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Pathology

A CLINICOPATHOLOGICAL STUDY OF INTRAEPIDERMAL IMMUNOBULLOUS DISEASES

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ABSTRACT **Background:** Immunobullous disorders are dermatological disorders involving the formation of fluid filled skin blisters as a result of an immunological reaction against different epidermal antigens. Such disorders can be categorized into intraepidermal and subepidermal based on the plane of epidermis in which the blister is present. **Aim:** To describe the clinical features and histopathological patterns of intraepidermal immunobullous diseases. **Method:** It was an institution-based cross-sectional observational study. A total of 107 cases were studied over a period of eight years in the Department of Pathology of a tertiary care hospital. Relevant clinical details of these cases were collected and punch biopsies were obtained from the site of lesion for routine histopathology. **Results:** Among the 107 cases included in our study, Pemphigus vulgaris was the predominant type with 86 (80.37%) cases followed by 17 (15.88 %) cases of Pemphigus foliaceous and 4 (3.73%) cases of Pemphigus vegetans. The age of the patients ranged from 10-78 years and females were found to be more commonly affected. Most of the pemphigus vulgaris patients presented in 7th decade with cutaneous blisters and oral mucosa involvement. Pemphigus foliaceous patients showed cutaneous lesions only with no involvement of oral mucosa. Intraepidermal vesicles containing acantholytic and inflammatory cells were characteristic histological features. All patients of pemphigus vulgaris showed suprabasal blisters. Of the 90 clinically diagnosed cases of PV, 86 cases (95.5 %) were proven histopathologically.**Conclusion:** Both the clinical findings and histological features are invaluable in arriving at a definite diagnosis in immunobullous diseases.

KEYWORDS : Immunobullous disorders, Intraepidermal, Pemphigus, Blisters.

INTRODUCTION

Intraepidermal immunobullous diseases are one type of autoimmune bullous diseases (AIBDs) characterized by pathogenic autoantibodies directed against target antigens, which are components of desmosome complex. Pemphigus vulgaris (PV) is the most common with a worldwide prevalence of 0.1-0.5/1,00,000 population followed by pemphigus foliaceus (PF).[1]It develops primarily in the older individuals (peak incidence is between 30-60 years) and equally affects males and females. PV presents with large, flaccid bullae involving the oral mucosa, scalp, midface, sternum, groin and pressure points.[2,3] These bullae break easily and leave the denuded areas that tend to increase in size by progressive peripheral detachment of the epidermis.[2] Pemphigus foliaceous usually develops in middle aged individuals and is sometimes also referred as superficial pemphigus as it manifests as recurrent shallow erosions accompanied by erythema, scaling and crusting. As they are superficial, blisters break easily resulting in erosions. Oral lesions are uncommon.[2]

Diseases of the pemphigus group are characterized by acantholytic intraepidermal blisters.[4] The diagnostic approach after the clinical suspicion and determination of clinical subtype includes: a) histopathological analysis of a fresh (<24h) vesicle or 1/3 of the peripheral portion of a blister and 2/3 perilesional skin; b) direct immunofluorescence microscopy (DIF) of perilesional skin (up to 1 cm from a fresh lesion, even though the skin is seemingly healthy); c) indirect immunofluorescence microscopy (IIF); d) serological detection of specific serum autoantibodies (Dsg1, Dsg3, BP180, BP230) by commercially available enzyme-linked immunosorbent assay (ELISA) kits; and e) immunoblotting that specifies the identity and molecular weight of target antigens.[5,6,7]

Considering the prevalent load of these diseases, the proportion of studies undertaken to study the aspects of immunobullous disorders is surprisingly low. Many studies have been done in Western World; the concern is deeper in developing countries like India.

This study was undertaken to evaluate the clinical and histopathological features of intraepidermal immunobullous disorders of skin for the diagnostic potential and to correlate them for greater diagnostic accuracy.

