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Editorial

Equidistant and Expanded-Paget's Disease of Breast

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Mammary Paget's disease is configured of proliferating malignant glandular epithelial cells or an *in situ* carcinoma confined within epidermal surface of nipple areola complex.

Initially scripted by James Paget in 1874, lesion manifests as an uncommon clinical representation of invasive carcinoma breast.

Mammary Paget's disease is additionally designated as Paget disease of breast, Paget disease of nipple or ductal carcinoma *in situ* (DCIS) involving nipple skin. Mammary Paget's disease frequently expounds subclinical or histological evidence of disease.

The lesion preponderantly represents as an eczematous or erythematous alteration of cutaneous surface of nipple areola complex. Precise cutaneous manifestations emerge due to tumour cells disseminated through the epidermis with consequent disruption of intercellular junctions.

Majority of Paget cells and tumour cells configuring associated, subjacent carcinoma appear immune reactive to HER2+.

Lesion preponderantly (> 95%) expounds a subjacent high grade ductal carcinoma *in situ* (DCIS) or invasive carcinoma breast. Exceptionally, < 5% lesions of mammary Paget's disease appear non concurrent with subjacent invasive carcinoma breast.

Mammary Paget's disease may be associated with infiltration of subjacent dermis wherein Paget cells migrate through epidermal basement membrane. Generally, miniature foci of tumour invasion are discerned [1,2].

Secondary Paget's disease is comprised of deep seated foci of invasive carcinoma infiltrating superimposed cutaneous surfaces wherein foci of invasive carcinoma implicating breast parenchyma appear enlarged.

Infrequently observed, mammary Paget's disease implicates up to 4% of female subjects and ~2% of male subjects demonstrating invasive carcinoma breast [1,2].

Lesion arises within 20 years to 90 years and demonstrates a peak incidence within 6^{th} decade to 7^{th} decade. Mean age of disease emergence is 64 years. Up to 30% premenopausal female subjects may be incriminated [1,2].

Mammary Paget's disease commonly implicates nipple or areolar region. Lesion may expand into adjacent cutaneous surface of breast. Preponderantly unilateral, lesion may exceptionally be bilateral. Additionally, supernumerary nipples may be involved. Mammary Paget's disease is devoid of specific genetic mutations.

Paget cells predominantly (~80%) represent with genetic features identical to concurrent carcinoma cells [1,2].

Of obscure aetiology, mammary Paget's disease is posited to arise due to migration of Paget's cells or cells of ductal carcinoma *in situ* along basement membrane of the nipple. Cellular migration is mediated through motility factor heregulin α which is generated by keratinocytes and appears efficacious through HER2 receptor. Aforesaid 'epidermotropic theory' is applicable on account of comprehensive (~100%) emergence of ductal carcinoma *in situ* (DCIS) cells confined to deep seated breast tissue, identical to Paget cells [2,3].

Alternatively, the 'transformation theory' designates Paget cells engendered by malignant transformation of keratinocytes or Toker cells. According to 'transformation theory', pre-Paget cell emerges as an intermediate cell between a keratinocyte and Paget cell, thereby indicating the genesis of epidermal cells demonstrating characteristics of ductal cells during malignant metamorphosis [2,3].

Lesions devoid of concordant invasive carcinoma breast may possibly be associated with instances of undiscerned tumefaction or neoplasms with absence of cogent surgical tissue sampling [2,3].

Mammary Paget's disease predominantly represents with gradually evolving, morphological alteration within the nipple. Preponderant clinical manifestations emerge as nipple erythema, crusting, scaling, cutaneous ulceration, pruritus, focal haemorrhage or eczematoid type rash. Uncommonly, bloody nipple discharge, pain, retraction of superimposed cutis or absence of distinct alterations of the nipple may be uncommonly observed. Lesion may represent as a pigmented macule and necessitates demarcation from malignant melanoma [2,3].

