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A cross-sectional study of clinical, histopathological and direct immunofluorescence diagnosis in autoimmune bullous diseases

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ABSTRACT

Background: Immunobullous diseases are morphologically heterogeneous and the differentiation between various subtypes is essential for proper treatment and prognosis. Aim of our study was to analyze and correlate clinical, histopathological and immunofluorescence findings in autoimmune bullous diseases. **Materials and Methods:** A cross-sectional study was done over a period of two years (2010-2012) after approval of the ethics committee. Sixty patients, who met the inclusion criteria of immunobullous disease, were included in the study. Skin biopsy for histopathology and direct immunofluorescence (DIF) examination was taken. DIF using salt-split technique was done in few of the cases. The final diagnosis was based on clinical, histopathology and DIF findings. Pearson's coefficient of correlation (r) was calculated. Statistical Analysis was done using Epi info version. 7.0. **Results:** Fifty-three cases with clinical diagnosis of autoimmune bullous diseases were evaluated. In 88.6% of cases, histopathology diagnosis was consistent with clinical diagnosis and in 75.5% of cases, DIF findings were consistent with clinical diagnosis. A positive relation was seen between clinical and DIF findings with $r = 0.65$ and between histopathology and DIF findings with $r = 0.75$. DIF positivity was seen in 100% cases of bullous pemphigoid (BP) and pemphigus foliaceous and 94.7% cases of pemphigus vulgaris, which was statistically significant with $P < 0.05$. In DIF salt-split test, deposition was seen on roof of blister in BP whereas on floor in epidermolysis bullosa acquisita. **Conclusion:** Our study provides evidence-based guidance for the diagnosis and classification of various immunobullous disorders. DIF test should be done in conjunction with histopathology for definitive diagnosis and to minimize both: False-positive and false-negative results.

Key words: Histopathology, immunobullous, immunofluorescence

INTRODUCTION

Dermatopathology, as pioneered by Unna, affords a keystone not only for modern dermatology but also for the use of immunofluorescence in studies of skin immunopathology.[1] Histopathologic studies of Walter Lever differentiated what we now call pemphigus and pemphigoid.[2] Immunofluorescent studies by Ernst Beutner and his group revealed the autoimmune etiologies of pemphigus and pemphigoid.[1] Now, other immunologic methods also contribute to our understanding.[3,4]

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Autoimmune blistering diseases are associated with an autoimmune response directed to structural proteins mediating cell-cell and cell-matrix adhesion in the skin.[5] Autoimmune blistering diseases are classified based on the ultrastructural site of deposition of immunoreactants and on the molecular target of autoantibodies.[6]

Diseases of the pemphigus group are associated with autoantibodies to epidermal components mediating cell-cell adhesion and are characterized by acantholytic

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blisters within the epidermis.[7] Tissue-bound and circulating autoantibodies to the dermal-epidermal junction are characteristic immunopathological features of subepidermal autoimmune bullous diseases.[5,8]

Direct immunofluorescence (DIF) is more sensitive and also more frequently positive than indirect immunofluorescence (IIF) in patients in clinical remission and more valuable for detection of immunological activity of the disease.[9]

MATERIALS AND METHODS

A cross-sectional study was conducted in Department of Dermatology, Smt. S. C. L Hospital, Smt. N. H. L Municipal Medical College from June 2010 to November 2012 after being approved by the Institutional ethics committee Board. The patients were selected from the in and outpatient department of the Department of Dermatology, and informed consent was obtained. Patients with a clinical diagnosis of autoimmune bullous disorders, irrespective of age and gender and willing to participate in the study were included. Patients not willing to be the part of the study or undergo the required investigations were excluded.

Clinical data were recorded in the form of:

- Demographic information
- Detailed clinical history taking
- General and dermatological examination
- Clinical photographs
- Routine investigations
- Tzanck smear
- Skin biopsy for histopathological evaluation
- Direct immunofluorescence staining of peri-lesional skin specimen.

A total of 53 cases, clinically diagnosed with autoimmune bullous dermatological disorders were included in the study. Skin biopsy sample (punch biopsy/excision biopsy) was the standard procedure for obtaining samples.

