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TZANCK SMEAR: AN ORAL PATHOLOGIST'S PERSPECTIVE

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ABSTRACT

Tzanck smear has been widely used for diagnosing various cutaneous dermatoses as it is simple, rapid and reliable technique. There are various diseases which clinically present as oral ulcerations or erosions. Differentiating between these diseases is important as treatment for these may vary greatly. Tzanck smears can be useful in such diseases when diagnosis is unclear. The presence of acantholytic cells on cytology readily diagnose pemphigus group of disorders from other immunological diseases like bullous pemphigoid, oral lichen planus, lichenoid reaction, erythema multiforme and aphthous stomatitis. However to differentiate among pemphigus group of disorders in addition to evaluation of Tzanck smears clinical correlation is a must. Infective diseases like herpes infections, staphylococcal infections, candidiasis, leishmaniasis and molluscum contagiosum show pathognomonic features on cytology which helps in rapid diagnosis and prompt treatment. In oral squamous cell carcinoma clinically presenting as an ulcerated lesion typical cytological features facilitate early diagnosis, thus improving prognosis. So when used along with proper history and clinical examination Tzanck smears can serve as rapid adjunctive diagnostic tool in oral ulcerative and erosive lesions in which diagnosis is obscure.

KEYWORDS: Cytology, Tzanck smear, adjunctive diagnostic tool, acantholytic cells, multinucleated giant cells, Leishman Donovan body.

INTRODUCTION

Cytology can be defined as the study of individual cells and their intrinsic characteristics and functions. Word 'Cytology' is derived from Greek word *'kytos'* which means 'hollow vessel'.[1] Cytology was first used in cutaneous disorders by Tzanck in 1947 for the diagnosis of vesiculobullous disorders, particularly herpes simplex.[2] Since then cytology became common practice for diagnosing various cutaneous dermatoses.[3,4,5,6]

There are many diseases which present as erosive or ulcerative lesions in the oral cavity. In the absence of definitive diagnostic clinical presentation, it's difficult to readily diagnose these lesions and provide prompt treatment. Tzanck smears from these lesions can serve as an effective chair-side diagnostic tool. Thus, this articles aims to discuss method of preparation of Tzanck smear and its findings in various oral ulcerative and erosive lesions.

PREPARATION AND STAINING OF TZANCK SMEAR

Tzanck smear is simple and very rapid chair-side diagnostic tool. In case of vesicle, bulla and pustule, the intact roof of lesion is incised along one side and folded back and then base of the lesion is scraped with a scalpel or edge of a spatula. Erosive areas without intact roof are directly scraped whereas in case of crusted lesions, first crusts should be carefully removed with the help of sterile forceps and then the sample should be collected.[5] In case of viral infections, a fresh vesicle should be used for sample collection than a crusted one to yield proper number of virus infected cells to facilitate diagnosis. Cellular material thus obtained then transferred to clean glass slide by touching the spatula to glass slide repeatedly and gently. While sampling, inclusion of blood and smearing of bulla or vesicle fluid should be avoided as it will lead to inappropriate results.[1]

Once smears are prepared they should be fixed immediately. Method of fixation varies according to staining method to be used. If Giemsa stain to be used then smears are allowed to air dry whereas if Papanicolaou stain to be used, the smear should be immediately fixed in alcohol. Tzanck smears can be stained by different methods; most common is use of diluted or undiluted Giemsa stain. Other stains used are Papanicolaou, hematoxylin and eosin, Wright, methylene blue and toluidine blue. Once stained, smears are then washed with water, dried and observed under microscope.[1]

TZANCK SMEAR FINDINGS IN VARIOUS ORAL ULCERATIVE AND EROSIVE LESIONS [Table 1]

Table 1: Tzanck smear findings in various oral ulcerative and erosive lesions.

