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Resident's Page

Cytodiagnosis in dermatology

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Cytodiagnosis – a simple, rapid, cheap, and often reliable method of diagnosis in fresh tissues – was introduced by Dudgeon and Patrick, in 1927, though George Papanicolaou is considered as the father of exfoliative cytology. Various methods of cytodiagnosis include Tzanck smear, imprint smear, tissue smear, exudate smear, skin scraping smear, and aspiration cytology.

TZANCK SMEAR

Tzanck test or Tzanck smear was first introduced in 1947 by Arnault Tzanck.

Preparation

Samples are taken from a fresh vesicle. The vesicle is unroofed and the floor is gently scraped. Material thus obtained is smeared onto a microscopic slide, allowed to air dry, and stained with Giemsa or Leishman stain. Other stains used are hematoxylin and eosin, Wright, Papanicolaou, methylene blue, and toluidine blue.

Table 1 shows the Tzanck smear findings in various dermatoses.[1]

Tzanck smear in pemphigus group of disorders

Tzanck smear is a very useful test for the diagnosis of pemphigus vulgaris, particularly in the early stages of oral pemphigus. A typical Tzanck cell is a large round epithelial cell or keratinocyte with a large nucleus, hazy or absent nucleoli, perinuclear halo, and peripheral condensation of basophilic cytoplasm ("mourning edged" cells).

There may be features of cell adherence such as "Sertoli rosette cells" and "Streptocytes" which are relatively less characteristic cytodiagnostic signs in pemphigus vulgaris. "Sertoli rosette" is aggregates of cells with a keratinocyte at the center surrounded by a ring of leukocytes. There may be adherent chains of leukocytes formed by filamentous, glue-like substances called "Streptocytes."

Tzanck smear in infections

Herpes simplex, varicella and herpes zoster[2-4]

A fresh vesicle <3 days old must be chosen as older lesions may get crusted or secondarily infected and the characteristic cytological features may not be there. Characteristic feature is the presence of typical multinucleated giant cells. The cells are swollen ("ballooning cell or pregnant cell") and large, 60–80 μ in diameter. Nuclei exhibit molding so that they can fit together in a jigsaw puzzle-like fashion within the cell. The nuclei show great variation in size and shape. Intranuclear

Table 1: Tzanck smear findings in various dermatoses.

Disease	Tzanck smear findings
Immunobullous	
Pemphigus vulgaris	Numerous larger acantholytic cells (Tzanck cells) and few eosinophils [Figure 1]
Pemphigus vegetans	Acantholytic cells and many inflammatory cells – especially eosinophils
Pemphigus foliaceous	Smaller, cuboidal, and less numerous acantholytic cells
Bullous pemphigoid	Eosinophils and few lymphocytes and neutrophils
Cutaneous infections	
Herpes infections	Multinucleated epithelial giant cells [Figure 2]
Staphylococcal scalded skin syndrome	Dyskeratotic acantholytic cells, absent or few inflammatory cells, absent cocci
Bullous impetigo	Dyskeratotic acantholytic cells, neutrophils, and Gram-positive cocci in clusters
Candidiasis	Yeast cells with pseudohyphae
Genodermatoses	
Hailey–Hailey disease	Plenty of acantholytic cells
Darier's disease	Corps ronds, grains, and few acantholytic cells
Spongiotic dermatitis	
Allergic contact dermatitis	Tadpole cells [Figure 3], lymphocyte predominance[1]
Irritant contact dermatitis	Tadpole cells, neutrophil predominance[1]

inclusion bodies surrounded by a clear halo are characteristic of herpetic infection but are often difficult to find. Varicella in adult patients and paucilesional or atypical forms of herpes zoster, i.e., cases where lesions are non-dermatomal in distribution but generalized (so-called herpes zoster varicellosus), is often misdiagnosed as bacterial folliculitis. Tzanck smear may help in these instances.

Bullous impetigo, staphylococcal scalded skin syndrome (SSSS), and toxic epidermal necrolysis (TEN)

SSSS and TEN have some clinical similarities. Tzanck smear taken from a fresh bulla shows abundance of dyskeratotic keratinocytes without inflammatory cells in SSSS, whereas in TEN necrotic keratinocytes, fibroblasts and inflammatory cells are seen.[3,5] Cytodiagnosis should be confirmed either by a frozen section taken from the bulla roof or by a biopsy.

