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ORIGINAL ARTICLE

A Clinico-pathological Study Of 22 Cases Of Pemphigus

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ABSTRACT

Background : The term pemphigus refers to a group of autoimmune blistering diseases of the skin and the mucous membranes . Pemphigus affects 0.1- 0.5 patients per 1,00,000 population per year .**Aim:** To evaluate the clinical findings in association with histopathological findings, to study the histopathological findings in various vesiculobullous lesions of skin and to confirm with immunofluorescence wherever possible. **Materials And Methods:** Histopathological evaluation of biopsies received from the department of Dermatology was done in the Department of Pathology, JSS hospital, Mysore, from August 2006 to July 2008. **Results:** A total number of 648 skin biopsies were received, out of which 22 cases were of the pemphigus group of diseases. Pemphigus vulgaris accounted for 81 % (18) of cases and pemphigus vegetans accounted for 9.01 % (2) of cases. The less common types were pemphigus erythematosus and IgA pemphigus constituting 4.1 % (1) of the cases. Pemphigus vulgaris formed the most common variant. The male to female ratio was 1.35:1. The age incidence was between 21-70 years .The trunk and extremities were the frequently involved sites and had classical flaccid bullae in 90.9% of cases. Oral mucosa was involved in 66% of the cases of pemphigus vulgaris. Apart from the common histopathological changes in pemphigus vulgaris, we also observed: 1.Spongiosis of adjacent epidermis (11 cases) 2. Acantholysis in adnexa (4cases) 3. Hair shaft and sebaceous gland inside bulla (biopsy artifact)(3cases). Both the cases of pemphigus vegetans showed hyperkeratosis, papillomatosis and acanthosis, along with suprabasal bulla containing inflammatory infiltrate. **Conclusion;** Histopathological features were conclusive in most of the cases of primary vesiculobullous lesions of the skin. The study also revealed additional histopathological findings which are not encountered normally. Analysis of the subtle light microscopic features apart from the classical diagnostic features assisted in the diagnosis of difficult cases. The immunofluorescence study done, helped in confirming the diagnosis where histopathology and clinical features alone were inconclusive.

Key Words: Pemphigus vulgaris ; pemphigus vegetans; biopsy artifact

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Introduction

The bullous diseases have a history as old as that of medicine. In the early 1950's, Lever was able to differentiate most of these by using histological criteria [1]. The term pemphigus refers to a group of autoimmune blistering diseases of skin and mucous membranes which are characterized histologically by intraepidermal blisters due to acantholysis.

Acantholysis is the characteristic feature of the bullae of pemphigus and is defined immunopathologically by the finding in vivo, of bound and circulating IgG directed against the cell surface of keratinocytes [1].

As first demonstrated in 1943, acantholysis is the characteristic feature of the bullae of pemphigus [2].

Although a few studies are available on this relatively uncommon disease, apart from the classical histopathological features, this study highlights some interesting and rarely encountered histological findings.

Materials and methods

A total number of 648 skin biopsies were received from the Department of Dermatology during the study period of 2 years, out of which 22 cases were the pemphigus group of diseases accounting to 3.3% of the cases. The histopathological evaluation of biopsies was done in the Department of Pathology, JSS hospital, Mysore, from August 2006 to July 2008.

The biopsy material was sent in 10% formalin. The biopsies were subjected to routine processing and paraffin embedding. Multiple serial sections (upto 18) were taken for each biopsy and were stained with hematoxylin and eosin. Immunofluorescence was done wherever possible.

Results

Out of the 22 cases of the pemphigus group of diseases, pemphigus vulgaris accounted for 81 % (18) of the cases and pemphigus vegetans accounted for 9.01 % (2) of the cases. The less common cases were pemphigus erythematosus and IgA pemphigus constituting 4.1 % (1) of the cases [Table/Fig 1].

