Clinical and Biological Characteristics of Breast Cancer in Women with Mammary Paget's Disease: A Retrospective Study of 36 cases

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ABSTRACT

Objective: Identification of clinical and biological characteristics of breast cancer in women with mammary Paget's disease (MPD).

Methods: We performed a retrospective analysis for 36 women with a primary diagnosis of mammary Paget's disease, patients were treated in Sant' Orsola-Malpighi Breast Unit in Italy, between 2000 and 2016. Patients demographics, clinical data, radiologic and pathologic reports were extracted from electronic health records.

Result: 36 cases of patients with a diagnosis of MPD were involved. The mean age was 64.28 years (Range, 36-86 years). Only 14 patients (38.9%) were found to have an underlying breast mass. Invasive breast carcinoma was diagnosed in 23 patients (63.9%), 7 patients (19.4%) had ductal carcinoma in situ. All patients with associated breast mass were diagnosed with invasive breast carcinoma and they had a higher rate of axillary lymph node metastasis. Most invasive breast carcinomas were HER2 positive (65.2%), estrogen and progesterone receptors negative (56.5% and 69.6%).

Conclusion: Mammary Paget's disease is a rare type of cancer that can be localized to nipple-areola complex or it can be associated with underlying breast carcinoma. Breast MRI has a higher sensitivity for identifying underlying breast pathology. Once MPD is associated with an underlying mass, the likelihood of carcinoma is higher so a biopsy is recommended. The expression of ER/PR is lower in breast carcinomas with MPD, while they have higher HER2/neu expression. Unless multifocality or multicentricity is excluded, mastectomy is the recommended surgical treatment. Sentinel lymph node biopsy should be performed to evaluate the axilla when the invasive disease is identified or a mastectomy is planned.

Key words: invasive breast carcinoma, mammary Paget's disease (MPD), Nipple Dermatitis

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INTRODUCTION

Mammary Paget's disease (MPD) of the breast is a rare type of cancer of the nipple-areola complex that was first described in 1874 by Sir James Paget and accounts for approximately 1-4.3% of all breast cancers (1, 2), it is

often associated with underlying invasive or in situ carcinoma. It is defined clinically as a chronic, eczematous rash of the nipple and adjacent areolar tissue that is more commonly encountered in older postmenopausal women (mean age 57 years) (3). Two patterns of MPD are identified based on physical examination (4); with or without underlying breast mass, while it is classified pathologically into three patterns: MPD with underlying invasive carcinoma, MPD with underlying ductal carcinoma in situ (DCIS) and MPD without underlying pre-cancerous or cancerous conditions of the breast (5).

The prevalence of MPD associated carcinoma ranges from 67% to 100%, the presence of underlying breast mass or parenchymal pathology makes the probability of diagnosing invasive carcinoma higher in comparison to patients without breast mass (6, 7, 8).

As Paget's disease of the breast usually presents as a thickened, eczematous, erythematous or crusted lesion of the nipple and adjacent areola, it can be easily mistaken for eczema or other inflammatory nipple conditions, so treatment with topical steroids is falsely practiced by physicians in these cases regardless transient improvement that can be noticed (9, 10). Manifestations of pain, itching, nipple discharge or nipple deformity are also frequent.

MATERIALS AND METHODS

We reviewed the medical reports of all patients with clinical and histological diagnosis of Mammary Paget's Disease who were treated in Sant' Orsola-Malpighi Breast Unit, between 2000 and 2016. The clinical presentation, menstrual status, personal and family history of breast cancer, pregnancy history, and smoking status were all extracted from the case notes.

Mammographic and ultrasound reports were reviewed to identify cases of MPD with an associated underlying mass. Operative reports as well as final pathological reports were evaluated for the type of procedure, lymph node status, and clinicopathological classification of associated carcinoma.

Our study aims to evaluate differences between MPD cases in the presence or absence of an underlying breast parenchymal pathology.