The biopsy specimen for histopathology was sent in 10% formalin and for DIF in Michel medium. In the laboratory, specimens were processed, stained and findings were recorded. DIF using a salt-split method was performed in a few cases, on the specimen that has previously been investigated by routine DIF. The specimen was incubated in 10 ml 1mol/L NaCl at 40°C for 48-72 hours. Epidermis was separated from dermis easily and DIF staining was carried out. Facilities for IIF were not available at our center, hence not performed. While reporting DIF finding of skin biopsy, the fluorescent staining was described under the following headings:

1. Type of immunoreactant: IgG, IgA, IgM, C3, and fibrin
2. Location of immune deposits: Intercellular spaces (ICS) in epidermis/basement membrane zone (BMZ)/blood vessels/hair shaft
3. Pattern of immune complex deposits: Granular or linear.

The description of all these staining characteristics leads to immunopathological diagnosis. Digital photography was done to document the results. In this way, both histopathological and DIF examination were carried out in all included cases and findings were recorded. The definite diagnosis of these patients was based on clinical, histopathological and immunofluorescence findings.

Statistical analysis

Analysis was done in Epi info version 7 and word excel. The Z-test of significance of difference in proportions of large samples was used. The Chi-square test with Yates correction was used to find the significance of difference in two more than two proportions. Pearson's correlation coefficient (r) was found. Above tests were used where ever applicable according to the sample size and type of data.

RESULTS

The study group comprised of 53 cases of autoimmune bullous disorders of the skin, with 30 females (56.4%) and 23 males (43.6%). The age range of cases was between 5 months and 88 years with mean value 39.7 years.

The clinical diagnosis of the predominant cases were pemphigus vulgaris (PV) in 19 cases (31.6%), dermatitis herpetiformis (DH) in 11 (18.3%), bullous pemphigoid (BP) in 10 (16.6%) and pemphigus foliaceous (PF) in 3 cases (5%). Two cases (3.3%) each of pemphigus erythematosus (PE), bullous SLE, linear IgA dermatosis (LAD), were seen in Table 1.

Discordance between clinical, histopathological and DIF diagnosis was noted [Table 2]. Overall, in 47 cases (88.6%), histopathology findings were consistent with the clinical diagnosis, and in 40 cases (75.5%), DIF findings were consistent with the clinical and histopathology diagnosis. Figure 1 shows the correlation

between clinical and histopathology diagnosis. On applying Pearson's correlation coefficient, a positive relation was seen between clinical and histopathology diagnosis with $r = 0.97$. Figure 2 shows correlation between clinical and DIF diagnosis. A positive relation was seen between clinical and DIF diagnosis with $r = 0.65$. Figure 3 shows correlation between histopathology and DIF diagnosis. A positive relation was seen between histopathology and DIF diagnosis with $r = 0.75$.

DIF pattern of deposition of immunoreactants in different disorders are shown in Table 3.

1. Pemphigus vulgaris: Out of total 19 cases, 94.7% showed DIF positivity ($N = 18$). IgG was the

Table 1: Types of blistering disorders on clinical examination

Clinical types of disease	No.	Percentage
Pemphigus vulgaris	19	31.6
Pemphigus foliaceous	3	5
Pemphigus vegetans	1	1.6
Pemphigus erythematosus	2	3.3
Bullous pemphigoid	10	16.6
Lichen planus pemphigoid	1	1.6
Pemphigoid gestationis	1	1.6
Linear IgA dermatosis	2	3.3
Bullous SLE	2	3.3
Dermatitis herpetiformis	11	18.3
CBDC	1	1.6

SLE: Systemic lupus erythematosus, IgA: Immunoglobulin A, CBDC: Chronic bullous disease of childhood

