

Cytological and histopathological evaluation of skin lesions with special reference to bullous lesions

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Abstract

Introduction: Various lesions afflict the skin ranging from non-specific dermatoses to inflammatory diseases to neoplastic changes in various components of the skin.

Aims and Objectives: This study aims to evaluate cytology and histopathology examination for the diagnosis of bullous lesions of the skin and to correlate the clinical diagnosis with the histopathological findings.

Materials and Methods: This was a prospective study carried out in the Department of Pathology, over a period of two and half years. The study included 31 patients who presented with various types of bullous lesions. A detailed history and clinical examination was carried out in all the cases. Cytological (Tzanck smear) and histopathological examination was done for all the patients and the results were correlated with the clinical diagnosis.

Results: The study group comprised of a total of 31 patients. Out of 810 new cases with various skin problems 31 cases were of blistering disorders. There were 17 males and 14 female patients in the study. The male: female ratio being 1.21:1. The patient age ranged from 1 year to 68 years. The maximum number of cases observed were of immunological variety followed by unknown etiological type and lastly was the infective type and congenital variety. Pemphigus vulgaris was most common in the immunological group and more of female patients were affected. Tzanck smear examination was useful in most of the cases and supported the histological diagnosis.

Conclusions: Cytological examination of skin lesions by way of Tzanck smears is a simple and reliable test for the presumptive diagnosis of pemphigus and pemphigoid groups of disorders. It is also helpful in the diagnosis of viral infections. Complete clinical details, cytology and routine histopathology, all together help in the diagnosis of most bullous lesions of skin. In some cases, additional studies such as immunofluorescence tests are required.

Keywords: Bullous lesions of skin, Skin biopsy, Tzanck smears.

Introduction

Various lesions afflict the skin ranging from non-specific dermatoses to inflammatory diseases to neoplastic changes in various components of the skin. Histopathological diagnosis based on clinical correlation and the use of special stains and immunofluorescence techniques as and when required, form the basis of differential diagnoses in dermatoses that appear similar on clinical examination. Most of the cutaneous lesions are easily accessible and hence biopsy is the preferred method for diagnosis. However, cytological examination by Tzanck smear is helpful as it gives a presumptive diagnosis and is much more rapid.

This study aims to evaluate cytology and histopathology examination for the diagnosis of bullous lesions of the skin and to correlate the clinical diagnosis with the histopathological findings.

Materials and Methods

This was a prospective study carried out in the Department of Pathology, Mamata Medical College, Khammam, over a period of two and half years. The study included 31 patients who presented with various types of bullous lesions.

A detailed history and clinical examination was carried out in all the cases. Cytological and histopathological examination was done for all the patients and the results were correlated with the clinical diagnosis.

In all the patients, a small, early representative lesion was selected for preparation of the Tzanck smear. The roof of the blister was removed, the contents were allowed to flow, and the base of the blister gently scraped with a blunt scalpel, so as not to produce bleeding. The material obtained was spread thinly and uniformly on a clean glass slide. The smear was then fixed with 95% ethyl alcohol, stained with Giemsa stain and was examined for acantholytic cells, inflammatory cells and for viral changes under light microscope. Skin biopsy was also taken from all the patients, fixed in neutral formalin, was subjected to routine histopathology processing and sections were stained with hematoxylin and eosin (H and E).

Interpretation

In the microscopic diagnosis of various bullous dermatoses, following features were noted:

1. Level of biopsy separation i.e., intraepidermal (subcorneal, intragranular, suprabasal) and subepidermal.

2. Changes in the epidermis and dermis.
3. Inflammatory infiltrate-density, location and type of cells.

Results

The study group comprised of a total of 31 patients during a period of two and half years. During this period there were 810 new cases with various skin problems. Out of 810 cases 31 cases were of blistering disorders. There were 17 males and 14 female patients in the study. The male:female ratio being 1.21:1. The patient age ranged from 1 year to 68 years.

