiculobullous lesions from one of the predominant groups. Vesicles [blisters less than 0.5 cm in diameter] and bullae [blisters greater than 0.5 cm in diameter] occur in a number of skin conditions[1]. These blistering disorders are the most visually dramatic of skin disease. Each entity in this group has distinct clinical features and these lesions share a number of histologic features, but only to some extent have common pathogenic mechanisms. For example: bullous pemphigoid and pemphigus vulgaris are autoimmune in nature, most notably inherited epidermolysis bullosa are caused by non-immunologic mechanisms [2,3]. Pathologic evaluation of a blister involves systematic analysis which include, the blister separation plane, the mechanisms of blister formation and the character of the inflammatory infiltrate including, it's presence or absence [2]. Studies, including both western and Indian literature on these lesions have highlighted one particular entity or a specific aspect of it. But a detailed histo-morphological study including the entire spectrum of the disease has been attempted by a very few people, especially in this part of India. Histologic study is one of the most valuable means of diagnosis in dermatology. The greatest diagnostic accuracy is obtained by correlating the clinical and histological findings[2,4].

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MATERIALS AND METHODS

SOURCE OF DATA

Material for this study included patients who were clinically diagnosed as having Vesiculobullous disease from the Department of Skin and S.T.D of Victoria hospital and Bowring & Lady Curzon hospital attached to Bangalore medical college, Bangalore. Skin biopsies measuring 3mm – 4mm from 74 patients, who had an intact vesicle or bullae at the time of presentation received on a random basis were selected. The pertinent clinical history like the age, sex, duration of the lesion; site of the lesion, significant family and personal history, history of associated diseases and other relevant history, like any drug intake was taken. Findings of the detailed general and local examination were recorded. The biopsy studied included epidermis, dermis and subcutaneous fat below the lesion as well as the uninvolved perilesional area. The perilesional area is required to prevent the detachment of the roof of the blister from its base.

GROSS EXAMINATION OF THE SKIN BIOPSY

The three dimensional size and shape of the skin biopsy was assessed including the circular or elliptical shape of the biopsy and any gross lesion like, bulla or surface ulceration was noted. The entire skin biopsy is submitted for routine processing and embedded in paraffin wax.

HISTOLOGICAL EXAMINATION OF THE SKIN BIOPSY.

3-5 µ thick paraffin sections of the skin biopsy were stained with Hematoxylin and Eosin. Each skin biopsy was subjected to systematic, critical interpretive assessments in sequence as follows:

The separation plane, whether subcorneal, intraepidermal, suprabasilar, subepidermal or intradermal was observed.

The mechanisms of blister formation; whether by spongiosis, acantholysis, mechanical separation, dermoepidermal separation and edema was observed.

The character of the inflammatory infiltrate, its presence or absence, its pattern, the type of the inflammatory cell infiltrate in the blister, and in the dermis was separately recorded.

In the dermis, localization of the inflammatory infiltrate whether, in the superficial dermis, perivascular or periadnexal location was also observed.

RESULTS AND OBSERVATION

The total number of skin biopsies received inclusive of Vesibulobullous lesions was 354. Among them, the number of patients with Vesiculobullous lesions was 74 accounting for around 21% of the total number of skin biopsies.

GENERAL ASPECTS IN CLINICAL PRESENTATION:

The vesiculobullous lesions arise from a vast array of underlying pathologies, the spectrum of disease encountered ranged from inherited disorders to acquired disease liked drug reactions. Bullous pemphigoid, occurring as multiple, tense bullae of varying sizes commonly in adults, had the highest incidence, followed by pemphigus vulgaris, in which oral lesions were predominant with skin involvement showing flaccid bulla of varying sizes, erythema multiforme, presenting as popular erythematous eruptions caused by a variety of unrelated stimuli, dermatitis herpetiformis, which occurred along with gluten sensitive enteropathy with skin involvement showing vesicles on erythematous bases and pemphigus foliaceus, which had characteristic positive Nikolsky's sign and a few uncommon conditions like Darier's disease and superficial pustular dermatoses were also encountered.

The entire list of the lesion and the number of the cased in category is listed in descending order (table 1).