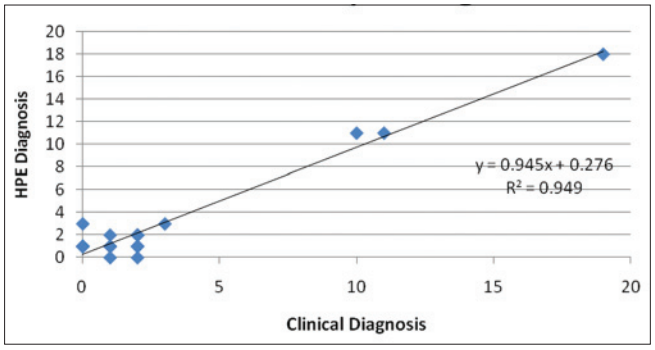

Figure 1: Correlation between clinical and histopathological diagnoses

Table 2: Clinical, histopathological and DIF findings in 53 cases

Disease entity	Clinical diagnosis	Consistent histopathological diagnosis		DIF findings		Final diagnosis
		Positive	Negative	Positive	Negatives	
Pemphigus vulgaris	19	18	1	18	1	PV (*N*=18)
Dermatitis herpetiformis	11	11	0	3	8	DH (*N*=3)
Bullous pemphigoid*	10	11	0	11	0	BP (*N*=11)
Pemphigus foliaceous**	3	4	0	4	0	PF (*N*=4)
Linear IgA dermatosis	2	0	2	0	2	BP (*N*=1), HSV (*N*=1)
Pemphigus erythematosus	2	2	0	2	0	PE (*N*=2)
Bullous SLE	2	2	0	2	0	Bullous SLE (*N*=2)
Pemphigus vegetans	1	1	0	1	0	PVG (*N*=1)
Lichen planus pemphigoid ±	1	2	0	2	0	LPP (*N*=2)
pemphigoid gestationis	1	1	0	0	1	PG (*N*=1)
CBDC	1	0	1	0	1	Bullous mastocytosis (*N*=1)
EBA[€]	0	1	0	1	0	EBA (*N*=1)
Pemphigus herpetiformis	0	1	0	1	0	PH (*N*=1)

PV: Pemphigus vulgaris, PF: Pemphigus foliaceous, DH: Dermatits herpetiformis, PVG: Pemphigus vegetans, PE: Pemphigus erythematosus, CBDC: Chronic bullous disease of childhood, EBA: Epidermolysis bullosa acquisita, LPP: Lichen planus pemphigoid, PH: Pemphigus herpetiformis, PG: Pemphigoid gestationis, SLE: Systemic lupus erythematosus, *one case of LAD showed features of BP in HPE and DIF, **one case PV on histopathology and DIF showed features of PF, ±one case with d/d DH and bullous LP, turned out to be LPP on HPE and DIF, [€]final diagnosis based on DIF salt-split study, DIF: Direct immunofluorescence

Table 3: Summary of DIF findings

Types of disease*	DIF positivity	IgG	IgM	IgA	C3	Site of deposits	*P* value	Results*
Pemphigus vulgaris (*N*=18)	18	15	-	-	3	ICS, epidermis	<0.0001	Significant
Bullous pemphigoid (*N*=11)	11	11	-	-	10	BMZ	0.3000	NS
Pemphigus foliaceous (*N*=4)	4	4	-	-	1	ICS, epidermis	<0.0001	Significant
Dermatitis herpetiformis (*N*=3)	3	-	1	2	1	Dermal papillae	<0.0001	Significant
Pemphigus erythematosus (*N*=2)	2	2	-	-	1	ICS+BMZ	<0.0001	Significant
Lichen planus pemphigoid (*N*=2)	2	2	1	-	-	BMZ	<0.0001	Significant
Bullous SLE (*N*=2)	2	2	-	-	2	BMZ	0.5000	NS
Pemphigus vegetans (*N*=1)	1	1	-	-	1	ICS, epidermis	0.5000	NS
Pemphigus herpetiformis (*N*=1)	1	1	-	-	-	ICS, epidermis	0.5000	NS
EBA (*N*=1)	1	1	-	-	-	BMZ	0.5000	NS
Total	60							

*Type of disease on final diagnosis as mentioned in table 2, EBA: Epidermolysis bullosa acquisita, ICS: Intercellular space, BMZ: Basement membrane zone, NS: Not significant, DIF: Direct immunofluorescence

commonest immunoreactant, deposited in 83.3% cases, followed by C3 in 16.7% [Figure 4]

2. Pemphigus foliaceus: 100% cases showed DIF positivity ($N = 4$). IgG was found in 100% cases followed by C3 in 25% ($N = 4$) cases
3. Pemphigus erythematosus: IgG and IgM deposition at ICS and BMZ was found in 100% cases ($N = 2$)
4. Bullous pemphigoid: 100% ($N = 10$) had DIF test positive. One case clinically diagnosed having LAD, showed histopathological and DIF findings consistent with the diagnosis of vesicular variant of BP. So total 11 patients had DIF findings, suggestive of BP [Table 2] IgG with C3 were predominant immunoreactant, found in 90.9% ($N = 10$) cases, IgG alone was present in only one case that is 9% [Figure 5]
5. Dermatitis herpetiformis: Out of total 11 cases, clinically diagnosed having DH, only 27.27% ($N = 3$) cases had a positive DIF test. IgA was the principal immunoreactant deposited in 67% of cases. IgM deposit along dermal papillae was seen in one case [Figure 6].