Disease	Findings
Immunological	
Pemphigus vulgaris	Acantholytic cells, degenerating epithelial cells
Pemphigus foliaceous & Pemphigus erythematosus	Few acantholytic cells, dyskeratotic cells
Bullous pemphigoid	Few epithelial cells, numerous eosinophils
Oral lichen planus & Lichenoid reactions	Necrotic epithelial cells, inflammatory cells, fibroblasts and large tissue fragments
Toxic epidermal necrolysis	Necrotic basal epithelial cells, inflammatory cells and fibroblasts.
Recurrent aphthous stomatitis	Epithelial cells, mixed inflammatory infiltrate and occasional Anitschkow cells.
Infective	
Bullous impetigo	Dyskeratotic acantholytic cells, neutrophils, clusters of cocci
Staphylococcal scalded skin syndrome	Dyskeratotic acantholytic cells, no clusters of cocci
Herpes simplex & varicella-zoster virus infection	Multinucleated giant cells with intra-nuclear inclusion bodies
Herpangina	Non-specific findings
Candidiasis	Candidial hyphae on PAS staining
Leishmaniasis	Leishman-Donovan bodies
Molluscum contagiosum	Henderson-Patterson bodies
Genodermatoses	
Epidermolysis Bullosa	Melanophages, necrotic epithelial cells, inflammatory cells
Hailey-Hailey disease	Multiple acantholytic cells
Malignanacy	
Oral squamous cell carcinoma	Non-cohesive pleomorphic squamous cells with abnormal mitoses

I. Immunological Diseases

a) Pemphigus Vulgaris (PV)

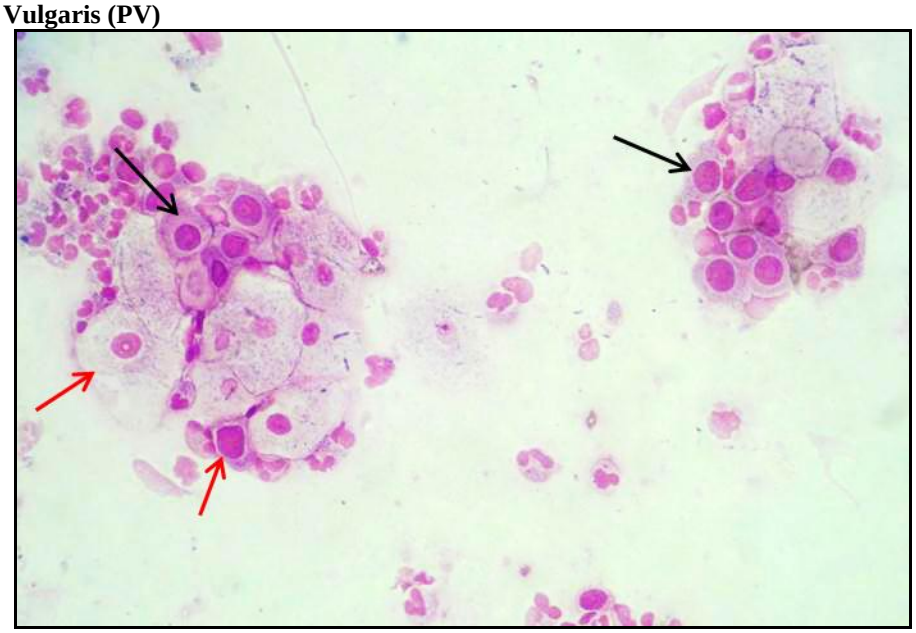

Fig. 1: Tzanck smear showing presence of abundant acantholytic or Tzanck cells (black arrows) and degenerating epithelial cells (red arrows) with inflammatory cells in PV.

