

## &lt;Case Report&gt;

## A case of Pagetoid carcinoma confined to the nipple

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**Key words** : Paget, nipple, breast cancer

**ABSTRACT**

We report a rare case of Pagetoid carcinoma with underlying invasive ductal carcinoma confined to the nipple. A 75-year-old postmenopausal Japanese woman presented with a chief complaint of a mass involving the right nipple with bleeding and erosion of 2 years' duration. The tumor, which was confined to the right nipple, measured 4.5 × 4.0 × 3.0 cm. Cytological analysis of a smear of nipple tissue showed class V disease. The patient underwent modified radical mastectomy with level III lymph node dissection. The histopathological diagnosis was papillo-tubular type of invasive ductal carcinoma, and Paget's cells, with large, clear cytoplasm and large nuclei, were found in the epidermis of the nipple. Thus, this case was considered Pagetoid carcinoma confined to the nipple. Histological examination showed metastases to multiple axillary and infraclavicular lymph nodes. The clinical stage was III C of T4N3M0, according to the classification of the International Union Against Cancer. Immunohistochemical studies of invasive ductal carcinoma cells showed strongly

positive staining for HER-2 and p53 proteins in the cell membrane and in the nucleus, respectively, but those of Paget's cells showed weakly positive staining. The patient died of multiple metastases to the lung and carcinomatous pleuritis 18 months after surgery despite receiving combination chemotherapy. We consider that, in Pagetoid carcinoma, intensive treatment, including radiotherapy or chemotherapy, is needed in addition to mastectomy with lymph node dissection, even though the tumor is confined to the nipple.

**INTRODUCTION**

Paget's disease of the breast has been recognized as a distinct clinical entity since being described by Sir James Paget in 1874<sup>1)</sup>. Paget's disease of the breast is rare, accounting for 0.5% to 4.3% of breast cancers<sup>2-5)</sup>. It is characterized by progressive, marginated, eczematoid changes in the nipple or areola and by the spreading of typical cells of ductal origin in the corresponding epidermis due to the presence of carcinoma of the breast<sup>3)</sup>. Sakamoto et al have demonstrated that Paget's disease can be divided into Paget carcinomas and

Pagetoid carcinomas based on morphology and biology<sup>6)</sup>. Pagetoid carcinomas have a palpable mass with invasive ductal carcinoma in the underlying breast, whereas Paget carcinomas dose not demonstrate palpable masses<sup>6)</sup>. Here, we report a rare case of Pagetoid carcinoma with underlying invasive ductal carcinoma cells confined to the nipple.

### CASE REPORT

A 75-year-old Japanese postmenopausal woman presented on October 24, 1997, with a chief complaint of a mass of the right nipple with bleeding and erosion. She had noted blood-stained discharge from the nipple for 2 years. The tumor, which was confined to the right nipple, measured 4.5 × 4.0 × 3.0 cm (Figure. 1). The surface of the nipple was erosive, eczematoid, and irregular. Cytological examination of a smear of nipple tissue showed carcinoma cells, including Paget's cells, and disease was classified as class V. Firm lymph nodes, 5.0 cm in size, were palpated in the right axilla.



Figure. 1

There were no palpable masses in the right breast outside the nipple area. Imaging studies, including mammography, ultrasound, and computed tomography, also showed that the tumor was confined to the nipple (Figure. 2). There were no

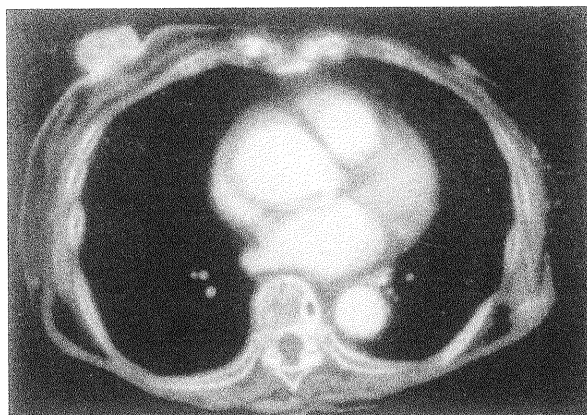


Figure. 2

apparent distant metastases on chest CT, abdominal ultrasound, or bone scintigraphy (data not shown). Of serum tumor markers examined before surgery, carcinoembryonic antigen was elevated at 8.1 ng/ml. After obtaining informed consent, modified radical mastectomy with dissection of axillary and infraclavicular lymph nodes was performed at the Department of Surgery, Otsu Red Cross Hospital, on November 10, 1997.