(Table /Fig 1) Distribution of lesions of pemphigus

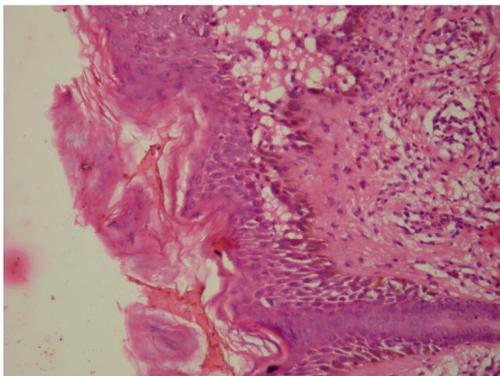
Sl No	Disorder	No. of Cases	%
1	Pemphigus Vulgaris	18	81
2	Pemphigus Vegetans	2	9.01
3	Pemphigus Erythematosus	1	4.1
4	IgA Pemphigus	1	4.1
Total		22	100%

A majority of the lesions in pemphigus vulgaris were distributed in the oral cavity- 12 (66%), followed by trunk- 7 (38%) and extremities -6 (33%), back -5 (27%) and axilla- 4 (22%). Most of them were flaccid bullae (90.9%) which were situated on a non erythematous base. A majority of pemphigus vulgaris patients were between 21 - 60 years of age (83%) and between 61-70 years of age (16.6%). IgA pemphigus and pemphigus vegetans were found in the 5th and 6th decades of life, respectively. The male to female ratio of pemphigus was 1.35:1.

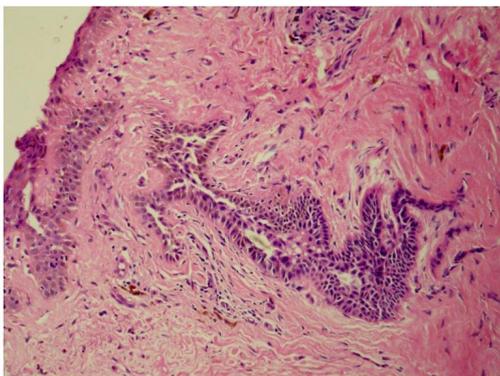
The histopathological features observed in 18 cases of pemphigus vulgaris [Table/Fig 2] were, a suprabasal split in 94.4% (17) of the cases. Neutrophils, eosinophils and acantholytic cells in clusters inside the bulla were observed in 94.4% (17) of the cases. Adjacent epidermis showed acantholysis in 11.3% (4) and spongiosis in 61.1% (11) of the cases [Table/Fig 3]. Acantholysis of the follicular sheath [Table/Fig 4] were seen in 22.2% (4) cases and prominent villi in 27.5% (5) cases. All of them showed dermal inflammatory infiltrate. Apart from these classical findings, we also noted acanthosis of the epidermis in 16% [3] of the cases. Interestingly, we also observed hair shafts inside the bulla cavity in 2 cases [Table/Fig 5] and sebaceous glands in the bulla cavity in one case. Tzanck smear was done in 15 cases. All the 15 cases showed the presence of acantholytic cells and mixed inflammatory cells which were composed of eosinophils and lymphocytes. Both the cases of pemphigus vegetans [Table/Fig 6] showed hyperkeratosis, papillomatosis and acanthosis. Suprabasal lacunae, with a few acantholytic cells were seen.

(Table/Fig 2) Histopathological changes in pemphigus vulgaris

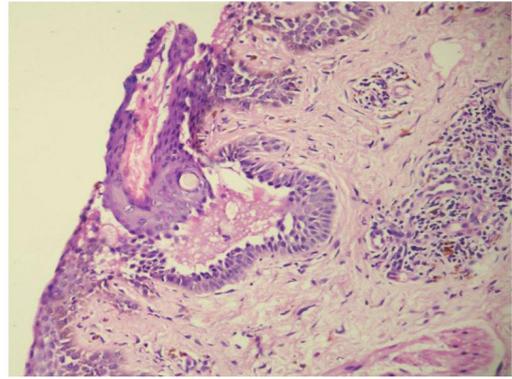
Sl No	Parameters	Hp Changes	No. of cases	Percentage(%)
1	Level of Split	Suprabasal	17	94.4%
2	Bulla Content	Neutrophils, Eosinophils Acantholytic Cells	17	94.4%
3	Adjacent Epidermis	Acantholysis	2	11.3%
		Spongiosis	11	61.1%
4	Involvement of adnexa	Acantholysis	4	22.2%
5	Dermal infiltrate	Neutrophils, Lymphocytes	18	100%
6	Others	Prominent Villi	5	27.7%
		Acanthosis	3	16%
		Hair shaft in bulla/ Sebaceous gland in bulla cavity	3	16%
7	Tzanck smear	Positive	15	100%