Vaccinia, orf, Milker's nodules, and variola[2,3]

Smears show a variable number of acantholytic or detached squamous keratinocytes. These keratinocytes may contain eosinophilic cytoplasmic inclusion bodies called a "Guarnieri bodies," frequently surrounded by a clear halo. In orf and Milker's nodules, there will be a background of inflammatory cells and necrotic squamous keratinocytes.

Pustular or bullous superficial fungal infections[2,3]

Candida and dermatophytes (especially geophilic or zoophilic strains) can present with pustules or bullae. Although KOH preparation is quite helpful in diagnosis, the presence of hyphae or pseudohyphae can also be easily identified in Giemsa stained smears.

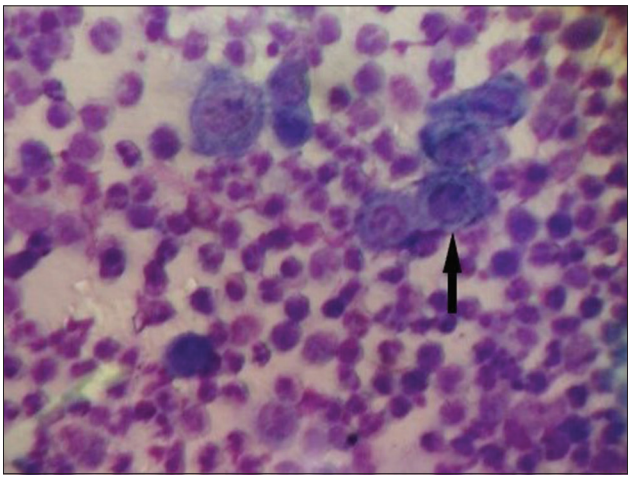

Figure 1: Acantholytic cells in pemphigus showing large nucleus, perinuclear halo, and peripheral condensation of cytoplasm.

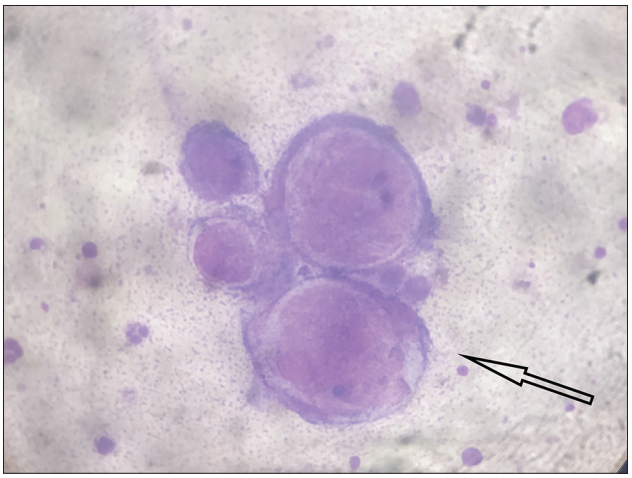

Figure 2: Multinucleated giant cells with secondary acantholytic cells in varicella.

Tzanck smear in genodermatosis

i. Hailey–Hailey disease: Cytodiagnosis is helpful in differentiating Hailey–Hailey disease from intertrigo, flexural psoriasis, or eczema, which are close simulators of this genodermatosis. Tzanck smear shows numerous acantholytic cells.
ii. Darier's disease: Cytology reveals "corps ronds" and "grains." "Corps ronds" are isolated round keratinocytes with an eosinophilic cytoplasm, which is retracted from the nucleus and denser peripherally. Grains are small, hyaline, eosinophilic ovoid bodies resembling pomegranate seeds.

Tzanck smear in vesicular and pustular dermatosis in neonates

Smears from pustules in transient neonatal pustulosis and infantile acropustulosis show predominance of neutrophils, whereas eosinophils are predominantly seen in erythema toxicum neonatorum and eosinophilic pustulosis.

