Paget's Disease of the Breast: Clinical Analysis of 45 Patients

Mingtian Yang
Hao Long
Jiehua He
Xi Wang
Zeming Xie

Department of Thoracic Oncology, Cancer Center of Sun Yat-sen University, Guangzhou 510060, China.

OBJECTIVE Paget's disease is an uncommon breast malignancy and often misdiagnosed. If the patient is treated at an early stage, the prognosis is satisfactory. Our study analyzed the clinical characteristics of the disease and the factors influencing the prognosis.

METHODS Fourty-five patients with Paget's disease who were admitted to our hospital were analyzed retrospectively.

RESULTS The most common symptoms of the disease were erosion and a bleeding-like eczematoid change at the nipple/areola. Of the 40 patients with an eczematoid change, 11 patients had verified Paget's disease with a palpable mass on physical examination, and 29 patients had verified Paget's disease with a nonpalpable mass. Only 5 patients manifested a mass with no eczematiod change. Thirteen patients had ipsilateral axillary lymphadenopathy. In this study, 25 cases were treated by radical mastectomy and 20 cases were treated by modified radical mastectomy. Five and 10-year survival rates for the patients with nonpalpable masses and for those with palpable masses were 95.5%, 78.6%, and 53.8%, 36.4% respectively. The former were significantly higher than the latter (P <0.01 and <0.05 respectively). Five and 10-year survival rates for the patients without underlying carcinoma (DCIS/IDC) and for the patients with underlying carcinoma were 100%, 88.9% and 69.6%, 43.8% respectively. The former were significantly higher than the latter (P <0.05) Five and 10-year survival rates for the patients with negative lymph nodes and for the patients with positive lymph nodes were 92.0%, 76.5% and 50.0%, 25.0% respectively. The former were also significantly higher than the latter (P <0.05).

CONCLUSION Treatment at an early stage is very important and influences the prognosis directly for Paget's disease of the breast. The survival rates of patients with nonpalpable masses without underlying carcinoma and without lymphadenopathy, were significantly higher than patients with palpable masses with underlying carcinoma and with lymphadenopathy respectively. There was significant statistical difference between each of the 2 groups.

KEYWORDS: breast cancer, Paget's disease, mastectomy, ductal carcinoma, invasive ductal carcinoma.

Paget's disease of the breast is named after James Paget who initially reported the disease which is a malignancy with a low incidence. In its early stage it can often be overlooked or misdiagnosed, which may greatly influence the outcome, leading to poor prognosis.[1,2] From December 1, 1966 to September 31, 2001, totally 45 cases of Paget's disease were admitted to our hospital; all were verified by a pathological examination and followed-up. In this study, the

Received May 13, 2004; accepted June 14,2004.

clinicopathological manifestations and treatment outcome of all patients were analyzed to explore the main factors that influence prognosis, so as to improve understanding and treatment of the disease.

MATERIALS AND METHODS

General data

A total of 45 cases were included in the all-female group. Their ages ranged between 34 and 76 years, with a median age 50. The lesions were in the left breast for 26 cases and in the right side for 19. Their course of disease ranged from 2 to 48 months, averaging 18.4 months. Forty of the 45 patients manifested eczematoid changes like erosion at the nipple/areola (11 cases with tumor masses), 5 patients only showed underlying masses at the nipple/areola, maximal diameters of tumor masses were 2 to 7 cm, median 3.5 cm. Thirteen cases had enlarged ipsilateral axillary lymph nodes.

Method of treatment

All 45 patients underwent a radical mastectomy or modified radical mastectomy (a radical mastectomy was performed on all 25 patients before the year 1988 after which a modified radical mastectomy was subsequently performed on the other 20 patients). After the year 1988, CMF or FAC regimen was routinely administrated for patients with positive axillary lymphadenopathy. Tamoxifen was added if hormone receptors were positive.

Pathology and grouping

Typical Paget's cells were detected in all 45 cases (Fig. 1). Twenty-six cases were accompanied by a deep major ductal carcinoma at the nipple. Among these 26 cases, 8 were major ductal carcinoma in situ (DCIS) (Fig.2) and 18 were invasive ductal carcinoma (IDC) (Fig.3). Ten cases were found to have ipsilateral axillary lymph node metastasis.

