Case Reports in Oncology

Case Rep Oncol 2023;16:1482–1488
DOI: 10.1159/000534847
Received: August 21, 2023
Accepted: October 17, 2023
Published online: November 24, 2023

Case Report

HER2-Positive Metaplastic Breast Cancer with Resistance to Neoadjuvant Chemotherapy: Case Report

Kaho Tateishi[a] Megumi Kiyoi[a] Miwako Miyasaka[a] Mari Kawaji[a] Hitomi Nakanishi[a] Yuki Furuta[a] Mana Nishimatsu[a] Yuichi Takahashi[b] Mizuki Nishikawa[b] Yoshiharu Nishimura[a]

[a]Department of Thoracic and Cardiovascular Surgery, Wakayama Medical University, Wakayama, Japan; [b]Department of Human Pathology and Diagnosic Pathology, Wakayama Medical University, Wakayama, Japan

Keywords

Metaplastic breast cancer · HER2-positive · Neoadjuvant chemotherapy · Squamous cell carcinoma · Breast cancer

Abstract

Introduction: Metaplastic breast carcinoma (MBC) is a rare histologic subtype of breast carcinoma, which is usually negative for estrogen receptor, progesterone receptor, and HER2. HER2-positive MBC is therefore extremely rare. Most MBCs have poor response to chemotherapy. HER2-targeted neoadjuvant chemotherapy (NAC) is widely performed and has high efficacy in treating HER2-positive breast cancer. We report an atypical case of HER2-positive breast cancer that had poor response to NAC and was diagnosed with MBC after the surgery. ***Case Presentation:*** A 73-year-old woman noticed a mass in her right breast and visited our hospital. The mass was diagnosed as hormone receptor-negative, HER2-positive invasive ductal carcinoma, T2N0M0 stage IIA. She received HER2-targeted NAC comprising trastuzumab + pertuzumab + docetaxel. Despite three courses, we observed disease progression. The next NAC regimen was composed of two courses of epirubicin + cyclophosphamide, but the cancer continued to grow. She stopped receiving NAC and underwent a unilateral mastectomy and sentinel lymph node biopsy. Although the preoperative pathological result of core needle biopsy specimen showed invasive ductal carcinoma, the postoperative pathological result of the surgical specimen was MBC. ***Conclusion:*** In this case, when the patient had undergone three courses of trastuzumab + pertuzumab + docetaxel, it would have been appropriate to review the result of the core needle

Correspondence to:
Kaho Tateishi, k.tate@wakayama-med.ac.jp

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biopsy with pathologists or to perform vacuum-assisted breast biopsy. This case suggests the importance of considering the possibility of special histologic subtypes such as MBC when a tumor with the diagnosis of invasive ductal carcinoma is resistant to NAC.

Introduction

Metaplastic breast cancer (MBC) is a rare subtype of breast carcinoma, accounting for less than 1% of all breast cancers [1–3]. Clinical features include older age, larger tumor size, and lower incidence of axillary lymph node involvement than conventional invasive ductal carcinoma (IDC). In addition, MBCs are mostly negative for estrogen receptor (ER), progesterone receptor (PgR), and HER2. In other words, they are a triple-negative phenotype [1–4]. Most types of MBC have been suggested to have poor response to conventional chemotherapy [5–7]. MBC is a heterogeneous group of tumors with variable morphology and clinical outcome. There are several different subtypes, including low-grade adenosquamous carcinoma, carcinoma with pure or mixed squamous cell differentiation, spindle cell carcinoma, fibromatosis-like carcinoma, and metaplastic carcinoma with heterologous mesenchymal differentiation [8].

HER2-positive breast cancer accounts for approximately 20–25% of breast cancer and is defined by overexpression of HER2 protein in the tumor surface or by HER2 gene amplification [9]. HER2-targeted chemotherapy usually has high efficacy and is commonly used in HER2-positive breast cancer. However, the effect of neoadjuvant chemotherapy (NAC) in HER2-positive MBC is unclear. Here, we report a case of a patient with HER2-positive breast cancer who had poor response to NAC and was diagnosed with MBC after the surgery.