Table 1: Age wise distribution of 31 cases

Age (yrs.)	Males	Females	Total (%)
0-10	2	-	2 (6.41%)
11-20	1	1	2 (6.41%)
21-30	4	3	7 (22.58%)
31-40	4	4	8 (25.80%)
41-50	2	4	6 (19.35%)
51-60	4	1	5 (16.12%)
61-70	-	1	1 (3.22%)
Total	17 (54.83%)	14 (45.16%)	31 (100 %)

Age wise distribution of blistering diseases:

Maximum number of blistering disorders was observed in fourth decade while least number was seen in the seventh decade. Among genetically mediated blistering disease, 1 case was seen between 21-30 years age group. For immunologically mediated blistering dermatoses the youngest patient was a one year old boy and the oldest patient was a 68 year old female. Pemphigus vulgaris (PV) was observed mostly in fifth decade. Two cases were observed in third and seventh decades. Pemphigus vegetans (P. Vg) was observed in sixth decade while one case of pemphigus erythematosus (PE) was seen in the third decade. Cases of pemphigus foliaceus (PF) were in fourth and fifth decades. Patients of bullous pemphigoid (BP) were observed in first, third, fourth and sixth decades. Dermatitis herpetiformis (DH) cases were seen in third and sixth decades. A single case of chronic bullous dermatosis of childhood (CBDC) was seen in the first decade. A single case of bullous discoid lupus erythematosus (BDLE) was observed in the third decade. Two cases of bullous erythema multiforme (BEM) were seen in second and fourth decade. A single case of sub corneal pustular dermatosis (SCPD) was seen in fifth decade. One case of urticarial vasculitis case was seen in fourth decade. One case of bullous erythema nodosumleprosum (BENL) case was seen in second decade. While one case of bullous lichen planus (BLP) was seen in third decade. One case of staphylococcal scalded skin syndrome (SSSS) was seen in first decade. One case each of herpes simplex (HS) was seen in third while

herpes zoster (HZ) was present in fourth decade; one case of TAD was seen in third decade.

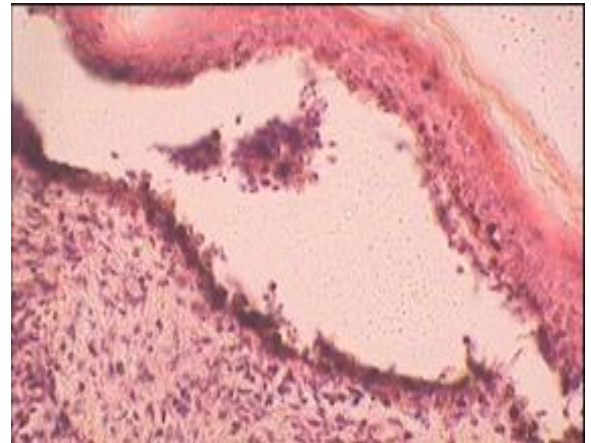


Fig. a: Suprabasilar clefting with moderate number of acantholytic cells

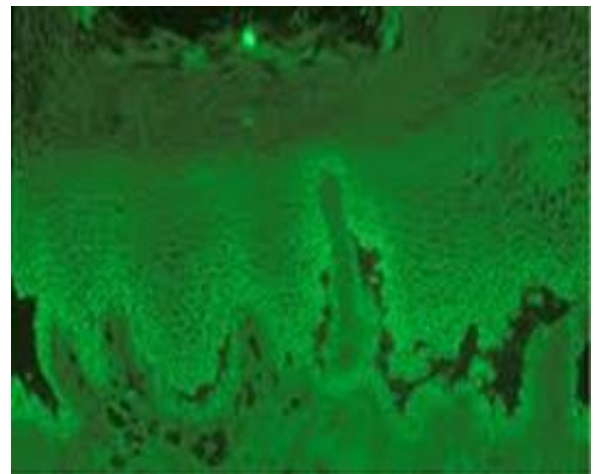


Fig. b: IgG deposited in a network pattern at intercellular spaces (ICS)