On applying Z-test between various types of immunoreactants among various blistering disorders, it was found that immunoreactant deposition was statistically significant in pemphigus vulgaris, pemphigus foliaceous, pemphigus erythematosus, lichen planus pemphigoid and dermatitis herpetiformis, with $P < 0.05$ [Table 3].

Among subepidermal group of disorders, bullous pemphigoid (BP) can mimic epidermolysis bullosa acquisita (EBA) in clinical presentation, histopathological and DIF findings. In the present study, 4 cases having clinical and histopathological differential diagnosis of BP and EBA, direct salt-split immunofluorescence test was performed. Predominantly IgG and/or C3 deposition on the roof of blister cavity was seen in 3 out of 4 cases, favoring diagnosis of BP. In one case, IgG deposits were seen along floor of blister cavity, favoring diagnosis of EBA [Figure 7].

DISCUSSION

The diagnosis of autoimmune bullous diseases is based on the evaluation of clinical findings, histopathology,

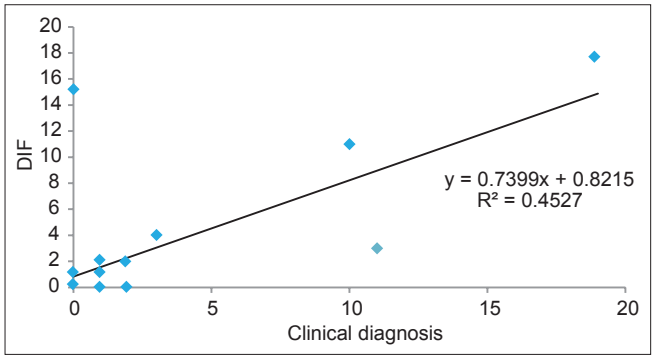

Figure 2: Correlation between clinical and DIF diagnoses

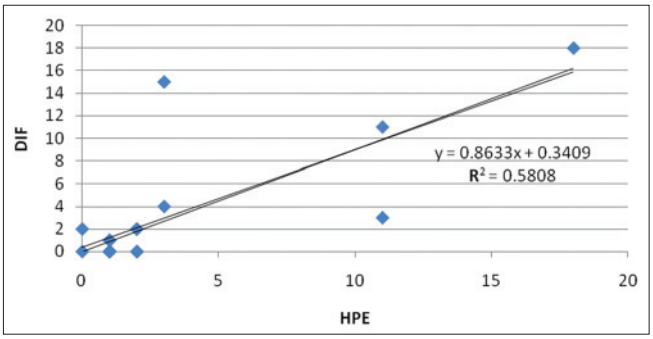

Figure 3: Correlation between histopathological and DIF findings

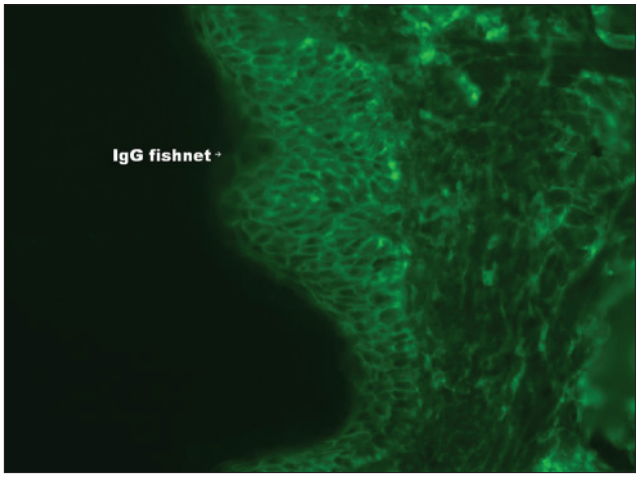

Figure 4: DIF photomicrograph of a case of pemphigus vulgaris showing IgG deposits in ICS of epidermis in fishnet pattern (×20)