MATERIALS AND METHODS

- This cross-sectional observational study was conducted after approval from institutional ethical committee in the Department of Pathology of a tertiary care hospital, over a period of eight years (January 2013 to November 2020). All the cases presenting with vesicobullous lesions in OPD or IPD during the study period and underwent skin biopsy for histopathology were included in the study. Patients presenting with vesicobullous lesions but not undergoing skin biopsy, patients undergoing skin biopsy for skin lesions other than vesicobullous lesions and inconclusive skin biopsies on histopathology were excluded from this study.
- A detailed clinical history, general and local examination with particular reference to the mode of onset, characteristic & distribution pattern of the lesions was done.
- A total of 107 patients who were diagnosed as intraepidermal immunobullous lesions were included in the study.
- An informed written consent was obtained from these patients, prior to biopsy. Ideal lesion site for biopsy was chosen with intact vesicle or bulla.
- Under local anaesthesia, skin biopsies were taken using punch biopsy needles of 3 mm to 5 mm diameter or excisional biopsy was performed. One biopsy was of the lesion with intact vesicle or bullae and second biopsy from perilesional site (few mm to 1 cm from the lesion preferably uninvolved skin). Intact vesicle or bulla biopsy was preserved in 10% buffered formalin and subjected for routine histopathological processing.
- All the hematoxylin and eosin (H & E) stained slides were studied under microscope along with clinical data. The histopathological diagnosis was made. The separation plane of the blister, the mechanism of blister formation and the character of the inflammatory infiltrate were observed. The results obtained were analyzed to derive percent proportion of cases based on gender, age of presentation, duration of disease, site of occurrence, morphological diagnosis, level of vesicle formation, content of blister, mechanism of vesicle formation, etc. The results were

compared with previous similar studies.

RESULTS

In our study, out of a total of 107 cases, PV was found to be the predominant type with 86 (80.37%) cases followed by 17 (15.88%) cases of PF and 4 (3.73%) cases of Pemphigus vegetans. The age of the patients ranged from 10-78 years with a mean age of 45.4 years. Overall, there was a female preponderance in the study group with male to female ratio of 1:1.14. Acute onset of the disease was noted in 26 (24.3 %) patients and the duration ranged from less than a week to one month. Majority (68 / 107 cases, 63.55 %) of the patients presented with symptoms of one to six months duration. Cutaneous blisters (Figure 1) were present in 89 / 107 (83.2%) cases along with oral mucosa involvement in 48 / 86 (55.8 %) patients of PV. Secondary skin lesions such as erosions (67.6 %), crusting (67.6%), plaques (8%), papules (5 %) and scaling (5%) were also noted (Figure 2).

Table 1: Distribution of immunobullous disorders according to presence of symptoms.

Symptom	Present	Absent	Total
Cutaneous Blisters			
PV	71	15	86
PF	14	03	17
P.Vegetans	04	--	04
Oral mucosa involvement			
PV	48	38	86
PF	00	17	17
P.Vegetans	--	--	04

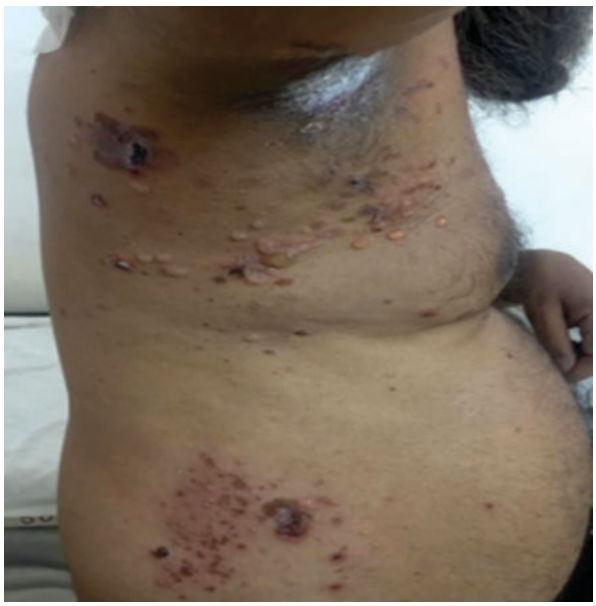

Fig 1. Multiple flaccid vesicles and bullae filled with pus, erosions and crusted plaques in a patient of PV.