Cogent cellular modifications commence at the nipple or areola. Lesion may spontaneously retrogress. Alternatively, gradual progression with extension into cutaneous surface of the breast may be discerned.

An estimated 50% subjects demonstrate an associated palpable breast mass, indicative of subjacent invasive carcinoma breast.

Notwithstanding, lesion may be clinically misinterpreted as cutaneous inflammatory disease or infection. Thus, cogent disease discernment may be challenging or delayed [2,3].

Male subjects implicated by mammary Paget's disease manifest with clinical representations identical to female subjects [2,3].

Cytological smears exhibit tumour cells amalgamated upon epidermal surface and scaly crust. Smears from scalpel scrapings of the nipple may be prepared and optimally stained with Papanicolaou stain or May-Grünwald-Giemsa (MGG) stain. Nipple scrapings may adequately discern mammary Paget's disease in ~90% instances [3,4].

Cytological and morphological features as isolated cells and loose clusters of malignant glandular epithelial cells permeated with pale cytoplasm, enlarged nuclei and prominent nucleoli appear disseminated within a population of squamous epithelial cells. Cytological distinction is required from lesions as nipple adenoma or squamous cell carcinoma.

Lesions challenging to ascertain may be subjected to morphological assessment of cutaneous punch biopsy in addition to cytological scrape smears [3,4].

Grossly, nipple areola complex exhibits reddish to pink crusting lesion, cutaneous discoloration, thickening, cutaneous ulceration, nipple retraction or exudate from the lesion [3,4].

Typically, a well demarcated lesion is observed. Epidermal surface is commonly implicated as a grossly evident lesion. Besides, the scaly crust necessitates eradication prior to surgical intervention.

Upon microscopy, singular cells or cellular clusters are disseminated within the epidermis. Tumour cells are impregnated with abundant, pale cytoplasm and enlarged, irregular nuclei with prominent nucleoli. Paget cells appear to phagocytose melanin pigment, thereby simulating melanocytes [3,4].

Subjacent dermis enunciates focal aggregates of chronic inflammatory cells. Superimposed epidermis demonstrates hyperkeratosis and possible focal ulceration. Florid lesions of mammary Paget's disease enunciate glandular articulations [3,4].

Paget's disease appears to superimpose carcinoma breast, commonly high grade invasive carcinoma of no special type (NST). Alternatively, ductal carcinoma *in situ* (DCIS) may be concurrent [3,4].

Ultrastructural examination exhibits desmosomal attachments between Paget cells and adjoining epidermal keratinocytes [3,4].

	Various conditions	Paget's disease
Eczema	Bilateral. Common in premenopausal women. Intact nipple. Itchy. No subjacent lump. Responds to steroids	Unilateral. Common in postmenopausal women. Nipple distorted. Subjacent lump present. Itchiness absent. Non responsive to steroids.
Psoriasis	Vesicles or pustules	No vesicle or pustules.
Irritant contact dermatitis	Limited to areola. No change in nipple.	Nipple retraction or deformation. Involves nipple, extends to areola.
Mammary duct ectasia	Bilateral	Unilateral
Drug eruption	No palpable mass	Palpable mass
Toker cell	Arise in younger age	Occur in older age
Nipple duct adenoma	Normal mammogram	Abnormal mammogram
Bowen's disease	Nipple skin uninvolved. Intercellular bridges. Occurs on sun exposed skin. Contributory factors are UV radiation, HPV infection, immunosuppression.	Lesion starts at nipple, extends to areola and beyond. Epidermal glandular formations are common. No association to sun exposure or HPV infection.

Table: *Differential diagnosis of Mammary Paget's disease [4].*

Mammary Paget's disease appears immune reactive to CK7, HER2, CAM5.2, oestrogen receptors (ER) and progesterone receptors (PR). Tumour cells appear immune non reactive to human melanoma black45 (HMB45) antigen, Melan A, CK5/6, CK20 and S100 protein [5,6].