Tzanck test is helpful in providing provisional diagnosis of pemphigus vulgaris especially in very early stage of disease when only oral lesions are present and biopsy can be uncomfortable to patient.[7] Typical acantholytic cells called as Tzanck cells are present in abundance (Fig.1). There is also a presence of epithelial cells showing different stages of ballooning degeneration of nucleus. (Fig. 1 and Fig. 2) These acantholytic cells or Tzanck cells (Fig. 3) are round epithelial cells with hypertrophic centric or eccentric nuclei and basophilic cytoplasm. There is presence of perinuclear halo due to tendency of the cytoplasm to be condensed at the periphery.[1]

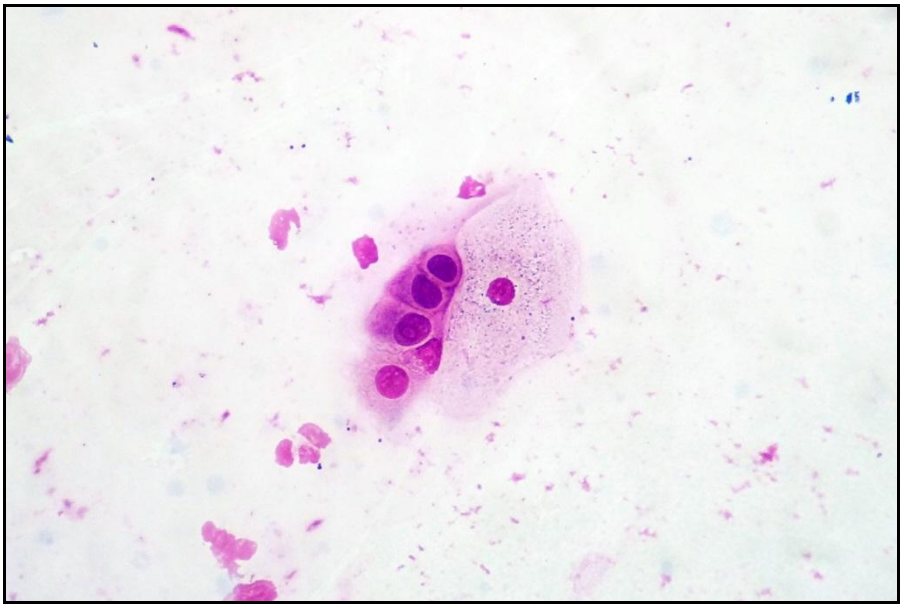

Fig. 2: Tzanck smear with epithelial cells showing different stages of ballooning degeneration of nucleus in PV.

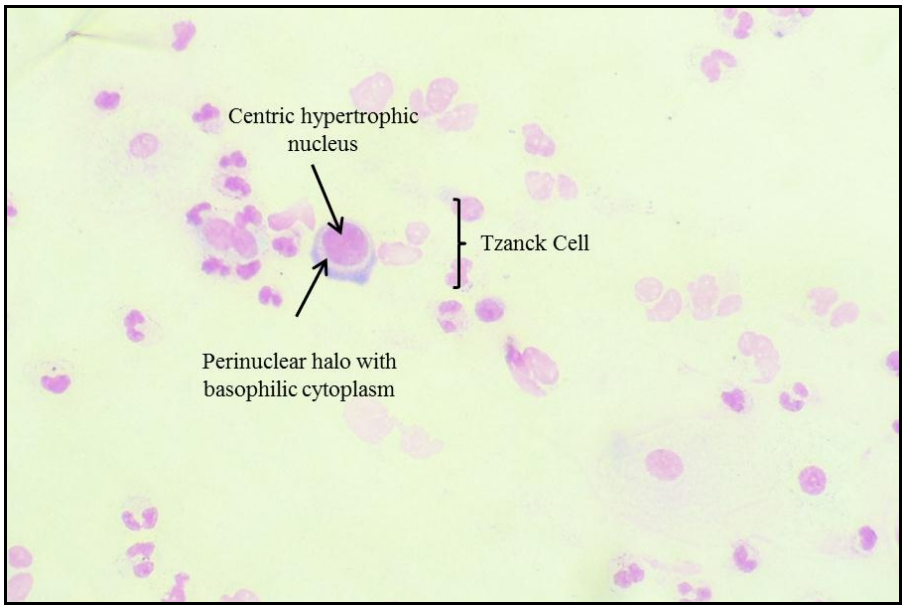

Fig. 3: Typical Tzanck cell showing hypertrophic centric nucleus and perinuclear halo with basophilic cytoplasm.