RESULTS

In the period between 2000 and 2016, a total of 3571 cases of invasive breast carcinoma and 484 cases with carcinoma in situ were diagnosed in our hospital. Only thirty-six cases of women with MPD were

collected from our hospital records. The mean age was 64.28 years (Range, 36-86 years). Breast mass was identified in 14 cases (38.9%) while 22 cases (61.1%) didn't have an underlying mass. Although it was not statistically significant, the mean age for cases with an associated mass was found to be less than cases without an associated mass (59.57 vs. 67.27 years). The Mean age of menarche was 12.53 years. 30.3% of women were pre-menopausal and the mean age of menopause was 49.7 years (Range, 32 – 55 years). Smoking was prevalent in 27.7% of all Paget's cases. A personal history of breast cancer was found in 3 patients of MPD with a mass group (21.4%), and in 6 patients of Paget's only disease (27.3%). Only one patient of Paget's with mass had a family history of breast cancer while five patients (22.7%) had this risk factor in Paget's only disease group. Regardless of all preceding figures, there were no statistically significant differences between both groups. 22.2% of women with MPD were nulliparous, and 16.6% had their first pregnancy at the age of 30 or older. *Table 1* illustrates general features for patients with MPD.

Clinically, 11 patients had clinically palpable breast mass in association with MPD while in 3 patients, breast parenchymal mass or distortion was identified using breast mammogram and ultrasound. Patients were labeled as Paget's only disease when we failed to demonstrate masses or parenchymal distortion either clinically or radiologically. Nipple eczema or ulceration was the most frequent clinical sign in clinically diagnosed Paget's disease; 32 women experienced significant nipple changes (88.9%) while 4 women (11.1%) have only very little changes that were not recognized by their practitioners. Nipple discharge was noticed in 44.4% of cases (16/36). Seven patients in Paget's with the mass group had spontaneous nipple

Table 1 - General features for patients with MPD

Number of Cases	36
Site of pathology	
Right	24
Left	12
Menarche age (mean)	12.53
Menopause age (mean)	49.7
Smoking	10/36 (27.7%)
Personal history of Breast Cancer	9/36 (25%)
Family History of Breast Cancer	6/36 (16.6%)
Nulliparity	8/36 (22.2%)
1st Pregnancy < 30 years	21/36 (58.3%)
1st Pregnancy ≥ 30 years	6/36 (16.6%)

discharge (50%) while 9 women (40.9%) experienced it in Paget's only group. Palpable axillary lymphadenopathy was found only in two patients of Paget's with mass (15.4%) (*table 2*).

Mammographic findings associated with Paget's disease ranged from a normal mammogram (55.6%), malignant microcalcifications only (13.9%), and a mass (or parenchymal distortion) with or without microcalcifications (30.5%). *Table 3* compares the mammographic findings in both groups of PD.

Surgical Management and Clinicopathological Features

As a preoperative confirmation of diagnosis, a nipple biopsy was performed for 29 patients, and it proved the diagnosis of MPD. The remaining 7 patients were diagnosed clinically and histopathologic diagnosis were confirmed retrospectively. Out of 16 women with pathologic nipple discharge, cytological examination of this discharge was ordered for 14 patients, the presence of malignant cells have been proved in 11 of them.

Mastectomy was the procedure of choice for 32 cases (89%) and central quadrantectomy in 4 cases only (11%). In the mastectomy group, 22 patients had mastectomy alone, 2 patients had a mastectomy with expander while the remaining 8 patients performed skin-sparing mastectomy with an expander/implant reconstruction.

A total of 23 patients had a final diagnosis of invasive ductal carcinoma (IDC) in association with MPD, the majority of them were labeled based on the AJCC 8th edition TNM staging system as T1 tumors (n = 20, 87%). All patients with a mass (n=14) were found to have an underlying IDC, three of them (21.4%) had ductal carcinoma in situ (DCIS) in association with their invasive component. In comparison, only 9 patients (41%) of MPD patients without a mass had an invasive carcinoma (P = 0.0012). 7 patients of this group (31.8%) had only DCIS and 6 patients (27.2%) had nipple Paget's that was limited only to the dermis without an underlying carcinoma *table 4*.