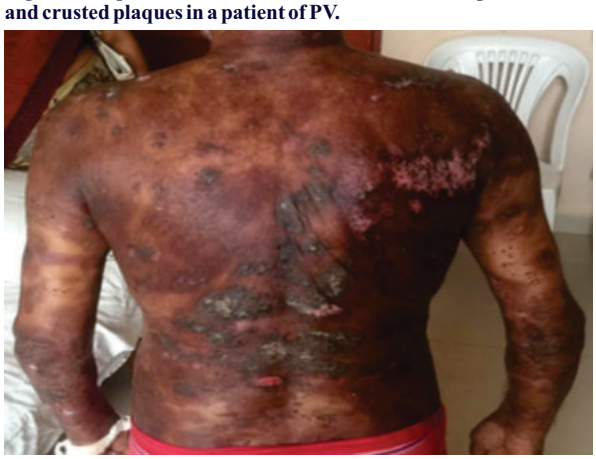

Fig. 2. Extensive areas of erosion, crusting, pigmentation over trunk, both upper limbs and neck in a patient of Pemphigus vulgaris.

On histopathological examination, all cases of PV and P.vegetans showed suprabasal (Figure 3) blisters, 16 cases of PF showed subcorneal (Figure 4) blisters while 1 case of PF showed supracorneal blister. Acantholytic cells were seen in majority (84/107, 78.5 %) of cases. Row of tombstone (Figure 3) appearance of basal layer was present in 67 (77.9%) cases out of 86 PV patients. Dermis showed perivascular inflammatory infiltrate in 80 (93 %) cases of PV and all cases of PF and P. vegetans.

Table 2: Histopathological features of study population.

Parameters	PV (n=86)	PF (n=17)	P.Vegetans (n=04)
Acantholytic cells	70	10	04
Neutrophils	64	12	03
Eosinophils	23	05	02
Tombstone	67	--	--
Acanthosis	33	07	02
Orthokeratosis	38	05	03
Spongiosis	32	08	02
Dermal edema	31	03	--
Perivascular infiltrate	80	17	04
Pigment incontinence	22	06	01

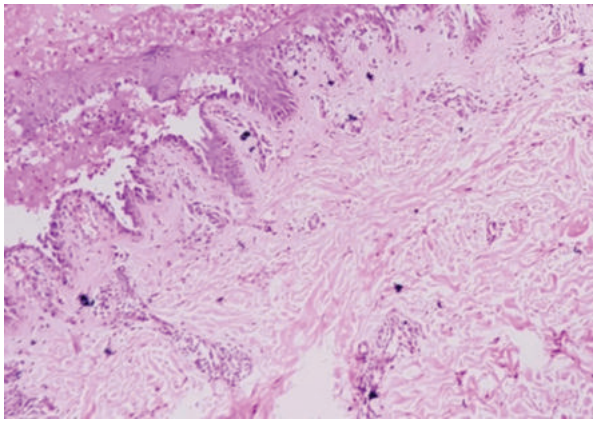

Fig.3. Microphotograph showing suprabasal blister formation and row of tombstone appearance of keratinocytes characteristic of pemphigus vulgaris. (10x,H&E)