Table - Distribution of the cases

Lesions	No of cases	Percentage.
Bullous pemphigoid	16	21.6 %
Pemphigus vulgaris	14	18.9 %
Erythema multiforme	06	8.1%
Pemphigus foliaceus	06	8.1%
Dermatitis herpetiformis	06	8.1%
Chronic bullous dermatoses of childhood	06	8.1 %
Epidermolysis bullosa	04	5.4%
Darier's disease	02	2.7%
Pemphigus vegetans	02	2.7%
Liner IgA dermatoses	02	2.7%
Subcorneal pustular dermatosis	02	2.7%
Pemphigus erythematosus	01	1.3%
Hailey–Hailey disease	01	1.3%
Bullous systemic lupus erythematosus	01	1.3%
Allergic contact dermatitis	01	1.3%
Bullous herpetic lesion	01	1.3%
Bullous impetigo	01	1.3%
Staphylococcal scalded skin syndrome	01	1.3%
Drug induced blisters	01	1.3%

Correlation between clinical and histological diagnosis:

Table 2 showing clinical and histological correlation		
Correlation	Number of cases	percentage
Histological confirmation	48	64.8%
Diagnosed only on histology	19	25.6%
Histologically ambiguous	07	9.4%

Out of the 74 cases studies (table 2), 48 cases were clinically diagnosed as one of the varieties of Vesiculobullous lesion, which were confirmed on histology. In remaining 19 cases, the diagnosis was mainly established on histology, which included the early lesions of bullous pemphigoid, early lesions of pemphigus vulgaris and all cases of subcorneal pustular dermatosis and chronic bullous disease of childhood. But ambiguity still remained in about 7 cases where in, only histological suggestion was offered. Out of these 7 cases, 2 cases were of bullous pemphigoid, which showed mixed inflammatory infiltrate and 2 cases were linear IgA dermatoses, 2 cases were of suspected staphyloccal infection and one case was of bullous herpetic lesion.

Distribution of cases based on age:

The age of onset ranged from the neonate to 70 years. Most of the entities occurred more commonly in adults than in children from e.g. bullous pemphigoid.

The distribution of Vesiculobullous lesions among various age groups have been tabulated in table 3:

Table 3 showing age incidence		
Age group	No of cases	percentage
Birth 10 years	07	9.4 %
11 to 20 years	11	14.8%
21 to 30 years	23	31.0%
31 to 40 years	15	20.3%
41 to 50 years	15	20.3%
Above 50 years	03	04%

In the present study (table 3). Maximum number of cases occurred in the middle aged adults with age groups 21 to 50 years, in which there were, 14 cases of pemphigus vulgaris, 13 cases of bullous pemphigoid, 5 cases of erythema multiforme, 5 cases of dermatitis herpetifomis, 5 cases of pemphigus foliaceus, 5 cases of darier's disease, 2 cases of linear IgA dermatosis, 2 cases each of pemphigus vegetans, 2 cases subcorneal pustular dematosis and one case each of bullous systemic lupus erythematosus, drug induced blisters, pemphigus erythematosus and hailey-hailey disease.

In the age group above 50 years all the patients were only of bullous pemphigoid, out of which 2 cases were aged above 60 years.

Among the cases occurring in the age group birth to 10 years (table 3) the youngest, aged 3 years was a case of chronic bullous dermatosis of childhood which also constituted the predominant entity in this group. A single case of bullous herpetic lesion was also observed in this age group.

There were more varieties observed in the age group between 11 to 20 years, which include 3 cases of epidermolysis bullosa, 2 cases of dermatitis herpetiformis and one case each of allergic dermatitis, drug induced blister, bullous impetigo, staphylococcal scalded skin syndrome, erythema multiforme and pemphigus foliaceus.

Table 5 showing distribution in mechanism of blister formation		
Mechanism	Number	Percentage
Epidermal basement membrane zone Destruction / disruption	31	41.8%
Acantholysis	24	32.4%
Spongiosis	10	13.5%
Keratinocytes degeneration & cytolysis	08	10.8%

Sex distribution:

Table 4 showing sex incidence				
Type of lesion	Male	Percentage	Females	Percentage
Bullous pemphigoid	12	75%	04	25%
Pemphigus vulgaris	08	57%	06	43%
Erythema multiforme	04	67%	02	33%
Pemphigus foliaceus	03	50%	03	50%
Dermatitis herpetiformis	05	83%	01	17%
Chronic bullous dermatosis	04	67%	02	33%
Epidermolysis bullosa	03	75%	01	25%
Darier's disease	02	100%	0	0
Pemphigus vegetans	01	50%	0	0
Linear IgA dermatosis	01	50%	01	50%
Superficial pustular dermatosis	01	50%	01	50%
Pemphigus erythematosus	0	0	01	100%
Hailey – Hailey disease	01	100%	0	0
Bullous S.L.E	0	0	01	100%
Allergic contact dermatitis	01	100%	0	0
Bullous herpetic lesion	0	0	01	100%
Bullous impetigo	0	0	01	100%
Staphylococcal scalded skin syndrome	0	0	01	100%
Drug induced blisters	0	0	01	100%
Total	**45**	**61%**	**29**	**39%**

In the present study, out of the 74 cases, 61% (45 cases – table 4) were male and 39% (29 cases – table 4) were female. Most of the least common lesion were encountered in the female.

Mechanism of blister formation.

Table 5 showing distribution in mechanism of blister formation		
Mechanism	Number	Percentage
Epidermal basement membrane zone Destruction / disruption	31	41.8%
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Spongiosis	10	13.5%
Keratinocytes degeneration & cytolysis	08	10.8%

In the present study (table 5), epidermal basement destruction leading to subepidermal bullae formation was the most common mechanism involved (41.8% - 31 cases), followed by acantholysis (32.4% -24 cases). Others mechanisms like spongiosis (13.5% - 10 cases) and keratinocytes degeneration and cytolysis (10.8% - 8 cases) were also observed.

Inflammatory cells:

Table 6 distribution of the predominant inflammatory cell		
Inflammatory cell	Number of cases	percentage
Mixed	31	41.8%
Eosinophils	22	29.7%
Neutrophils	09	12.2%
Lymphocytes	08	10.8%
Absence of inflammation	03	4.0%

In the present study among the various types of Vesiculobullous lesions, the lesions showing mixed inflammatory infiltrate (41.8%- 31 cases) were the most common followed by lesions showing predominantly eosinophils (29,7%- 22 cases), lesions showing neutrophils (12.2%- 9 cases) and lymphocytes (10.8%- 8 cases) shown in descending order (table 6). There were 3 cases (4%), which showed characteristic absence of inflammation, of which 2 cases were of Darier's disease and one case was of Hailey-Hailey disease.

Fig 1: Equipment: Surgical Gloves, Scalpel Blade, Easy Punch Instruement and Toothed Forceps

Fig. 2. Tzanck Smear 400x – Acantholytic cells seen in blister fluid.

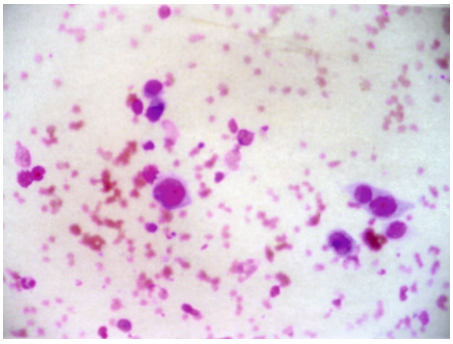


Fig.3. Bullous pemphigoid 400x – Subepidermal bulla with eosinophils.

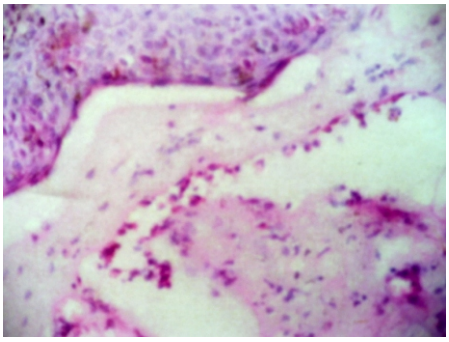


Fig.4. Pemphigus Vulgaris 400x – Suprabasal bulla with acantholytic cells.

