Paget's Disease of the Breast (PDB) – A Review

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Abstract: Paget's disease of breast is a cutaneous malignancy of the breast involving the nipple-areolar complex that is often associated with underlying neoplastic lesions of breast parenchyma. This condition is often mistaken for a wide range of dermatological conditions, leading to delay in diagnosis. This review article revisits the etiology, clinical presentation, differential diagnosis, diagnostic work-up, natural history, management and prognosis of Paget's disease of breast.

Keywords: Paget disease, ductal carcinoma in situ, invasive breast cancer, eczema, nipple-areola complex.

INTRODUCTION

Paget's disease of breast (PDB) is a rare malignancy that accounts for about 1–3 % cases of breast cancer. This condition was first described by Sir James Paget in 1874 when he reported chronic eczematous ulcerative or vesicular lesions with clear yellowish exudate, over the nipple and the areola in fifteen women. Initially, these lesions were thought to be benign in nature, but subsequently in 1881 malignant cells were discovered in them by George Thin [1]. PBD is associated with neoplasia of underlying breast parenchyma and mimics many cutaneous disorders and misdiagnosis results in patients receiving extended courses of a topical treatment without complete resolution and hence the resultant delay in the initiation of treatment for breast cancer [2]. This review article discusses the etiology, clinical presentation, differential diagnosis, diagnostic work-up, natural history, management and prognosis of PDB.

METHODS AND MATERIALS

Systematic literature search was conducted through electronic databases, including PubMed, Research Gate, SEMANTIC SCHOLAR and Scopus using the key-words "Paget's disease of breast, Mammary Paget's disease". The search was carried out by using individual keywords with a combination of Boolean Logics (AND). Studies published in English language were used and the studies in the time frame of 2000-2022 were preferred and only those earlier references were used that have historical significance or have concepts that have not been revalidated in recent years.

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Epidemiology

PDB accounts for about 1-4 percent of overall clinical presentations of breast cancer which is much less as compared with other common features like breast lump, nipple discharge etc. This condition is predominantly found in females though rarely men can get afflicted. Though PBD can manifest at any age [3], the peak incidence is in sixth decade. There are certain epidemiological studies that point towards the probability of decrease in incidence over the last few decades. According to the surveillance, epidemiology, and end results (SEER) database, the overall incidence was high between 1988-2002 but had registered a decrease by 45% after that due to unexplained factors. This decreasing trend was displayed in particular for PDB associated with invasive cancer or DCIS [4].

Xu *et al*. recently conducted a population-based study aimed at estimation of the prevalence of PDB and its pattens by sex, age and area in China [5]. The study found the prevalence of PDB to be 0.42 per 100,000 population (95% CI 0.19 to 0.73), with marked female predominance. The prevalence rates peaked at 40-59 years and above 80 years in females and males, respectively. The prevalence rates varied among different regions, ranging from 0.06 (95% CI 0.00 to 0.23) in Northeast China to 1.21 (95% CI 0.07 to 3.72) in Northwest China. Chinese female patients were much younger, with lower prevalence than that in the United States.

Etiopathogenesis

Two theories have been propounded to explain the possible pathogenesis of Paget's disease as following [6]:

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Intraepidermal Transformation Theory

According to this theory, Paget cells arise by degeneration and malignant transformation of pluripotent keratinocyte stem cells or cells of apocrine gland of nipple-areola complex (Figure **1A**). This theory is backed by the following observations:

a. in some cases of Paget's disease, just the nipple-areolar complex (NAC) is affected, and no underlying DCIS or invasive malignancy is present.

b. there is a morphological similarity between Paget cells and Toker cells, which are non-malignant, cytoplasm-rich epithelial cells of sebaceous-gland origin detected in the areolar epithelium of 10% of normal women [7].

Epidermotropic Theory

According to this theory, malignant cells from ductal carcinoma in situ migrate along the basement membrane of the lactiferous ducts and ductules to reach the NAC (Figure **1B**). This theory is more widely accepted by researchers and is supported by two significant evidences [8]:

a. there is high incidence of PDB with underlying malignancy

b. Paget cells and the underlying cancer have the same immunohistochemical profile manifested as high level of HER2/neu oncogene expression.

