ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 2 Issue 8 November 2018

Research Article

Clinicopathological Study of Vesiculobullous Disorders

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Received: September 24, 2018; **Published**: October 10, 2018

Abstract

Introduction: Blistering disorders are known to man since ancient times. The immunobullous diseases are characterized by pathogenic auto-antibodies directed against target antigens whose function is either cell-to-cell attachment within epidermis or attachment to dermis. The target antigens are components of desmosomes or components of basement membrane zone. The most important techniques for the investigation of patients with immunobullous disease are histopathology and direct-indirect immunofluorescence (DIF, IIF).

Methods: Total of 45 cases presenting with autoimmune and genetic etiology of vesiculo-bullous disorders attending the outpatient department were included in the study. All patients were subjected to routine and specialized investigations like tzanck, histopathology, DIF and IIF.

Results: Amongst the 45 patients enrolled, 25 (55.5%) were males and 20 (44.4%) were females. Pemphigus vulgaris was the predominant group with 57.77%. Concordant results on histopathology were obtained in all cases (100%) of pemphigus.

Conclusion: Collaboration of clinical findings, histopathology, DIF and IIF is needed to come to diagnosis of autoimmune vesiculobullous disorders.

Keywords: Vesiculobullous Disorders; Blistering Disorders

Introduction

Blistering disorders are known to man since ancient times [1]. First recorded episode of pemphigus disease was by Hippocrates (460 - 370 B.C) who described pemphigoid fever as "pemphigoides pyertoi" and Galen (AD 131 to 201) named a pustular disease of the mouth as "febris pemphigoides".

The immunobullous diseases are characterized by pathogenic autoantibodies directed against target antigens whose function is either cell-to-cell attachment within epidermis or attachment to dermis [2]. The target antigens are components of desmosomes or components of basement membrane zone [3]. The most important techniques for the investigation of patients with immunobullous diseases are histopathology and direct-indirect immunofluorescence [4].

DIF is a one-step histological staining procedure to identify in vivo antibodies bound to tissue antigens [5-7]. The utility of this technique is limited by cost, site and time of the biopsy, technical and tissue processing factors, history of treatment and nature of the disease [8,9].

Techniques such as immunoblotting and immunoelectron microscopy may refine the diagnosis [10]. Histologic findings alone may not be sufficient to classify correctly the subtype of eruption [11]. Histopathologic studies of Walter lever differentiated what we now call pemphigus and pemphigoid [12]. Immunofluorescent studies by Ernst Beutner and his group revealed the autoimmune etiologies of pemphigus and pemphigoid [13].

Materials and Method

This study was done over a period of one year. All the cases presenting clinically with vesiculobullous lesions suggestive of autoimmune, genetic etiology were included in the study. The following infectious causes were excluded from study.

Infectious diseases

- Viral - herpes simplex, varicella, hand-foot-mouth disease, herpes zoster.
- Fungal - candidiasis.
- Bacterial - congenital syphilis, bullous impetigo, staphylococcal scalded skin syndrome.

Other rare causes of vesiculobullous disorders like drug induced, metabolic, pustular psoriasis, erythema toxic neonatorum, transient neonatal pustular melanosis, friction blisters, allergic and irritant contact dermatitis, phototoxic and photoallergic reactions were also excluded.

In this study, a total of 45 cases presenting with autoimmune vesiculobullous lesions in all age groups and both sexes attending the in and out patient department were included. Clinical details of the patient including history, clinical examination findings were recorded in pre-set proforma.

All the patients were subjected to

Blood investigations like CBC, RFT, LFT, RBS; Urine investigations like urine routine, stool for occult blood, ova and cyst; Biopsy from skin and mucous membrane; Radiological investigations like X Ray, USG abdomen/pelvis, Tzanck smear; DIF (direct immunofluorescence) and IIF (indirect immunofluroscence) was done in select cases

Results

A total of 45 patients were enrolled for study over a period of one year. Amongst the 45 patients, 25 (55.5%) were males and 20 (44.4%) were females. The male to female ratio was 1:25. Out of total 45 patients, the maximum number of patients i.e. 12 (26.66%) were in age group of 31-40 followed by 10 (22.22%) patients in the age group of 21-30 years. Our study showed that female to male ratio is 0.04 (Table 1). Study by Krina., *et al*. showed female to male ratio to be 1.30:1 [10].