Statistical analysis

SPSS was employed to analyze the data. Five and 10-year survival rates were compared by the χ^2 test, with a significance set at < 0.05.

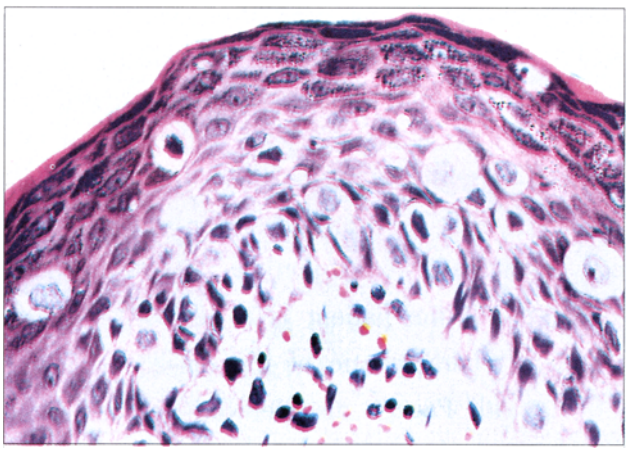

Fig. 1. Typical Paget's cells in breast cancer: large cells, circular or oval, with large nucleus, cytoplasm lightly-dyed or transparent H&E × 400.

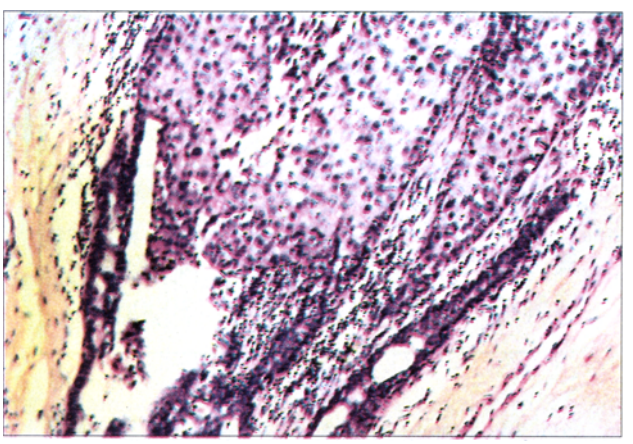

Fig. 2. Paget's disease with ductal carcinoma H&E × 100.

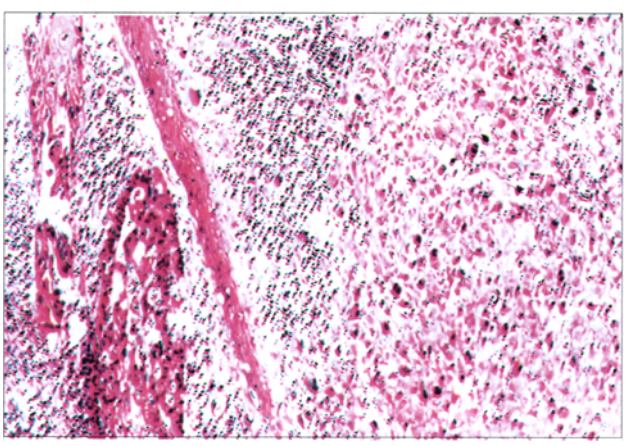

Fig. 3. Paget's disease with invasive ductal carcinoma H&E × 100.

RESULTS

We conducted follow-up for all the patients. Overall survival rates for 5 and 10 years were 80.0% (28/35) and 60.0% (15/25) respectively. Five and 10-year survival rates for patients without an underlying tumor

mass were 95.5% and 78.6% respectively and 53.8% and 36.4% respectively for patients with underlying mass. Comparison of the 5 and 10-year survival rates for the two groups showed a statistically significant difference (P <0.01 and <0.05, respectively). Five and 10-year survival rates for patients without underlying carcinoma (DCIS/IDC) and for the patients with underlying carcinoma were 100%, 88.9% and 69.6%, 43.8% , respectively, the former were significantly higher than the latter (P <0.05); Five and 10-year survival rates for the patients with negative lymph nodes and for the patients with positive lymph nodes were 92.0%, 76.5% and 50.0%, 25.0% respectively, the former also being significantly higher than the latter (P<0.05), Table 1.