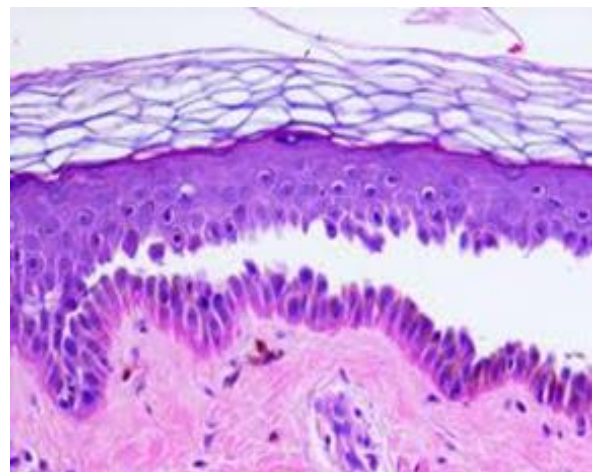


Fig. c: Suprabasal clefting with moderate number of acantholytic cells. Dermis showed perivascular lymph mononuclear cells infiltration

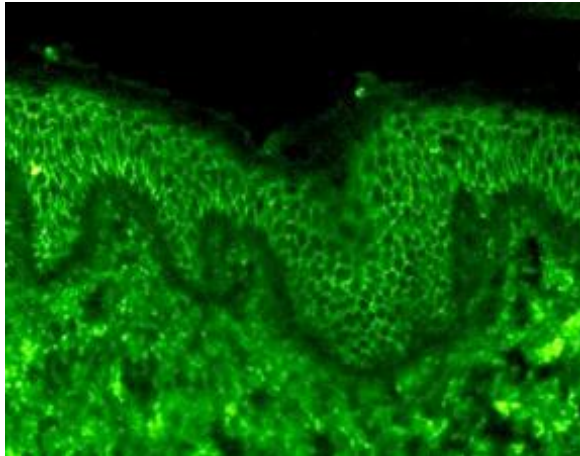


Fig. d: Intercellular granular deposits of IgG in Pemphigus vulgaris

Incidence

Out of 810 cases of various skin lesions, 31 bullous skin lesions were encountered and all of the cases were selected for this study. The overall incidence of vesiculo-bullous disorders was 3.82% in our study. Vesiculo-bullous diseases recorded were categorized into 4 groups based on the etiology.

Table 2: Incidence of types of blistering disorders

Type	No. of cases	Percentage (%)
Congenital	1	3.23
Immunological	20	64.52
Infective	4	12.90
Unknown	6	19.35
Total	31	100

The maximum number of cases observed were of immunological variety (64.52%) followed by unknown etiological type (19.35%), infective type (12.90%) and congenital variety (3.23%).

Among immunologically mediated blistering disorders following incidence was observed: Out of 20 cases, 11 cases belonged to pemphigus group (55%), 5 cases to pemphigoid group (25%), 2 cases of DH (10%), 1 case of CBDC (5%) and 1 case of bullous DLE (5%).

Sub types of pemphigus group: Out of 11 cases in pemphigus group, 7 cases (63.64%) belonged to pemphigus vulgaris, 2 cases to pemphigus foliaceus (18.18%), 1 99.09%) each to pemphigus vegetans and pemphigus erythematosus.

Gender wise distribution: In the present study of 31 cases it was observed that there was increased male (54.83%) preponderance compared to female (45.16%).

The male to female ratio was 1.21:1. In this study 10 cases (50%) male and 10 cases (50%) of female patients were found to be affected in immunological blistering group of disorders. Among unknown etiological cases 12.9% males and 6.45% females were affected. In the infectious category 9.68% males and 3.23% females were affected.

Table 3 Gender wise distribution in 31 cases

Type	Males	Females
Congenital	1 (3.23%)	0 (0)
Immunological	10 (32.26%)	10 (32.26)
Unknown	4 (12.90%)	2 (6.45%)
Infectious	3 (9.68%)	1 (3.23%)
Total	18 (58.07%)	13 (41.94%)

Among unknown etiological disorders 66.67% males and 33.34% females are found to be affected. There were 4 male patients (66.67%), out of which 2 cases were of bullous erythema multiforme and one case each of transient acantholytic dermatoses and of urticarial vasculitis. There were 2 female patients (33.34%), one case each of subcorneal pustular dermatosis and bullous lichen planus.

Infectious blistering disorders observed in this study affected males, 3 cases (75%) more commonly when compared to female patients 1 case (25%). There was single case each of herpes simplex, herpes zoster and staphylococcal scalded skin syndrome in male patients. There was a single case of bullous erythema nodosum/leprosum in a female patient who was a known case of leprosy.