Sentinel lymph node biopsy was utilized as a procedure for axillary staging in 26 patients (72.2%), and 6 patients had ALND without SLNB. The axillary staging was omitted in 3 patients due to their previous history of breast cancer and ALND and in one patient with a history of DCIS because of its advanced age and poor medical condition. Sentinel lymph node macrometastasis was found in 3 patients (11.5%), micrometastasis in only one patient (3.84%), and all of

Table 2 - Clinical presentation of mammary Paget's disease (MPD)

Clinical Presentation	MPD with a mass (N = 14)	MPD without a mass (N= 22)
Palpable breast mass	11	0
Nipple changes (eczema / ulceration)	12 (85.7%)	20 (90.9%)
Nipple Discharge (Bloody)	7 (50%)	9 (40.9%)
Axillary Lymphadenopathy	2 (14.3%)	0

Table 3 - Mammographic features of mammary Paget's disease

Mammographic Features	MPD with a mass (N=14)	MPD without a mass (N=22)
Normal	1 (7.1%)	19/22 (86.4%)
Microcalcifications	2 (14.3%)	3/22 (13.6%)
Mass/Parenchymal distortion	9 (64.3%)	0
Mass with microcalcification	2 (14.3%)	0

(MPD): Mammographic findings

them were operated with an ALND subsequently. 50% of patients who performed axillary node dissection as the primary procedure for axillary staging were found positive for metastasis. Axillary lymph node metastasis was more common in patients with a mass (38.5%) than those without a mass (5.5%), P = 0.029.

Among patients with a diagnosis of IDC (n=23), Estrogen receptors (ER) were positive in 10 patients (43.5%), 7 patients (30.4%) were PR positive and 15 patients (65.2%) were HER2 positive. *Table 5* shows the biologic classification of MPD associated IDC in our patient group.

DISCUSSION

MPD is often mistaken for a benign dermatologic condition such as nipple dermatitis. Once the diagnosis is suspected, a skin biopsy of the eczematous lesion should be obtained. Nipple biopsy could be in a form of wedge biopsy, superficial "shave" biopsy of the epidermis, or punch biopsy (3). No one of these methods is always successful, so a second biopsy or

Table 4 - Histopathologic findings in MPD

	MPD with a mass (N=14)	MPD without a mass (N=22)
IDC	14*	9
DCIS only	0	7
Nipple Paget's only	0	6

*Additional DCIS have been demonstrated in 3 cases

Table 5 - Biologic classification of MPD associated IDC (n=23)

Biologic Subtype *	Number of cases (%)
Luminal A (ER and/or PR positive, Her2 negative, Ki-67 <14%)	4 (17.4%)
Luminal B (HER-2 negative) (ER and/or PR positive, Her2 negative, Ki-67 ≥14%)	3 (13%)
Luminal B (HER-2 positive) (ER and/or PR positive, Her2 overexpressed or amplified, any Ki-67)	4 (17.4%)
HER-2 overexpression (ER and PR absent, HER2 overexpressed or amplified)	11 (47.8%)
Triple negative (ER and PR absent, HER2 negative)	1 (4.4%)

ER: estrogen receptor; PR: progesterone receptor,
HER2: human epidermal growth factor receptor 2

nipple excision may be performed to reach a diagnosis (10). A wedge biopsy is the most useful method because it can show sufficient epidermis as well as lactiferous ducts (3). The cytological examination is not sufficient to confirm the MPD diagnosis.

Once the diagnosis of MPD is confirmed, further imaging studies are needed to exclude underlying breast parenchymal pathology as the presence of a mass is linked to a higher probability of underlying breast carcinoma. The reported multifocality and multicentricity of breast carcinoma prevalence in MPD are 41% and 34%, respectively (11). Ultrasound and mammography sensitivity for detecting IDC multifocality or multicentricity in MPD is 79% and 74% respectively while it is lower for DCIS (39% and 19% respectively). On the other hand, MRI was shown to be 100% sensitive for IDC and 44% for DCIS, so it can help better in identifying patients with localized diseases (12, 13, 14). If a lesion is identified, biopsy should be taken for further assessment.

