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Mammary Paget Disease

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Continuing Education Activity

Paget's disease of the breast is an uncommon manifestation of underlying breast cancer in postmenopausal female patients. Underlying breast lesion is usually a ductal carcinoma in situ (DCIS) but can be invasive cancer. The condition can easily be overlooked or misdiagnosed as the presentation is very similar to many common skin rashes that a woman experiences in her life. This activity highlights the role of the interprofessional team in the evaluation and management of mammary Paget disease.

Objectives:

- Summarize the epidemiology of Paget disease of the breast.
- Describe the typical presentation of Paget disease of the breast.
- Review the diagnostic techniques to differentiate and confirm Paget disease of the breast.
- Summarize an interprofessional team approach to the evaluation and treatment of Paget disease of the breast.

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Introduction

Sir James Paget, in 1874, identified 15 female patients with chronic nipple lesions; all of them developed breast cancers later on. These lesions were described as eczematous ulcerative or vesicular lesions with clear yellowish exudate. Initially, these lesions were considered benign in nature, but it was subsequently discovered that these epidermal lesions, which are usually present over nipple and areola, had malignant cells. This condition was later described as mammary Paget disease (MPD) or Paget disease of the breast (PDB). A similar disease process was identified in female and male external genitalia, known as extramammary Paget's disease. The histological features of both conditions are the same, but the pathogenesis is different.

Etiology

It is widely accepted that Paget disease is associated with some underlying breast malignancy, usually ductal carcinoma in situ (DCIS) or invasive ductal carcinoma. It is theorized that these malignant ductal epithelial cells migrate toward the skin through the lactiferous ducts and ductules. There are no clearly identified distinct risk factors except those which are common to other breast cancers.

These risk factors are as follows: old age (above 50 years old), a personal history of breast abnormalities like lobular carcinoma in situ or atypical hyperplasia, family history of breast or ovarian cancer, or both, dense breast tissue as identified by the mammogram, radiation exposure, particularly to the chest, increase the risk of breast or ovarian cancers due to inherited gene mutations like BRCA1 and BRCA 2, hormone replacement like estrogen therapy after menopause, high-risk ethnicity for breast cancer, e.g., White race women are more likely to develop breast cancer than black or Hispanic women, drinking large amounts of alcohol.

Epidemiology

The Presentation of PDB is much less common as compared to the other presentations of breast malignancy like palpable mass or mammographic findings, accounting for about 1-4 percent of overall presentations.[1] While this condition is typically presented in women, rarely men can also present with similar presentations. The usual range of presentations is 26 to 88 years, with the peak incidence in postmenopausal females in the sixth decade.

Although this is an uncommon presentation, any patient with a chronic persistent skin rash of the nipple should be evaluated for PDB. There is some epidemiological data that suggests that the incidence of PDB is decreasing over time. Although the overall incidence was high in the data between 1988-2002, according to one estimation provided by the surveillance, epidemiology, and end results (SEER) database, the incidence is decreased by 45% after that due to unknown reasons. This decreasing incidence was greatest for PDB associated with invasive cancer or DCIS.[2]

Pathophysiology

A couple of hypotheses have been proposed to explain the pathogenesis of PDB.

1. Epidermotropic theory: proposes the Paget cell arises from an underlying mammary adenocarcinoma, with the *neoplastic ductal epithelial cells migrating through the ductal system of the breast and reaching the epidermis of the nipple.* In many case series, it was found that the immunohistochemical (IHC) staining properties were common between Paget cells and the ductal epithelial cells. In comparison, this was not the case between Paget cells and the epidermal keratinocytes of the surrounding nipple tissue.[3] Similarly, several molecular markers were discovered in Paget cells that were also found in many parenchymal breast tumors like *overexpression or amplification of the gene for HER2*. Almost over 85% of the cases of PDB, Paget cells are stained with an anti-HER2 monoclonal antibody. It is hypothesized that the spread of Paget cells to the nipple epidermis from the duct system may be mediated through a motility factor that exerts its effect via the HER2 receptor. These data support a common genetic alteration and/or possibly a common progenitor cell for both the Paget cells and the underlying ductal carcinoma. Epidermotropic theory is, by far, the more widely accepted.[4]

2. Transformation theory: proposes that the *PDB arises from epidermal keratinocytes independent of underlying breast malignancy* and actually represents an epidermal carcinoma in situ. George Thin in 1881 proposed this theory claiming that the secretions from the breast ducts continuously damage the epithelium, which leads to the transformation of these keratinocytes into cancer cells. This theory was supported by certain facts and observations that a small percentage of PDB did not have underlying parenchymal cancer. And whenever an underlying malignancy was present, it was often located peripheral to the nipple that would suggest two independent neoplastic processes. In one series of 80 female patients with PDB and breast cancers, underlying malignancy was located more than 2 cm away from the areolar margin in 29 cases.[5][6] Also, there have been demonstrations of specific "pre-Paget cells with the appearance intermediate between keratinocytes and Pagets cells, suggesting the epidermal cells can acquire the characteristics of ductal cells as they undergo malignant transformation. This theory has fallen out of favor because if enough sections are taken in biopsy and studied, the involvement of the large (lactiferous) ducts immediately beneath the nipple can usually be demonstrated.

