

Case Report

Diagnosis and treatment of Paget's disease of the breast: an analysis of 72 cases

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Abstract: Objective: Clinical features, prognostic factors and principle of surgical treatment for Paget's disease of the breast were analyzed, so as to optimize the treatment of Paget's disease of the breast. Method: Seventy-two cases of Paget's disease of the breast treated at Affiliated Union Hospital and Hospital of Integrated Traditional Chinese and Western Medicine, Huazhong University of Science and Technology, from January 1991 to January 2010 were recruited. Their clinical data were analyzed retrospectively. Results: Among 72 cases, 52 cases had nipple-areolar complex lesions, 43 had palpable masses and 18 had palpable, enlarged axillary lymph nodes; 45 cases received radical mastectomy or modified radical mastectomy. Intraoperative pathological examination was performed for 9 cases who were not discovered to have breast lumps or enlarged axillary lymph nodes preoperatively; and 4 of them were diagnosed as lower axillary lymph node metastasis or invasive ductal carcinoma, and modified radical mastectomy was adopted for these cases. Fifty-two cases received postoperative pathological examination to reveal that the average number of metastatic lymph nodes was 3.1. Among the cases presenting with lymph node metastases, those negative for ER/PR accounted for 78%; Her-2-positive cases accounted for 56%. Thirty-seven cases were followed up for an average of 29 months postoperatively, and 5 of them were found with local recurrence and 7 with distant metastases. Conclusion: Most cases of Paget's disease of the breast were associated with invasive ductal carcinoma and lymph node metastases. These cases had low ER/PR positive rate, high Her-2 positive rate and poor prognosis.

Keywords: Breast carcinoma, Paget's disease of the breast, treatment, axillary lymph node dissection

Introduction

Paget's disease of the breast was first reported by Paget in 1874. The major presentation is eczematoid lesion of the nipple, from which the name of eczematoid carcinoma of breast was derived. Paget's disease of the breast is a rare type of breast carcinoma and more common in females aged over 40 years old with a high misdiagnosis rate. The main histological characteristic is the presence of Paget cells. Seventy-two cases of Paget's disease of the breast treated at Affiliated Union Hospital and Hospital of Integrated Traditional Chinese and Western Medicine, Huazhong University of Science and Technology, from January 1991 to January 2010 were recruited. The clinical data of these cases were reviewed.

Clinical data and outcome

General data: All 72 cases were females and affected unilaterally; 33 cases were affected

on the left and 39 on the right. The age of onset was 30-79 years old with an average of 58, and the course of disease was 1-56 months with an average of 12.2 months. Fifty-two cases showed ulceration, crusting and bleeding of nipple-areolar complex, accounting for 72.2%; 43 cases had palpable masses, accounting for 59.7%, all of which occurred singly and measured 0.6-4.5 cm with an average of 2.1 cm; 18 cases had palpable, enlarged axillary lymph nodes, accounting for 25.0%. Fifty-one cases were examined for cytological smear, and 22 of them were diagnosed with Paget's disease of the breast, showing an accurate diagnosis rate of 43.1%. Nineteen cases received skin biopsies, and 16 of them were diagnosed as Paget's disease of the breast, with an accurate diagnosis rate of 84.2%. Twenty-three cases received preoperative color Doppler ultrasound examination, and 11 cases were found with hypoechoic masses behind the areola. Twenty-five cases received molybdenum target X-ray examination;

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8 cases were found to have no obvious abnormalities; 12 cases had periareolar skin thickening; 8 cases had fine sand like calcification; 6 cases presented with breast lump or anatomical distortion of ducts. Masses were discovered behind the nipple-areolar complex in 3 out of 8 cases receiving MRI.

Surgical method

Eight cases received radical mastectomy, and 37 cases modified radical mastectomy; 18 cases received simple mastectomy, and 9 cases mastectomy + low axillary lymph node resection + intraoperative frozen section examination. Among 45 cases receiving radical mastectomy or modified radical mastectomy, 43 cases had palpable masses or enlarged axillary lymph nodes. Intraoperative pathological examination was performed for 9 cases who were not discovered to have breast lumps or enlarged axillary lymph nodes preoperatively; 2 of them had low axillary lymph node metastases with ductal carcinoma in situ or invasive ductal carcinoma; 1 case had invasive ductal carcinoma without low axillary lymph node metastases; and 1 case had low axillary lymph node metastases but no ductal carcinoma. These 4 cases received modified radical mastectomy. The remaining 5 cases had neither low axillary lymph node metastases nor ductal carcinoma, and therefore were not treated by extended radical mastectomy.