Other less frequent findings include, Sertoli rosette cells which consists of aggregates with an epithelial cell at the center surrounded by neutrophils and streptocytes which are chains of white blood cells.[7] However presence of acantholytic cells is not pathognomonic of PV. So, to confirm the diagnosis direct immunofluorescence staining can be directly applied to these Tzanck smears thus removing necessity for biopsy.[8]

b) Pemphigus Vegetans

Cytological features in Pemphigus vegetans are identical to Pemphigus vulgaris but it has usually more inflammatory cells. Clinically, it can be easily distinguished from pemphigus vulgaris due to characteristic vegetating lesions. Thus, clinical correlation is must along with evaluation of Tzanck smears.[1]

c) Pemphigus Foliaceous and Pemphigus Erythematosus

Cytology shows fewer acantholytic cells and presence of dyskeratotic cells with hyalinised cytoplasm.[1, 7]

d) Bullous Pemphigoid

Cytological findings are non-specific in this case and it just serves to rule out the diagnosis of pemphigus group of disorders. Smear shows presence of few epithelial cells and marked inflammatory infiltrate especially significant number of eosinophils.[6]

e) Erosive oral lichen planus and Lichenoid reactions

Here, cytological findings are nonspecific with necrotic keratinocytes, mixed inflammatory cell infiltrate, large tissue fragments and occasional fibroblasts.[1,7]

f) Erythema Multiforme (EM)

When target lesions are absent on skin and oral lesions predominate, erythema multiforme must be differentiated from primary herpes simplex infection as treatment for these two varies greatly.[9] EM can be readily distinguished from herpes infection by Tzanck smear which shows absence of multinucleated giant cells, syncytium and ballooning degeneration of the nucleus in EM which are present in Herpes infection.[1,4]

Tzanck smear can be used to differentiate between Toxic epidermal necrolysis (TEN) and Staphylococcal Scalded Skin Syndrome (SSSS). In Steven Johnson Syndrome and TEN necrotic basal cells, leukocytes and fibroblasts are evident whereas SSSS shows dyskeratotic acantholytic cells and few inflammatory cells on cytology.[1,7]

g) Recurrent Aphthous Stomatitis

It is characterized by recurrent ulcers confined to oral mucosa with no other sign of disease in patients. It is usually diagnosed by exclusion of other diseases. Tzanck smears help in diagnosis from viral stomatitis, pemphigus, pemphigoid based on typical cytological findings seen in these diseases.[9]

Cytological picture in RAS is nonspecific with many squamous epithelial cells and abundant to moderate degree of mixed inflammatory infiltrate. Occasionally Anitschkow cells are evident.[10]

II. Infective diseases

a) Bullous Impetigo

Tzanck smears show presence of dyskeratosis, acantholytic cells with numerous neutrophils. On gram staining, clusters of cocci can be seen which differentiate it from SSSS as cocci are absent in SSSS as it is caused by toxin and bacteria reside at a distant site.[1,11]

b) Herpes Simplex and Varicella-zoster Virus Infection

Though viral culture remains the standard method, rapid confirmation of herpetic infections can be obtained by Tzanck smear.[4] In Herpes simplex infection, Tzanck smear shows presence of multinucleated giant cells with intra-nuclear inclusion bodies, syncytium and ballooning degeneration of the nucleus.[9] Cellular changes seen in epithelial cells include enlargement of cells, multinucleation and crowding of nuclei with nuclear molding, alteration of ground substance which can be either coarse or can have ground glass appearance. Nuclear changes include, ballooning degeneration with peripheral margination of nuclear chromatin and intra-nuclear inclusion bodies surrounded by halo. Papanicolau stain provides a better visualization of these intra-nuclear inclusion bodies. Necrotic syncytial giant cells are seen in lesions that are more than 72 hours old.[4]