Histopathology

The histologic hallmark of PDB is the presence of Paget cells, which are malignant, intraepithelial adenocarcinoma cells of variable sizes usually large in size, present singly or in the form of small groups within the epidermis of the nipple. Cells may be ovoid, round, or signet-ring forms, usually mucin positive, and the cytoplasm may contain periodic acid-Schiff (PAS)–positive, diastase-resistant granules, indicating the presence of neutral mucopolysaccharides. The cells possess microscopic features of glandular cells with pale to clear vacuolated cytoplasm, and nuclei are usually high-grade with prominent nucleoli. It has been postulated that cells may derive from glandular stem cells or epidermal Toker cells (clear cells of the nipple epithelium).

Toker cells are benign and have been found in about 10% of normal nipples and rarely in supernumerary nipples. Like Paget cells of PDB, Toker cells contain prominent, clear vacuolated cytoplasm, and *they are considered benign counterparts of Paget cells*.[7][8] Histologically, PDB can mimic malignant melanoma, particularly if the cells have incorporated melanin from the adjacent epidermis. By using special stains such as mucicarmine, which may highlight

the cytoplasmic mucin vacuoles in the Paget cells, it is possible to differentiate PDB from melanoma. These invasive cancer associated with this condition were estrogen and progesterone receptors negative and had high-grade pathology.[9]

History and Physical

A detailed history should be taken, focusing mainly on the length of time the lesion has been present and any associated symptoms, including nipple discharge, pain, bleeding, burning, redness, scaling, and itching. A long-standing eczematous pruritic lesion should prompt to think about underlying parenchymal breast malignancy. Early symptoms and signs of PDB include excoriation from itching and resolution & recurrence of small vesicles within the skin lesion. The history should also cover the patient's individual risk profile for breast cancer like personal or family history of breast or ovarian cancer, hormone replacement therapy, social history, etc.

Bilateral breast examination should be performed, focusing on associated breast abnormalities. Usually, in PDB, there is unilateral involvement in comparison to eczema, which usually involves the breast bilaterally, but bilateral breast involvement in PDB has also been reported. On physical exam, typically an erythematous, scaly, crusty, and thickened plaque-like lesion is present on the nipple spreading to the surrounding areolar areas. This erythematous patch is sharply demarcated and deeply infiltrated, unlike eczematous dermatitis, but it is often difficult to distinguish PDB from eczematous dermatitis or melanoma.

Lesions are usually present centrally (within 2 cm of the areola) but occasionally may be present peripherally. The size usually ranges from 3 mm to 15 cm in diameter and may be associated with serosanguinous discharge. An underlying malignancy is present in up to 88 percent of the cases with these skin lesions. *An associated palpable mass may be present in 50 percent of the cases*.[1][10] Other nipple changes may be present like nipple retraction or invagination, and these findings are usually indicative of underlying breast tissue infiltration.

Evaluation

After a careful history and physical exam, the workup may be started either with mammography or a biopsy of the lesion. Scrape cytology is a quick, easy, non-invasive method of screening eczema of the nipple in the out-patient clinic. Bilateral mammography should be done to look for underlying mass. Approximately 50% of cases of PDB have associated abnormal mammographic findings. *In 20 percent of cases, a mammographic abnormality is present without a palpable mass*. The mammographic findings may include simply a mass or suspicious microcalcifications, architectural distortion, and asymmetric thickening of the nipple-areolar complex. A negative mammogram does not rule out underlying malignancy. In one case series, mammography failed to find underlying Ductal carcinoma in situ (DCIS) in 17 women, five of them had the extensive multicentric disease. Whole breast ultrasound can be done for further evaluation, but the addition of ultrasound to mammography has not been found to increase the overall sensitivity to detect underlying lesion as compared to mammography alone. However, ultrasound can be used to further categorize or to guide core biopsy from any palpable mass or mass-like abnormality found in mammography.

Magnetic resonance imaging (MRI) is a sensitive imaging tool for invasive breast cancer. As the neoplasm may be multifocal and multicentric, MRI has been recommended to evaluate the true extent of disease. *Approximately 12 to 15 percent of cases are not associated with any palpable mass or a mammographic abnormality*.[11] MRI may disclose occult cancer in some women with PDB and no findings on mammography or physical examination, potentially allowing directed treatment of the ipsilateral breast. However, a negative preoperative study cannot reliably exclude underlying occult cancer. In a case series of 34 female patients who had 32 patients with biopsy-proven PDB, MRI did not detect cancer in 3 patients (two unifocal DCIS and one invasive cancer).[12] conversely, 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.[13] Thus, if MRI is to be performed, it should only be undertaken at an institution that has the capability of performing MRI-guided biopsies, and the patient should be counseled regarding the high false-positive rate of breast MRI and the possible need for additional biopsies.