Results of pathological examination

Pathological examination was performed for all 72 cases; 9 cases had simple nipple-areolar complex lesions without ductal carcinoma; 12 cases had simple nipple-areolar complex lesions with ductal carcinoma in site; 45 cases had simple nipple-areolar complex lesions with invasive ductal carcinoma. For cases presenting with ductal carcinoma but no obvious nipple-areolar complex lesions, the diagnosis of Paget's disease of the breast was made in 6 cases based on the discovery of Paget cells in postoperative pathological examination. A total of 52 cases were shown to have axillary lymph node metastases by postoperative pathological examination; among them, 19 cases had 1-3 metastatic lymph nodes, 15 cases over 3 metastatic lymph nodes, and 18 cases no metastatic lymph nodes; the average number of axillary lymph node metastases was 3.1. Of the

cases with ductal carcinoma in situ, 2 cases had lymph node metastases (2/9); of the cases with invasive ductal carcinoma, 32 cases had lymph node metastases (32/43). Among 59 cases tested by immunohistochemical staining, 13 cases were positive for ER/PP, 46 cases negative for ER/PR, and 31 cases positive for Her-2. Further analysis revealed that ER/PR-negative cases accounted for 78% (25/32) of the cases presenting with lymph node metastases, while Her-2-positive cases accounted for 56% (18/32).

Follow-up

Thirty-seven cases were followed up for an average of 29 months postoperatively (7-116 months). Five cases had local occurrence, with average time to recurrence of 51 months. Seven cases had distant metastases, with average time to metastasis of 62 months. Thirty-two cases were followed up for as long as 5 years, and the 5-year survival was 81.3 (26/32); 22 cases were followed up for 10 years, and the 10-year survival was 45.5% (10/22).

Discussion

Paget's disease of the breast accounts for only 1%-3% of primary breast carcinomas, usually presenting as infiltrative growth of tumor in nipple-areolar complex. Paget's disease of the breast is divided into 3 types clinically: (1) Simple nipple-areolar complex lesion with no ductal cancer; if not penetrating beyond basilar membrane, the cancer is considered in-situ carcinoma; (2) Nipple-areolar complex lesion with ipsilateral breast lump (carcinoma in the breast parenchyma); (3) Lumps in the breast parenchyma as the primary presentation, without obvious nipple-areolar complex lesion. The diagnosis is generally based on the presence of Paget cells using postoperative pathological examination. The incidence of Paget's disease of the breast associated with carcinoma in the breast parenchyma is 67-100%, and generally over 90% [1, 2]. However, only about 50% of these patients have palpable masses [3], with hard texture, indistinct borders, unsmooth surface and low mobility. These symptoms are similar to the clinical presentation of invasive carcinoma and enlarged axillary lymph nodes are usually observed. In the present study, 87.5% (63/72) of the cases were associated

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with carcinomas in the breast parenchyma, and 59.7% had palpable masses, which were consistent with the previous statistics.

There is still on-going dispute over the histogenesis, clinical diagnosis and treatment for Paget's disease of the breast. Two hypotheses are proposed as to the pathogenesis: one states that Paget cells are derived from breast parenchyma or ducts and then spread to epithelium of the nipple; the other believes that Paget cells are derived from the flat epithelial cells that line the opening of the nipple [4]. Ultrastructural observation by electron microscope and genetic analysis find that Paget cells are tumor cells with multi-directional differentiation capacity. Therefore, it is not reasonable to explain the pathogenesis for all cases through the assumption of unidirectional differentiation.

Paget's disease of the breast is susceptible to misdiagnosis. The accurate diagnosis rate can be improved by skin biopsy. Imaging examination is mainly intended to identify intraductal lesions and to evaluate axillary lymph node metastases, so as to optimize the surgical treatment.

The prognostic factors of Paget's disease of the breast include concurrent ductal carcinoma and the histological type and lymph node metastasis. Fu reported that the rate of axillary lymph node metastasis in Paget's disease of the breast with breast lumps was 69%, and that of Paget's disease of the breast without breast lumps was 29%; the rate of axillary lymph node metastasis in the former was obviously higher than that of the latter; moreover, the overall survival of the two types of cases also showed significant difference ($P < 0.05$) [5]. Sheen-Chen studied 31 cases of Paget's disease of the breast. The 5-year survival of those with breast lumps was 19%, while that of those without breast lumps was 94% ($P < 0.01$) [6]. Some scholars collected 965 cases of Paget's disease of the breast from 15 researches. It was found that 93% of the cases with breast lumps had invasive breast carcinoma, and 7% had ductal carcinoma in situ; 34% of the cases with breast lumps had invasive breast carcinoma, 65% had primary ductal carcinoma, and only 1% had Paget's disease of the breast. It was also demonstrated that the cases

combined with breast lumps had a higher rate of axillary lymph node metastasis [7].

