

Case Report

Invasive Cancer Confined to the Nipple of the Conserved Breast: A Case Report

Miyuki Kitahara^a Yasuo Hozumi^a Naoto Takeuchi^a Satoko Ichinohe^a
Mitsuki Machinaga^a Tatsuo Iijima^b

^aDepartment of Breast Surgery, Ibaraki Prefectural Central Hospital, Ibaraki Cancer Center, Kasama, Japan; ^bDepartment of Diagnostic Pathology, Ibaraki Prefectural Central Hospital, Ibaraki Cancer Center, Kasama, Japan

Keywords

Breast-conserving surgery · Invasive breast cancer · Nipple · Metachronal ipsilateral · True recurrence

Abstract

Invasive breast cancer deriving from the milk duct and lobule that develops in the nipple is extremely rare, except in Paget's disease and skin cancer. This is the second reported case of the development of invasive cancer confined to the nipple after breast-conserving surgery. A 69-year-old woman visited our department due to redness, swelling, and bloody discharge of the right nipple in the last month. A needle biopsy was suggestive of invasive ductal carcinoma; we performed a removal surgery of the right residual breast tissue and a second sentinel lymph node biopsy. She underwent these procedures 10 years previously as well. Thus, we diagnosed the present lesion as a local recurrence, but it was unknown whether the lesion was a true recurrence or second cancer, namely, metachronal ipsilateral breast cancer. The present case helps promote awareness that invasive cancer rarely develops in the nipple after conserving surgery. Patients should be encouraged to visit a medical facility if experiencing skin changes and swelling of the nipple. Additionally, breast cancer patients must be carefully selected for breast-conserving surgery; failure to do so may later result in nipple-specific local recurrence.

© 2020 The Author(s).
Published by S. Karger AG, Basel

Miyuki Kitahara
Department of Breast Surgery, Ibaraki Prefectural Central Hospital and Cancer Center
6528 Koibuchi
Kasama, Ibaraki 309-1793 (Japan)
m-kitahara@chubyoin.pref.ibaraki.jp

Introduction

Invasive breast cancer confined to the nipple is rare except in Paget's disease, which is reported to account for 0.18% of overall invasive breast cancer [1]. This is the second case to report the development of invasive cancer deriving from the milk duct and lobule in the nipple after breast-conserving surgery. Here, we report a case of invasive cancer confined to the nipple of the conserved breast that developed 10 years after the first treatment for breast cancer.

Case Report

The subject was a 69-year-old woman. She had no family history of breast cancer or any malignancy. She underwent partial mastectomy of the right breast for breast cancer in the lower outer quadrant of the right breast and a sentinel lymph node biopsy 10 years ago. The histopathological examination results showed microinvasive carcinoma, pT1micN0M0 pStage1, negative resection stump, negative for estrogen receptor (ER), negative for progesterone receptor (PgR), and positive for human epidermal growth factor receptor 2 (HER2) (Fig. 1). After surgery, she underwent chemotherapy (TC treatment [T: docetaxel, C: cyclophosphamide]), anti-HER2 therapy (trastuzumab), and radiation therapy for the right breast and the tumor bed. Due to redness, swelling, and bloody abnormal discharge of the right nipple in the last month, she visited our department. The right nipple was enlarged from 0.8 to 1.5 cm in diameter, and single-pore bloody discharge was observed (Fig. 2a). A breast ultrasound showed the formation of a hypoechoic mass accompanied by hyperechoic dots within the right nipple, and a breast MRI showed strong enhancement localized in the right nipple (Fig. 2a, c). Based on the results of a needle biopsy of the right nipple, the patient was diagnosed with invasive ductal carcinoma. We judged it as a local recurrence in the conserved breast tissue.