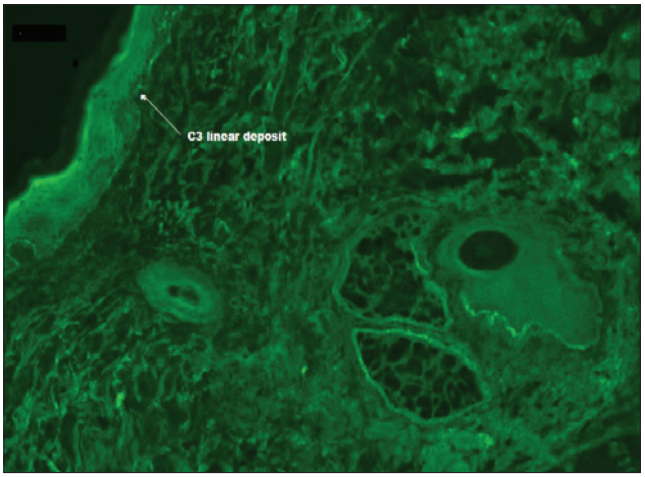

Figure 5: DIF photomicrograph of a case of bullous pemphigoid showing C3 deposits in linear pattern at dermoepidermal junction (×20)

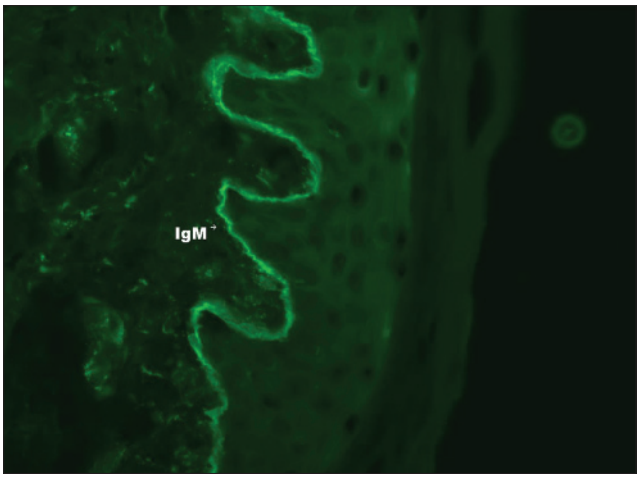

Figure 6: DIF photomicrograph of a case of dermatitis herpetiformis showing IgM deposits at dermal papillae (×20)

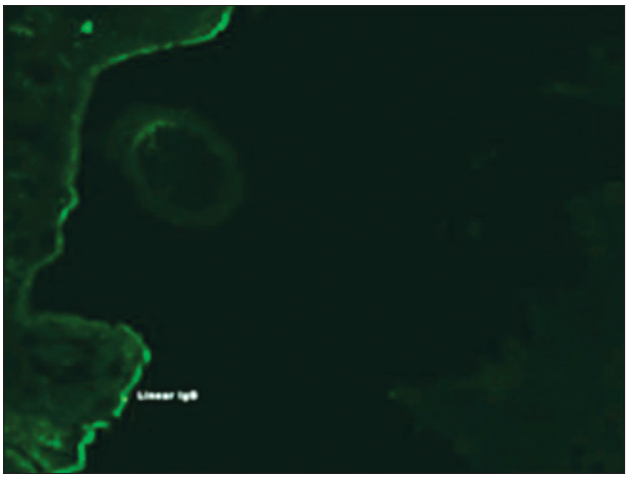

Figure 7: DIF salt-split skin photomicrograph showing linear C3 band at BMZ showing roof pattern in BP (×20)

direct immunofluorescence (DIF) and indirect immunofluorescence.[10]

The differentiation between the entities is important for both treatment modalities and prognosis.[11] Our study validate that DIF is requisite for accurate diagnosis of autoimmune bullous disorders of the skin. Thus, improved detection and affirmation of clinical diagnosis of diseases like DH, LAD, chronic bullous disease of childhood (CBDC), bullous SLE is attainable with DIF only. In the present study, DIF was able to confirm 75.47% of clinically diagnosed cases. In a study by Minz *et al*., DIF was able to detect 70% of clinically diagnosed vesicobullous lesions of the skin.[12]

Out of 19 cases, clinically suspected as pemphigus vulgaris, DIF was found to be consistent with the clinical diagnosis in 18 cases. In all the 3 clinically suspected cases of pemphigus foliaceous, light microscopy and DIF diagnosis was consistent with the clinical diagnosis. One case, clinically suspected as pemphigus vulgaris, after histopathology and DIF examination features turned out to be of pemphigus foliaceous [Table 2]. A total of 10 cases of clinically suspected bullous pemphigoid were analyzed by DIF, 100% cases were consistent and one additional case, clinically diagnosed as LAD was picked up on DIF and light microscopy [Figure 8] when there was no clinical finding in favor of BP. [Table 2] In DIF microscopy, linear IgG and/or C3 deposition in BMZ were observed in all cases [Table 3].