ER, PR and Her-2 testing can aid the choice of therapy and help predict the prognosis. Endocrine therapy usually achieves a better outcome and prognosis for cases positive for ER and PR. Breast carcinomas positive for Her-2 are associated with stronger invasiveness and poor prognosis. In the study by Kothari et al., the 10-year survival of Paget's disease of the breast associated with invasive ductal carcinoma was lower than that of Paget's disease of the breast without invasive ductal carcinoma (49% vs. 64%). They attributed the difference in survival to Her-2 overexpression [4]. Luminal A and luminal B types had a higher 3-year disease-free survival than that of triple-negative and Her-2 overexpression [8]. Many studies have shown that Her-2 is overexpressed in 20%-30% of breast carcinomas, with ER and PR positive rate of about 60%. Her-2-positive rate in breast carcinomas with Paget's disease of the breast is higher than that in breast carcinomas without Paget's disease of the breast; the ER/PR positive rate in breast carcinomas with Paget's disease of the breast is lower than that in breast carcinomas without Paget's disease of the breast [9]. In the present study, the Her-2-positive rate was 53% (31/59), and ER/PR positive rate was 22% (13/59). Most cases had unfavorable prognostic factors, which would affect the clinicians' selection of therapies.

Surgical treatment is the preferred choice for Paget's disease of the breast. The commonly used treatments include modified radical mastectomy, simple mastectomy and breast-conserving surgery, depending on whether Paget's disease of the breast is associated with ductal carcinoma, the histological type of ductal carcinoma and axillary lymph node metastases. Marcus suggested the performance of simple mastectomy for palpable ductal cancers, positive imaging findings or primary ductal carcinomas during intraoperative pathological examination [10]. Stanislawek and Sakorafas et al. believed that modified radical mastectomy was necessary for Paget's disease of the breast associated with breast lumps, considering the higher probability of invasive ductal carcinoma. For cases with no ductal cancer, the probability of primary ductal carcinoma is much higher

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than that of invasive ductal carcinoma, and axillary lymph node metastases are rare. Therefore, simple mastectomy + axillary lymph node dissection, or simple mastectomy + lower axillary lymph node dissection is recommended [11, 12].

In the present study, 87.5% of the cases were associated with carcinomas in breast parenchyma, and 59.7% of the cases had palpable breast lumps. Therefore, radical mastectomy or radical mastectomy was performed; simple mastectomy was adopted for a few cases presenting with nipple-areolar complex lesions instead of breast-conserving surgery. Sentinel lymph node biopsy has facilitated the study on the route of lymph node metastasis in breast carcinomas. Many studies indicate that low axillary lymph nodes may be the first to get involved in cancers near the nipple-areolar complex and combined with lymph node metastases; the rate of low axillary lymph node involvement is 90%, which is far higher than that of lymph nodes in other positions [13, 14]. During operation, it is easy to expose the site for breast resection and to carry out dissection of low axillary lymph nodes. These procedures usually have a low risk of damage to local nerves and blood vessels. For cases who were not found to have breast lumps and enlarged axillary lymph nodes preoperatively, the major ducts behind the nipple-areolar complex and the low axillary lymph nodes were resected and subject to intraoperative frozen section examination. Four out of 9 cases showed positive pathological findings and were transferred to radical mastectomy.

It is now recognized that breast carcinoma is a systemic disease. Survival of the patients can be prolonged by comprehensive treatment instead of enlarging the surgical scope improperly. The tumor to be resected needs to be delineated accurately using technical means, so as to prevent residual tumors. According to clinical data, local recurrence can reduce survival. Local treatment for early breast carcinomas will help lower the probability of local recurrence and distant metastasis and thus prolong the survival. In contrast, improper narrowing of the surgical scope may cause incomplete tumor resection and shorten the survival. Since most cases with Paget's disease of the breast neither belong to luminal A nor luminal B

type, their survival rate is generally low. Therefore, it is crucial to determine whether Paget's disease of the breast is associated with breast lump. If the breast lumps are found intraoperatively, the scope of surgical resection may be modified, so as to achieve complete tumor resection.

Disclosure of conflict of interest

None.

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