Usually herpes zoster can be readily diagnosed by its typical clinical appearance. But, when there are no intact vesicles and only erythema, edema and ulceration are seen, such isolated herpes Zoster can be misdiagnosed. In such cases Tzanck smear is useful in diagnosis.[9] However it cannot be used to differentiate between varicella virus and herpes virus infection as both these infections show same cytological findings.[1] Viral cultures then serve as a only way to distinguish herpes simplex from varicella-zoster infection.[9]

c) Herpangina

In addition to several clinically distinguishing criteria, Tzanck smear picture is different in Herpangina than in Herpes simplex and varicella zoster infection. Smears in Herpangina don't show ballooning degeneration or multinucleated giant cells which are constant findings in herpes simplex and varicella zoster infection.[9]

d) Candidiasis

Candidiasis is often diagnosed based on clinical findings and in detail history. However, sometimes, erythematous candidiasis needs to be differentiated clinically from erosive lichen planus, lichenoid reaction and erythema multiforme. In such cases, smears stained with periodic acid Schiff reagent can serve as useful adjunctive diagnostic tool. Magenta red colored candidial hyphae can be visualized in between keratinocytes on cytological smears.[12]

e) Leishmaniasis

Oral leishmaniasis usually presents as ulceration on hard or soft palate. However any site can be affected and sometimes, lesion can also appear as exophytic, nodular and indurated lesion. Thus, mimicking a malignant lesion. Histopathological findings in mucosal leishmaniasis are usually nonspecific and seen as subepithelial non-necrotizing granulomatous inflammatory reaction. Daneshbod etal studied histological and cytological features of mucosal leishmaniasis in 11 patients and concluded that cytology is more reliable than histopathology in making a diagnosis.[13]

Cytology reveals many mature squamous cells, plasma cells, neutrophils, histiocytes and protozoa in a typical 'swarm of bees' pattern along with presence of numerous extracellular and intracellular leishman Donavan (LD) bodies.[14] LD bodies are seen as light blue ellipsoid bodies which are 2-4 μ long with an eccentric nucleus and have smaller kinetosome at the opposite pole. LD bodies can be detected on cytology in early untreated cases of leishmaniasis but not in chronic form of the disease.[1]

f) Molluscum contagiosum

Clinically, it usually presents as raised nodule with umbilicated centre but sometimes when isolated and non-umbilicated, these lesions can be misdiagnosed.[1, 15] Here cytology shows keratinocytes in an inflammatory background. These keratinocytes may be nucleate or anucleate. Additionally, intracytoplasmic and extracytoplasmic eosinophilic to basophilic, homogenous or heterogenous bodies enclosed in a well-defined membranous sac are seen. These bodies are called as 'molluscum bodies' or 'Henderson-Patterson' bodies.[15]

III. Genodermatoses

a) Epidermolysis Bullosa

Cytology reveals presence of necrotic keratinocytes, inflammatory cells and melanophages. Presence of melanophages suggest damage to epithelial and connective tissue junction. Thus, identification of melanophages in cytological smears is beneficial for diagnosis of variants of epidermolysis bullosa which elicit lichenoid reaction pattern and obscure diagnosis.[7]

b) Hailey- Hailey disease

Hailey- Hailey disease also called as familial benign chronic pemphigus shows multiple typical Tzanck cells on cytology.[1,7]

IV. Oral Squamous Cell Carcinoma (OSCC)

Cytology can be of great help in diagnosis of soft, ulcerated varieties of OSCC but not in keratotic or verrucous lesions.[1] Cytomorphological features seen in OSCC include cellular pleomorphisms and absence of cohesiveness of cells. Nuclei are hypertrophic, hyperchromatic, anisodiametric with abnormal mitoses. Furthermore, there is loss of translucent quality of cytoplasm.[1,16]

CONCLUSION

Tzanck smear is a simple, rapid, inexpensive chair-side technique which does not require any specialized equipment. Negative Tzanck smear test is useful in exclusion of pemphigus group of diseases. Similarly, positive Tzanck smear test in infections like herpes, molluscum, candidiasis and leishmaniasis helps clinician to diagnose disease readily and start treatment promptly. Thus, it can be useful as an adjunctive investigative tool in oral ulcerative and erosive lesions whose diagnosis is obscure.

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