Mammary Paget's disease requires segregation from neoplasms as squamous cell carcinoma *in situ* (Bowen's disease), malignant melanoma, cutaneous squamous cell carcinoma *in situ* or Bowen's disease, melanoma *in situ*, Toker cells or pagetoid dyskeratosis [5,6].

Symptomatic instances of mammary Paget's disease may be appropriately discerned with cogent clinical examination. Palpable breast lumps require appropriate evaluation [6,7].

Mammographic evaluation is recommended in order to ascertain subjacent tumour masses or tissue anomalies which may be additionally subjected to core needle tissue sampling or fine needle aspiration cytology (FNAC) [6,7].

Notwithstanding, tissue sampling with open surgical techniques or wedge excision may be necessitated in instances where aforesaid methodologies are inadequate for ascertaining the condition [6,7].

Asymptomatic lesions or unsuspected instances of mammary Paget's disease may be incidentally discovered within mastectomy specimens. However, cogent detection of Paget cells is contingent to extent of surgical tissue sampling of the nipple with precise morphological assessment and adoption of pertinent immunohistochemistry [6,7].

Imaging is preponderantly employed for detecting and evaluating extent of concurrent malignant neoplasms and appropriate therapeutic strategies.

Mammography appears beneficial in discerning a breast mass, breast distortion or focal calcification. Notwithstanding, an estimated 50% subjects with mammary Paget's disease display normal mammograms. Ultrasonography expounds ductal ectasia or alterations within nipple areola complex as flattening, asymmetry or cutaneous thickening. Magnetic resonance imaging (MRI) is a sensitive technique adopted for discerning occult or concurrent disease undetected upon mammography. MRI may depict an anomalous nipple enhancement, thickened nipple areola complex, association with emerging ductal carcinoma *in situ* (DCIS), invasive carcinoma breast or an amalgamation of aforesaid manifestations [7,8].

Cytological smears of nipple scrapings may aptly discern tumour cells aggregated upon epidermal surface or within the scaly crust. However, the manoeuver may be painful and is exceptionally adopted. Confirmatory analysis is achieved by histological assessment of cutaneous tissue samples obtained with techniques such as punch biopsy, shave biopsy or infrequently with core needle biopsy. On account of cosmetic countenance of the nipple, miniature tissue samples may be excised [7,8].

Mammary Paget's disease may be appropriately subjected to surgical excision. Extent of surgical eradication pertains to magnitude of subjacent focus of carcinoma breast. Subjects with limited disease may appropriately be managed with manoeuvers as breast conservation therapy comprised of centric lumpectomy and irradiation of whole breast. Extensive disease as represented by multi-centric carcinoma or diffuse calcification may be subjected to surgical procedures as simple mastectomy [7,8].

The entire nipple areola complex requires excision within comprehensive (100%) lesions wherein reconstruction of nipple may be achieved by a variety of techniques [7,8].

Assessment and strategies of therapeutic intervention within the axilla implicated by mammary Paget's disease and varieties of invasive carcinoma breast appear identical [7,8].

Systemic therapy with neoadjuvant or adjuvant chemotherapy appears contingent to associated invasive carcinoma breast or ductal carcinoma *in situ* (DCIS) [7,8].

Prognostic outcomes are contingent to occurrence, extent and morphological characteristics of subjacent carcinoma breast. Mammary Paget's disease associated with ductal carcinoma *in situ* (DCIS) is associated with excellent prognostic outcomes with > 95% overall survival at 20 years [7,8].

Singular mammary Paget's disease in the absence of parenchymal tumour demonstrates superior outcomes with 5 year and 10 year proportionate survival at ~100%, in contrast to lesions associated with ductal carcinoma *in situ* (DCIS) [7,8].