Most important is to biopsy the underlying abnormalities, not only the nipple lesion but any underlying masses or mammographic abnormalities to assist further management plan, including the further need for evaluation of the axilla. A full-thickness punch biopsy is more widely used. A wedge biopsy may contain lactiferous ducts, which may identify DCIS as the etiology of PDB. Nipple scrape cytology can also accurately diagnose PDB but does not involve

the biopsy of the underlying mass. If nipple discharge is present, a sample may be taken and studied to detect the presence of Paget cells.[14]

Immunohistochemical (IHC) staining for a nipple biopsy that does not involve tissue from the underlying mass is very helpful to differentiate from other similar lesions, especially if squamous cell carcinoma of epidermis and melanoma are the in the list of differential diagnosis. The usual diagnostic panel includes CK7 and CK20, which are low molecular weight cytokeratins, carcinoembryonic antigen (CEA), Estrogen receptor (ER), HER2, S-100, and either MART-1 or HMB-45 if melanoma is suspected. PDB is usually positive for CEA and negative for S-100 protein. However, in some cases, PDB may also express S-100.[15]

MART-1 or HMB-45 may be more useful than S-100 in confirming malignant melanoma. Squamous cell carcinoma of the epidermis contains high molecular weight cytokeratins, while PDB contains low molecular weight cytokeratins. CK7, a low molecular weight cytokeratin, is probably the most useful marker, but the interpretation must also consider other typical features of PDB as CK7 may also be expressed by benign Toker cell hyperplasia. Additionally, Hormone receptor (estrogen/progesterone) positivity is also very helpful. Unfortunately, only 50% of the PDB is positive for these receptors. This finding is not surprising as PDB is a high-grade malignant lesion, and many high-grade breast malignancies do not express these hormone receptors. Instead, most of them are positive for HER2 receptors as PDB. Over 80% of PDB have HER2 overexpression or amplification, the finding consistent for the worse prognosis of such malignancies.[16]

Treatment / Management

Paget's disease of the breast might be classified with *TNM classification and staging system* in the same manner as other breast malignancies. In other words, the presence of Paget disease of the breast does not change the stage of underlying breast cancer. If associated invasive breast cancer or DCIS is not identified, Paget disease is classified as Tis (Paget) disease. A most important aspect of this condition that influences the plan of treatment is underlying breast malignancy. Simple mastectomy has been the standard of treatment for PDB with or without underlying mass previously. Recently, Breast conservative treatment (BCT) has been the treatment of choice for DCIS. No guidelines are available for invasive breast malignancy. When PDB is present in association with a palpable mass or defined mammographic abnormality, the associated breast cancer tends to be a more advanced stage. The chances of underlying multifocal or invasive disease or axillary lymph node positivity are higher than if a mass is absent. The underlying lesion must be removed with a nipple-areolar complex. If wide local excision can be performed with negative margins and acceptable cosmetic results, BCT is the appropriate treatment of choice followed by whole breast radiation therapy (RT).[6][17][18]

Women with multicentric cancer or diffuse calcifications should be treated by mastectomy with axillary evaluation, for example, by sentinel lymph node biopsy (SLNB). Many patients with PDB and a palpable mass are not the candidates for BCT because of the remarkable distance between the primary tumor and the nipple-areolar complex.[6] If there is no underlying mass, Still there is a higher chance that there is some underlying lesion is present likely DCIS. The chances of underlying invasive cancer range from 25 to 33 percent. Mastectomy and BCT, followed by radiation therapy, are both the acceptable treatment of choices. Most of the current data suggest that complete resection of the nipple-areolar complex with central lumpectomy, as clinically appropriate, followed by whole-breast RT is a reasonable alternative to mastectomy for women with PDB and no palpable mass or mammographic abnormality, providing good cosmetic outcome and negative margins can be achieved.[19][20]

The risk of axillary involvement is higher if there is a palpable mass or invasive cancer and need axillary investigation. Patients with DCIS do not require axillary investigation unless the disease is extensive enough to choose mastectomy. If a mastectomy is planned, sentinel lymph node (SLN) biopsy is often performed in order to avoid complete axillary lymph node dissection in case an invasive component is identified at final pathology. Patients with clinically suspicious axilla should undergo an initial ultrasound-guided fine-needle aspiration (FNA) or core needle biopsy of the palpable axillary nodes; if the disease is confirmed histologically, full axillary lymph node dissection (ALND) is recommended. In contrast, if the FNA or core biopsy is negative, SLB biopsy should be performed.[21][22]