Age (in years)	Male	Female
1 - 10	3	0
11 -20	1	2
21 - 30	10	0
31 - 40	3	9
41 - 50	1	3
51- 60	3	3
61 - 70	3	3
71 - 80	1	0
Total	25	20

Table 1: Age and sex distribution of people with vesiculobullous disorders.

Pemphigus vulgaris (PV) was the predominant group with 57.77% of the patients studied with the disease. The pemphigus group included PV (n = 0), oral pemphigus (n = 6), PF (n = 3), 1 case of PH and 1 case of PN (Table 2 and 3). Oral mucosal involvement was the initial manifestation in majority (> 90%) of PV patients. The pemphigus group included Pemphigus vulgaris (PV) (57.77%), Pemphigus folliaceous (PF) (6.66%), Pemphigus herpetiformis (PH) (2.22%), Paraneoplastic pemphigus (PNP) (2.22%).

Diseases	Number of patients	Percentage
PV Cutaneous	20	44.44
PV Oral	6	13.33
PF	3	6.66
PH	1	2.22
PNP	1	2.22
BP	6	13.33
DH	1	2.22
HHD	2	4.44
CBDC	1	2.22
SCPD	1	2.22
EB Simplex	3	6.66
Total	45	100

Table 2: Distribution of diseases.

Diseases	Males	Females
PV Cutaneous	10	10
PV Oral	0	6
PF	1	2
PH	0	1
PNP	1	0
BP	6	0
DH	1	0
HHD	1	1
CBDC	1	0
SCPD	1	0
EB Simplex	3	0
Total	25	20

Table 3: Type of disease and sex distribution**.**

Tzanck smear preparations were studied in all 45 cases. A skin biopsy was performed in all 45 cases. Concordant results were obtained in all cases (100%) of pemphigus. No differentiation could be made between the subtypes of pemphigus on the basis of cytology. Smears from the patients with sub epidermal blistering disorder revealed non-specific findings with inflammatory cells. Histopathology examination proved helpful in such cases.

DIF was done in only 6 (13.33%) cases because of low affordability of the patients. DIF is complementary to histopathology for the diagnosis of pemphigus and not a substitute for it. IIF is helpful for the monitoring of disease activity. It was done only in 2 (4.44%) cases. Rituximab was given to 4 (8.88%) patients of exten-sive PV not responding well to high dosage of steroids.

Discussion

DIF is more sensitive and also more frequently positive than indirect immunofluorescence in patients in clinical remission and more valuable for detecting immunological activity of the disease [14,15].

Pemphigus

Distinction between PV and PF was not possible on cytology. Histopathology revealed suprabasal intraepidermal blister in PV, PNP (in addition to keratinocyte necrosis and vacuole interphase dermatitis) and sub corneal intraepidermal blister in PF and PH. On histology, 20 cases were diagnosed as cutaneous PV, 6 cases as oral PV, 3 cases as PF, 1 case as PH, 1 case as PNP. Findings on histopathological examination of PV were similar to those seen by Camacho-Alanso., *et al* [16]. Histopathological findings of PF were similar to those observed by Park., *et al* [17]. Concordant results were obtained in all the cases (100%).

In our study, the characteristic features were the presence of many acantholytic cells in all the cases of PV, PF, PNP. The acantholytic cells are epithelial cells lying in groups or singly. Many of the cells seem to be detached or loosely attached to neighbouring cells rather than in a tightly adherent sheet. The typical acantholytic cell (tzanck cell or tzanck-like cell) contains a large, centrally located, hyper chromatic nucleus with prominent nucleolus. Moderate to large number of cells was present in PV and PF (Table 4) (Figure 1-6).

Bullous pemphigoid

Tzanck smears from 6 patients with BP showed small to large number of eosinophils, neutrophils and occasionally lymphocytes. No acantholytic cells were seen in these smears.

Dermatitis herpetiformis

Cytology from 1 patient demonstrated inflammatory cells. No cantholysis was seen. Biopsy showed subepidermal blisters, infiltrates of neutrophils at tips of dermal papillae and papillary dermal enema.