There are no clearly identified distinct risk factors except those which are common to other breast cancers [4] as shown in Table **1**.

Clinical Presentation

PDB develops insidiously as a unilateral skin lesion, that evolves gradually over months to years by centrifugal extension from the nipple into the areola and in more advanced cases may also involve the periareolar skin [9-10]. The skin lesions are associated with several symptoms, including redness, fine scaling, itching, burning sensation, pain, and oozing with serosanguineous discharge / bleeding [11-12].

On physical examination, the typical findings include sharply demarcated, fine scaly, erythematous, crusty, and thickened plaques on the nipple, spreading to the surrounding areolar areas (Figure **2**). In advanced stages, the cases are often accompanied by skin ulceration/fissures and nipple retraction. The lesion range in size from 3 mm to 15 cm in diameter and the mean size is about 2.8 cm in diameter. PDB can arise from the axillary accessory breast tissue or the supernumerary nipples [3,13]. Hyperpigmented lesions

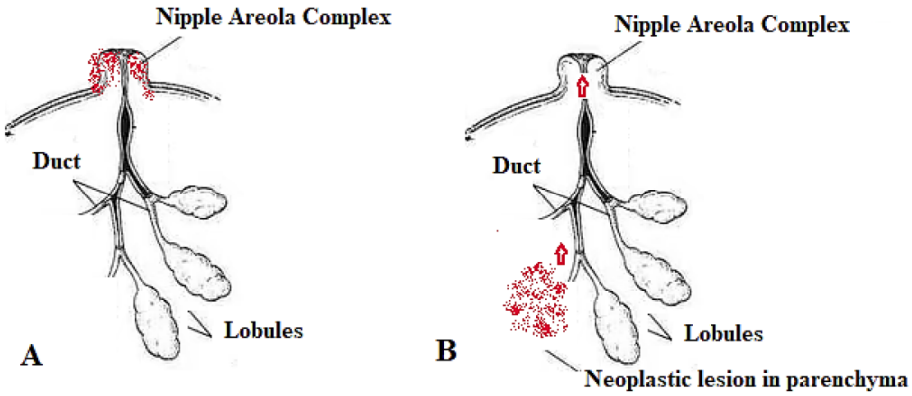

Figure 1: Etiopathogenesis of Paget's Disease of Breast. **A**: Intraepidermal transformation theory **B**: Epidermotropic theory.

Table 1: Risk Factors for Paget Disease of Breast

Risk factors for Paget disease of breast		
i. Old age (above 50 years old)	ii. Inherited gene mutations like BRCA1 and BRCA 2	iii. Increased breast density as identified by the mammogram
iv. Personal history of breast abnormalities like lobular carcinoma in situ (LCIS) or atypical hyperplasia	v. Hormone replacement like estrogen therapy after menopause	vi. History of radiation exposure, particularly to the chest
vii. Family history of breast or ovarian cancer, or both	viii. High-risk ethnicity for breast cancer, e.g., white race	ix. Alcoholism

that resemble malignant melanoma have also been reported in the literature [8, 14-17].

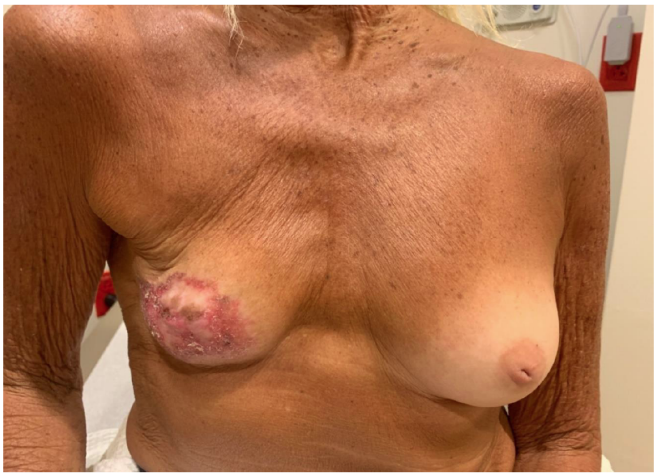

Figure 2: Clinical presentation showing right breast nipple-areolar complex obscured by skin changes. (Source: https://www.cureus.com/articles/71558-invasive-pagets-disease-of-the-breast-rash-or-recurrence).