Table 4: Clinical diagnosis, Tzanck smear and biopsy findings

Clinical Diagnosis	No. of Cases	Tzanck Smear	Biopsy
Pemphigus vulgaris	7	Acantholytic cells	Pemphigus vulgaris
Pemphigus foliaceus	2		Pemphigus foliaceus
Pemphigus vegetans	1		Pemphigus vegetans
Pemphigus erythematosus	1		Pemphigus erythematosus
Bullous pemphigoid	5	Eosinophils	Bullous pemphigoid
CBDC	2	Negative	CBDC
Bullous erythema multiforme	2	Negative	Bullous erythema multiforme
Dermatitis herpetiformis	1	Negative	Dermatitis herpetiformis
DH/BP	1	Negative	Nonspecific findings

BDLE	1	Negative	BDLE
Transient acantholytic dermatosis	1	Negative	Transient acantholytic dermatosis
Urticarial vasculitis	1	Negative	Urticarial vasculitis
SCPD	1	Neutrophils	SCPD
SSSS	1	Acantholytic cells	SSSS
Herpes simplex	1	Multinucleated cells	Herpes simplex
Herpes zoster	1	Multinucleated cells	Herpes zoster
Bullous lichen planus	1	Negative	Bullous lichen planus
CBFP	1	Acantholytic cells	CBFP
Total	31		

Discussion

Blistering diseases of human skin are due to various etiologies and have variable clinical appearances. These diseases may respond to a variety of therapeutic agents. It is necessary to diagnose and treat these conditions early as some of them are potentially life threatening. Histopathological examination is a simple and consistent method for diagnosis of blistering disease.

Incidence

In the present study, the incidence of bullous dermatoses was 3.82% of all skin lesions. Exact incidences of these cases are not reported from India. A 0.3% incidence of various bullous dermatoses was reported by Kanwar et al.^[1] from Libya. The higher incidence in the present study could be due to geographical variations and availability of improvised diagnostic methods.

In the present study, majority of cases belonged to immunological blistering diseases followed by unknown etiological cases and then by the infective blistering cases. Congenital blistering dermatoses were sporadic.

Among immunologically mediated blistering disorders, pemphigus groups accounted for more number of cases followed by the pemphigoid group while DH, CBDC and BDLE were sporadic in incidence. This is in agreement with the observation of Kanwar et al.^[1] Pemphigus group is reported to be common in India.^[2] Highest number of blistering cases was seen in fourth decade (25.80%) and lowest in seventh decade (3.22%). Immunological blisters especially that of PV formed the bulk in fourth decade. An overall gender ratio for immunological blistering lesions was 1:1 in this study.

Immunologically mediated blistering disorders: Out of 810 cases, there were 11 cases (1.35 %) of pemphigus group. The incidence of pemphigus among

the dermatology out patients has variation from 0.09 to 1.8%.^[3,4]

These constituted a major segment in the study (64.52%). Among the 20 cases of immunological disorders, there were 11 cases (55%) of pemphigus group. In the present study, Pemphigus vulgaris accounted for 11 cases (63.63%) followed by pemphigus foliaceus 18.18%. This is in concurrence with observations made by Bedi et al.^[2] and Sehgal et al.^[5]

Pemphigus vulgaris: Seven cases of pemphigus vulgaris were seen in the present study. Clinically, all cases of PV presented with itchy or burning, tense or flaccid vesicles, bullae and erosions predominantly affecting trunk and extremities. These findings have been described by many authors.^[6,7] Only two cases (28.57%) showed oral mucosal involvement. Oral involvement is usually observed in 40-50% cases of PV.^[7,8] Presence of grouping and variability of Nikolsky sign and AHS (Asboe Hansen sign) lead to differential diagnosis of BP and DH. Acantholytic cells were demonstrable in all cases. Histopathology showed suprabasalclefting and acantholysis in all the 7 cases, leading to histological diagnosis of PV.

Tzanck smears are especially useful in the diagnosis of vesiculo-bullous lesions of pemphigus vulgaris, where the typical acantholytic cells are seen on the smear and are also called as 'Tzanck cells'^[9] whereas, the presence of numerous eosinophils points to a diagnosis of bullous pemphigoid. In a study by Durdu et al.^[10] the sensitivity of 'acantholytic cells' for pemphigus vulgaris was reported as high as 100%.

