

Correlation of Histology of Vesiculobullous Disorders With Immunofluorescence: A Study at A Tertiary Care Centre

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ABSTRACT

Introduction: Vesiculobullous disorders present with varied clinical manifestations. Vesicles and bullae are fluid filled cavities present within or beneath the epidermis. They are autoimmune blistering disorders in which autoantibodies are directed against target antigens present in the epidermis and dermoepidermal junction.

Aim: To study and analyse the clinical, histopathological and immunofluorescence findings in bullous lesions of the skin and to determine the contribution of immunofluorescence in diagnosing these conditions when there is a histological overlap.

Materials and Methods: A total of 50 cases were selected in a two years span. Punch biopsy specimens of the skin taken from early lesions, sent for histopathological examination and Direct Immunofluorescence (DIF), were processed routinely. The light microscopic and immunofluorescence stained slides were studied and correlated with the clinical findings.

Results: Pemphigus vulgaris was the most common vesiculobullous disorder (36%) followed by bullous pemphigoid (28%), pemphigus foliaceus (10%), hailey-hailey disease (8%), dermatitis herpetiformis (8%) and others (10%).

Conclusion: The present study concludes that all the patients of vesiculobullous disorder may not present clinically with classical morphological features. In such conditions where clinical diagnosis is a problem, biopsy from the lesion helps in arriving at the final diagnosis. In cases where histopathological findings are not typical, DIF helps to diagnose the disease which shows typical pattern of immune deposition at the appropriate site. So, a separate specimen should be submitted for DIF. In order to make a final diagnosis, it is important to correlate the clinical details, history of prior treatment, histomorphological and DIF findings.

Keywords: Antibodies, Histomorphology, Histopathology, Skin Biopsy

INTRODUCTION

Vesiculobullous disorder is an autoimmune disease which is rare with an incidence of 0.5 to 3.2 cases/100,000 population [1]. It is a dermatological disorder in which the autoantibodies are directed against antigens present in epidermis or dermoepidermal junction [2,3]. Vesiculobullous diseases are the manifestations of skin response to various external and internal stimuli and it is one of the most important primary morphological patterns of skin reaction. Blisters include both vesicles and bullae which are cavities filled with fluid present either in or underneath the epidermis. Cavities which are less than 0.5 cm in diameter are called vesicles and those which are greater than 0.5 cm in diameter are called bullae [4]. Vesiculobullous disorders can involve mucosal surface of oral cavity, conjunctiva, nasopharynx, oesophagus, urethra, vulva, cervix, scalp, chest, face and upper back. Lesions may also involve the flexor surfaces of the arms and legs, abdomen, axillae and groin [5].

Autoimmune bullous disorders are classified into various groups based on clinical, histomorphological and immunological criteria. They are divided into intraepidermal and subepidermal based on the location of the bulla. Among intraepidermal bullous disorders, pemphigus vulgaris (PV) is most common accounting for around 70%. It is a disease of middle age. It is slightly more common in Asian and Jews and is endemic in parts of Brazil [6]. The exact pathogenesis of these disorders is not known. A genetic predisposition in the pathogenesis of the disease has been suggested as these antibodies can be seen in healthy relatives of the patients [7]. The HLA haplotypes DRB1*0402 and DQB1*0503 are associated with over 95% of PV patient [7]. The association of pemphigus vulgaris with other autoimmune diseases like Rheumatoid arthritis, Sjogren's syndrome, Pernicious anaemia, Systemic Lupus Erythematosus, Scleroderma, Hashimoto's thyroiditis, Addison's disease, Bullous pemphigoid and Myasthenia gravis with or without Thymoma have been reported [7,8,9]. Formation of intraepidermal

blisters result due to loss of adhesion of keratinocytes which occur due to directed pathogenic autoantibodies against intercellular junctions of keratinocytes [10]. Bullous pemphigoid (BP) is the most common subepidermal disorder in which two antigens located within epidermal desmosomes are identified which are BPAg1 (plakin family protein BP230) and BPAg2 (transmembrane collagen 7 or BP180) [11]. Hemidesmosomes mediates the linkage of intermediate filament proteins to the basement membrane proteins. The principal antigen, BPAg1, is associated with cytoplasmic attachment site of hemidesmosomes and is largely within the basal keratinocytes. BPAg2 is a transmembrane collagen that extends through the lamina lucida [11,12]. Subepidermal blister formation is due to loss of attachment of basal keratinocytes to the basement membrane [10,13]. There are various mechanisms which are involved in formation of blisters such as acantholysis, spongiosis, reticular degeneration, cytolysis and basement membrane zone disruption or destruction [Table/Fig-1] [14].

