

Paget's Disease of the Breast: Review of Literature Focusing on Various Imaging

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Introduction

Paget's disease of the breast was first described in 1874 by Sir James Paget observing 15 women with chronic nipple ulceration who all went on to develop cancer of the involved breast within two years (1). It is a clinical entity which became known as Paget disease of the breast (PDB) and was subsequently discovered that the characteristic malignant cells are present within the epidermis of the nipple and it is frequently associated with breast parenchymal malignancy (2, 3). Although PDB is a less common presentation of breast cancer than is palpable mass or mammographic abnormality, it is an important consideration in the differential diagnosis of a chronic persistent abnormality. We will review of the disease with characteristic radiologic findings that would facilitate early and precise detection and appropriate treatment.

Epidemiology and Clinical Presentation

PDB accounts for 2 to 3 percent of all breast cancers. It rarely occurs in men. The peak incidence is in age between 50 and 60. The hallmark of PDB is a scaly, raw, vesicular, or ulcerated lesion that begins on

the nipple and then spreads to the areolar (Fig. 1). Nipple retraction, skin thickening and bloody nipple discharge could be also present with or without palpable mass (4). Despite the superficial nature of the findings, the median duration of the symptoms prior to histologic diagnosis is between 6 to 8 months (5). Subclinical histologic evidence of PDB may be more frequent. In a series of 3000 consecutive mastectomy specimens, the incidence of clinical Paget disease was 0.7 percent, but histologic evidence of the disease was present in 4.9 percent of the mastectomy specimens (6).

Histologic Features and Pathogenesis

Definitive diagnosis of PDB can be made by full-thickness wedge or punch biopsy of the nipple showing typical malignant, intraepithelial adenocarcinoma cells (Paget cells) occurring singly or in small groups within the epidermis (7). Controversy exists over the origin of Paget cells but two theories have been proposed to explain the pathogenesis of PDB. They are the epidermotrophic theory, which is by far the more widely accepted, and the transformation theory. The epidermotrophic hypothesizes that Paget cell arises from an underlying mammary adenocarcinoma, with the neoplastic ductal epithelial cells migrating through the ductal system of the breast into the epidermis of the nipple. This theory is supported by immunohistochemical staining concordant in Paget cells and the ductal epithelial cells and several molecular markers concordant in

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PDB and underlying parenchymal breast tumors (8, 9). In contrast, the transformation theory proposes that epidermal keratinocytes within the nipple transform into malignant Paget cells, and that PDB in fact represents an epidermal carcinoma in situ that is independent of any underlying ductal carcinoma. This theory is bolstered by the observations that no parenchymal cancer is associated in a small percentage of cases and when an underlying parenchymal carcinoma is present, it is often located peripheral to the nipple (10, 11).



Fig. 1. A 54-year-old woman with erythematous nipple areola complex with ulcerative, eczematous inflammatory skin change which is typical clinical presentation of Paget's disease of the breast.

Radiologic Features

Bilateral mammography is mandatory to identify an associated mass. Approximately one-half of cases of PDB have an associated mammographic abnormality. The mammographic findings included suspicious microcalcifications, a mass, architectural distortion, nipple retraction and asymmetric thickening of the nipple-areolar complex with or without discrete mass (Fig. 2). The mammographic abnormalities can be located distant from the nipple-areolar complex (12). Presence of invasive breast cancer is less likely with a negative mammogram particularly in the absence of a palpable mass. However, an occult associated intraductal carcinoma may be present without detectable abnormality on mammography (12, 13).

Ultrasound (US) examination may be helpful and should be considered as a part of initial evaluation especially when mammography is negative (14). Skin thickening more than 2 mm and/or skin of involved breast thicker than the contralateral breast, interruption of the echogenic line or the skin, the dermis/subcutaneous fat interface could be detected on ultrasonography (Fig. 3). Lobulated or irregularly contoured mass, mostly without posterior acoustic shadowing could be noted for the