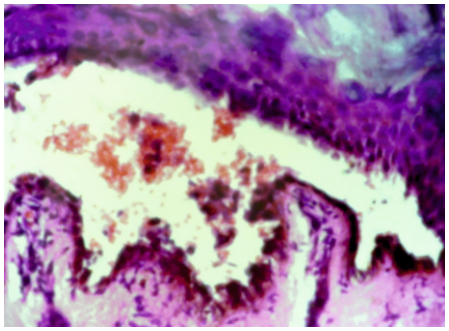
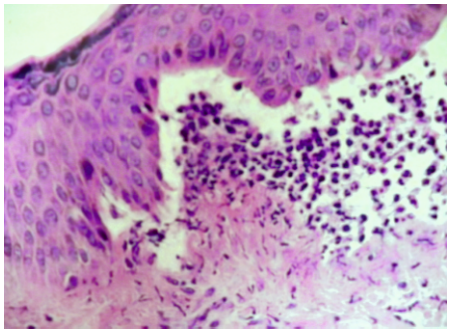


Fig.5. Dermatitis Herpetiformis 400x – dermal papillary microabscess



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DISCUSSION

The Vesiculobullous skin diseases comprise a group of eruptions of widely different etiology and prognosis, which share a common characteristic, the formation of blister cavities with in different layers of the epidermis or beneath the epidermis. Investigators in the past have studied the prevalence of these disorders in various population subgroups and have tried to define differences in mode of presentation, age of onset, the sex ratio, clinical or histological features and etiologic features 2,3

Bullous pemphigoid:

Bullous pemphigoid shows clinical similarity to pemphigus (hence its name) but the blisters are sub-epidermal, not intra-epidermal [56]. It is most common in people over the age of 50 years, with male preponderance [14]. It is a commoner disease in Europe and north America as the average age of the population increases and is characterized by the presence of large, tense bullae, usually on the thighs, arms and abdomen [1]. In the present study bullous pemphigoid occurred in the age group above 40 years [table 3]. The patients above 50 years were only of bullous pemphgioid, of which 2 cases were aged above 60 years with male predominance [table 4]. This minimal variation is attributed to the fact that the bulk of cases in the present study were in the age group 21 to 50 years [table 3]. Bullous pemphigoid is a sub epidermal blistering disorder with a predominance of eosinophils in the bulla and early lesions show a characteristic eosinophilic spongiosis 54. Nishioka et al studies 25 cases of bullous pemphigoid out of which 40% of the cases showed eosinophilic spongiosis. In the present study, of the 16 cases of bullous pemphigoid 5 cases (31%) showed eosinophilic spongiosis.[57]

Pemphigus group:

Among the Vesiculobullous, in the pemphigus group, pemphigus vulgaris is the commonest variety[6]. Shafi, M et al have studies 109 cases of pemphigus from Tripoli, libya and have found that the incidence of pemphigus in Libya is very high, with predominant variant being pemphigys foliaceus [58]. In his study Shafi. M et al also found out that males were predominantly affected than females [58]. In the present study (table 1) it was observed that bullous pemphigoid occurred at a greater frequency (21.6%) as compared to pemphigus vulgaris (18.9%), eight had characteristic clinical findings, and in the rest of the six cases, the diagnoses were established by histo-morphological studies, This variation in clinical presentation was probably due to prior administration of therapeutic agents. The present study also showed similar male predominance except for pemphigus foliaceous, which had equal sex distribution (table 4)

Fabbri P et al in another study of 112 cases of pemphigus group stated that acantholysis was the major mechanism involved and in pemphigus vulgaris and its variant pemphigus vegetans there was suprabasilar clefting, which was the hallmark of these diseases23. In pemphigus foliaceus and its variant pemphigus erythematosus,

the pathologic alteration of the epidermis occurs superficially i.e in the granular layer [9,23]. Similar observations were made in the present study in the pemphigus group, with all the cases of pemphigus group showing acantholysis as the predominant mechanism of bulla formation (table 5). The reason for the intrinsic difference between pemphigus foliaceus and pemphigus vulgaris has been poorly understood, but has long been of interest to clinicians as well as the investigators [27].

Erythema multiforme:

Erythema multiforme is a distinctive clinical and histological reaction to many different stimuli[44]. Barbazan. C and Sopena et al in their study of 67 cases of erythema multiforme documented 85% having past history of infection, either viral or bacterial and 15% past history of drug intake [59]. Similarly, correlating with the above study the present study showed 6 cases of erythema multiforme, of which 4 cases (67%) had a consistent history of past infection predominantly involving the respiratory tract and 2 cases (33%) with drug intake. The reason for this variation may be attributed to the small study group and self-limiting nature of the lesions [44]. The histological picture was of blister formation at either the epidermal or dermal level or both. The associated features observed were basal cell vacuolation with necrosis of basal keratinocytes. Several investigators like Han KD, Kim TH, Ackerman.A.B. and Ragaz.A in their study of post infective erythema multiforme with high male preponderance have described a predominant Lymphocytic infiltrate in the dermo-epidermal junction in about 90% of the cases . 43.60 the present study also showed similar male preponderance (table 4) with similar predominant Lymphocytic infiltrate (table 6) in the dermo-epidermal junction.