Mechanism of blister formation	Diseases
Acantholysis	Pemphigus, Darrier's disease, Hailey-Hailey disease
Spongiosis	Pemphigus(early), Eczematous dermatitis, Miliaria
Cytolysis	Erythema multiforme, Epidermolysis bullosa simplex
Reticular degeneration	Viral infections
Basement membrane zone destruction	Bullous pemphigoid, Cicatricial pemphigoid, Linear IgA dermatosis, Dermatitis herpetiformis, Epidermolysis bullosa dystrophica, Epidermolysis bullosa acqutisa

[Table/Fig-1]: Disease and their mechanisms of blister formation 14.

Conventional histopathology and immunological tests like direct and indirect immunofluorescence are important techniques for the investigation of patients with vesiculobullous diseases [4]. Immunofluorescence (IF) plays an important role in diagnosis as well as understanding the pathophysiology [15,16]. Positive DIF findings in remission cases also help us to predict early relapse of the disease [17].

Immunofluorescence is a gold standard method for diagnosis of autoimmune vesiculobullous diseases which detects the antibodies bound to the antigen either in the tissue or circulating fluids. The relative simplicity and accuracy has made immunofluorescence a powerful tool in the diagnosis of vesiculobullous disease [1,2,18].

Fluorescence is the property of some substances to absorb light of certain wavelength, remit the light of longer wavelength and such substances are known as fluorochromes. Fluorescein Isothiocynate (FITC) is the most commonly used fluorochrome which produces apple green colour in fluorescence microscope by using mercury vapor

or xenon light source with appropriate exciter and barrier filters [19].

In this technique immune complexes are seen under ultraviolet microscope by using the corresponding antibodies which are attached to a fluorochrome [2,19]. There are two main methods of immunofluorescence - direct and indirect. In direct immunofluorescence, fluorescent bound antibodies are detected on the sample (skin, mucosa), whereas in indirect immunofluorescence, two types of antibodies known as primary and secondary antibodies are used. First, the unlabelled primary antibody specific for the molecule of interest is used and then a second anti-immunoglobulin antibody tagged with a fluorescent dye called as secondary antibody is directed towards the constant portion of first antibody and is done on the sera of patients [20].

DIF method has been used in the present study. DIF test depends upon the primary site of immune deposition, class or types of immunoglobulin, number of immune deposits, intensity of deposits and deposition in other sites besides the main site. All these features help to make a final diagnosis [21].

MATERIALS AND METHODS

This is a prospective study which constitutes clinical, histopathological and DIF features of vesiculobullous diseases conducted on 50 cases received in the department of histopathology of Apollo hospitals, Chennai over a period of two years (November 2014-November 2016). The clinical details were obtained from the histopathology data base of the hospital. Only cases which had the above details were taken up for the study.

After obtaining institutional ethical clearance and patient's consent, a detailed history with particular emphasis on the mode of onset, characteristics and distribution of the lesions were obtained. Biopsies without immunofluorescence, inadequate tissue and cases with incomplete clinical information were excluded from the study. Vesiculobullous lesions secondary to infections, eczema and burns (chemical and thermal) were also excluded from the study. Punch biopsy skin specimens taken from early lesions which were sent for histopathological examination and direct immunofluorescence (DIF) were processed routinely. The light microscopic and immunofluorescence stained slides were studied and correlated with clinical findings.

Histological diagnosis was based on the plane of separation, content of bulla, types of inflammatory cells and changes in the dermis. On the basis of these features vesiculobullous lesions were divided into four categories: subcorneal, intraepidermal, subepidermal and suprabasal. The DIF results were based on primary site of immune deposits, class of immunoglobulin deposits, pattern and the intensity of deposition complex. Based on these features, the cases were grouped into intercellular or dermoepidermal junction deposits of IgG, IgM, IgA or C3. They displayed linear or granular deposits with different intensity.

STATISTICAL ANALYSIS

The sensitivity of DIF and histopathology was looked into which is depicted in the table.