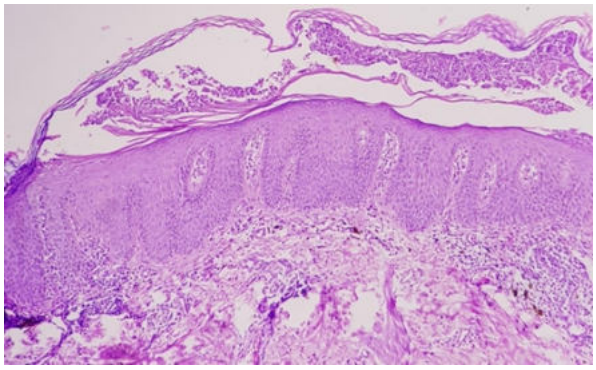

Fig.4. Microphotograph of Pemphigus foliaceous showing Subcorneal bulla with roof, floor and contents. (10x, H&E)

DISCUSSION

Autoimmune vesiculobullous disease, like other inflammatory dermatoses are morphologically heterogenous. They do not present with classical morphology and distribution of lesions which is most likely due to prevalence of the disease, severity of disease at presentation and status of treatment. Therefore, an accurate diagnosis is required in these cases to minimize the morbidity and mortality. For confirmation of diagnosis, histopathological examination is necessary. Very few studies in India have dealt with the clinicopathological features of intraepidermal bullous diseases. In the present study, a comprehensive analysis of the clinical and histomorphological features of intraepidermal bullous diseases was done.

Out of the 107 cases of pemphigus studied, PV was the predominant type with 86 cases (80.37%) followed by 17 cases (15.88%) of PF and 4 (3.73%) cases of Pemphigus vegetans. This is in concordance with

earlier studies by Mittal H et al,[8] Mohanty S et al,[9] Deepti S.P et al.[10] and Basu K et al.[1] which also showed PV as the commonest entity. The age of the patients ranged from 10 - 78 years with a mean age of 44.5 years. This finding is similar to the studies done by Basu K et al,[1] Khannan et al,[11] and Prakash et al.[12] There was a slight female preponderance with male : female ratio of 1 : 1.14. It was in concordance with the studies done by Basu et al,[1] Chowdhury et al,[13] Deepti et al,[10] and Mittal et al.[8]

In our study, acute onset of the disease was noted in 26 (24.3 %) patients and the duration ranged from less than a week to one month. However, majority (68 / 107 cases, 63.5 %) of the patients presented with symptoms with duration of one to six months which is similar to the study done by Basu et al.[1]

Of all the 107 cases, oral mucosal involvement was seen in 48 (44.8%) cases which was comparable to the studies done by Basu et al,[1] Prakash et al.[12] and Chowdhury et al.[13]

In our study, on histopathological examination, 100 % cases of PV and P.vegetans showed suprabasal blisters which is similar to the findings of Basu et al. [1] (100 %), Chanabasayaa V et al.[14] (100%), Mohanty S et al.[9] (93.75%), Deepti et al.[10] (88.2%) and Arundhati et al.[15] (93.2%). 16 cases (94.1 %) of PF showed subcorneal blisters while 1 case of PF showed supracorneal blister, a finding similar to the study done by Mittal et al.[8] Row of tombstone appearance of basal layer was present in 67 (77.9%) cases out of 86 PV patients, similar to the study done by Prakash et al.[12]

Acantholysis is the hallmark and a prerequisite for the diagnosis of pemphigus. Lever first described it and later on it was confirmed by several other authors like Handa et al.[16] and Arya S.R. et al.[17] Acantholytic cells were seen in majority (84/107, 78.5 %) of cases, a finding similar to the study done by Basu et al.[1] and Khannan et al.[11]

Of the 90 clinically diagnosed cases of PV, 86 cases (95.5%) were proven histopathologically, while 4 cases (0.04%) were discordant histologically as one case each of Steven Johnson syndrome, PF and two cases of Bullous pemphigoid.

CONCLUSION

Considering the socioeconomic situations of the patients and unavailability of immunofluorescence technique widely, histopathological diagnosis with clinical correlation still plays a major role in arriving at the diagnosis.

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