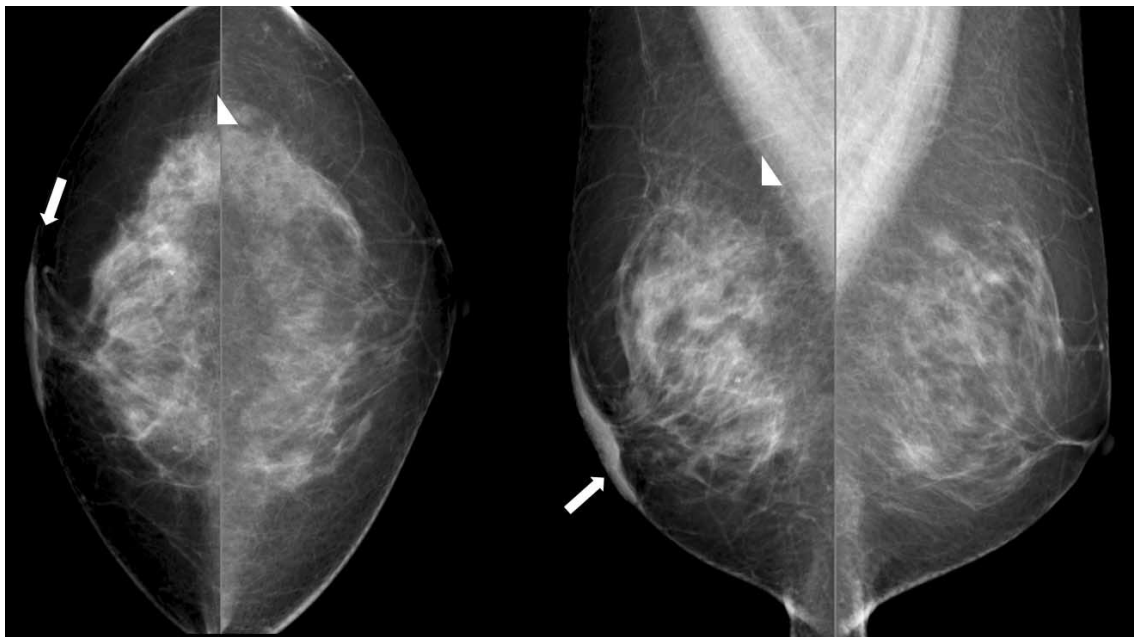


Fig. 2. A 58-year-old woman with palpable mass in her right breast. Mammography of both breasts show skin thickening of areola and inverted nipple (arrow). A focal asymmetry at right upper outer breast is associated (arrow head).

associated breast cancer (15).

Computed tomography (CT) findings of PDB has never been mentioned in the published literature but asymmetrical skin thickening, nipple retraction, architectural distortion in the involved breast could be demonstrated with or without mass or masses. Asymmetrical enhancement of nipple-areolar complex and linear ductal enhancement connecting underlying breast tumor with nipple could also be noted on contrast enhanced CT (Fig. 4).

Magnetic resonance imaging (MRI) is now well known for its high sensitivity in detecting mammographically and clinically occult breast neoplasm. There are few data addressing the utility of breast MRI in women with PDB and a negative mammogram (16–20). The largest series included 34 women with PDB, 32 of whom had a histologically confirmed breast cancer (seven invasive carcinoma and 25 DCIS). In that study, MRI detected four otherwise occult breast cancers (three DCIS, one

invasive cancer) in patients with biopsy proven PDB and negative mammography. Abnormal MRI findings of PDB include an enhancement of the tip of the nipple extending into the retroareolar region with ill-defined borders and irregular margin, clear asymmetric morphology and enhancement pattern of nipple areolar complex which show early enhancement with subsequent washout (17, 19). Breast parenchymal abnormal findings compatible with higher than BI-RADS category 3 could be revealed if underlying breast cancer is combined (16) (Fig. 5). While MRI could be of much help disclosing occult breast cancer allowing directed treatment of the ipsilateral breast, a negative preoperative study cannot be used to reliably exclude an underlying cancer. In addition, because MRI is highly sensitive but not highly specific, MRI may reveal abnormalities that might lead to the overuse of mastectomy rather than breast conserving therapy. Therefore, it was proposed MRI guided biopsy is crucial for ultimate treatment options.