We performed a removal surgery of the right residual breast tissue and a second sentinel lymph node biopsy. The resected specimen showed an oval white solid mass with a well-defined border in the right nipple (Fig. 3a). This was separate from the scar of the previous surgery and macroscopically, and there were no findings that suggested the continuity between the scar of the previous surgery and the present lesion. The histopathological exam-

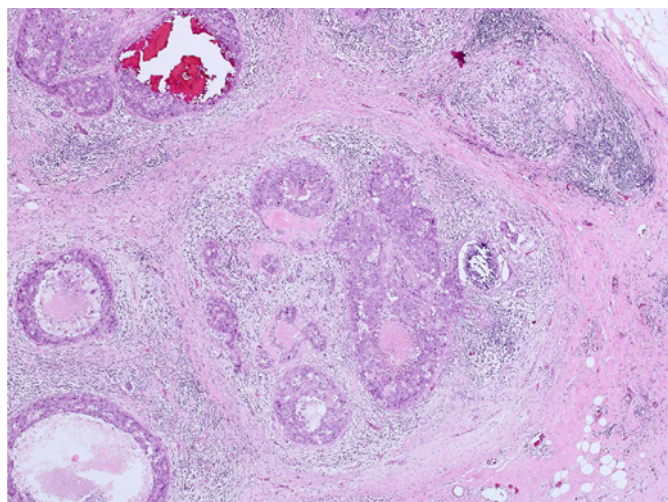


Fig. 1. Histopathological findings at the time of the first surgery. Microinvasive carcinoma was negative for ER and PgR, and positive for HER2/FISH. Tumor diameter in the invading area: 1 mm. Tumor diameter including the area of progression in the milk ducts: 15 × 8 mm (magnification, ×40). ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.

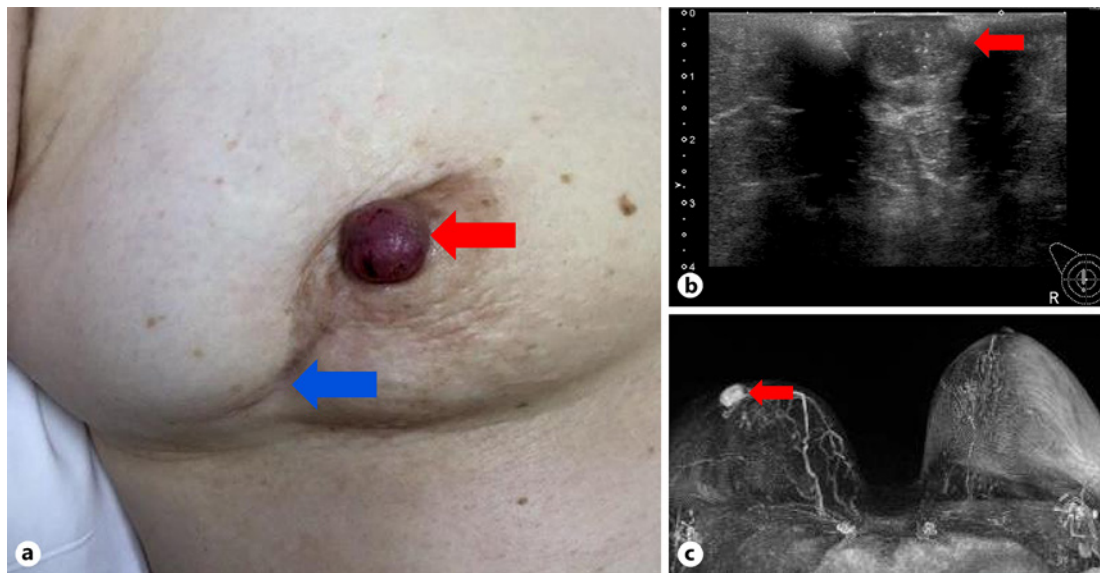


Fig. 2. Findings of the right nipple; ultrasound and MR images of the breast. **a** Redness and swelling of the nipple and single-pore bloody discharge are seen. **b** Ultrasound image of the mammary gland. A hypoechoic mass accompanied by hyperechoic dots in the nipple is observed. **c** Breast MR image. Strong enhancement localized in the right nipple is observed. Red arrow: the right nipple. Blue arrow: site of the first surgical scar. MR, magnetic resonance.