Pemphigus vegetans: Only one case of P. Vg was observed. Clinically, there was history of vesicles and erosions few months prior to presentation. The patient gave history of lesions in rural areas for almost three days which were associated with mild burning type of pain. Discharge was present from these lesions. Nikolsky sign was demonstrable. Similar clinical findings were described by various authors.^[7,8]

Cytology showed few acantholytic cells which was consistent with pemphigus group. Histologically, the presence of moderate acanthosis, mild hyperkeratosis and suprabasal cleavage confirmed it to be P. Vg.^[11]

Pemphigus erythematosus (PE): Single case of PE was seen in this study making it sporadic in incidence. Clinically, patient had erosive, scaly lesions accompanied by burning sensation over malar area of face, neck, trunk and extremities. Nikolsky sign and AHS are usually present while it was absent in this case. A diagnosis of PE was considered clinically. Cytology showed acantholytic cells which placed this case in pemphigus group.

Histological presence of hyperkeratosis and mild acanthosis with suprabasalclefting supported the

diagnosis of PE partially fulfilling the criteria by Lever et al.^[11] In this case few melanophages were observed in upper dermis which was not described previously.

Pemphigus foliaceus: In this study, two cases of PF were seen. Clinically, presence of vesicles, bullae, erythematous erosions, crusting and scaling at periphery with generalized distribution, absence of Nikolsky sign lead to the diagnosis of PF.

Cytology for acantholytic cells was consistent for pemphigus group. Histopathological presence of subcorneal clefting and acantholysis favored a possible diagnosis of PF.

Bullous pemphigoid (BP): There were five cases of bullous pemphigoid. The age varied from 1 year to 54 years. Bullous pemphigoid is known to have a wide variation in age at presentation.^[12] In one case, patient was 1 year old and had blisters from 15 days after birth and clinically was thought of having Epidermolysis bullosa or CBDC. Another patient a 25 year old female presented in third trimester of pregnancy with clinical diagnosis bullous pemphigoid or herpes gestationis. Histopathologically, subepidermal bullae were present in all cases. The bullae showed fibrinoid material and inflammatory cells within. One case showed wiping out of basal cells in one section where bulla was present while other sections adjacent to blister showed hydropic degeneration. All cases showed eosinophilic infiltration in the dermis and were consistent with the diagnosis.^[8,11]

Dermatitis heretiformis (DH): In the present study, two cases of DH were encountered. Ages of the patients were 34 and 53 years. The mean age of onset was considered as fourth decade which coincides with present study. DH cases have been reported from an age of 10 months to 90 years.^[12] Both cases presented with severely pruritic vesicles with urticarial lesions showing grouping on trunk, upper extremities and one case had lesions over the scalp also. Excoriations were present. One case showed targetoid lesions elsewhere giving clinical suspicion of EM. Nikolsky sign and AHS were negative. The presence of erythematous base suggested considering BP also as a differential diagnosis for one of the patient. The clinical features described by Eileen PD and John J. Z. were satisfied so the differential diagnosis of BP was suggested.^[12]

Tzanck smears were negative for any cells. Histopathology of one case showed sub epidermal bulla without any contents. Dermis showed papillary neutrophilic micro abscesses. There was neutrophilic, eosinophilic and lymphocytic infiltration in upper dermis. A histological diagnosis of DH was confirmed as it satisfied the histological features described by Lever and Provost et al.^[11,12] The other case did not show any other typical findings except for sub epidermal bulla and was reported as having nonspecific

findings. Immunofluorescence studies may be helpful in such cases.

Chronic bullous disease of childhood (CBDC): Only one case of CBDC was encountered in the present study. The patient was a boy aged 5 years. The case showed multiple discrete and grouped tense vesicles and bullae which had generalized distribution. Vesicles showed 'cluster of jewels' configuration in few areas. Nikolsky sign and AHS were negative. CBDC was made as first diagnosis as it satisfied the clinical features and age of occurrence mentioned by various observers.^[7,8] BP of childhood and juvenile DH were also thought of.