RESULTS

During the study period of two years from November 2014 to November 2016, there were 50 cases of vesiculobullous disorder. Majority of the patients presented between 41-60 years of age. There was a slight female preponderance with a female to male ratio of 3:2. Pemphigus vulgaris constituted 18 cases (36%) followed by 14 cases (28%) of bullous pemphigoid, 5 cases of pemphigus foliaceus (10%), 4 cases of dermatitis herpetiformis (8%), 4 cases of hailey-hailey disease (8%), 2 cases of subcorneal pustular dermatosis (4%), one case each of pemphigus vegetans and erythema multiforme (2% each) and others constituted 2%. Majority of the lesions were distributed in the upper extremities (28%) followed by the trunk (22%), lower extremities (18%) and other locations constituted 32%.

15 of 18 cases of pemphigus vulgaris (83.3%) showed suprabasal separation, 12 of 14 cases of bullous pemphigoid (85.71%) showed sub epidermal separation and all the cases of dermatitis herpetiformis (100%) showed sub epidermal separation. All cases of pemphigus foliaceus showed separation at sub corneal level. 3 cases of bullous pemphigoid showed festooning of dermal papillae. The content in suprabasal bullae were acantholytic cells, neutrophils and eosinophils. Subepidermal bulla were composed of eosinophils and neutrophils.

The clinical diagnosis, histopathological features, DIF pattern of different vesiculobullous disorders are shown [Tables/Fig-2&3].

A slight discordance between clinical, histological and DIF diagnosis was noted in the present study.

Out of 26 cases clinically diagnosed as pemphigus vulgaris, 17 were proved to be pemphigus vulgaris, 3 were bullous pemphigoid, 2 were pemphigus foliaceus, (PF), 1 was pemphigus vegetans, 1 was hailey-hailey disease, 1 was erythema multiforme and 1 was subcorneal pustular dermatosis (SPD) by Histopathological examination (HPE) and immunofluorescence (IF). Out of 16 clinically diagnosed cases as bullous pemphigoid, 11 proved to be bullous pemphigoid, 3 were dermatitis herpetiformis, 1 was pemphigus vulgaris and 1 was hailey-hailey disease. Two cases of bullous impetigo turned out to be PF and hailey-hailey. One case of bullous eczema/Pemphigus vegetans turned out to be SPD. Thus the percentage of concordance and discordance between clinical and IF findings in this study is 62.22% and 37.78% respectively.

Out of 50 cases, 42 cases which showed positive result with immunofluorescence were taken into account to find out concordance rate between histopathology and immunofluorescence and to calculate sensitivity of both. In present study, there is good concordance between histological and direct immunofluorescence results. Histology was conclusive in 17/18 cases of PV and 13/14 cases of BP which were also supported by DIF. One case each of PV and BP in which histopathology was not diagnostic, DIF helped us to make final diagnosis. There was 100% concordance between histopathology and DIF in all cases of PF. Three out of five cases were proven to be DH both by histopathology as well as by DIF. One case in which the histological findings were specific for DH but DIF was negative and in one case

Final histopathological diagnosis	Intraepidermal	Suprabasal	Subepidermal	Subcorneal	Total
Pemphigus vulgaris	3	15			18
Pemphigus foliaceus				5	5
Hailey-Hailey disease	1	3			4
Pemphigus vegetans	1				1
Bullous pemphigoid		2	12		14
Dermatitis herpetiformis			4		4
Subcorneal pustular dermatosis				2	2
Erythema multiforme		1			1
Others			1		1
Total	5	21	17	7	50

[Table/Fig-2]: Plane of Separation.

Site of immune deposit	Frequency (n)	Percentage (%)
Dermoepidermal junction	17	34
Intercellular junction	25	50
No deposits	8	16
Total	50	100

[Table/Fig-3]: Primary site of immune deposition.

where histology was not conclusive, DIF was positive. One case which was histologically diagnosed as pemphigus vegetans showed intercellular fluorescence [Table/Fig-4].

In remaining 8 cases, DIF was negative. One case by histomorphology was suggestive of DH, but no granular deposits was seen by DIF as already described above. Other cases were hailey-hailey (4), erythema multiforme

(1), subcorneal pustular dermatosis (2). Histomorphological features in all these cases were typical with negative DIF which helped in making the correct diagnosis. The sensitivity of immunofluorescence in both pemphigus and pemphigoid group were 100% whereas, sensitivity of histopathology was 95.83% and 92.85% respectively [Table/Fig-5].

Final Diagnosis	Histopathology		Immunofluorescence	
	Diagnostic	Non-diagnostic	Positive	Negative
PV (n=18)	17	1	18	0
PF (n=5)	5	0	5	0
BP (n=14)	13	1	14	0
DH (n=4)	3	1	4	0
P Veg (n=1)	1	0	1	0

[Table/Fig-4]: Comparison of Histopathology and Immunofluorescence findings in Vesiculobullous disorders.