In a series by Dalberg *et al*. involving 223 women with histological verified Paget's disease, a vast majority (98%), had eczema or ulceration of the nipple as the main presenting complaint [18]. In a series by Kawase *et al*., similar results were seen and eczema or ulceration of the nipple was seen in 98 percent of the 104 enrolled cases whereas bloody nipple discharge was present in 10 percent [19].

Workup

The timely diagnosis of PDB requires awareness about the fact that if after four to six weeks course of topical corticosteroids, an apparently benign skin lesion does not show any signs of complete resolution or shows only marginal improvement , then a high-quality diagnostic breast imaging work-up and biopsy should be performed [6].

Imaging is important to rule out malignancy as there is a high probability of associated breast carcinoma. PDB co-exists with DCIS or invasive cancer in more than 90% of cases, while palpable mass is found in 10 -60 % of cases.

In a series by Challa and Deshmane , 12 out of 20 cases (60%) had retroareolar lump with three patients (25%) having the lump extending to the upper outer quadrant [20].

In a series by Lim *et al*., more than 90% of cases of PDB were associated with an additional underlying breast malignancy and multifocality and multicentricity were reported in 41 and 34% of MPD cases. Mammographic findings were negative in 50% of cases and it was suggested that further imaging modalities like magnetic resonance (MR) imaging be conducted in patients with Paget disease for evaluation of the nipple-areolar complex and identification of an additional underlying malignancy in the breast [21].

Kothari *et al*. retrospectively reviewed the cases of 70 women with a clinical diagnosis of Paget disease. They found that the underlying malignancy was invasive in 58% of cases. Only one third of women presented with a palpable mass, but the malignancy was frequently extensive, being confined to the retroareolar region in only 25% of cases. Mammography failed to estimate the true extent of the disease in 43% of cases. All patients with a palpable mass had multifocal disease, and 30% had multicentric disease. Among those who did not have a palpable mass at presentation, 63% had multifocal or multicentric diseases [22].

Mammography should be used as the primary diagnostic imaging modality for detection of the underlying malignancy but must be followed by breast ultrasound /MRI if the mammogram is negative as mammography is 97% sensitive in detecting an underlying malignancy in PDB cases if a palpable mass is present clinically; however, it only detects underlying malignancy in 50% of cases if no palpable mass is present [21-22]. The findings on mammograms may include skin thickening of the nipple-areolar region, asymmetric density, nipple retraction, a discrete mass, and suspicious microcalcifications [23]. Breast ultrasound findings may include a mass, asymmetry, microcalcifications, ductal ectasia, and thickening of the NAC [21]. Ultrasound may further assess the status of the axillary nodes.

In cases with positive mammogram or ultrasound findings, contrast-enhanced breast magnetic resonance imaging (MRI) may also be used to gauge the extent of the disease, especially when breast-conserving surgery is being contemplated as a treatment option. Furthermore, when these studies are negative, contrast-enhanced breast MRI can detect occult, multifocal, or multicentric lesions. By MRI, the abnormal NAC may be characterized by asymmetric nodular, discoid, or irregular enhancement in comparison to the unaffected, contralateral breast [21, 23-24].

Whether the associated malignancy is identified by imaging studies or not, patients presenting with a

persistent NAC rash should raise suspicion of PDB and must undergo a full-thickness biopsy of the nipple or areolar using a 2–4 mm diameter punch biopsy tool or else a wedge-shaped full-thickness incisional biopsy [6]. There are reports in literature wherein diagnosis have been achieved by quick and non-invasive means like scrape smear cytology test [25-26].