The tumor was curatively resected macroscopically and was found to be confined to the nipple (Figure. 3). The

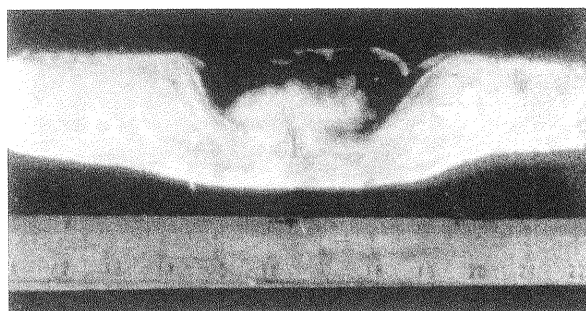


Figure. 3 (A)



Figure. 3 (B)

histopathological diagnosis was papillo-tubular type of invasive ductal carcinoma (Figure. 4A), and Paget's cells, with large, clear cytoplasm and large nuclei, were found in the epidermis of the nipple (Figure. 4B). Thus, this case was considered Pagetoid carcinoma confined to the nipple. Histological examination of the carefully prepared section of the resected specimen did not show any carcinoma cells in the breast outside the nipple area.

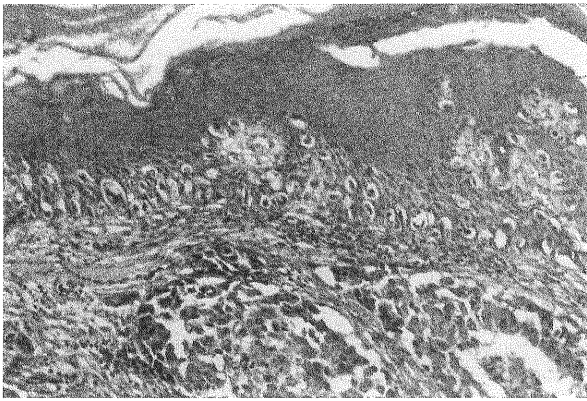


Figure. 4A

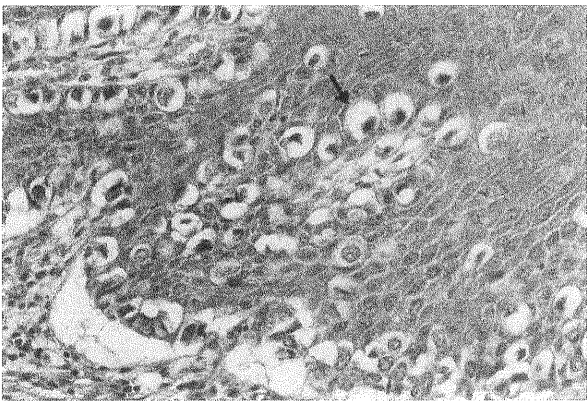


Figure. 4B

Immunohistochemical studies of invasive ductal carcinoma cells showed strongly positive staining for HER-2 and p53 proteins in the cell membrane and in the nucleus, respectively, but those of Paget's cells showed weakly positive staining (Figure. 5A, 5B). Metastases to multiple axillary and infraclavicular lymph nodes

were found on histological examination. The clinical stage was III C of T4N3M0, according to the classification of the International Union Against Cancer. On enzyme-linked immunosorbent assay of tumor specimens, neither estrogen nor progesterone receptors were positive.

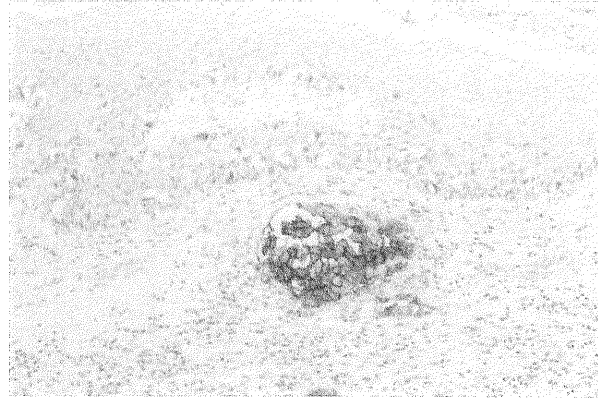


Figure. 5A

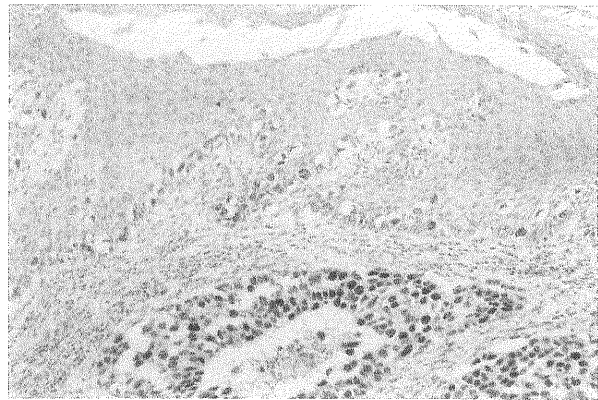


Figure. 5B

Lymphadenopathy was noted in the right supraclavicular region on December 16, 1997. From that day, 4.5 Gy of irradiation to the right supraclavicular region was administered daily for 4 weeks to control lymph node metastases. The lymphadenopathy decreased, and the patient was discharged without major complications due to irradiation. The patient and her family refused chemotherapy.

