Case Report

Imprint Cytology Can Be a Better Option for Diagnosis of Mammary Paget's Disease!!!: A Case Report with Review

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Abstract

Mammary Paget's disease (MPD) is a rare form of pruritic eczematous skin lesion involving the nipple areola complex usually associated with an underlying *in-situ* or invasive carcinoma of breast, accounting ≤ 4% of overall breast carcinoma. The patient may present with nipple discharge, eczema, plaque, or nipple destruction with or without a lump which is resistant to common remedies. Diagnosis of MPD is usually accomplished by a punch biopsy, but imprint cytology is found to be an effective modern technique yet less explored. Cytological diagnosis is advantageous over surgical excisional biopsy; advantages being easy practicability, cost-effective, quick non-invasive, and above all can lead the physician for breast-preserving surgeries in selective cases rather than more aggressive standard mastectomies. We report one such case of MPD in a 52-year-old female diagnosed on imprint cytology with the aim to emphasize that imprint cytology can be a better option to improve the treatment protocol.

Keywords: Breast-conserving surgery, imprint cytology, mammary Paget

Introduction

Paget's disease of the breast/mammary Paget's disease (MPD) is an uncommon entity and accounts for 1–4% of overall patients with breast carcinoma.[1] In 43% of the cases, mammography may not show any abnormality.[2] Sir James Paget first described an eczematous lesion that precedes a mammary cancer in 1874.[3] Whether MPD is a locally advanced carcinoma or not is a controversial issue. It occurs commonly in post-menopausal nulliparous woman, with peak incidence between 6th and 7th decades (mean age being 54 years) and less common in men with worse prognosis.[4] Traditionally, diagnosis relies on radiology but confirmed by biopsy. Imprint cytology is now utilized to diagnose MPD quickly and reliably. Herein we report a case of Paget's disease diagnosed on imprint cytological examination of eczematous nipple discharge unlike the biopsy as the first line of diagnostic procedure.

Case History

A 52-year-old-female referred to the Department of Cytology with eczematous lesion in the right side nipple and whitish pus-like oozing noticed for 3 months. On palpation, no lump found in either breasts. There was no axillary/supraclavicular lymphadenopathy nor family history of breast cancer. Ultrasonography of bilateral breast showed no mass lesion. By touching nipple discharge imprint smears were taken, then spread on the whole slide, and stained with routine cytology stain, e.g., Diff Quik, Hematoxylin and Eosin, and Papaniculaou's stain. The imprint cytosmears showed good number of dispersed, highly pleomorphic cells having high N: C ratio, hyperchromatic nucleus, abundant pale cytoplasm along with stripped nuclei. The background showed plenty of polymorphs, lymphocytes, histiocytes, foamy macrophages admixed with scattered/clusters of mature squamous epithelium. Thus a cytological diagnosis of Paget's disease was given [Figure 1A and B]. Cone biopsy was followed which showed large polygonal to round Paget cells

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Access this article online

Quick Response Code:

Website: www.jcasonline.com

DOI: 10.4103/JCAS.JCAS_145_21

How to cite this article: Mohanty P, Das P, Mohapatra AS. Imprint cytology can be a better option for diagnosis of mammary Paget's disease!!!: A case report with review. J Cutan Aesthet Surg 2022;15:196-8.

with hyperchromatic nucleus limited to nipple areola complex (NAC) skin. Underlying breast stroma was free of tumor [Figure 1C and D]. Supplementary PAS stain was negative, and immunohistochemistry of EMA and CK7 markers showed intense membranous positivity for tumor cells and Her2/neu showed intense and complete membranous positivity (Score 3+) [Figure 2A-D]. Hence, a final diagnosis of Paget's disease involving NAC was rendered. The patient was found disease-free on 1-year follow-up.

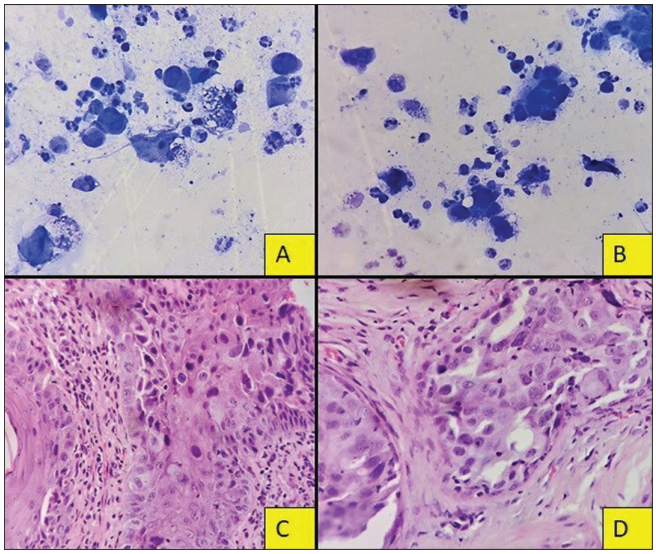

Figure 1: (A and B) Cytology showing Paget's cells in an inflammatory background (Diff Quik, ×100). (C-E) Photomicrograph showing large polygonal to round Paget's cells with hyperchromatic nuclei (H&E, ×400)