Histopathological Features

PDB is characterized by the presence of Paget's cells (Figure **3**) in the basal region of the epidermis either as single layers or as clusters of cells forming gland-like structures or nests [27]. These cells have characteristic enlarged pleomorphic and hyperchromatic nuclei, with discernible nucleoli, and abundant pale, clear cytoplasm, which often contains mucin. The cells do not form intercellular bridges with adjacent prickle cells. Mitotic figures and melanin pigments may also be observed. Because of the shrinkage artifact due to retraction from the surrounding keratinocytes, the Paget cells may appear to lie within intraepidermal lacunae/ vacuole.

The epidermis may be eroded or hyperplastic, covered by ortho- or parakeratosis. The underlying dermis displays reactive changes including variable degrees of telangiectasia and chronic inflammation, which result in the characteristic clinical appearance [27].

Immunohistochemistry aids in the diagnosis of the Paget's disease as wells as its differentiation from other skin lesions. Paget's cells overexpress low molecular weight cytokeratins (CKs), such as CK7, and they typically do not expression of high molecular weight CKs, such as CK10, CK12, CK14 and CK20 [27-28].

Paget's cells express other glandular antigens too, such as epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), gross cystic disease fluid protein 15 (GCDFP-15) and several mucins, but neither express high molecular weight CKs nor melanocytic antigens [29]. Paget's cells are often estrogen and progesterone receptor negative and present the reactivity of underlying carcinoma. Negative hormone receptor reactivity does not exclude a diagnosis of Paget's disease [30].

Furthermore, there is overexpression of ras oncogene product p21 p53, cell cycle related antigens, such as p21, Ki-67, cyclin D1, androgen receptors and oncoprotein Her-2 [31]. Some reports suggest the possibility of a correlation between positive staining for Her-2 oncoprotein of Paget's cells and underlying *in situ* or invasive breast carcinoma [32]. Some recent studies suggest that NY-BY-1 expression or loss of pRb expression may have a role to play in the pathogenesis of Paget's disease [33].

Differential Diagnosis

The differential diagnosis includes various benign and malignant conditions [34] as depicted in Table **2**.

Bilateral Paget

Synchronous bilateral PDB is exceptionally rare and isolated cases are reported in literature. Choridah *et al*. [35] and Franceschini *et al*. [36] have reported synchronous bilateral PDB in females and in both there

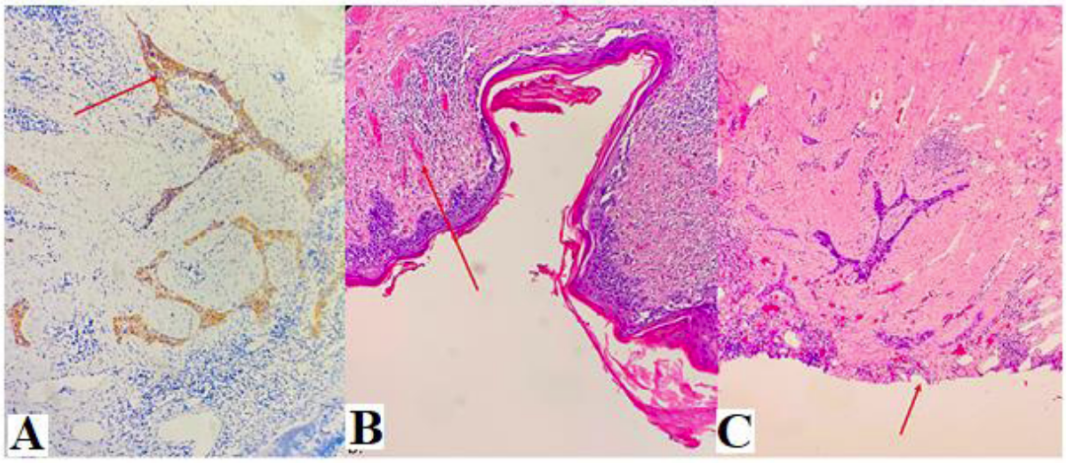

Figure 3: A. HER2 (human epidermal growth factor receptor 2) positive nests of invasive Paget's disease (arrow); **B**. Neoplastic cells in the epidermis (arrow); **C**. Invasive Paget's disease, epidermis was ulcerated and sloughed off at this focus (arrow). (Source: https://www.cureus.com/articles/71558-invasive-pagets-disease-of-the-breast-rash-or-recurrence).

