

Case Report

Effect of estrogen receptor expression on prognosis in male mammary Paget's disease: a case report and literature review

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Abstract: Male mammary Paget's disease (PD) is extremely rare. The pathogenesis, treatment and prognosis have not been clearly defined. The relationship between molecular subtypes and prognosis is still unknown. Here, we presented a case of a 60-year-old man with erythema and erosion of his left nipple-areolar complex. The diagnosis of PD was confirmed by an excisional biopsy of areolar skin. Left total mastectomy and sentinel lymph node biopsy were performed. Histopathological examination revealed PD with underlying ductal carcinoma *in situ*. No metastasis was found in sentinel lymph nodes. Immunohistochemical tests revealed that Paget cells were positive for human epidermal growth factor receptor-2, while negative for estrogen receptor (ER) and progesterone receptor. We also reviewed ER status of male mammary PD described in the literature. We found that patients with ER negative mammary PD maybe more prone to having concomitant infiltrating ductal carcinoma, which may contribute to poor prognosis.

Keywords: Paget's disease, male, molecular subtypes, hormone receptor, estrogen receptor

Introduction

Approximately 1% of all breast cancers occur in male breasts [1], and Paget's disease (PD) accounts for 1.45% of all male breast cancers [2]. Therefore, male mammary PD is extremely rare. The clinical presentation is varied and non-specific. The most common symptoms include eczematoid changes, erythema, erosion and ulceration of nipple-areolar complex (NAC). It may be mistaken for benign skin disease such as eczema or dermatitis, thus the diagnosis and the effective therapy are often delayed.

According to the NCCN guideline of breast cancer (2016, version 2) and St Gallen international expert consensus, classifying of molecular subtypes plays an important role in tailoring therapy of breast cancer. Meanwhile, immunohistochemical tests of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her-2) are widely used for subtype classifying. But the value of

molecular subtypes in male mammary PD is unclear. Here, we describe a case of male mammary PD treated in our department. Moreover, we reviewed the literature and tried to get clue of the relationship between molecular subtypes and clinical outcome in this disease.

Case report

A 60-year-old male was referred to our breast clinic with symptoms of erythema and erosion of his left NAC for 3 years duration. The diagnosis of PD was confirmed by an excisional biopsy of areolar skin 10 months ago. However, the treatment was delayed due to the patient's will. The patient denied family history of breast cancer.

On clinical examination, the NAC looked erythematous with eczematous crust formation, measuring 3.5 cm in diameter (**Figure 1A**). The examinations of both breasts and axillae were unremarkable. Ultrasonography of breast revealed a hypoechoic lesion measuring 11×9 mm

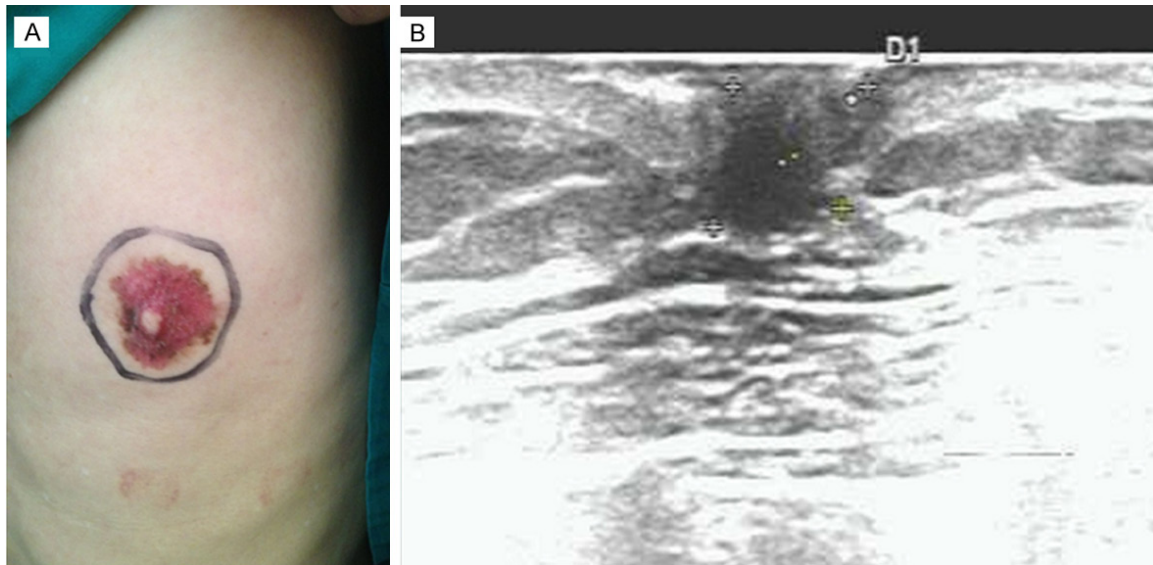


Figure 1. Clinical presentation and image of left nipple. A: NAC with irregular erythema. B: Ultrasonography showing hypoechoic lesion with irregular shape under the nipple.