ination results showed invasive ductal carcinoma, solid-type, pT1cN0M0 pStage1, positive for ER, negative for PgR, and positive for HER2 (Fig. 3b, c). The tumor cells grew to fill the nipple, but progression to the surrounding milk ducts was not observed. There was no tumor lesion at the site of the previous surgery scar. Based on the facts that the scar of the previous surgery and the present lesion were distinct and that both histological images and immunohistochemical findings were different, we judged the present case not a true recurrence, but as a second cancer: metachronal ipsilateral breast cancer. As postoperative therapies, we planned chemotherapy (paclitaxel), anti-HER2 therapy (trastuzumab), and hormone therapy (letrozole).

At the first administration of paclitaxel, allergies such as shortness of breath and hypoxia appeared and it was discontinued. Currently, the patient has been receiving trastuzumab and letrozole. At present, 12 months after surgery, she is alive with no recurrence.

Discussion

The majority of breast cancer develops from terminal duct lobular units and the cancer rarely develops in the nipple, which is the farthest from the lobules [1]. A large-scale case study of breast cancer that developed in the nipple was first reported in 1956 [1]. Of 10,000 patients undergoing surgery, 25 (0.25%) patients developed cancer in the nipple. Of them, 18 (0.18%) patients had invasive cancer and 7 (0.07%) patients had ductal cancer in situ. A study in 2018 reported that the frequency of invasive cancer that developed in the nipple was 0.30% (24 of 8,000 patients), of which 10 (0.12%) patients developed Paget's disease and 14 (0.18%) patients developed invasive cancer deriving from the milk duct and lobule [2].

There are 2 hypotheses for why invasive cancer deriving from the milk duct and lobule develops in the nipple. The first hypothesis is that the lobules were shown to be present in