Dermatitis Herpetiformis:

Olbricht et al in their study of 21 cases have demonstrated papillary micro-abscesses containing predominantly neutrophils in almost all the cases and they were common in males and the predominant age group was between 20-40 years [36]. Correlating with the observations of Olbricht et al[36], the present study showed 6 cases (table 1) of Dermatitis Herpetiformis, out of these 83% (5 cases table 4) were males and all the cases showed similar papillary micro-abscesses containing predominantly neutrophils (table 6). The findings were consistent with the classical description of dermatitis herpetiformis as a subepidermal blistering disorder with predominantly neutrophils. Connor.B.L et al in his study of 105 cases of gluten sensitive enteropathy noted skin manifestations in 52% of the cases and all showed neutrophilic papillary microabcesses[61]. This variation was attributed to the fact that study group was large and only half of the total number of cases showed skin manifestations.

Linear IqA dermatosis and Chronic bullous dermatosis of childhood:

Smith SB et al reported sub epidermal blisters with mixed inflammatory infiltrate in both adults and children and histology of the lesions in adults showed predominantly plasma cells [62]. Similar to the study of Smith SB et al the present study showed 8 cases, of which 6 cases (table 1) were of chronic bullous dermatosis of childhood between the age of birth to 10 years (table 3) and 2 cases (table 1) were of adult IgA dermatosis in the age group 20 to 30 years (table 3). Histological features of our study also correlated with those of Smith SB et al [62], all cases showed a sub-epidermal bullae with a mixed inflammatory infiltrate (table 6) and more plasma cells in the adults. In another study by Leonard.J.N et al, which included only linear IgA dermatosis in adults reported similar histological features in 92% (40 cases)[47].

Epidermolysis bullosa [mechanobullous] group:

Paller.A.S et al and Furve M et al in their separate studies reported blistering disorders with history of minimal trauma in 25 and 32 cases respectively 80% of them showed sub-epidermal blisters with scantly inflammatory infiltrate and fragmented basal keratinocytes[64,65]. Present study comprised only 4 cases (table 1) of Epidermolysis bullosa in which biopsy was done, microscopic examination revealed similar histological features with subepidermal blisters with minimal mixed inflammatory infiltrate (table 6) and few degenerated keratinocytes. The less number of cases were due to the fact that most of the clinically diagnosed Epidermolysis bullosa cases presented with increased skin fragility over and around the lesion, which is classical in mechano-bullous lesions[41], and obtaining biopsy with intact bulla was very difficult.

Other rare groups:

Rare entities like Darier's disease, Superficial bullous dermatoses, Bullous systemic lupus erythematosus, Hailey-Hailey disease, Staphylococcal scalded skin syndrome, Bullous impetigo and Allergic contact dermatitis were reported. Mittal RR et al in their study of 12 patients of subcorneal pustular dermatosis during summer months reported in all cases the presence of subcorneal bulla containing mixed inflammatory infiltrate39. In the present study only 2 cases (table 1) of subcorneal pustular dermatosis were reported showing similar histological features as the above study with a characteristic sub-corneal bulla containing mixed inflammatory infiltrate along with the papillary dermis showing a perivascular neutrophilic infiltrate.

Burge SM et al in their study of review of clinical and histological features in 13 patients of Darier's disease observed hyperkeratosis, parakeratosis, acanthosis, and formation of suprabasilar clefting due to acantholysis and degenerated dyskeratotic keratinocytes termed as corps ronds and grains in the suprabasilar plane 49. 2 cases (table 1), both male patients (table 4) of Darier's disease were reported in the present study and both the cases correlated histologically with the above study.

Anne.H.Kettler et al in their study reported a case of 34-years-old female having bullous systemic lupus erythematosus with a subepidermal bulla and neutrophilic papillary micro-abscesses[15]. Our study also showed only a single case of bullous systemic lupus erythematosus, it was female of 23 years of age showing similar histology as the above study with subepidermal splitting and also papillary micro-abscesses but our case showed a mixed inflammatory infiltrate. This change may be because of the reason that the lesion selected for biopsy was old and the case was already on steroid therapy.