TISSUE SMEAR

For cytodiagnosis, lesion should be incised with a sharp, pointed scalpel. The incision should be superficial to avoid bleeding. A sample of tissue is then obtained with either a blunt scalpel or a small curette and the tissue obtained is pressed between two slides, air dried, and stained.

Table 2 shows the tissue smear findings in various dermatoses.

Leishmaniasis

In Leishmaniasis, the cytological smear is obtained by gentle scarification along with the margins of the lesion. It shows the presence of numerous protozoa (Leishman-Donovan bodies) within histiocytes known as Wright's cells [Figure 4]. Intracellular Leishmaniae are seen as bee-swarm-like formations.[6] They can also be extracellular. In oil immersion, Leishmaniae appear as small blue ovoid, ellipsoid, or pyriform bodies with a deeply basophilic cytoplasm, a trophonucleus, a paranucleus or kinetoplast, and a minute endocytoplasmic flagellum. In older lesions, cytological testing is of limited diagnostic use as protozoa are rarely seen.

Donovanosis

Tissue smear is more sensitive than biopsy. It may show Greenblatt/Pund cells which are large macrophage/epithelioid

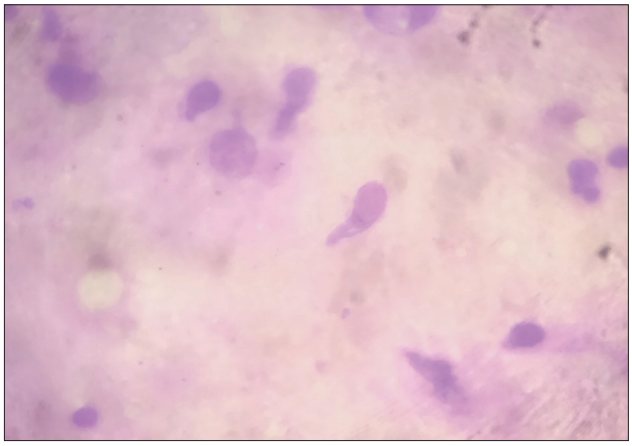

Figure 3: Tadpole cells with few neutrophils in irritant dermatitis.

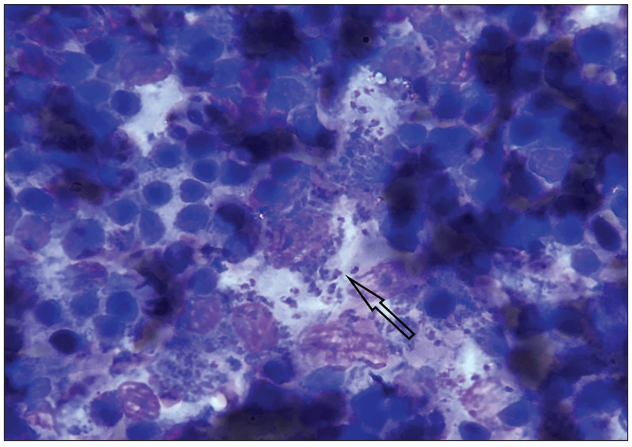

Figure 4: Leishman stained smear of cutaneous leishmaniasis demonstrating numerous LD bodies.

Table 2: Tissue smear findings in various dermatoses.

Disease	Tissue smear findings
Cutaneous infections	
Leishmaniasis	Leishman-Donovan bodies, Wright's cells
Donovanosis	Greenblatt and Pund cells, Donovan bodies
Molluscum contagiosum	Henderson-Patterson bodies
Cutaneous tumors	
Basal cell epithelioma	Clusters of basaloid cells
Squamous cell epithelioma	Isolated atypical squamous cells
Paget's disease of breast	Paget's cells
Erythroplasia of Queyrat	Poikilokaryosis (variation in size, shape, and staining of nuclei), naked and clumped nuclei
Bullous mastocytosis	Mast cells with metachromatic granules
Langerhans cell histiocytosis	Atypical Langerhans cells

cell containing cystic spaces, with nuclei pushed to one side and darkly staining inclusions called Donovan bodies. Donovan bodies are blue-black bipolar condensations with a safety pin appearance.