Currently, there are no data that the endocrine therapy, including tamoxifen or aromatase inhibitors, reduce the risk of recurrence of local disease in patients with PDB without an underlying invasive carcinoma or DCIS who are treated

with breast-conserving therapy. Recommendations regarding endocrine therapy, as well as other forms of adjuvant systemic therapy such as chemotherapy and trastuzumab, should be based solely upon the characteristics of any associated invasive carcinoma or DCIS. Radiation therapy alone does not always control occult breast cancer; however, it may be used for patients who refuse mastectomy or those who are medically unfit for surgery. Recently, there have been some clinical trials for a procedure called photodynamic therapy for the treatment of mammary and extramammary Paget disease. This procedure involves the use of a drug known as a photosensitizer, along with a special type of light. During this procedure, this drug is injected into the system and absorbed by the affected cells. The drug is activated by the light at a specific wavelength, which destroys the affected cells. Initial results have shown that photodynamic therapy is safe and well-tolerated and, possibly, a less invasive alternative to the surgery. However, the data is limited and more research is needed to determine the effectiveness and long-term safety of the procedure.[23][24]

Differential Diagnosis

It is very important to identify and differentiate Paget disease of the breast from other mimics like inflammatory dermatosis, pre-malignant skin conditions, and breast neoplasms. A list of differential diagnosis should be kept in mind to carry out proper investigations and treatment. Following is the list of the differential diagnosis for MPD of the breast;

- Various skin inflammatory conditions like atopic dermatitis, factitious dermatitis, irritant contact dermatitis & other forms of eczema
- Various skin cancers like malignant melanoma, Squamous cell carcinoma or basal cell carcinoma, etc
- Pre-malignant skin conditions like Bowen's disease
- Erosive adenomatosis of the nipple which is a benign neoplasm of the major nipple ducts
- Nipple duct adenoma, which presents as a palpable nipple nodule with cutaneous erosion and sometimes a discharge in middle-aged women
- Benign Toker cell (clear cell of the nipple epidermis) hyperplasia
- Drug eruptions.

Eczematous dermatitis of the nipples is usually bilateral; it is without any induration and responds rapidly to topical glucocorticoids. Nevertheless, be suspicious of Paget disease if "eczema" persists for more than three weeks with the treatment.

Prognosis

The prognosis of PDB is dependent upon the initial presentation of the disease and the presence 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 cases without a palpable mass. When breast mass is not palpable, 92% of patients survive five years after excision; 82% survive ten years. When breast mass is palpable, 38% survive five years; 22% survive ten years. Prognosis is worse when there is lymphadenopathy.[3][6][25]

Complications

It is not uncommon that the diagnosis of mammary Paget disease is initially overlooked and missed. Longer the delay, the longer the chance for the underlying neoplasm to spread, potentially leading to lymph node metastasis, if not occurred already, worsening the stage of the disease. The more widespread disease will need more extensive tissue dissection. The complications of breast cancer treatment in the patients of mammary Paget's disease are the same as for the treatment of any breast cancer surgery. The excision of lymph nodes may lead to lymphedema in the long run. The use of chemotherapy and radiation therapy might increase the risk for other cancers as well. Hormonal therapy and radiation therapy might also increase the risk of early menopause or infertility.

Deterrence and Patient Education

Here are some important points:

1. Paget disease of the breast is an unusual and different form of presentation of underlying breast cancer. The skin rash may actually indicate the underlying neoplasm in the breast that might need extensive work up as soon as possible.
2. Most nipple rashes are simply a minor skin infection or a reaction to some irritant. A nipple rash that does not get better with topical steroid treatments requires further evaluation with advanced imaging and biopsy to rule out serious conditions like Malignant melanoma or mammary Paget disease, etc.
3. The treatment depends on the stage of the condition, presence or absence of an underlying tumor, lymph nodes are involvement, hormone receptors & HER2 receptor status, and overall general condition of the patient.
4. Surgical therapy, followed by whole breast radiation, is the treatment of choice for the best survival and prognosis.

Enhancing Healthcare Team Outcomes

A well-coordinated effort is required from a team of medical professionals, including the medical oncologist, breast surgeons, radio-oncologist, etc., combined with the patient's preferences for the best outcome of the patient. The treatment of each individual is made on the basis of the extent of the disease and the general condition of the patient to withstand the surgical procedure. Traditionally, the treatment of PDB consisted of removal of the breast with lymph node dissection and possible dissection of chest wall muscles and other related tissue (Radical Mastectomy or Modified Radical Mastectomy). Recent efforts have been made to find out the exact extent of the disease and carry out Breast conservative surgery followed by Radiation therapy with the aim to conserve as much breast tissue as possible.

Review Questions

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