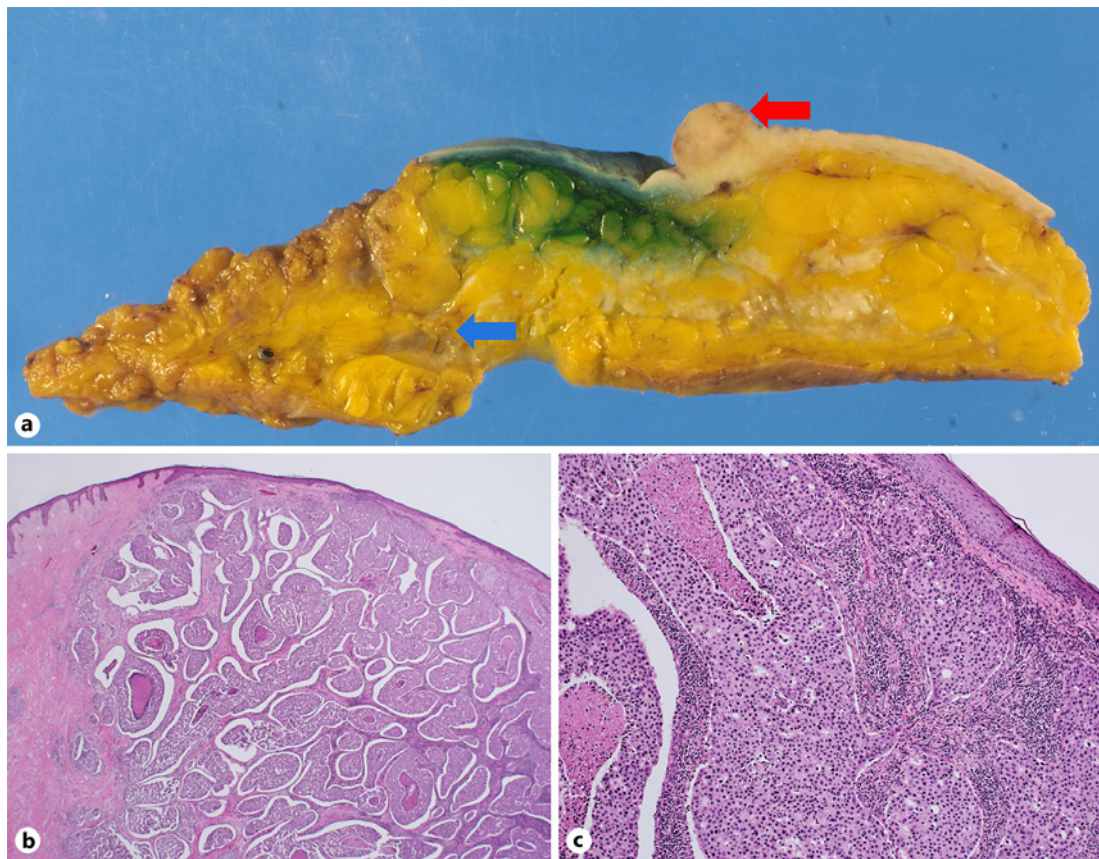


Fig. 3. Macroscopic and histopathological findings of the resected specimen. **a** An oval solid mass of 14 × 8 mm in size with a well-defined border in the nipple is observed. Red arrow: the right nipple. Blue arrow: site of the first surgical scar. **b** Invasive ductal carcinoma, solid type, positive for ER, negative for PgR, positive for HER2/FISH (magnification, ×20). **c** The tumor formed various-sized solid alveoli and grew to fill the nipple (magnification, ×100). ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.

26% of the nipple and directly meet the major milk ducts [3]; thus, the cancer presumably develops from the lobule in the nipple. The second hypothesis is that ductal carcinoma develops in the peripheral mammary gland and through progression in the milk duct, invasive cancer presumably develops in the nipple [2].

The incidence of local recurrence from breast-conserving surgery in early breast cancer is reported to be as high as 14.3% [4]. The tumor may recur at the surgical scar or the surrounding quadrants of the affected breast. The reason for this phenomenon is unknown, but unclear resection margins or unidentified occult tumor tissue may be the cause.

Isolated local recurrence in the nipple in the ipsilateral breast after breast-conserving surgery or nipple-sparing mastectomy is rare [5]. There was only 1 case reported in the literature with each surgical technique [6, 7]. This is the second case to report the development of invasive cancer deriving from the milk duct and lobule in the nipple after breast-conserving surgery.

The real reason for an isolated ipsilateral nipple recurrence after a breast-conserving surgery remains a mystery. It is believed that unclear surgical margins, implantation phenomenon, or occult tumor at the nipple-areolar complex may give rise to this phenomenon

[8]. Several studies showed that the tumor grade, size, and stage, tumor-nipple distance, and HER2 positivity were significant predictors of occult nipple involvement in breast cancer [9], but other studies reported contrasting findings [8, 10]. However, all of them agreed that the location of the tumor has an influence on nipple involvement [8–10]. The incidence of nipple recurrence is higher for tumors located at the central or retroareolar area compared with the other 4 quadrants of the breast [9, 10]. Therefore, the decision to perform breast-conserving surgical procedures should not be based on the tumor location alone, but also on the size and stage of the cancer as well as the immunohistochemistry results and HER2 status.

At present, there are no established criteria that clearly classify local recurrences within the breast as either true recurrences or second cancers (metachronal ipsilateral breast cancers). Based on previous studies, these differ in prognoses and therapeutic strategies [11, 12]. In our present case, if histopathological status of the nipple was ductal carcinoma in situ, we agreed that the lesion was a second cancer. However, it was unknown whether the lesion was a true recurrence or a second cancer except for objective evidence (e.g., genetic mutations).

In addition, an increase in the number of prophylactic nipple-sparing mastectomies is expected in the current situation where hereditary breast and ovarian cancer syndrome surveillance is conducted in routine clinical practice. There have been 9 of 776 (1.2%) cases in which breast cancer developed after prophylactic nipple-sparing mastectomy, of which 1 (0.3%) case developed cancer in the conserved nipple [13, 14]. Several contrived surgical procedures to conserve the nipple, such as a procedure of hollowing out the mammary gland in the nipple, have been shown [15]. However, there is no unified view regarding long-term prognoses [15].