The surgical treatment of MPD is controversial. Because of its low incidence, no randomized studies are evaluating the optimal surgical management (15). Mastectomy with or without ALND was the standard surgical treatment of MPD (3). The reason behind this approach is the high association either with IDC or DCIS (14). Kothari and colleagues showed that 60% of patients with MPD having underlying invasive carcinoma, more than 40% of those had multicentric and/or multifocal disease and more than 60% had axillary lymph node involvement (11). In a meta-analysis including 7 studies comparing the local recurrence of MPD after mastectomy and breast conservative surgery (BCS), the local recurrence rate in the mastectomy group was 5.6% while it was 13.2% in the BCS group. The pooled OR for local recurrence was

0.38 (95% CI 0.21–0.69). It was shown that relapse cases tend to develop invasive carcinoma with poor prognosis after previous BCS (16). According to surveillance, epidemiology, and end results (SEER) data for patients with MPD during 2000 – 2011 (17), 2631 patients were identified. Of these patients, 7% had MPD of the nipple only, 36.2% had MPD with DCIS (MPD-DCIS) and 56.7% had MPD with invasive ductal carcinoma (MPD-IDC). The overall rates of mastectomy for these groups were 47, 69, 88.9% respectively.

Axillary lymph node metastasis was observed more in MPD patients with underlying breast mass (18). According to Wong SM et al. in their cohort study for the SEER database for MPD-IDC patients (17), MPD-IDC had higher odds of axillary lymph node metastasis in comparison to patients with IDC alone (OR 1.83; $P < 0.001$). Retrospective studies regarding the use of sentinel lymph node biopsy in cases of MPD showed that nearly 11% of cases were positive for metastasis even in the absence of radiologic features of breast cancer, so SLNB should be performed to evaluate the axilla when the invasive disease is identified or a mastectomy is planned (19, 20).

In comparison to other invasive breast carcinomas, MPD-IDC showed larger tumor size, more multifocal disease, lower ER/PR expression, and higher HER2 overexpression (21, 22). In our study, ER, PR and HER2 were positive in 43.5%, 30.4%, and 65.2% of MPD associated carcinomas respectively. In comparison, both ER/PR were positive in more than 75% of patients and HER2 is lower than 40% in patients without MPD. Based on Arsenal et al data, MPD-IDC patients showed expression of ER and PR in 38.5% and 33.3%, respectively, and HER2 overexpression in 41% (23). In another study, overexpression of the HER2/neu (c-erb-B2) oncogene was detectable in 83% of cases (11).

Patients with MPD with associated underlying breast carcinoma have been shown to have poor survival. The 5 and 10-year survival rates have been reported to be 32-43% and 31-49%, respectively (24). In one study conducted by Kothari, the 10-year overall survival for MPD with IBC was 49% while for patients with IBC alone it was 64% (11). This poor survival was attributed to the high incidence of HER2/neu positive cells, but this difference was eliminated if they were also matched for HER2 status.

MPD had been reported by several investigators as the first local recurrence event after breast-conservative surgery or nipple-sparing mastectomy. In one study, seven cases of MPD were reported as a recurrence after nipple-sparing mastectomy, which accounted for 19.4% of total recurrences (25), one

explanation for this is the possible existence of MPD before the operation.

CONCLUSION

Mammary Paget's disease is a rare disease that can be localized to nipple-areola complex or it can be associated with underlying breast carcinoma. According to the literature, breast MRI has a higher sensitivity for identifying underlying breast pathology. Once MPD is associated with an underlying mass, the likelihood of carcinoma is higher so a biopsy is recommended. The expression of ER/PR is lower in breast carcinomas with MPD, while they have higher HER2/neu expression. Unless multifocality or multicentricity is excluded, mastectomy is the recommended surgical treatment. Sentinel lymph node biopsy should be performed to evaluate the axilla when the invasive disease is identified or a mastectomy is planned.

Statement conflict of Interest

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