Basal cell carcinoma[2,3,7]

Cytology reveals clusters of basaloid cells with some of them showing retention of peripheral palisading, as in the histology. Basaloid cells are similar to normal basal keratinocytes in appearance but are larger and more deeply basophilic. They are uniform in size, elongated and the nucleus is central oval, intensely basophilic and occupies four-fifths of the cells.

Squamous cell carcinoma[2,3]

Cytology is helpful in the nodular, soft, or ulcerated non-keratotic varieties of squamous cell carcinoma (SCC), but not in keratotic or verrucous lesions. The two characteristic cytodiagnostic features of SCC are the absence of cluster formation by cells and pleomorphism. At higher magnification, abnormal nuclear changes (hypertrophic, hyperchromatic, or multilobated nuclei and abnormal mitoses) and bizarre changes in cytoplasm staining (basophilic in some, eosinophilic in others) are seen.

Paget's disease[3]

Paget's cells appear larger than keratinocytes and are seen as round to oval cells with weakly eosinophilic or amphophilic, vacuolated cytoplasm, and a hypertrophic nucleolated nucleus. They occur singly or in small clusters and stains with special stains for epithelial mucin such as mucicarmine, Alcian blue, and periodic acid–Schiff stain.

Erythroplasia of Queyrat[3]

Smear shows spindle-shaped, polyhedral, and round cells with pleomorphic nuclei, which is practically diagnostic.

Bullous mastocytosis[3]

Cytodiagnosis of mastocytoma is especially useful in pediatric cases, in which performing a biopsy under local anesthesia may be very difficult. Tzanck smear from bullous lesions is stained with 1% methylene blue for 1 min, which shows plenty of mast cells, which are identified by their irregular shape and metachromatic staining of granules as purple.

Langerhans cell histiocytosis[3]

Smear shows multinucleate atypical Langerhans cells which are 12–15 mm sized with pale, weakly eosinophilic or amphophilic, granular cytoplasm and large lobulated, convoluted, reniform, or centrally grooved nuclei. Although the cytological findings are quite suggestive, we should always perform a histological examination and immunophenotyping to confirm diagnosis.

FINE-NEEDLE ASPIRATION CYTOLOGY[8]

Fine-needle aspiration cytology (FNAC) is a useful cytodiagnostic method in differentiating benign tumors from malignant and also in various cutaneous infections. Epidermal inclusion cyst [Figure 5], trichilemmal cyst, basal cell carcinoma (BCC), SCC, melanoma, sebaceous carcinoma, Merkel cell tumor, pilomatricoma, granular cell tumor, Kaposi sarcoma, and various skin adnexal tumors are some of the lesions that can be diagnosed on FNAC. Subcutaneous nodules due to metastases from various solid organ malignancies such as cervix, lung, breast, prostate, ovary, liver, kidney, and gallbladder can be diagnosed using FNAC.

In pilomatricoma, cytological examination of smear may show ghost cells, basaloid cells, and numerous acute inflammatory cells. In BCC, there will be predominance of basaloid cells which are seen cytologically as cohesive cellular fragments with sharp borders and peripheral palisading. FNAC of foreign body granulomas shows multinucleated giant cells, acute inflammation, and demonstrable foreign bodies. FNAC of lipoma shows adipose tissue. The fat cells are with a single large vacuole in the cytoplasm with nuclei pushed to the periphery. FNAC from gouty tophi reveals needle shaped crystals of monosodium urate [Figure 6] and negatively birefringent crystals under polarised light [Figure 7].

Another important application of FNAC in dermatology is in the diagnosis of many infective conditions presenting as cutaneous nodules such as parasitic infections like cysticercosis, fungal infections such as aspergillosis, erythema nodosum leprosum, lepromatous leprosy, and molluscum contagiosum.