Disease	Sensitivity of DIF (%)	Sensitivity of histopathology(%)
Pemphigus group (n=24)	24 (100%)	23 (95.83%)
Pemphigoid group (n=14)	14 (100%)	13 (92.85%)

[Table/Fig-5]: Sensitivity of DIF and Histopathology

DISCUSSION

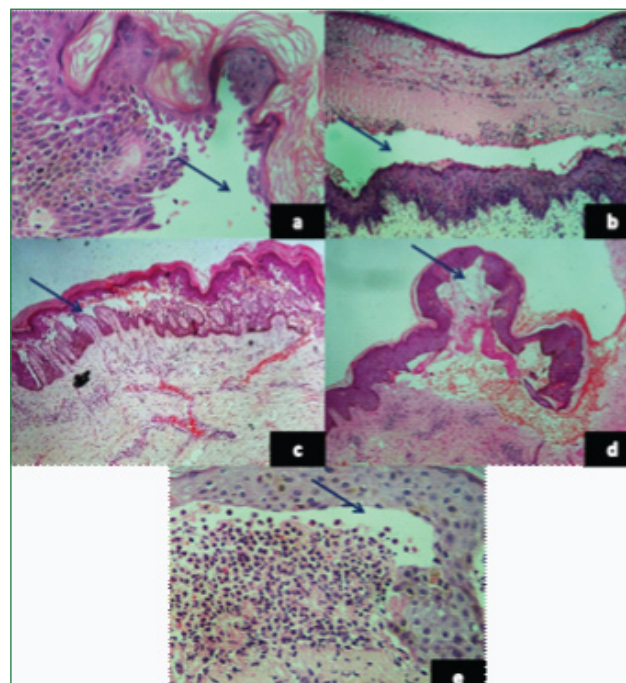
Vesiculobullous disorders present clinically with various cutaneous manifestations based on the severity of the lesion [3]. It also depends on stage of the disease and prior treatment received for the disease. Early and accurate diagnosis of disease is essential to prevent morbidity and mortality which is highlighted by this study. All patients may not present clinically with classical morphological features. In such conditions where clinical diagnosis is difficult, biopsy from the lesion helps in arriving at a diagnosis. In cases where histopathological findings are not typical, DIF helps to diagnose the disease which shows typical pattern of immune deposition at the appropriate site. In some cases DIF can be negative, which may be due to stage of the disease or prior treatment received [3,6].

In this study, an attempt was made to study the clinical, histopathological and direct immunofluorescence findings of various autoimmune bullous disorders. In the current study, pemphigus vulgaris constituted the most common vesiculobullous disorder followed by bullous pemphigoid and pemphigus foliaceus as seen in study of Rizvi SR et al., [22]. Pemphigus vulgaris constituted 36% (18 out of 50 cases) which is comparable with the results of Bhalara R et al., [23] with 35.8%. Bullous pemphigoid constituted 28%, which is similar to the study of Deepti SP et al., [24]. Pemphigus foliaceus and pemphigus vegetans were found to be 10% and 2% similar to the study by Ahmed K et al., [25]. We found that vesiculobullous disorders were more common in

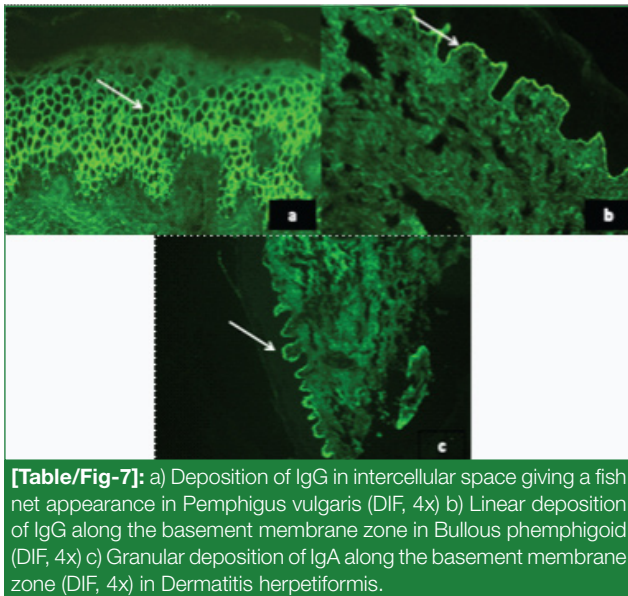
females with a male to female ratio of 2:3 which is comparable with the result by Deepti SP et al., [24] and Patel PR et al., [4]. Majority of disorders were seen in patients between 40 to 60 years of age. Most common site of involvement was upper extremity followed by trunk, lower extremity whereas, trunk and extremities were the frequently involved sites as observed by Leena J B et al., [26].