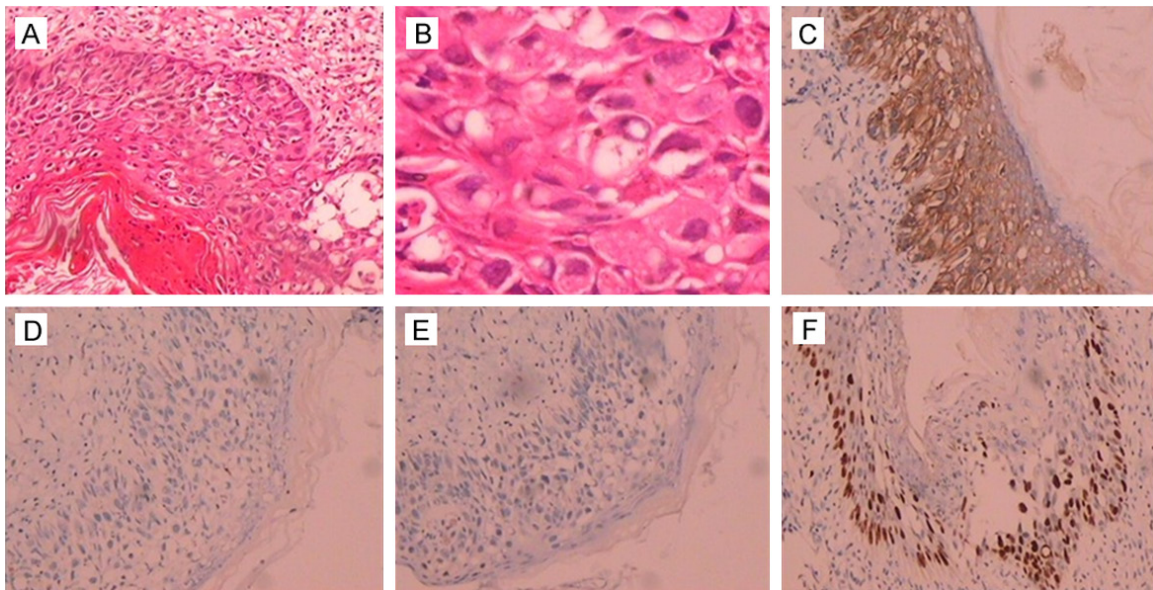


Figure 2. Histological analysis and immunohistochemical characteristics of the specimen. A: The epidermis of nipple infiltrated by Paget cells (H&E, $\times 100$). B: Paget cells with large nucleus and light stain cytoplasm (H&E, $\times 400$). C: Paget cells were positive for Her-2 ($\times 100$). D: Paget cells were negative for ER ($\times 100$). E: Paget cells were negative for PR ($\times 100$). F: About 10% of the Paget cells were positive for Ki67 ($\times 100$).

with irregular shape under the left nipple (**Figure 1B**). Mammogram wasn't performed due to small volume of the patients' breasts. The serum prolactin was 20.48 ng/ml (normal: 2.58-18.12 ng/ml). The rest of laboratory tests were unremarkable.

The patient received left total mastectomy and left sentinel lymph node biopsy. Histopatholo-

gical examination confirmed PD (**Figure 2A, 2B**) with underlying ductal carcinoma in situ (DCIS) by the hematoxylin-eosin (H&E) stained sections. No metastasis was found in 3 sentinel lymph nodes. Immunohistochemical tests revealed that Paget cells were positive for cyto-keratin 5/6 (CK5/6), CK8/18 and Her-2 (**Figure 2C**), but negative for ER (**Figure 2D**), PR (**Figure 2E**), human melanoma black 45 (HMB45) and

ER expression and male mammary PD

Table 1. Data on male mammary PDs in the literature

	Year	Author	Age	ER	PR	Her2	IDC	DCIS
1	1988	Serour F	73	-	NA	NA	+	NA
2	1989	Sano Y	61	-	-	NA	NA	+
3	1996	Desai DC	47	-	-	NA	+	+
4	2000	Hayes R	65	-	+	+	+	+
5	2001	Nakamura S	83	+	+	NA	NA	+
6	2003	Piekarski J	86	-	NA	NA	+	NA
7	2006	Pimentel CL	59	+	NA	+	NA	+
8	2008	Bernardi M	52	+	-	-	NA	NA
9	2015	Leibou L	63	+	-	+	NA	+
10	2015	Choudhury B	69	+	+	NA	NA	+
11	2016	Current study	60	-	-	+	NA	+

Notes: + in Age/ER/PR/Her2, positive; -, negative; NA, not available; + in IDC/DCIS, existing.