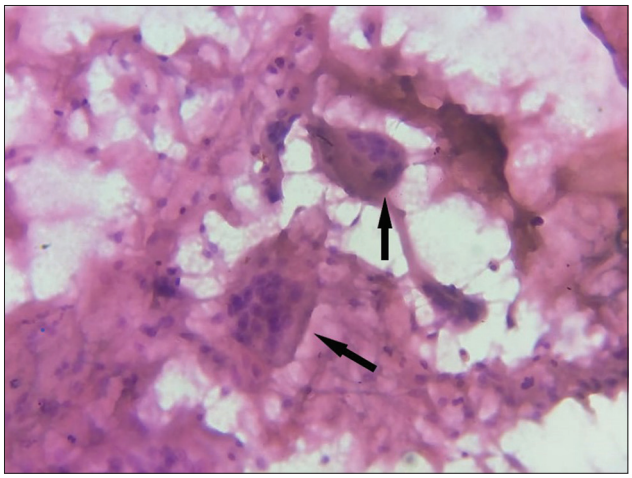

Figure 5: Papanicolaou stained smear showing keratin debris with multinucleated giant cells in epidermal cyst.

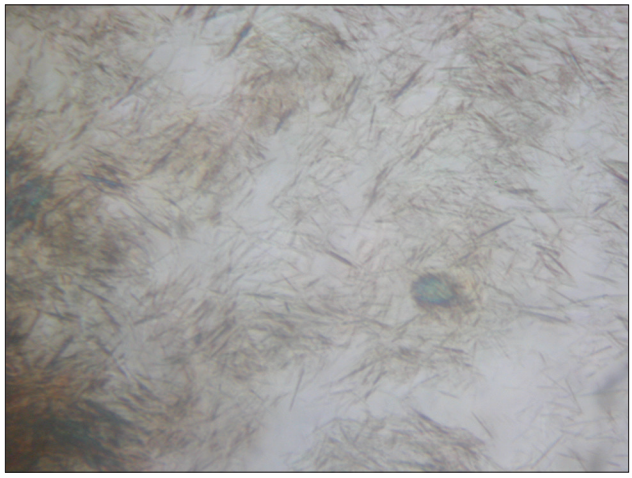

Figure 6: Needle-shaped monosodium urate crystals in gouty tophi.

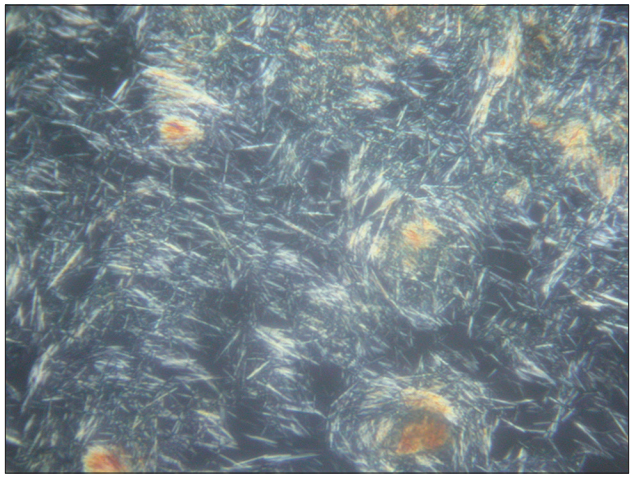

Figure 7: Negatively birefringent monosodium urate crystals in polarized microscopy.

FNAC of skin lesions and nerves of lepromatous leprosy shows increased cellularity, numerous foamy macrophages, and few lymphocytes with acid-fast bacilli (AFB) positivity, whereas in tuberculoid leprosy, there will be cohesive epithelioid granulomas with negative AFB.

In actinomycosis, cytology demonstrates acute inflammatory cell infiltrate and epithelioid cell granulomas in a proteinaceous background. Gram stain should be done which shows Gram-positive filamentous structures.

IMPRINT CYTOLOGY[9]

Imprint cytology is a method of pathological assessment of cells by taking imprint from the cut surface of a wedge biopsy specimen or from the resected margins of a surgical specimen. It is a rapid and simple technique of analyzing the margins of a resected tumor for the presence of malignant cells.

CONCLUSION

Cytodiagnosis can be a valuable aid in the diagnosis of various infectious and non-infectious dermatoses. The architectural patterns of disease are studied in standard histological sections, whereas the exact cell types involved in the disease process are analyzed in cytodiagnostic smears. Hence, it may be said that histology examines the "house," while cytology examines the "bricks" which forms the house. It is particularly useful when rapid diagnosis is important as in SSSS, TEN, or disseminated herpes when the lesions are at sites where biopsy may be difficult, such as eyelids.

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Conflicts of interest

There are no conflicts of interest.

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