DISCUSSION

The main clinical manifestations of Paget's disease occur at the nipple/areola area of breast. They involve erosion, flushing, skin thickening, desquamation and itching of the skin etc. These conditions mimic eczema, so the disease is also named eczematiod breast cancer. Paget's disease has a relatively long course and often progress slowly; it can be easily misdiagnosed as nipple eczema. In this group of 35 cases (77.8%) patient treatment was delayed because of misdiagnosis. This disease can be accompanied by an underlying mass at the nipple/areola area, which occurred in 27.5 %(11/40). It should be noted that some patients only showed an underlying mass at the nipple/areola area, with no other nipple symptoms. In our study, 11.1% (5/45) of the patients had an underlying mass, which was lower than the 22% reported by Fu et al.[3] The final diagnosis rested on a pathological examination.

There are various theories regarding the origin of Paget's disease. One theory holds that the disease originates from epidermal cells of the breast tissue, which invade deeply inferiorly into ducts underlying the nipple. The strongest evidence is that Paget's disease has different microscopic morphology from common breast cancer because underlying ductal invasion can not be detected in all Paget's disease cases. However, over the past 10 years, with the development of advanced detection techniques, most scholars agree that Paget's disease comes from carcinoma in situ or invasive ductal carcinoma of the breast.[4] Vielh et al.[5] reported that a focus of disease can be found in the breast in all Paget's disease patients. Potter et al.[6] found that Paget's cells in ducts invaded the epidermis when stimulated by nipple epidermal-cell chemotactic factors. Fu et al.[7] using multiple molecular markers to study Paget's disease, showed that tumors displaying strong invasion and poor prognosis expressed a high positive rate for various markers (for example: cerbB-2 was 92.9%, Cyclin D1 was 100% , Ki-67 was 85.7%). Those markers considered to be a sign of good prognosis were of a low positive rate (for example: bcl-2 was 14.2%, p53 was 42.9%, ER and PR were 28.6%). Such results were similar to studies of deep underlying ductal carcinoma in situ and(or) invasive carcinoma in Paget's disease, which also supported the theory that Paget's disease originates from mammary ducts.

Table1. Five and 10-year survival rates of Paget's disease of the breast after treatment % (cases)

Clinical Manifestations	Five-year	P	Ten-year	P
With underlying mass	95.5(21/22)	<0.01	78.6(11/14)	<0.05
Without underlying mass	53.89(7/13)		36.4(4/11)	
Simple Paget's disease	100(12/12)		88.9(8/9)	
With DCIS/IDC	69.6(4/6)	<0.05	43.8(7/16)	<0.05
With DCIS	70.6(12/17)		75.0(3/4)	
With IDC	92.0(23/25)		33.3(4/12)	
Negative lymphadenopathy	50.0(5/10)	<0.01	76.5(13/17)	<0.01
Positive lymphadenopathy	50.0(5/10)		25.0(2/8)	
Total	80.0(28/35)		60.0(15/25)	