Another case clinically mimicking linear IgA disease, turned out to be a case of disseminated herpes virus infection. Tzank smear and polymerase chain reaction (PCR) from vesicular fluid for herpes simplex was positive, patient responded well to antiviral treatment. Histopathology findings were also in favor of viral etiology and DIF was negative.

Histopathological findings were consistent with the clinical diagnosis in 100% ($N = 11$) cases of dermatitis herpetiformis (DH). Granular deposition of IgA and C3 in the papillary dermis and along the BMZ is diagnostic if DH deposition of IgG or IgM or both is less frequent and less intense.[13,14] However, only in 3 of 11 cases DIF findings were consistent with clinical diagnosis of DH. Our observation of only 27% of cases with a firm diagnosis of DH and actual negative findings by DIF (73%) is in agreement with the sensitivity of DIF reported in literature.[15] In a study of Banu Lebe *et al*.,[11] only in 3 of 58 cases of histopathology and DIF findings were in accordance with clinical diagnosis. The authors reported that the possible reason for this discordance may be due to pruritic papulovesicular eruptions of DH that evolved and disappeared rapidly and could be the inclusion of DH to clinical differential diagnosis by clinicians in many pruritic papulo-vesicular eruptions.[16] Selection of biopsy site, technical errors and treatment status may result in false negativity of DIF.

In one case, initial diagnosis was dermatitis herpetiformis, as histopathology showed subcorneal bullae, eosiniphilic spongiosis, and slight acantholyis. Immunofluorescence invariably showed IgG intercellular deposits in epidermis like pemphigus group. Therefore, diagnosis of pemphigus herpetiformis was considered. In view of atypical clinical manifestations, the lesions are, as a rule, initially diagnosed as various other bullous diseases. The recognition of pemphigus herpetiformis

as a variety of pemphigus is practically important since it differs clinically and histologically both from pemphigus vulgaris and foliaceous and requires a different therapeutic regimen.[17]

One cases with clinical differential diagnosis of EBA or DH, histopathology and DIF findings were in favor of BP or EBA. In DIF salt-split examination, immunoreactant deposition was seen in the floor of blister cavity, favoring the diagnosis of epidermolysis bullosa acquisita [Figure 7].

Out of 2 cases with final diagnosis of lichen planus pemphigoides (LPP), clinical diagnosis was consistent with histopathology and DIF diagnosis in one case. In second case, on basis of clinical presentation, differential diagnosis considered were bullous lichen planus, dermatitis herpetiformis. Histopathology and DIF findings were suggestive of features of LPP [Table 4], [Figure 9].

Lichen planus pemphigoides is an acquired autoimmune dermatosis and LP lesions usually precede the vesicobullous lesions. Clinically, LPP is characterized by developing blisters on lichenoid lesions and on uninvolved skin with more acral distribution of bullous lesions.[18-20] The differential diagnoses include bullous LP[21,22] or association of LP with erythema multiforme. Histological analysis reveals an intense lichenoid reaction with extensive liquefaction of basal keratinocytes. There is no linear immunostaining at the dermo-epidermal junction.

Table 4: Clinical and immunohistological features of cases of lichen planus pemphigoides

Data	Case 1	Case 2
Cutaneous examination	Violaceous maculopapules and plaques of the legs and forearms. Numerous tense blisters on both uninvolved skin and lichenoid lesions	Widespread hyperpigmented papular lesions on the trunk and limbs. Tense bullae on pigmented lesions and normal skin
Nail involvement	Yes	No
Oral mucosa	Erosions, white streak, whitish plaque	-
Histologic features* (biopsy specimen: Vesicle on normal appearing skin)	subepidermal blister containing numerous eosinophils with perivascular inflammatory cell infiltrates of eosinophils, histiocytes, and lymphocytes in the dermis	Subepidermal cleft with perivascular infiltrate of eosinophils and lymphocytes
DIF findings	Linear deposits on BMZ of IgG and IgM	IgG deposit of the BMZ

*Biopsy specimen of violaceous papular lesion showed features of lichen planus, BMZ: Basement membrane zone, DIF: Direct immunofluorescence, IgG: Immunoglobulin G

