Challenges in Diagnosis and Management of Paget's Disease of the Breast—a Retrospective Study

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Abstract Paget's disease of the breast is uncommon and patients may present with nipple discharge, eczema, plaque or nipple destruction with or without a lump. The aim of the present study was to evaluate the presentation, clinicopathological features and treatment given for patients presenting with Paget's disease of the breast. We performed a retrospective analysis of medical records of patients who were treated at our centre for Paget's disease of the breast from 2006–2011. Twenty patients were treated in this period. Twelve patients had associated lump and eight patients did not have a lump in the breast. Two patients did not have a lump or any detected abnormality in mammography. Multicentricity was present in five patients. Diagnosis of malignancy was made by fine-needle aspiration cytology for patients with palpable lump and nipple wedge biopsy for patients with no lump. Modified radical mastectomy was done in 10 patients: 2 patients underwent total mastectomy and sentinel lymph node biopsy and 8 patients underwent central quadrantectomy and sentinel lymph node biopsy. Eleven patients had invasive ductal carcinoma, one patient had ductal carcinoma in situ with foci of invasion and eight patients had ductal carcinoma in situ. Seven patients had lymph node metastases. Three patients had recurrence, one had local recurrence and two had distant recurrences. The mean follow up period was 28 months (range 15–64 months). Paget's disease of the breast is a rare entity and one needs imaging and biopsy to diagnose these patients as they have associated cancer. They can be considered for breast conservation surgery with good cosmetic and oncological results.

Keywords Paget's disease · Breast cancer · Ductal carcinoma in situ · Breast conservation surgery

Introduction

Eczematous disease of the nipple was first described by Velpeau in 1856 [1]. In 1874, Sir James Paget first described an eczematous lesion that precedes a mammary cancer [2]. After 15 years, extra mammary Paget's disease was first described by Radcliffe Cocker [3]. Paget's disease of the breast is a very rare entity and comprises 1–4 % of overall patients with breast cancer [4]. It is diagnosed by the presence of large, ballooned clear cells infiltrating the dermis. In the absence of an underlying lump, the diagnosis is more difficult. Mammography may not show any abnormality in 43 % of cases [5]. Though skin ulceration is considered as locally advanced malignancy, whether to consider Paget's disease as a locally advanced carcinoma is a controversial issue.

Paget's disease is a very uncommon presentation of breast cancer. We would like to share the presentation, diagnostic modalities, clinicopathological features and prognosis in this group of patients. To the best of our knowledge, this is one of the few studies which explored this issue in India.

Materials and Methods

A retrospective analysis of medical records of patients who presented with Paget's disease of the breast was done from the year 2006 to 2011 at Kidwai Memorial Institute of Oncology, Bengaluru. Clinical features, investigations, surgeries performed and pathological findings were analyzed. Cases with incidental finding of Paget's disease after mastectomy were excluded. Multifocality was considered in the presence of two or more discontinuous areas of carcinoma in the same

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Fig. 1 Various presentations of Paget's disease presenting as an eczema (a), nipple erosion and destruction with involvement of areola (b) and plaque-like presentation with no discharge (c)

quadrant and multicentricity when two or more quadrants were involved discontinuously.

Results

Twenty female patients with Paget's disease were diagnosed in the above-mentioned period. The mean age of presentation was 44.9 ± 10.5 years (range 26–65 years). All were unilateral, 10 on right side and 10 on the left side. Thirteen patients were premenopausal and seven were postmenopausal. The most common presentation was eczematoïd changes of nipple in 60 % of cases (12/20), nipple ulceration in 25 % (5/20) of patients and nipple areola complex destruction with plaques covering them in 15 % (3/20) of patients (Figs. 1 and 2). Nipple retraction was present in four patients (20 %). The most common symptom was itching in 25 % (5/20) and pain

in 20 % (4/20) patients. Nipple discharge was present in eight patients, five had bloody discharge and three had serous discharge.