Cytology was negative. Histopathology showed overlapping findings between DH, BP and CBDC due to presence of sub epidermal blister with dermal neutrophilic infiltrate.

Bullous discoid lupus erythematosus (BDLE): One case of BDLE was encountered in a 40 year old female. Vesicular lesions were limited to face (malar area), upper extremities and upper chest. The surrounding skin was depigmented and mildly scaly. Nikolsky sign and AHS were negative. The clinical features were like that as described by Pye et al.^[7,8] This lead to a clinical diagnosis of BDLE. Histology showed sub epidermal cleavage with neutrophils. Neutrophilic micro abscesses were present. Changes in upper dermis included dermo-epidermal separation at BMZ with relatively intact epidermis and an acute inflammatory infiltrate mainly of neutrophils in upper dermis. In many cases inflammatory infiltrate is accentuated in dermal papillae similar to DH.^[12] The observed findings coincided with these findings.

Transient acantholytic dermatosis (TAD): Single case of TAD was observed. The patient was a male aged 30 years. Pruritic papules and discrete tense vesicles on chest and back were observed. The lesions were AHS positive and were negative for Nikolsky sign. This case was considered clinically as PV or TAD. Histologically, acantholysis with suprabasal blister was present. Few lymphocytes and plasma cells were present in the dermis. The pattern may resemble PF although acantholysis is more pronounced in TAD. Due to the pronounced acantholysis and correlating with clinical details a diagnosis of TAD was entertained. It is necessary to correlate with clinical findings to make a diagnosis of TAD.

Bullous erythema multiforme (BEM): Two cases of BEM were seen. Both were male patients and gave a positive history to drug exposure; sulfa group in one case and other due to recurrent HSV infection. The vesicles and bullae were discrete and present over erythematous base. As features were consistent with those described in literature of BEM^[12,13] diagnosis of

BEM was made. Cytology was negative in both the cases. Presence of spongiosis and basal cell hydropic degeneration were the marked epidermal changes. Dermis was edematous and lymphomononuclear cell infiltration around blood vessels suggested BEM in one case. While in the other case, since epidermis was normal a possibility of BEM was thought of in view of available clinical details. Perivascular infiltration of mononuclear cells, epidermal basal cell degeneration, and necrosis of individual keratinocytes was described.^[11,12] Necrosis of individual keratinocytes was absent in both the cases in the present study.

Urticarial vasculitis: Single case of urticarial vasculitis was seen. A 35 year old male presented with recurrent attacks of vesicles. The vesicles were tense, targetoid lesions showing healing with depigmentation. The lesions were on extremities and back. A clinical diagnosis of EM was made with a differential diagnosis of urticarial vasculitis due to presence of erythematous macules which were asymptomatic. Cytology was negative. Histologically, urticarial vasculitis shows leucocytoclastic vasculitis.^[7,11] The biopsy from this case showed normal looking epidermis. The upper dermis showed nuclear debris and there were perivascular eosinophilic and fibrinoid deposits suggestive of urticarial vasculitis.

Subcorneal pustular dermatosis/Sneddon-Wilkson disease (SCPD): One case of SCPD was seen. The patient was a female aged 49 years. The disease occurs mostly in persons over 40 years of age and females are commonly affected.^[7] Patient had generalized, small oval pustular lesions which were flaccid and easily rupturable. Hypopyon formation was noted in two pustular lesions. Palms, soles, scalp and mucosa were unaffected. Circinate erosions and crusting were present. Nikolsky sign and AHS were negative. A clinical diagnosis of SCPD was made.

Cytological study showed numerous neutrophils. Lever et al.^[11] described presence of sub corneal pustules containing mostly neutrophils and occasional eosinophils, mild intercellular edema, spongiosis, presence of perivascular neutrophilic aggregation and vascular dilation. Sub corneal cleavage with neutrophilic infiltrate and mild epidermal spongiosis were observed. Perivascular lymphomononuclear infiltration was present. In our study no neutrophils were present perivascularly. With changes being consistent with above description, a diagnosis of SCPD was made.