Jeffrey JM et al in their case report of a single case of Hailey-Hailey disease associated with drug induced bulla noticed suprabasilar clefting with widespread partial acantholysis of the epidermis showing a characteristic 'dilapidated brick wall' appearance no inflammatory cells were seen in the blister cavity[48]. Similar histological features were observed in a single case of Hailey-Hailey disease in the present study, but there was no history of any associated drug intake.

Larsen WG et al in their study of 24 patients with contact dermatitis among workers of a perfume industry reported only 2 cases showing extensive intraepidermal spongiosis and blistering with predominant eosinophilic infiltrate in the blister cavity. Rest of the cases in their study showed predominant dermal involvement and minimal intraepidermal edema66. In the present study only one case of allergic contact dermatitis presenting as a bulla was reported, with a history of exposure to dye, in a male

aged 16 years showing similar histological features with extensive intraepidermal spongiosis forming a bulla with mixed inflammatory infiltrate. The paucity of cases of allergic contact dermatitis with bullous presentation was because routinely skin biopsy was not advised in such cases and bullous presentation is rare as seen in the study conducted by Larsen WG et al[66].

Several investigators like Sneddon.I.B et al in their study of pustular dermatosis have reported few cases of post staphyloccal infections[40]. Most of the cases presented as cutaneous ulcers mainly and bullous lesions with sub corneal bullae with minimal mixed inflammatory infiltrate were observed in few cases[40]. Similarly in the present study only two cases (table 1) of staphylococcal infection, one reported as bullous impetigo and one as staphylococcal scalded skin syndrome both presenting as bullous lesions showing sub-corneal bulla with minimal mixed inflammatory infiltrate and occasional degenerated acantholytic cells were seen. In the present study the small number of such cases was because of the reason that, before biopsy most of them were empirically treated with antibiotics and obtaining an intact blister was very difficult because of easy exfoliation of stratum corneum during the procedure.

One case of herpes zoster infection presented as perioral vesicles in a 5 year old girl and Tzanck smear showed multinucleate and degenerated acantholytic cells but skin biopsy was not done fearing cross infection.

Apart from the above-discussed cases, in the present study period many rare entities like paraneoplastic pemphigus, pemphigus gestationalis and cicatrical pemphigoid were not seen.

During our one-year study period, the cases of paraneoplastic pemphigus were seen occurring with various malignancies[30]. In our institution cases were referred to a separate cancer institute and lost for follow–up.

Entities like pemphigus gestationalis and cicatrical pemphigoid, which were supposed to be rare and not found during the present study period.

SUMMARY AND CONCLUSION

The Vesiculobullous lesions of the skin are a group of disorders having varied pathogenesis, but having in common the clinical presentation of vesicles, pustules or bullae. In histopathology, epidermal and dermal reaction patterns in such bullous disorders represented limited characteristic responses. When evaluated together with clinical presentation and microscopy they provide diagnostic information.

The present study showed a prevalence of 74 cases [21% of the total skin biopsies] of Vesiculobullous lesions among the 354 skin biopsies received in the department of pathology over a period of 1 year The age of onset varied from 3 years to 65 years. But the types of lesions varied between the various age groups. The commonest lesion overall was bullous pemphigoid[16] followed by Pemphigus vulgaris[14].

The mechanism of bullae formation was evident in all the cases. Epidermal basement membrane zone destruction was the most common form of blister formation leading to sub-epidermal bullae accounting for 35 cases [47.2%] followed by acantholysis leading to intra-epidermal bullae in 22 cases [29.2%].

Various types of inflammatory cells which included eosinophils, lymphocytes, neutrophils were seen individually or together as mixed inflammatory infiltrate providing clues for diagnosis as well as for pathogenesis. The lesions showing mixed inflammatory infiltrate were seen in maximum number of cases [41.8%] followed by lesions showing eosinophils [29.7%] and lymphocytes in 10.8% of the cases.

In the present study of 74 cases clinical diagnosis correlated with the histological diagnosis in 64.2% of the cases and in 25.6% of the cases, the diagnosis was done only on histology, where as in 9.4% of the cases it was difficult to offer a conclusive histological diagnosis. This establishes that along with clinical correlation, histo-morphological study forms one of the most useful tool in the diagnosis of Vesiculobullous skin disorders.

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