Associated lump in the breast was present in 60 % of patients (12/20). All of them had retroareolar lump with three patients having the lump extending to the upper outer quadrant. Mammogram was performed in 11 patients, of which 2 patients (18.1 %) didn't have any abnormality. Among nine patients with detected mammographic abnormality, five showed fine microcalcifications, two showed underlying mass and two showed increased skin thickening around the nipple (Fig. 3). Two patients showed multicentric calcification involving more than two quadrants. Overall, multicentricity was found in five patients (25 %). The demographic characters, management and histopathological results were described in Table 1.

Fig. 2 Patient presenting with pigmented lesion involving nipple, areola and surrounding breast skin with nodules diagnosed as Paget's disease (a); weeping type of Paget's disease with destruction of nipple and areola (b)

Fig. 3 **a** Mammogram of left breast (mediolateral oblique view) showing multiple fine calcifications involving central quadrant and upper quadrant; **b** Mammogram of the right breast (mediolateral oblique view) showing spiculated irregular hyperdense lesion with surrounding architectural distortion in retroareolar area (arrow head) with skin thickening and nipple destruction (arrow)

For the patients presenting with a lump, diagnosis was made by fine-needle aspiration cytology (FNAC) and for those without a lump, a wedge biopsy of the nipple was done. Ten patients underwent modified radical mastectomy, two

patients underwent total mastectomy with sentinel lymph node biopsy (SLNB) and eight patients underwent central quadrantectomy with SLNB (Fig. 4). One patient had positive sentinel lymph node for which she underwent complete axillary lymph node dissection (ALND). The final histopathology showed invasive ductal carcinoma (IDC) in 11 patients, ductal carcinoma in situ (DCIS) with foci of invasion in 1 patient and DCIS in 8 patients. Overall, lymph node metastases were present in seven patients, of which six were IDC and one was a case of DCIS.

The mean follow up was 28 months (range 15–64 months). One patient developed recurrence in the breast after 5 years of central quadrantectomy for which she underwent modified radical mastectomy (MRM). Another two patients with invasive cancer with axillary lymph node metastases developed distant metastases and expired 23 and 18 months after surgery.

Discussion

Paget's disease is an intraepithelial adenocarcinoma which can be mammary or extramammary. There are two hypotheses proposed for the origin of Paget's disease. The first one is epidermotropic theory which proposes ductal cancer cells have migrated along the basement membrane. The factors

Table 1 Clinicopathological features and management of patients with Paget's disease

S. No.	Age	Lump	Side	Multifocality or multicentricity	Surgery performed	Histological type	Lymph node metastases
1.	38	Present	Right	Yes	MRM	Invasive ductal cancer	Present
2.	45	No	Right	No	Central quadrantectomy + SLNB	DCIS	No
3.	42	Present	Left	No	MRM	Invasive ductal cancer	No
4.	26	No	Left	No	Central quadrantectomy + SLNB	DCIS	No
5.	55	Present	Left	No	Central quadrantectomy + ALND	Invasive cancer	Present
6.	57	No	Right	No	Central quadrantectomy + SLNB	DCIS	No
7.	36	No	Right	Yes	Simple mastectomy + SLNB	DCIS	No
8.	54	No	Left	Yes	Simple mastectomy + SLNB	DCIS	No
9.	35	Present	Right	No	MRM	Invasive ductal cancer	No
10.	65	No	Right	No	Central quadrantectomy + SLNB	DCIS with foci of invasion	No
11.	45	Present	Right	Yes	MRM	Invasive ductal cancer	No
12.	38	No	Left	No	Central quadrantectomy + SLNB	DCIS	No
13.	52	Present	Right	No	MRM	Invasive ductal cancer	Present
14.	46	Present	Left	Yes	MRM	Invasive ductal cancer	No
15.	33	Present	Right	No	MRM	Invasive ductal cancer	Present
16.	52	No	Left	No	Central quadrantectomy + SLNB followed by ALND	DCIS	Present
17.	36	Present	Left	No	MRM	Invasive ductal cancer	Present
18.	37	Present	Left	No	MRM	Invasive ductal cancer	No
19.	62	Present	Left	No	MRM	Invasive ductal cancer	Present
20.	45	Present	Right	No	Central quadrantectomy + SLNB	DCIS	No