Case Report

A 73-year-old Japanese woman presented with a mass in the right breast. Physical examination confirmed a mass in the lower inner quadrant of the right breast with a maximum diameter of about 3 cm, and the absence of axillary lymphadenopathy. Mammography showed a lobulated and high-density mass in the left lower inner quadrant of the breast (Fig. 1a). The margins of the mass were micro-serrated, there were no calcifications inside. Ultrasonography showed a well-circumscribed and amorphous mass measuring 2.7 cm in size. The mass had well-defined margins, enhanced posterior echoes, a halo, and low-level internal echoes (Fig. 1b). In ultrasonography, there was no observation of axillary lymphadenopathy. Contrast-enhanced magnetic resonance imaging (MRI) showed a 3.1 cm amorphous mass with a pattern of early enhancement and washout in the right breast (Fig. 1c). There was extensive ductal spread and a daughter nodule in the outside anterior of the mass. Core needle biopsy showed atypical spindle cells with cobblestone appearance (Fig. 1d), leading to diagnosis of IDC of no special type, T2N0M0 stage IIA. Immunohistochemistry confirmed that the lesion was positive for HER2 (score of 3+), negative for ER and PgR and 80% of MIB-1 positive cells. The patient received trastuzumab + pertuzumab + docetaxel (Tmab+Pmab+DTX) as HER2-targeted NAC. After three courses of Tmab+Pmab+DTX, ultrasonography showed the tumor growth to be 3.3 cm in size (Fig. 2a). The patient underwent two courses of epirubicin + cyclophosphamide (EC) as the next NAC regimen. However, the tumor was out of frame in ultrasonography (Fig. 2b) and grew to 3.8 cm in size with internal degeneration suspected of necrosis in MRI (Fig. 2c). She stopped receiving NAC and underwent a unilateral mastectomy and sentinel lymph node biopsy. The

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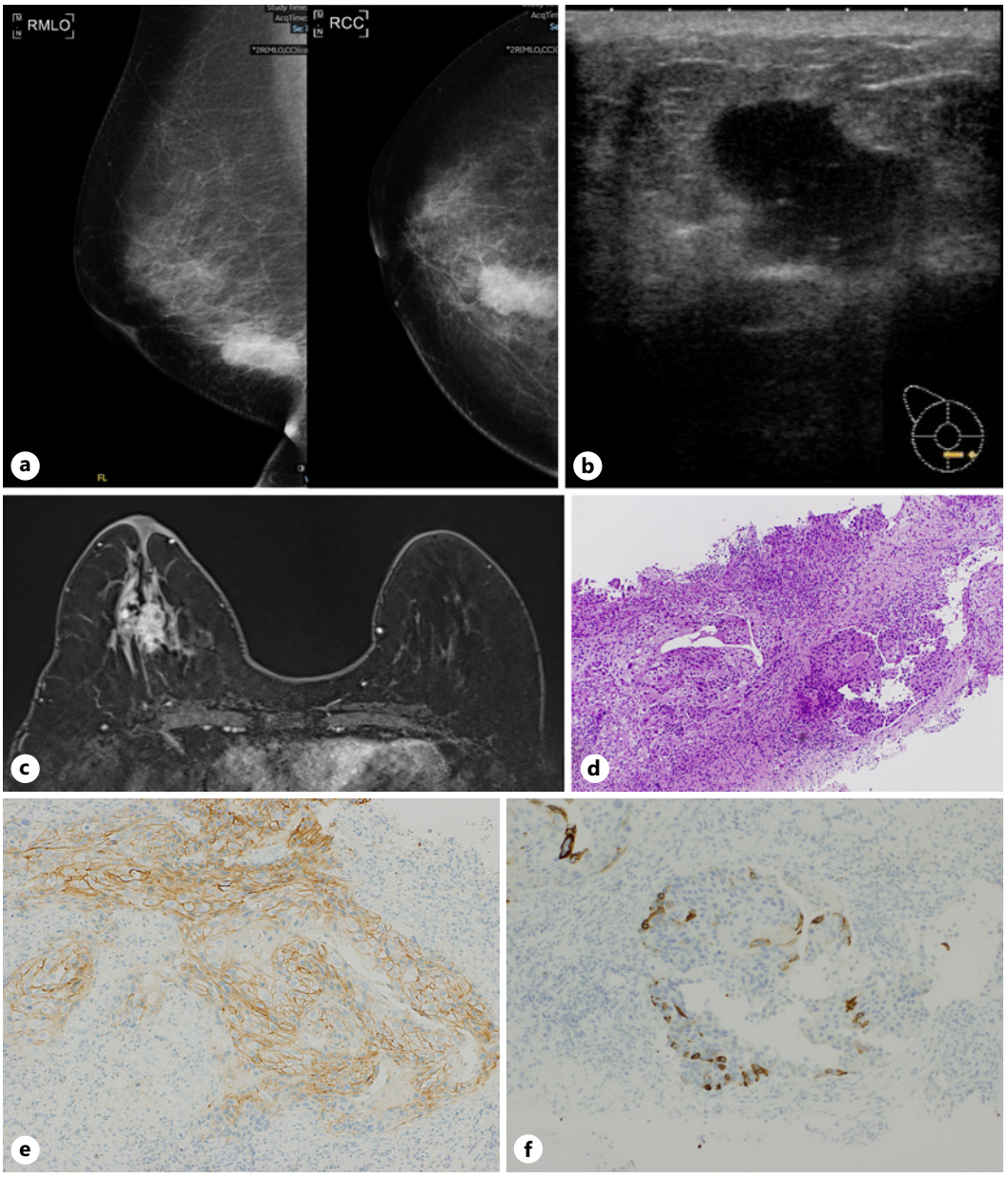