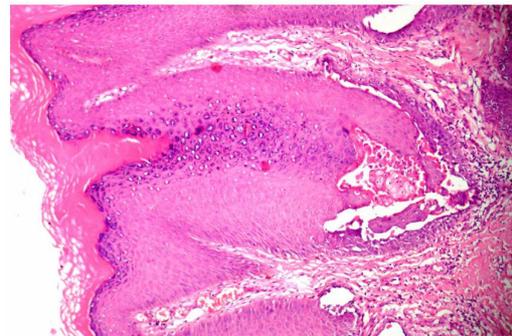
(Table/Fig 3) Pemphigus vulgaris – Spongiosis of the adjacent epidermis. H&E, 10x40



(Table/Fig 4) Pemphigus vulgaris – Acantholysis of the adnexa. H&E, 10x20



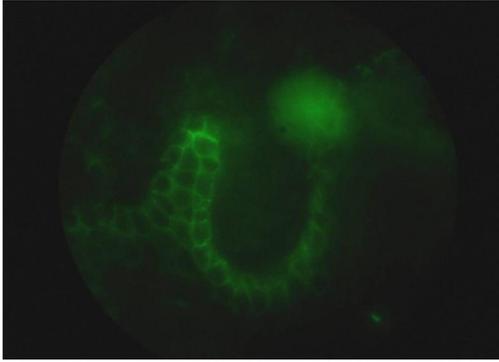
(Table/Fig 5) Pemphigus vulgaris- Hair shaft inside the bulla cavity (Biopsy artifact)H & E, 10X40



(Table/Fig 6) Pemphigus vegetans – Papillomatosis, acanthosis, suprabasal bulla with acantholytic cells. H & E : 10X40

One case each of pemphigus erythematosus and IgA pemphigus were seen, which presented with itchy lesions in a 35 year old female and in a 56 year old male respectively. Pemphigus erythematosus showed subcorneal bulla filled with neutrophils, eosinophils and acantholytic cells. Spongiosis of the adjacent epidermis and follicular sheath, along with acanthosis, were also noted. IgA pemphigus had both subcorneal and intraepidermal bullae with neutrophils and fibrin. The adjacent epidermis showed spongiosis. No cases of drug induced or paraneoplastic cases of pemphigus were seen in this study.

Direct immunofluorescence was done in 3 cases of pemphigus vulgaris, which showed intercellular lace like pattern [Table/Fig 7] with IgG and C3 in 2 cases and only IgG in one case.



(Table/Fig 7) Pemphigus vulgaris –DIF showing intercellular lace like IgG positivity

Discussion

Out of the 22 cases of the pemphigus group of diseases, pemphigus vulgaris accounted for 81% of the cases and pemphigus vegetans accounted for 9.01% of the cases. The less common cases were pemphigus erythematosus (4.5%) and IgA pemphigus (4.5%). Pemphigus vulgaris formed the most common variant in all the studies. Pemphigus foliaceus which was observed in other studies was not observed in the present study. Most of the patients presented with vesicles or pustules, with or without associated itching.

The male to female ratio was 1.35:1, with slight male preponderance in the present study. The male to female ratio was 1.4:1 and 1.3:1 in studies by Khandari et al and Arya et al respectively [3],[4], which correlated with our study. Most of the patients in the present study were in the age group of 21-70 years as compared to 9-70 years and 21-60 years in the studies conducted by Khandari et al and Arya et al respectively [3],[4].

The trunk and the extremities were frequently involved sites in most of the cases, which was also observed by Shafi et al. [5].