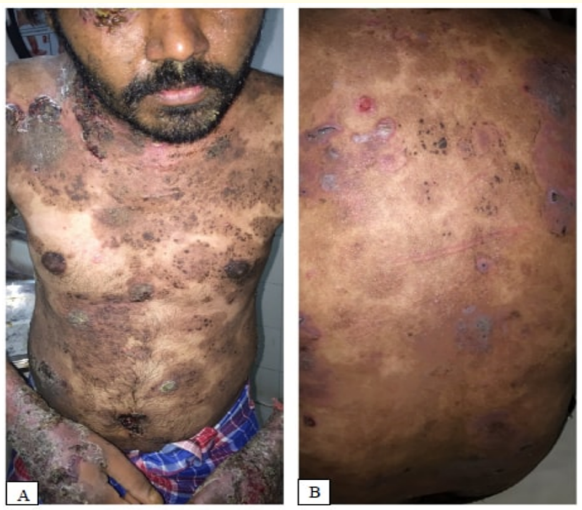

Figure 1: Pemphigus vulgaris.
A - crushing, erosion over chest and abdomen
B - crushing, erosion and Flaccid bullae over back

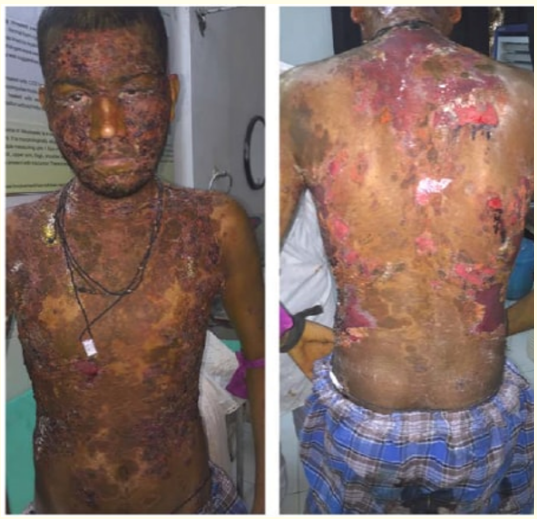

Figure 2: Prior to rituximab infusion, erosion and crushing over face and trunk.

Hailey disease

Tzanck smears from 2 cases didn't reveal any significant pathology. The histopathology was performed in both the cases showing characteristic loss of cohesion between keratinocytes (acantholysis) with suprabasal epidermal cleating. Widespread partial loss of the intercellular bridges between keratinocytes was seen as a "dilapilated brick wall".

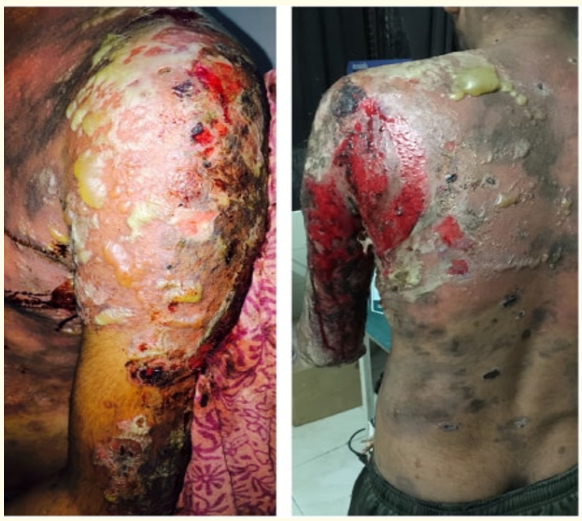

Figure 3: PDevelopment of herpes zoster after 4 weeks of rituximab 1st dose.

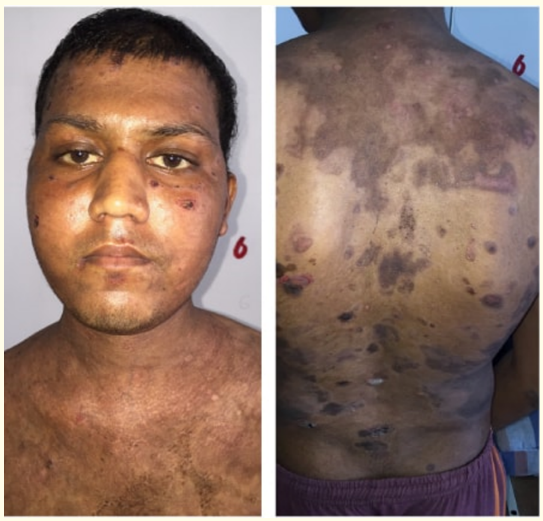

Figure 4: After 2 doses of rituximab therapy, majority of the lesions healed.