Table 2: Differential Diagnosis of Paget's Disease of Breast

Paget's disease of Breast	Eczema
Generally Unilateral	May be bilateral
More common in old postmenopausal females	More common in young premenopausal females
Nipple is involved	Nipple is usually intact
Underlying lump may be present	There is no underlying lump
Non-responsive to steroids	Responsive to steroids
	Psoriasis
No vesicles and pustules	Vesicles and pustules
	Contact Dermatitis
Involves nipple, and then extends to areola	No change in the nipple Limited to areola
	Mammary duct ectasia
Generally unilateral	Generally bilateral
	Drug eruption
Mass may be present	No mass
	Nipple duct adenoma
Mammograms frequently abnormal	Normal mammograms
	Bowen's Disease
Nipple is always involved. Glandular formation within the epidermis is more commonly seen in Paget's disease There is no association with sun exposure or human papillomavirus (HPV) infection.	Nipple is usually uninvolved. The presence of intercellular bridges favours Bowen's disease. Major risk factors for Bowen's disease include ultraviolet radiation due to sun exposure, HPV infection and immunosuppression
	Cutaneous Malignant Melanoma
Atypical neoplastic cells in the epidermic and dermis with hyperchromatic nuclei and wide pale cytoplasm; Neoplastic cells can contain granules of melanin; Some melanophages in the dermal papillae	Nests of atypical cells, or single atypical cells spread through the epidermis and dermis Melanophages and inflammatory cells in the dermal papillae
	Benign Toker cell hyperplasia
More common in old postmenopausal females	More common in younger age

was associated bilateral breast carcinoma. Ucar *et al*. has reported synchronous bilateral PDB with infiltrative ductal carcinoma in a 74-year-old male [37].

Paget Disease in Male Breast

Breast cancer occurring in the mammary gland of men is infrequent accounting for less than 1% of all breast cancers, and 0.2% of male cancer deaths [38]. And PDB in males is extremely rare and only a few cases are reported in peer-reviewed literature [39-41]. Clinical recognition of PDB is very important in males like in females, because it can be an indicator for an underlying invasive ductal breast cancer, often more aggressive than in females, with an estimated 5-year survival rate of 20–30% [27, 42].

Secondary Paget's Disease of the Breast

There are very rare reports of secondary PDB in literature wherein the disease presents as a local recurrence of the primary breast cancer.

Pourmoussa *et al*. in 2021 reported a 69-year-old female with secondary PDB, presenting as a diffuse pruritic rash and skin changes covering the entirety of the right breast including the NAC . Biopsy revealed dermal invasion and diagnostic mammogram and breast MRI revealed no underlying suspicious findings within the breast tissue. In her past, she had a history of right-sided early stage breast cancer 20 years ago which had been treated with lumpectomy and axillary lymph node dissection. She received adjuvant

treatment with chemotherapy, followed by whole breast radiation therapy, and had taken two years of tamoxifen, which had been discontinued due to uterine polyps.

She was managed with mastectomy with removal of the affected skin, resulting in a clear margin and clinically favourable outcome. Plastaras *et al*. also has reported PDB involving the nipple as a local recurrence after breast-conservation treatment for early-stage breast cancer.

Staging

The presence of PDB does not alter the stage of the underlying breast cancer. If an associated invasive breast cancer or ductal carcinoma in situ is not identified, PDB is classified as Tis (Paget) disease.

Treatment Options

i. **Surgical options:** Surgical management is the main treatment modality for PDB due to the underlying breast cancer and there is no unambiguous data in literature specifically addressing the local management of PBD.