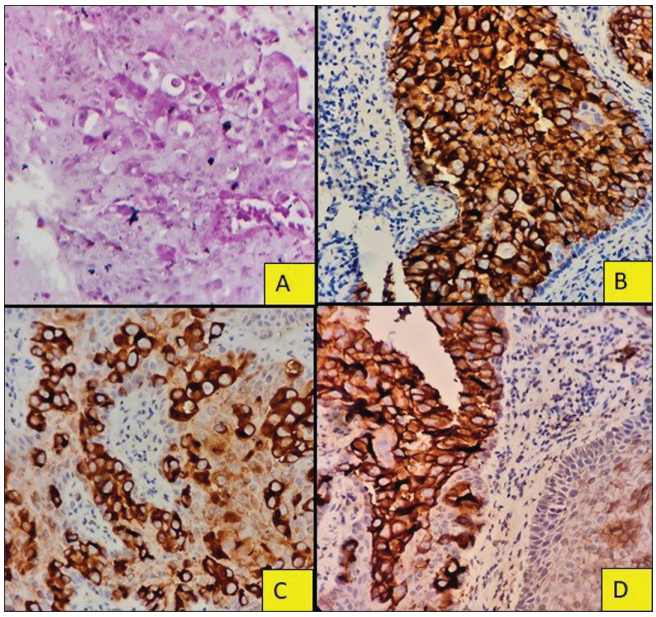

Figure 2: (A) PAS is negative in tumor cells (PAS, ×100). (B-D) Immunohistochemistry showing strong membranous positivity for CK7, EMA, and Her-2-neu, respectively (IHC, ×400)

Discussion

Paget's disease of the breast occurs exclusively on the NAC and may extend to the surrounding skin if left untreated. Histogenesis of Paget's diseases is controversial, yet important for treatment options. Two theories had been proposed toward its histogenesis: 1. epidermotropic theory and 2. *in-situ* malignant transformation theory. The first theory claims that changes typical for MPD arise in the ductal cells and spread along the basement membrane to the nipple, supported by several studies, reflecting the fact that in 82–92% cases, tumor cells have spread from underlying invasive carcinoma or ductal carcinoma *in situ* to skin of the nipple and areola, as evident by similar histomorphology. The second theory claims that MPD originates in the epidermal cells of the nipple by malignant transformation of keratinocytes and is not associated with any coexisting neoplastic process in the affected breast; supported by only very limited cases, those appear to have originated primarily within the nipple epidermis.[5] MPD is usually unilateral and may present as NAC lesions only/NAC lesion with palpable breast tumor/breast tumor only (subclinical Paget's diseases proved histologically); hence categorized as multicentric (two or more tumor foci in separate quadrant of breast) or multifocal (multiple carcinomatous foci in the same quadrant). Common differentials are chronic eczema, psoriasis, erosive adenomatosis, contact dermatitis, syphilitic chancre, adenoma/intraductal papilloma of nipple, superficial spreading melanoma, and squamous cell carcinoma.[4,5] Diagnosis of Paget's diseases cannot be made specifically in mammography or ultrasound of breast. However, MRI is highly sensitive in detecting malignancies that are missed by mammography or ultrasound and is of great help for pre-operative planning by evaluating the tumor extent. There are different modalities to diagnose Paget's disease such as cytology of the nipple discharge, FNAC, or incisional biopsy of the lump (if present) by shave/wedge/punch biopsy of the nipple aided by immunohistochemistry for CEA, CK7, EMA, and GCDFP-15.[6] Incisional biopsy is traditionally used as gold standard for primary diagnosis. But nowadays, cytologic diagnosis is proved to be a reliable and effective method with few literatures supporting, accounting its rarity. Cytology with touch (imprint)/scrape smears is very simple, easy, and quick-to-perform and non-invasive method of diagnosis. Above all, it can be done without anesthesia, hence better patient compliance. If the patient has an underlying mass, then FNA of mass becomes more helpful.[4,7] Early, prompt, and accurate diagnosis of Paget's disease by means of cytology enables breast-conserving surgery (BCS), as it is the preferred trend of surgery than historically performed mastectomy. However, the cytological evaluation technique encompasses several limitations due to both false positive and false negative results such as irregularity of the specimen surface, dryness, cautery effect, or overinterpretation of atypical

cells. False negative results are basically associated with poor sampling technique, improper tumor localization, small tumor size, and non-palpable breast lesions. Factors such as hypocellularity, presence of necrosis, degenerated apocrine cells, and epithelial hyperplasia are often encountered, making diagnosis challenging. Sometimes, different inflammatory and reactive squamous cell lesions also mimic MPD causing cyto-diagnostic errors, leading to false positivity. Extensive literature search revealed a study which reported 8 cases of MPD on nipple scrape smear cytology out of 14 patients with nipple change; another study with four positive cases of invasive ductal carcinoma with nipple scrape smear shows changes of Paget's disease out of 466 cases of nipple discharge and eczematous nipple lesion.[8,9] Association of Paget's disease with underlying carcinoma is variable in different studies from 55.2% to 100%.[10,11] Prognosis is poorer when underlying carcinoma becomes palpable than mammary carcinoma without Paget's disease, whereas the prognosis for Paget's disease with minimal intrinsic *in-situ* carcinoma is excellent.[4] The present case was diagnosed by imprint smear without underlying mass followed by biopsy and IHC confirmation. No optimal treatment strategy is established due to lack of randomized studies. As BCS is the most common emerging treatment modality for invasive breast cancer, this trend has also been tried in MPD. Studies concluded that BCS like central lumpectomy followed by adjuvant radiation is effective in patients with limited diseases, with some studies claiming similar results for both total mastectomy and BCS.[12,13] Others reported that cone excision of nipple–areola complex results in survival rates similar to those with mastectomy.[14]

Conclusion

Despite sparse documentation of MPD diagnosed by cytology, the efficacy of imprint cytology helps in early diagnosis and allows the surgeon optimal flexibility in casewise selective management for conservative surgery. But likelihood of an underlying carcinoma should be carefully evaluated with imaging before planning surgery. Yet, further studies are required to validate the method and till then it may be used as an adjunct to the histopathology.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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