Stage and Treatment

The presence of PDB does not change the stage of an underlying breast cancer and the most important aspect that influences the treatment decision is the presence or absence of an ipsilateral palpable breast mass or mammographic abnormality. If an associated breast cancer is not identified, PDB is classified as Tis. Recent trend treatment for PDB is breast-conserving surgery followed by radiotherapy which is thought to be a reasonable alternative to traditional mastectomy as long as nipple-areolar resection and wide local excision of non-

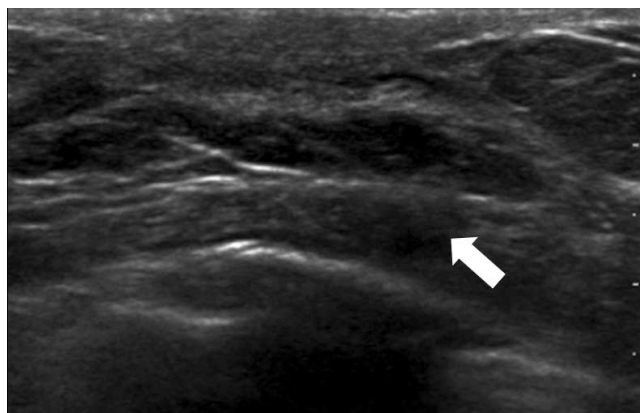


Fig. 3. A 71-year-old woman with eczematous skin change of her right breast, areolar area. Ultrasound reveals inverted nipple and skin thickening of around nipple and areola.

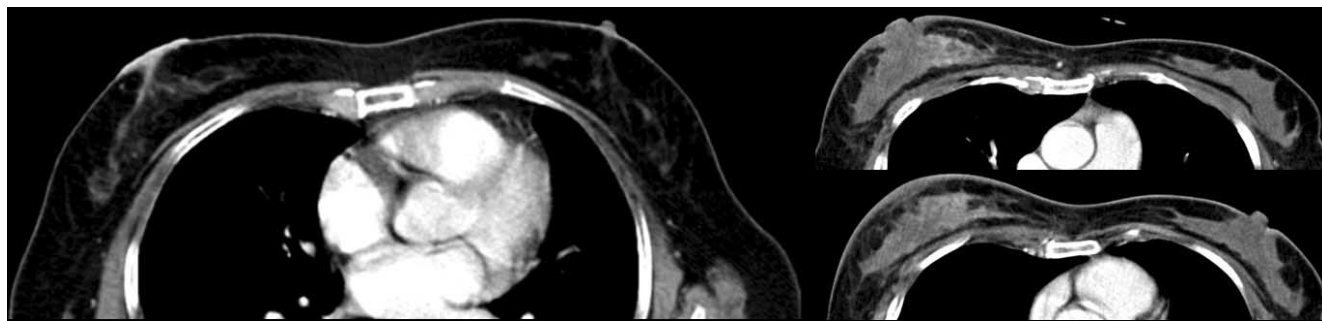


Fig. 4. Contrast enhanced computed tomography of two patients who had paget's disease, demonstrates linear ductal thickening with contrast enhancement and nipple retraction at the right breast (right). Dense soft tissue density is noted at subareolar area of the right breast, extending to the nipple (left upper). Slightly more enhancing lesion is found at medial side of the right breast, with skin thickening around nipple areola complex greater than that of contralateral side breast (left lower).

invasive mass, if there were any, is done. It is because favorable outcomes can be achieved with an acceptable cosmetic result and negative margins. If an invasive breast cancer is found, it should be treated like any other invasive breast cancer, with consideration of adjuvant systemic therapy. We experienced cases of PDB with locally advanced breast cancer which showed good response to neoadjuvant chemotherapy which yield curative surgery without recurrence or distant metastasis in five years follow up period (Fig. 6).

Conclusion

PDB is clinical entity referring typical malignancy in nipple areolar complex frequently associated with ipsilateral breast cancer. Familiarity of imaging findings of PDB with various modalities is import for radiologist in detecting underlying breast malignancy as well as in detecting subclinical nipple lesion to prevent under- or over evaluation and of the disease. And neoadjuvant chemotherapy is promising treatment for locally advanced breast cancer along with traditional combina-