This case promotes the awareness that, although uncommon, breast cancer may develop in the conserved nipple following breast-conserving surgery for breast cancer. In addition, this case highlights the importance of carefully selecting the appropriate breast conservation patients for nipple preservation. It is important to encourage patients to visit a medical organization immediately when experiencing nipple swelling or skin changes, such as redness, exudative crust, pigmentation, and itchiness.

Statement of Ethics

Institutional review board approval was obtained before writing the case report. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There were no funding sources.

Author Contributions

M.K. wrote the manuscript. M.K. and N.T. performed the operation. N.T., S.I., and M.M. managed the patient's perioperative course. T.I. contributed to the drafting of the pathological findings section of the manuscript. Y.H. approved the final manuscript. All authors read and approved the final manuscript.

References

- 1 Congdon GH, Dockerty MB. Malignant lesions of the nipple exclusive of Paget's disease. *Surg Gynecol Obstet*. 1956;103(2):185–92.
- 2 Sanders MA, Brock JE, Harrison BT, Wiczorek TJ, Hong X, Guidi AJ, et al. Nipple-invasive primary carcinomas: clinical, imaging, and pathologic features of breast carcinomas originating in the nipple. *Arch Pathol Lab Med*. 2018 May;142(5):598–605.
- 3 Kryvenko ON, Yoon JY, Chitale DA, Lee MW. Prevalence of terminal duct lobular units and frequency of neoplastic involvement of the nipple in mastectomy. *Arch Pathol Lab Med*. 2013 Jul;137(7):955–60.
- 4 Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*. 1995;333(22):1456–61.
- 5 Edge SB. Nipple-sparing mastectomy: how often is the nipple involved?. *J Clin Oncol*. 2009;27(30):4930–2.
- 6 Shahrun Niza AS, Rohaizak M, Naqiyah I, Srijit D, Noraidah M. Isolated ipsilateral nipple recurrence: important lessons to learn. *Malays J Med Sci*. 2011;18(2):82–4.
- 7 Srivastava A, Webster DJ. Isolated nipple recurrence seventeen years after subcutaneous mastectomy for breast cancer – a case report. *Eur J Surg Oncol*. 1987;13(5):459–61.
- 8 Laronga C, Kemp B, Johnston D, Robb GL, Singletary SE. The incidence of occult nipple-areola complex involvement in breast cancer patients receiving a skin-sparing mastectomy. *Ann Surg Oncol*. 1999;6(6):609–13.
- 9 Lambert PA, Kolm P, Perry RR. Parameters that predict nipple involvement in breast cancer. *J Am Coll Surg*. 2000;191(4):354–9.
- 10 Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of nipple/areolar involvement with mastectomy: can the areola be preserved?. *Ann Surg Oncol*. 2002;9(2):165–8.
- 11 Yoshida T, Takei H, Kurosumi M, Ninomiya J, Ishikawa Y, Hayashi Y, et al. True recurrences and new primary tumors have different clinical features in invasive breast cancer patients with ipsilateral breast tumor relapse after breast-conserving treatment. *Breast J*. 2009;16(2):127–33.
- 12 Sakai T, Nishimura S, Ogiya A, Tanabe M, Kimura K, Morizono H, et al. Four types of ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery: classification of IBTR based on precise pathological examination. *Pathol Int*. 2015;65(3):113–8.
- 13 Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med*. 1999;340(2):77–84.
- 14 Sacchini V, Pinotti JA, Barros AC, Luini A, Pluchinotta A, Pinotti M, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg*. 2006;203(5):704–14.
- 15 Murthy V, Chamberlain RS. Defining a place for nipple sparing mastectomy in modern breast care: an evidence based review. *Breast J*. 2013 Nov;19(6):571–81.