Out of two cases of pemphigus erythematosus, histopathology in first case showed subcorneal blister and acantholysis [Figure 10] and second biopsy specimen

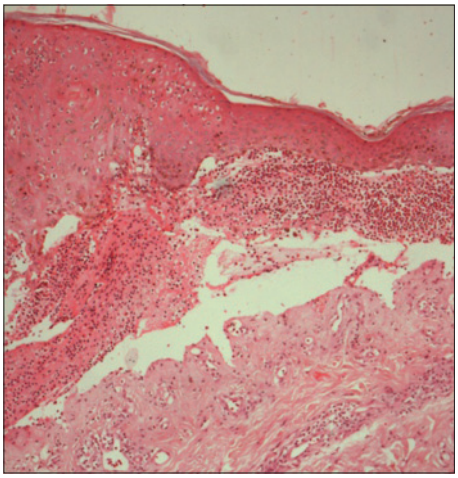

Figure 8: Bullous pemphigoid: Section showing subepidermal blister with eosinophilic infiltrate. (H and E, ×10)

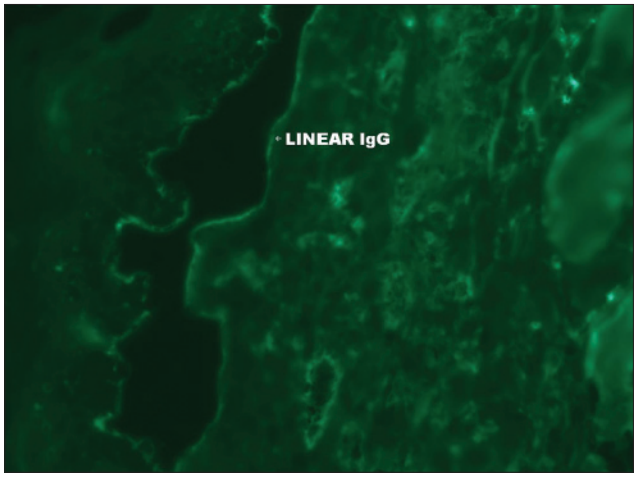

Figure 9: DIF photomicrograph of a case of lichen planus pemphigoid showing IgG deposits at dermoepidermal junction. (×20)

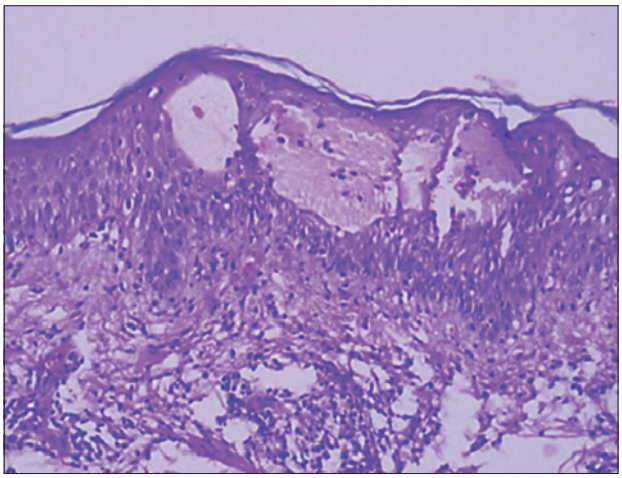

Figure 10: Pemphigus erythematosus: Section showing subcorneal cleft with acantholytic cells. HPE findings are same as of pemphigus foliaceous. (H and E, ×10)

showed intraepidermal blister with perivascular and interstitial dermal infiltrate. DIF of peri-lesional biopsy specimen in both the cases revealed IgG and/or C3 deposits in intercellular epidermis and dermoepidermal junction. So, DIF was helpful as both PE and PF show similar histopathology findings. Because histology is not always specific, immunopathology is very important.

One case clinically suspected of CBDC, histopathology showed subepidermal cleft with upper dermal mast cell infiltrate. Giemsa stain was done, DIF was negative. And a diagnosis of bullous mastocytosis was made.

Cases of limited number in our studies were CBDC, pemphigus vegetans, lichen planus pemphigoid and pemphigoid gestationis.

DIF microscopy evaluates tissue for the presence of autoantibodies, complements, and fibrin. It is important to take biopsy sample for DIF from appropriate site, to place it in correct transport media and to convey it to the laboratory without any delay. Failure at any of these points contributes to false negative results.

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