S100. Ki-67 was 10% positive (**Figure 2F**). The patient recovered uneventfully. He was disease free at the first 18 months follow-up.

Discussion

Mammary PD is characterized by eczematoid changes of NAC, which was first described by Sir James Paget in 1874 [3]. Since the male mammary PD is rare, current understanding of PD is mostly based on female cases. PD is commonly associated with an underlying DCIS or infiltrating ductal carcinoma (IDC). So a palpable mass may be found on physical examination, and mammography and ultrasonography are recommended in patients of suspected PD. The initial treatment of PD is surgery including mastectomy with or without axillary dissection. Breast-conserving surgery and sentinel lymph node biopsy are also acceptable alternative for some cases. Chemotherapy, biologic therapy and hormonal therapy are based on the stage and molecular subtype of underlying cancer. But the best treatment of PD with no detectable underlying malignancy is unclear.

PD is regarded as a non-invasive cancer. The epidermotropic theory postulates that ductal cancer cells that migrate along the basal membrane of the nipple are the origin of Paget cells [4]. The effect of PD on prognosis is under debate. A matched study showed that 5-year relapse-free survival and overall survival were both lower for patients of invasive breast carcinoma with PD than those without PD [5]. However, another study showed that the overall 5-year survival of patients with breast cancer and PD

have no significant difference with that of the non-PD group [6]. An analysis of The Surveillance, Epidemiology, and End Results (SEER) database found that IDC with PD is associated with an increased risk of axillary lymph node metastasis, but not with inferior survival, compared with IDC alone [7]. Additionally, the 5-year survival rate was reported to be lower in male mammary PDs than in female ones [2, 8]. It may due to the characteristics of underlying IDCs [9], not to the PDs themselves.

DCIS is also a non-invasive cancer. A prospective randomized trial showed that DCIS molecular subtype predicted for both overall and invasive recurrence, and high Ki67 expression was an independent predictor for invasive recurrence [10]. It is unknown if the male mammary PD with unfavorable molecular subtype, as the one we described in our case, has a relatively poor prognosis. Therefore, we searched for the literatures in English with full text links from January 1988 to August 2016 in PubMed for words: "male or man" and "Paget's disease or Paget disease". We found 25 cases of histopathologically proved male mammary PD. Among these reports, 10 cases described the ER expression of tumor cells [11-20]. We summarized these 10 cases as below (**Table 1**).

The proportions of ER, PR and Her2 positivity in female mammary PD cells are 10-41%, 0-25% and 80-100% respectively, based on primary research [4]. In comparison, analysis of SEER data found that ER and PR positivity is 47% and 35% in female PDs, while 93% and 74% in male cases [2]. In our study, 45% (5/11) cases were ER positive. The median age in ER positive group was 63 (range from 52 to 83), which was the same as that in ER negative group (range from 47 to 86). Her2 status of the Paget cells was described in five cases, and four of them were positive. Eight cases had underlying DCIS (four cases of ER positive and four cases of ER negative), while 4 cases had concomitant IDC.

Interestingly, all 4 cases with IDC in our review were ER negative, moreover, 3 of which had axillary lymph node metastasis [15, 17, 20]. Therefore, we assume that ER negative male mammary PDs might have higher incidence of complicating IDC, which may contribute to poor prognosis. More aggressive treatment and mo-

re close follow-up maybe needed in PDs of this subtype, even if the cases with no detectable underlying IDC. Because it is possible that the underlying malignance is not large enough to be identified using conventional imaging [21].

Due to the limited sample size in our review, solid conclusion can't be drawn yet. More data and longer time of follow-up are warranted. However, our work may imply that the importance of ER expression in male mammary PD can't be underestimated. From this point of view, we suggest a routine test of ER, PR, Her2 and Ki67 status for male mammary PDs.

Disclosure of conflict of interest

None.

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