Standard treatments for Paget's disease have been mainly mastectomy and modified radical mastectomy. Breast conserving therapy includes regional resection and cone excision with the nipple and aerola also excised. Fu et al. [3] reported quadrant excision for 8 cases without palpable masses, among them, 2 cases recurred, one after 3 years and the other 7 years after their operation. So because this disease is considered to have a high recurrent rate, breast conserving treatment should be carried out with caution. Bijker et al. [8] reported on the largest number of cases with Paget's disease who underwent breast conserving surgery. The surgical method used in all patients was excision of the nipple/areola area and subareolar mammary tissue (as deep as the negative surgical margins) and application of postoperative whole mammary radiotherapy. For all 61 patients, the postoperative 5-year recurrent rate was 5.2%, thereby concluding that for Paget's disease patients (including underlying DCIS), nipple/areola cone excision combined with postoperative radiotherapy proved acceptable. Marshall et al. [9] reported on 36 Paget's patients without palpable masses or obvious dense shadows in their breast X-ray. Of the 36 cases, 32 underwent total or partial excision of the nipple/areola area and 2 patients only had a biopsy, and routine postoperative radiotherapy. The total 5-, 10-, 15-year survival rates were 95%, 93% and 90% respectively. So they maintained that for Paget's disease patients without palpable masses or obvious dense shadows in the breast X-ray, whole mammary excision could be replaced by total or partial excision of nipple/areola area. Kothari et al.[10] had the viewpoint that a common complication in Paget's disease is inferior mammary tissue invasion. However, such invasion was almost undetectable clinically or by breast X-rays. For those who only underwent nipple/areola excision or cone excision, 76.5% were not treated with total excision, so extended partial resection and combined therapy were recommended.

Prognosis of Paget's disease of the breast has been determined by whether there were clinically palpable tumor masses. The survival rates were much higher for patients without clinically palpable tumor masses than those with palpable underlying masses. [2-3] In our group, the 5 and 10-year survival rates of patients without a clinically palpable tumor mass were 95.5% and 78.6% respectively, while the survival rates of patients with a palpable tumor mass were 53.8% and 36.4% respectively, the former rates being significantly better than the latter ($P<0.01$). Based on pathological examination, the prognosis was good in patients without an underlying invasion, but poor in patients with DCIS and even worse in patients with invasive breast cancer. In this group, the 5 and 10-year survival rates were 100% and 88.9% respectively in patients with only Paget's disease, while patients with DCIS/IDC the survival rates were 69.6% and 43.8% respectively. The former rates were significantly better than the latter ($P<0.05$). The prognosis was also greatly influenced by whether there was axillary lymphadenopathy. The 5 and 10-year survival rates were 92.0% and 76.5% respectively with negative lymphadenopathy, while the survival rates with positive lymphadenopathy were 50.0% and 25.0%, the former also being much better than the later. Obviously, the key to achieve the best outcome in Paget's disease is early diagnosis and treatment.

REFERENCES

1. Dixon AR, Galca MH, Ellis IO, et al. Paget's disease of the nipple. Br J Surg. 1991; 78: 722–723.
2. Sheen–Chen SM,Chen HS, Chen WJ, et al. Paget's disease of the breast– an easily overlooked disease? J Surg Oncol. 2001; 76: 261–265.
3. Fu W, Mittel VK, Young SC. Paget's disease of the breast: Analysis of 41 patients. Am J Clin Oncol. 2001; 24: 397–400.
4. Lloydl J, Flanagaan AM. Mammary and extramammary Paget's disease. J Clin Pathol. 2000; 53: 742–749.
5. Vielh P, Validire P, Kheirallah S, et al. Paget's disease of the nipple without clinical and radiological detectable breast tumor: Histological and immunohistochemical study of 44 cases. Pathol Res Pract. 1993; 189: 150–155.
6. Potter CR, Eeckhout L, Schelhout AM, et al. Keratinocyte induced chemotaxis in the pathogenesis of Paget's disease of the breast. Histopathology. 1994; 24: 349–356.
7. Fu W, Lobock CA, Siberberg BK, et al. Molecular markers in Paget's disease of the breast. J Surg Oncol. 2001; 77: 171–178.

8. Bijker N, Rutgers EJ, Duchateau L, et al. Breast-conserving therapy for Paget disease of the nipple: A prospective European Organization for Research and Treatment of Cancer Study of 61 Patients. Cancer. 2001; 91: 472-477.
9. Marshall JK, Griffith KA, Haffty BG, et al. Conservative management of Paget disease of the breast with radiotherapy. Cancer. 2003; 97: 2142-2149.
10. Kothari AS, Beechey-Mewman N, Hamed H, et al. Paget disease of the nipple. Cancer. 2002; 95: 1-7.