MRM modified radical mastectomy, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, DCIS ductal carcinoma in situ

Fig. 4 Breast conservation surgery performed for a patient with Paget's disease involving the central quadrant for which central quadrantectomy with sentinel lymph node biopsy was performed (a, b); followed by two-step purse string suturing for nipple reconstruction (c)

supporting this hypothesis are immunohistochemical correlation of these cells with underlying carcinoma and increased expression of Her-2 in these patients [6, 7]. It is proposed that epidermal cells secrete a tropic factor called heregulin—which binds to Her-2 receptor and mobilizes them to the surface. This hypothesis was supported by the fact that most of the patients in our and other series had associated lump in the breast [8]. Similarly, the other theory is an in situ malignant transformation hypothesis where the carcinoma develops in situ from the keratinocytes. This hypothesis can be considered in some cases of Paget's disease where there is no lump or detected abnormalities in mammogram [9–11].

Association of Paget's disease with underlying carcinoma is variable in different studies from 55.2 to 100 % [12–14]. In the present study, the association of Paget's disease with underlying carcinoma was 100 %. In patients associated with lump, there is an increased risk of invasive carcinoma in many studies [12–14]. In the present study, one patient with palpable mass had DCIS whereas the rest of them had invasive carcinoma. The mean age of presentation in our study was 44.9 years compared to other studies where they presented at a later age [12]. In our study, the risk of multifocality or multicentricity was less (25 %) compared to other studies which showed a risk of 32–63 % [13–16].

Various methods described to diagnose Paget's disease are cytology of the discharge, FNAC or biopsy of the lump if present, shave biopsy of the nipple, wedge biopsy of the nipple, punch biopsy of the nipple and immunohistochemistry for carcinoembryonic antigen (CEA), low molecular weight cytokeratins like CK7, epithelial membrane antigen (EMA) and gross cystic disease fluid protein 15 (GCDPF-15) [17]. Wedge biopsy gives good results as a part of lactiferous duct can be excised along with it for histopathological examination.

The risk of lymph node metastases increases in the presence of invasive component. In the present study, 35 % (7/20) had lymph node metastases, of which 6 had invasive carcinoma and 1 had DCIS. In our study, in presence of mass, 50 % (6/12) had axillary lymph node metastases whereas in absence of lump, 12.5 % (1/8) had axillary lymph node metastases. In literature, 50–60 % of patients with lump had axillary lymph node metastases whereas 0–21 % without lump had axillary lymph node metastases [15, 18–20].

Initial studies reported a high chance of multifocality and multicentricity in Paget's disease and also a high chance of local recurrence of 33–40 % when treated with wide excision alone [5, 21]. But with developing imaging modalities, surgical techniques (oncoplastic techniques) and better adjuvant treatment, more number of patients with breast cancer was considered for conservation. Conservative procedures in Paget's disease vary from partial to complete nipple excision and central quadrantectomy with radiotherapy with or without hormonal therapy [22]. The prognosis of these patients depends on the presence of lump and associated lymph node metastases. They have found that overall survival correlates with lymph node status, with node-negative patients having a survival of 75–95 % whereas in node-positive patients, it was 20–25 % [6, 23].

Conclusions

Paget's disease of the breast is a rare entity and is associated with malignancy even in the absence of lump or mammographic abnormality. Wedge biopsy of the nipple helps in the diagnosis of these patients. They can be considered for breast conservation therapy based on clinical and radiological assessment. Adjuvant therapies should be administered based on

the size of tumour, lymph node metastases, type of tumour and surgery performed.

Conflict of Interest None.

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