Staphylococcal scalded skin syndrome (SSSS): One case of SSSS was observed in a 6 month old male baby. There was a history of upper respiratory tract infection 6 days prior to the onset of skin lesions. Erosions and tenderness of skin was present and child was irritable. The lesions were diffuse and generalized. Nikolsky sign

was positive. Clinical features suggested a diagnosis of SSSS. Tzanck smear showed very few acantholytic cells. Histology is characterized by intra-epidermal split with acantholysis. Epidermal necrosis is absent.^[11,13] The biopsy of the case revealed presence of sub corneal clefting with mild acantholysis and no evidence of epidermal necrosis. Intact BMZ was present. Findings were in agreement with those put forth by Pyeet al.^[7] Tzanck smear is useful to differentiate between SSSS and toxic epidermal necrolysis. In SSSS, it shows many viable, acantholytic keratinocytes without inflammatory cells, and in TEN, a few necrotic keratinocytes, fibroblasts and inflammatory cells are evident.^[14]

Herpes simplex (HS): A diagnosis of Herpes Simplex was made in a 30 year old male patient who gave history of recurrent vesicles with itching and burning over the chin since one year. The surrounding skin was erythematous. Clinical diagnosis was of Herpes Simplex. Tzanck smear and histopathological findings were suggestive of viral infection.

Herpes zoster (HZ): One case of Herpes Zoster was encountered. The lesions were typical as described by various authors.^[7,13] Grouped vesicular lesions on erythematous base, with segmental involvement were present over the T10 dermatome. Excruciating burning pain was present in the patient. Tzanck smear showed viral inclusion bodies, and giant cells. Biopsy also showed viral changes.

Clinical diagnosis of viral infections like herpes simplex is easy but sometimes may mimic aphthous ulcers or other venereal diseases.^[15] In such cases, a Tzanck preparation reveals the pathognomonic, multinucleated keratinocytes thereby supporting the diagnosis. Orange et al.^[16] have reported a sensitivity and specificity of 90% for multinucleated giant cells for herpetic lesions.

Bullous lichen planus (BLP): A single case of bullous LP was seen in a 22 year old female with a history of six years. The patient had polygonal, discrete violaceous lesions showing koebnerisation along with some vesicular lesions which contained turbid fluid. The vesicles were present on the arms, forearms and on legs. A provisional clinical diagnosis of BLP was made. Also a differential of Lichen Planus Pemphigoides, was thought of.^[8] The Tzanck smear was negative and histopathology was suggestive of BLP.

Bullous erythema nodosumleprosum: A 20 years old female patient presented with tender nodular lesions and fever. Patient was a known case of Hansen's disease and was on multidrug therapy. The lesions observed were erythematous tender nodules a few of them showing vesicles which had ruptured to form ulcers.

A bullous form of ENL was thought of clinically as patient was in type 2 reaction, with erythema necroticans. Cytology was negative. Histopathology was confirmative as it revealed presence of neutrophilic and leucocytoclastic vasculitis. Special stain Fite-Faraco was positive for fragmented acid fast bacilli which was described as a feature by Jopling et al.^[17]

Chronic benign familial pemphigus (CBFP): One case of CBFP was noticed in the present study. The patient was 30 years old male with recurrent fluid filled lesions and erosions for a year. There was no family history of similar disease. Erosions were predominant and were spread peripherally along with a few vesicles. The lesions were confined to axilla, groin and perineal areas with discharge. Nikolsky sign and AHS sign were positive.

With these clinical findings PV and CBFP were thought of. The findings were consistent with observations of various authorities.^[8,13] Tzanck smear showed few acantholytic cells. Histopathology was confirmative showing sheets of acantholytic cells appearing as a dilapidated brick wall.

Conclusions

Cytological examination of skin lesions by way of Tzanck smears is a simple and reliable test for the presumptive diagnosis of pemphigus and pemphigoid groups of disorders. It is also helpful in the diagnosis of viral infections like herpes zoster and herpes simplex. The advantages of Tzanck smear are that it is easy to perform, inexpensive and reliable.

Among the cutaneous blistering disorders, those due to immune etiology are most common and usually do not have a gender predilection. Among the pemphigus group, pemphigus vulgaris affects females more. Complete clinical details, cytology and routine histopathology, all together help to arrive at a diagnosis for most bullous lesions of skin. In some cases, additional studies such as immunofluorescence tests are required.

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