Chronic bullous dermatoses of childhood

Tzanck smear was taken. On giemsa staining, no acantholytic cells were seen. Biopsy showed subepidermal split with superficial dermal infiltrate of neutrophils and eosinophils.

Sub corneal pustular dermatoses

Tzanck smear showed abundant neutrophils. Histopathology was concordant with sub corneal vesiculopustule formation with abundant neutrophils.

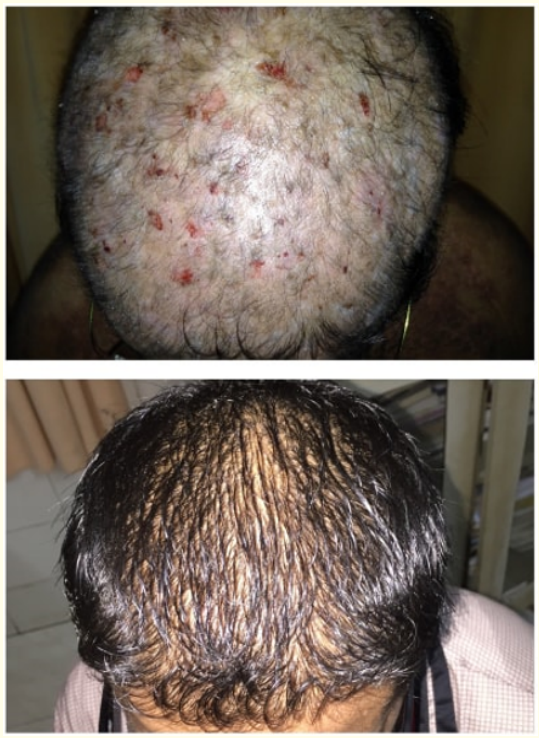

Figure 5: Hair regrowth after rituximab therapy in case of pemphigus vulgaris.

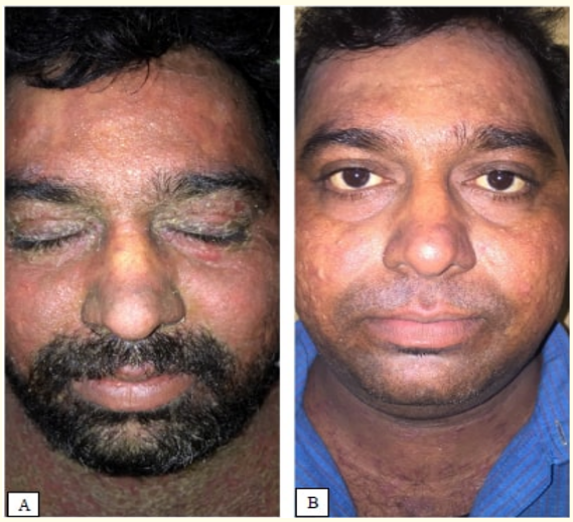

Figure 6: Pemphigus foliaceous.
A – Excessive scaling over face and neck
B – 3 weeks after rituximab therapy.

Epidermolysis bullosa simplex

- Smears failed to show acantholytic cells. Histologically, an intraepidermal separation was seen in epidermolysis bullosa simplex.
- Out of 45 cases, tzanck positivity (positive acantholytic cells) was seen in 30 (66.66%) cases.
- DIF was done in 6 (13.33%) cases of PV which showed epidermal intercellular deposition of IgG, C3.
- IIF was done in 2 (4.44%) cases of PV which showed higher desmoglein 3 titre.
- Rituximab (500 mg/50 ml diluted in 500 ml normal saline intravenously given every 15 days) was given to 4 (8.88%) patients of extensive PV not responding well to high dosage of steroids. Out of 4 patients receiving rituximab, one developed herpes zoster after infusion.

Conclusions

Collaboration of clinical findings, histopathology, DIF and IIF is needed to come to diagnosis of autoimmune vesiculobullous disorders.

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