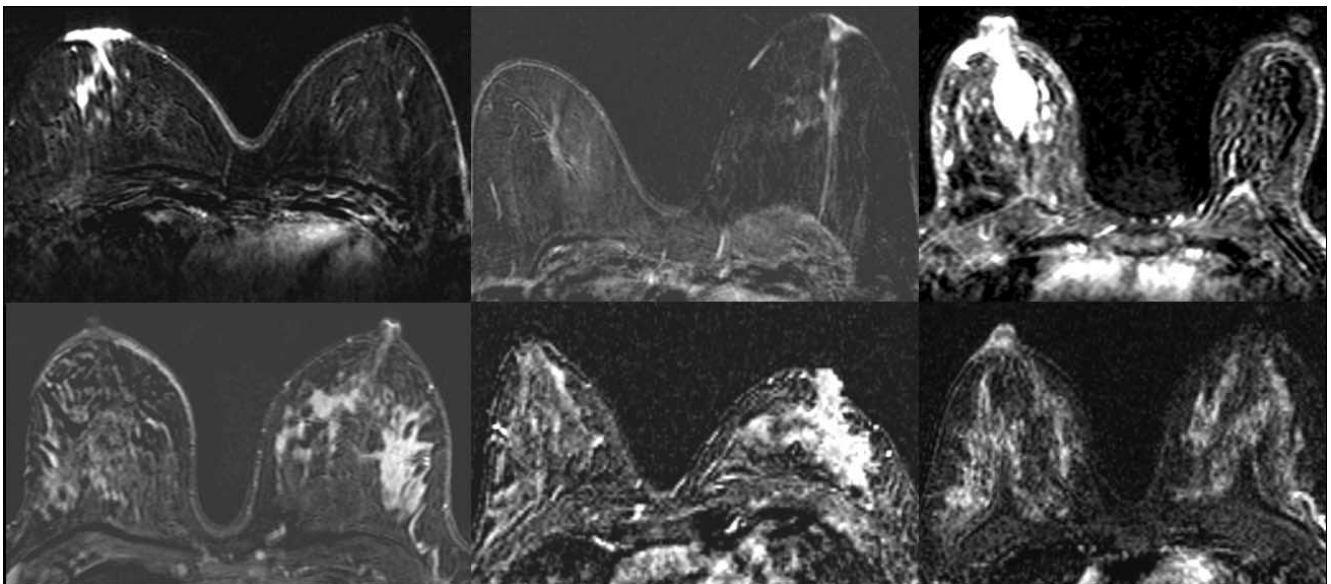


Fig. 5. Subtraction gadolinium-enhanced magnetic resonance images of six different patients show relatively prompt strong enhancement at nipple areola complex with several highly enhanced lesions in breast parenchyma at ipsilateral side. All are as well interpretable as highly suggestive of malignancy of the breast with nipple and areolar complex involvement, which were confirmed Paget's disease.

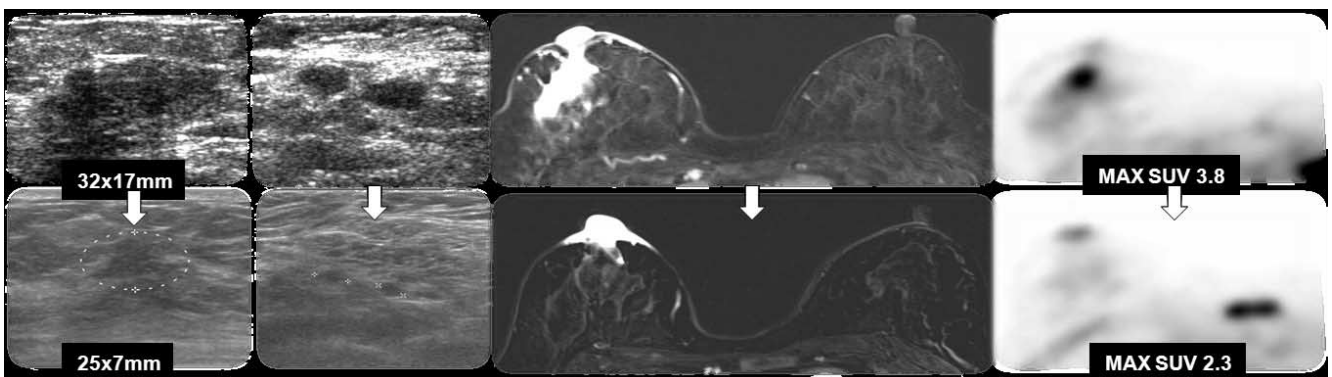


Fig. 6. A 54-year-old woman with invasive ductal carcinoma of her right breast. Pre- and post- neoadjuvant chemotherapy imaging studies of a case. Ultrasonogram (first two pictures in upper/lower row), subtraction gadolinium-enhanced magnetic resonance images (third picture in upper/lower row), and positron emission tomography (PET) (far left in the upper/lower row) show decreased size and metabolic activity of the lesion after three cycles of neoadjuvant chemotherapy. Obvious radiologic improvement of cancer suggests partial responsiveness. Pathology confirmed complete remission of malignant cells in the breast after following operation. Remaining enhancement at nipple areolar complex in third picture in the lower row is confirmed by fibrotic scarring change.

tion of surgery, CCRT and systemic chemotherapy.

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