All cases of pemphigus vulgaris showed deposits of IgG in intercellular space of epidermis in fishnet pattern as observed by Khannan CK [27] and Deepti SP et al., [24]. All cases of BP showed basement membrane zone deposits predominantly of IgG in a linear pattern and 13 of 14 cases mainly showed linear deposits of C3c. All cases of bullous pemphigoid also showed linear deposits of IgG and C3c in dermoepidermal junction in the study by Jindal A et al., [28] and Khannan CK et al., [27]. All cases of DH showed granular deposits of IgA and C3c deposition as seen by Jindal A et al., [28].

The histopathological and immunofluorescence characteristics are shown in [Tables/Fig-6 and 7]. Discordance between clinical, histopathological and DIF diagnosis was noted in the present study. Histopathologic features helped us to diagnose the variants of pemphigus such as pemphigus vegetans, pemphigus foliaceus and hailey-hailey disease based on negative IF. One case of erythema multiforme and one case of subcorneal pustular dermatosis was diagnosed by histomorphological features and negative DIF supported the



[Table/Fig-6]: a) Suprabasal blister with acantholytic cells in Pemphigus vulgaris (H & E, 10x) b) Subcorneal bulla with acanthocytes and inflammatory cells in Pemphigus foliaceus (H & E, 10x) c) Dilapidated brick wall appearance in Hailey Hailey disease (H & E, 10x) d) Subepidermal bulla with fibrin and inflammatory cells in Bullous pemphigoid (H & E; 10x) e) Subepidermal bulla with neutrophils in Dermatitis herpetiformis (H & E; 40x).



[Table/Fig-7]: a) Deposition of IgG in intercellular space giving a fish net appearance in Pemphigus vulgaris (DIF, 4x) b) Linear deposition of IgG along the basement membrane zone in Bullous pemphigoid (DIF, 4x) c) Granular deposition of IgA along the basement membrane zone (DIF, 4x) in Dermatitis herpetiformis.

correct diagnosis. Discordance was also seen in the study of Arundhati S et al., [15] in which out of 36 clinically diagnosed cases as pemphigus vulgaris, 26 were PV, 3 were BP, 2 were PF, 1 was bullous systemic lupus erythematosus, 1 was erythema multiforme and 1 was herpes gestations. Clinically diagnosed 4 cases of pemphigus foliaceus turned out to be PV (1), SPD (2) and non-specific (1). Out of 4 cases of DH, 1 was BP and 3 were non-specific. Thus, concordance and discordance was 57.77% and 42.22% respectively. Similar discordance was also seen in the study of Mysorekar W et al., [1].

DI findings were similar in pemphigus vulgaris, pemphigus foliaceus and pemphigus vegetans, but histopathology helps in differentiating them. Similarly, all cases of bullous pemphigoid and dermatitis herpetiformis showed basement membrane zone fluorescence. On the basis of histopathology, type and pattern of immune deposit, final diagnosis can be made. In the present study one case was suggestive of DH by histomorphology, but granular deposits were not seen by DIF. Similar finding was also observed by Mysorekar et al., [1] in which all the four biopsy proven cases of DH were negative in DIF but two of them responded to specific treatment for DH. The discrepancy is due to the absence of IgA deposition in early course of the disease and in such cases, clinical correlation is advised. Study by Leena JB et al., [26] and Sousa L et al., [29] also showed similar findings. On the other hand, another case diagnosed as dermatitis herpetiformis clinically, histology was not conclusive for DH but DIF showed granular deposit of IgA. Similar findings was also described by Huber C et al., [30] in which diagnosis was confirmed by serological studies which responded rapidly to dapsone treatment.

LIMITATION

A larger series needs to be evaluated to know the exact concordance and discordance rates of the vesiculobullous disorders.

CONCLUSION

DIF is helpful to support clinical diagnosis even if histology is non diagnostic and in the absence of characteristic DIF pattern, one should rely on the clinical features, serology and response to treatment which helps us to make the final diagnosis.

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FINANCIAL OR OTHER COMPETING INTERESTS:

None.

Date of Publishing: Oct 01, 2018