The characteristic clinical lesion has been the classical flaccid bullae, arising on normal skin in most of the cases, similar to that observed by Khandari et al in his study.

A majority of the cases had oral mucosal involvement in addition to skin lesions (66%). This observation was noticed in study by Fernandez et al [6]. Mucous membrane involvement is not always present or has a lesser incidence of involvement in pemphigus erythematosus [3], as in the present study.

Acantholysis, a process by which epidermal cells lose their cohesiveness is the essential abnormality in the pemphigus group of disorders. Cytological examination (Tzanck smear) of the intact bulla is one of the methods for the demonstration of these acantholytic cells. [7] Tzanck smear was done in 15 cases in the present study. All the 15 cases showed the presence of acantholytic cells, some of which showed degenerative changes and mixed inflammatory cells which were composed of eosinophils and lymphocytes. Direct immunofluorescence using fluorescein isothionate labelled anti IgG on Tzanck smears from the floor of the fresh bulla can be used for the rapid confirmation of the diagnosis of Pemphigus [7].

Arya et al and Fernandez et al observed suprabasal bulla with neutrophils, eosinophils and acantholytic cells which were similar to our findings in most of the cases. In one case of oral pemphigus, the bulla could not be identified because of the ulceration of the mucosa. The diagnosis was established by DIF studies of the perilesional area.

Spongiosis of the adjacent epidermis was noted in 61.1% of the cases. The follicular sheath also showed acantholysis in 22% of the cases. These findings were also noted by Arya et al. Acantholysis and spongiosis occurs due to the loss of syndecan 1 expression, a heparin sulfate which is present on the membrane of keratinocytes, which functions in intercellular adhesion. In spongiosis, desmosomal stretching occurs prior to cell separation, while in acantholysis, cell separation occurs without stretching [8].

Extrusion of the hair follicle in 2 cases and the hair follicle and sebaceous gland in 1 case into blister cavity, which is an uncommon finding, was also noted. Some of them consider this to be a natural phenomenon [9]. Some others explain it to be an artifact which is caused by the damage to the fragile sebaceous glands by the effects of the physicochemical changes that occur during tissue processing and the squeezing effect of the microtome knife as it slices through the paraffin block containing the biopsy tissue, pushing up the dislodged sebaceous gland outward through the common folliculo sebaceous conduit.[10]. This could also be possible because of the suprabasal clefting in the hair follicle sheath or the extension of the acantholysis along the adnexal epithelium.

Direct immunofluorescence was done in 3 cases of pemphigus vulgaris, which showed an intercellular lace like pattern with IgG and C3 in 2 cases and only IgG in one case.

Both the cases of pemphigus vegetans showed hyperkeratosis, papillomatosis and acanthosis, along with suprabasal bulla containing an inflammatory infiltrate which was similar to those observed by Arya et al.

The principal differential diagnosis of pemphigus vegetans is pyoderma vegetans. The histological features are similar, but neutrophils are more commonly found and intraepidermal eosinophilic abscess and acantholysis are rare [11].

We encountered 1 case of IgA pemphigus which showed intraepidermal and subcorneal bulla filled with fibrin and neutrophils. These histopathological features should be distinguished from that of subcorneal pustular dermatosis. Light microscopy alone may not be useful, in such cases, immunofluorescence study may be required. DIF testing shows IgA deposition in the squamous intercellular substance throughout the epidermis. Complement and other immunoglobulins

were usually not present [4]. However, immunofluorescence could not be done in this case and a diagnosis was offered, based on histopathological and clinical correlations.

An accurate histological diagnosis is essential for the therapy. The association of clinical and histopathological features helps to arrive at the diagnosis in most cases. The study also revealed additional features which are not encountered normally, like the extrusion of adnexal structures into the bulla cavity and the extension of spongiosis and acantholysis into the adnexal epithelium. Analysis of subtle light microscopic features, apart from the classical diagnostic features, threw light on the diagnosis of difficult cases. Immunofluorescence study helped in confirming the diagnosis where histopathology and clinical features alone were inconclusive.

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