During follow-up, serum levels of carcinoembryonic antigen gradually in-

creased. Multiple metastases to the lung were seen on chest X-ray films in October 1998 (data not shown). On January 5, 1999, the patient was readmitted for intravenous systemic chemotherapy. Despite 4 courses of combination chemotherapy consisting of cyclophosphamide, methotrexate, and 5-fluorouracil, metastases to the lung were increased in number and size on chest CT. Furthermore, large amounts of fluid were retained in the thoracic cavity bilaterally because of carcinomatous pleuritis. On April 14, 1999, the patient died of respiratory failure.

### DISCUSSION

In General Rules for Clinical and Pathological Recording of Breast Cancer, Paget's disease is described as a cancer, showing intradermal invasion in the nipple-areolar complex and intraductal spread with no or little extraductal invasion<sup>7)</sup>. Cases showing severe extraductal invasion are classified by the histological type of the underlying invasive ductal carcinoma<sup>7)</sup>. However, it is difficult to diagnose the extent of the extraductal invasion preoperatively<sup>8)</sup>. Thus, when Paget's cells are found in the nipple-areolar complex, it is often treated as Paget's disease<sup>8)</sup>. It is clinically useful to divide Paget's disease into Paget carcinomas and Pagetoid carcinomas based on morphology and biology<sup>6)8)</sup>. Pagetoid carcinomas show severe extraductal invasion, and often shows lymph node metastases, whereas Paget carcinomas have no or little extraductal invasion of carcinoma cells<sup>6)</sup>. Pagetoid carcinomas have a palpable mass and show a poor prognosis. However, Paget carcinomas have no palpable mass and show a fair prognosis. Sakamoto et al have indicated

that Pagetoid carcinoma cannot be an advanced stage of Paget carcinoma<sup>6)</sup>. In the present case, extraductal invasion of carcinoma cells and metastases to lymph nodes were found, and the survival was short due to multiple lung metastases and carcinomatous pleuritis. Thus, it is thought that the Paget's disease in the present patient should be classified as Pagetoid carcinoma, in which invasive ductal carcinoma cells were confined to the nipple.

For patients with Paget's disease without a palpable mass, treatment is usually conservative and includes nipple excision or quadrantectomy, excision plus radiation, or radiation only<sup>9-12)</sup>. However, many authors have indicated that, even in the absence of a palpable mass, conservative surgery should be selected cautiously because of a higher recurrence rate and multifocal lesions<sup>4)13)14)</sup>. Modified radical mastectomy with lymph node dissection is recommended for Pagetoid carcinoma showing a biologically aggressive phenotype with a palpable mass or lymph node metastases<sup>15)</sup>. Amplification or overexpression of HER-2 has been observed in invasive human breast carcinoma and correlates with a poorer prognosis, metastasis to lymph nodes, and rapid progression<sup>16)17)</sup>. In patients with breast cancer, overexpression of p53 indicates a poor prognosis<sup>18)19)</sup>. The incidence of overexpression of HER-2 and p53 in Paget's disease is much higher than that in invasive human breast carcinoma<sup>20-22)</sup>. This higher incidence indicates that both proteins can play important roles at an earlier phase of pathogenesis in Paget's disease than in invasive breast carcinoma. Immunohistochemical studies for both HER-2 and p53 proteins in the present case showed strong staining in the invasive

ductal carcinoma cells, but weak staining in Paget's cells. The poor outcome in this case can be explained by overexpression of both proteins in invasive ductal carcinoma cells rather than by weak expression of proteins in Paget's cells. However, it is not clear whether that is applicable to all cases of Pagetoid carcinoma. The details of the roles of HER-2 and p53 in both Paget and Pagetoid carcinomas remain to be clarified.

Trastuzumab (Herceptin), which is a monoclonal antibody against HER-2 protein, has been reported to be effective in patients with overexpression of HER-2<sup>23-25</sup>. It would be interesting to investigate whether trastuzumab can improve the prognosis of patients with recurrence or metastases of Pagetoid carcinoma overexpressing HER-2 protein.

In conclusion, we have reported a rare case of Pagetoid carcinoma confined to the nipple and forming a palpable mass. We consider that, in Pagetoid carcinoma, intensive treatment, including radiotherapy or chemotherapy, is needed in addition to mastectomy with lymph node dissection, even though the tumor is confined to the nipple.

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#### FIGURE LEGEND

Figure. 1. The tumor, which was confined to the right nipple, measured  $4.5 \times 4.0 \times 3.0$  cm. Its surface was erosive, eczematoid, and irregular.

Figure. 2. The tumor was detected only in the right nipple with CT.

Figure. 3. Examination of the gross specimen (a) and of hematoxylin and eosin-stained sections (b) showed that the tumor was confined to the nipple.

Figure. 4. Invasive ductal carcinoma cells were found throughout the nipple (a), and Paget's cells were found in the epidermis of the nipple (b), (arrow), (a)  $\times 100$ , (b)  $\times 200$

Figure. 5. HER-2 (a) and p53 (b) proteins were strongly positive in the cell membrane and in the nucleus of invasive ductal carcinoma cells, respectively, but were weakly positive in those of Paget's cells. (a)(b)  $\times 100$