Prognostic outcomes of concurrent invasive carcinoma breast occurring within subjacent breast are contingent to tumour magnitude and status of regional lymph nodes. Enhancing tumour stage delineates declining 5 year relative proportionate survival which is denominated within stage I (95.8%), stage II (77.7%), stage III (46.3%) and stage IV (14.3%) disease [7,8].

Generally, female subjects demonstrating mammary Paget's disease with concurrent palpable breast mass indicate the occurrence of advanced disease with inferior survival, in contrast to women devoid of a palpable breast mass [7,8].

Foci of tumour invasion into subjacent dermis may be engendered directly from epidermal foci of mammary Paget's disease and appear localized to the nipple. Characteristically, aforesaid invasive Paget's disease with antecedent detection is associated with favourable prognostic outcomes [7,8].

Mammary Paget's disease requires distinction from inflammatory carcinoma breast and invasive carcinoma breast with localized, advanced lesion with cutaneous ulceration which may be associated with adverse prognosis [7,8].

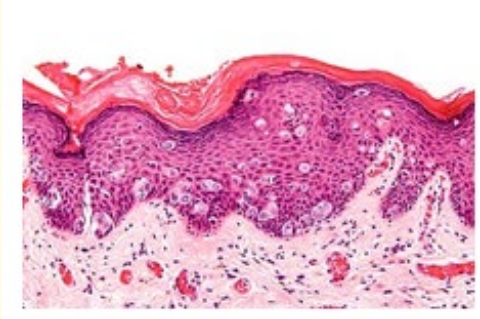

Figure 1: *Paget's disease demonstrating aggregates of epidermal cells impregnated with abundant, eosinophilic cytoplasm, enlarged nuclei and prominent nucleoli. Foci of hyperkeratosis and acanthosis are observed. Subjacent dermis exhibits foci of chronic inflammatory cells [9].*

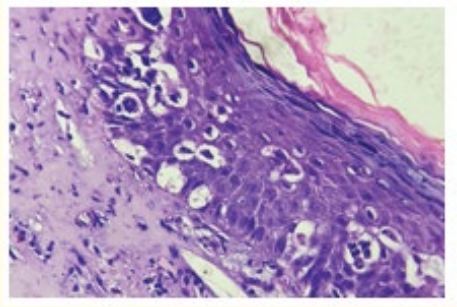

Figure 2: *Paget's disease exhibiting aggregates of epidermal cells impregnated with abundant, eosinophilic cytoplasm, enlarged nuclei and prominent nucleoli. Foci of hyperkeratosis and acanthosis are observed. Subjacent dermis exhibits foci of chronic inflammatory cells [10].*

Bibliography

1. Mariano L., *et al*. "A pictorial exploration of mammary Paget disease: Insights and perspectives". *Cancers (Basel)* 15.21 (2023): 5276.

2. Baysal H., *et al*. "The effects of clinicopathological and imaging findings on recurrence and survival in mammary Paget's disease". *Northern Clinics of Istanbul* 10.5 (2023): 541-549.

3. Yasir M., *et al*. "Mammary Paget Disease". Stat Pearls International. Treasure Island, Florida (2023).

4. Markarian S and Holmes DR. "Mammary Paget's disease: An update". *Cancers (Basel)* 14.10 (2022): 2422.

5. Sisti A., *et al*. "Paget disease of the breast: a national retrospective analysis of the US population". *Breast Diseases* 39.3-4 (2020): 119-126.

6. Dubar S., *et al*. "Paget's breast disease: a case report and review of the literature". *Frontiers in Surgery* 4 (2017): 51.

7. Liu X., *et al*. "Pathological and imaging features of Paget's disease and nipple adenoma: a comparative study". *Gland Surgery* 11.1 (2022): 207-215.

8. Hu T., *et al*. "Overall and cancer-specific survival in patients with breast Paget disease: a population-based study". *Experimental Biology and Medicine (Maywood)* 247 (2022): 187-199.

9. Image 1 Courtesy: Libre pathology.

10. Image 2 Courtesy: The pathologist.

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