For multicentric or multifocal disease, total or skin-sparing mastectomy with surgical axillary staging with or without breast reconstruction is frequently performed; however, for patients with unifocal disease limited to the nipple-areolar region breast-conserving therapy has become increasingly more common in recent years [23, 45]. Superior aesthetic outcomes can be attained with oncoplastic surgical techniques (e.g., Grisotti mastopexy, Wise-Pattern mammaplasty) combined with a contralateral mammaplasty or mastopexy, to maintain breast symmetry. Nipple-areolar reconstruction may be undertaken immediately or with a delay and dermatography (medical tattooing) may be performed to create a symmetrical, colour-matched NAC [6] .

In cases without any evidence of underlying malignancy, non-operative management have been tried as an alternative therapy to traditional breast-conserving therapy [46]. Stockdale *et al*. retrospectively reviewed the case records of 28 patients with Paget's disease of the nipple treated by radio-therapy alone. 16 of 19 patients who had no palpable underlying tumour and who were mammographically normal at the time of original treatment remain free of disease with a median follow-up of 5 years 3 months [47]. Similarly in a study by Bulens *et al*., 13 patients with PDB confined to the nipple or surrounding skin without any underlying malignancy were treated with radiotherapy alone, with no recurrences detected after 58.6 months of mean follow-up [48].

ii. **Minimally invasive options:** Photodynamic therapy (PDT) is a recent treatment modality which uses a topical or intravenous photosensitizing agent that is activated by a specific wavelength of light to ablate an abnormal tissue. This modality has been tried as a minimally invasive alternative for PDB with limited success [49]. Markarian *et al*. have employed cryoablation of subareolar lesions combined with local excision of the affected NAC to manage PDB limited to the skin and subareolar tissue [6].

iii. **Endocrine therapy:** Regarding role of endocrine therapy (tamoxifen or aromatase inhibitors), there are no data addressing their efficacy in reducing the risk for local recurrence in patients with PDB without an underlying invasive carcinoma or DCIS who are treated with breast-conserving therapy. Decisions regarding endocrine therapy as well as other forms of adjuvant systemic therapy such as chemotherapy and trastuzumab are hence based solely upon the characteristics of any associated invasive carcinoma or DCIS.

Prognosis

Without any active treatment, PDB and the underlying breast lesions are likely to progress to invasive breast cancer, followed by lymph node and visceral metastasis [6]. The prognosis of PDB is dependent upon the initial clinical presentation and the presence or otherwise, of an underlying invasive ductal carcinoma or axillary node metastases. If PDB presents initially with a palpable mass, it is usually associated with more advanced disease than the cases without a palpable mass. When breast mass is not palpable, 92% of patients survive five years after excision and 82% survive ten years. When breast mass is palpable, 38% survive five years; 22% survive ten years. Prognosis is worse when there is lymphadenopathy, high nuclear grade or age above 60 years [50].

Some studies have found that PDB negatively influences breast cancer survival, and that was attributed to its tendency to develop in association with

higher-stage disease. Zhou *et al*. found that PBD cases have more HER2 positivity (P<0.01) and hormone receptor negativity (P<0.01), and a worse outcome (Kaplan–Meier analysis, P<0.001 for disease-free survival and P=0.002 for overall survival) as compared to a matched group of patients diagnosed with breast cancer without PBD [51].

CONCLUSION

Eczematoid changes of the nipple-areola complex and persisting symptoms like soreness, burning or itching, without any obvious cause, should raise a high level of suspicion for Paget's disease of the breast and lead to thorough evaluation, including imaging and biopsy as the superficial lesion of Paget disease may be the only sign of an underlying breast neoplasm. PBD is associated with DCIS or invasive cancer in the ipsilateral breast, almost universally and since it mimics many cutaneous disorders and unawareness can lead to delay in diagnosis and worsen the outcome. Because these associated breast malignancies tend to be multifocal and multicentric, mammography and ultrasound often is insufficient and MRI may be necessary to evaluate the true extent of the disease. Management is generally surgical though in selected cases, non-surgical management has a role.

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DISCLOSURE

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