Fig. 1. a Mammography revealed a lobulated and high-density mass in the left lower inner quadrant of the breast. **b** Ultrasonography showed a well-circumscribed and amorphous mass in the right breast that was 2.7 cm in size, had well-defined margins, enhanced posterior echoes, halo, and low-level internal echoes. **c** MRI revealed an amorphous mass with a pattern of early enhancement and washout. There was extensive ductal spread and a daughter nodule in the outside forward of the mass (arrow). **d** Pathological findings of core needle biopsy, showing atypical spindle cells with cobblestone appearance. **e** HER2 was overexpressed on the surface of the cancer cells (score of 3+). **f** CK5 was expressed on the part of the cancer cells.

pathological tumor size was 3.5 × 2.5 cm (Fig. 3a), and the sentinel lymph node appeared to be normal. The postoperative pathological result of the surgical specimen showed that the tumor cells were pleomorphic and proliferated in sheets with necrosis and keratinization (Fig. 3b, c), leading to the diagnosis of metaplastic carcinoma (squamous cell carcinoma). Immunohistochemistry confirmed that the lesion was negative for ER and PgR and 80% of MIB-1 positive

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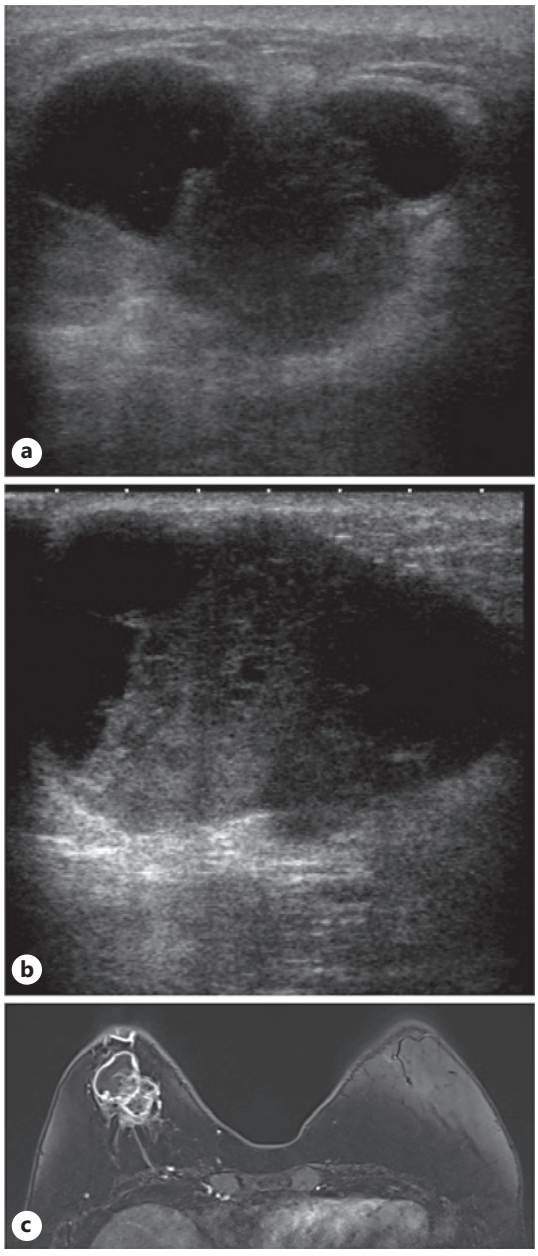

Fig. 2. a Ultrasonography after three courses of Tmab+Pmab+DTX showed the tumor growth to 3.3 cm in size. **b** Ultrasonography after two courses of EC showed that the tumor was enlarged and out of frame. **c** MRI showed the tumor with internal degeneration suspected of necrosis.

cells. The immunohistochemical score of HER2 was 2+, so we performed the fluorescence in situ hybridization test; the result was positive. The optimum postoperative treatment for MBC has not been determined, so we suggested follow-up observation could be an option. The patient nonetheless decided to receive adjuvant chemotherapy. She received trastuzumab emtansine as adjuvant chemotherapy, and there has been no recurrence as of 6 months after the surgery.

Discussion

There is no specific treatment for MBC; it is usually performed according to the treatment of typical IDC. NAC has been widely performed for not only early-stage cancer but also for inflammatory and locally advanced tumors. MBC is frequently larger in size and has an

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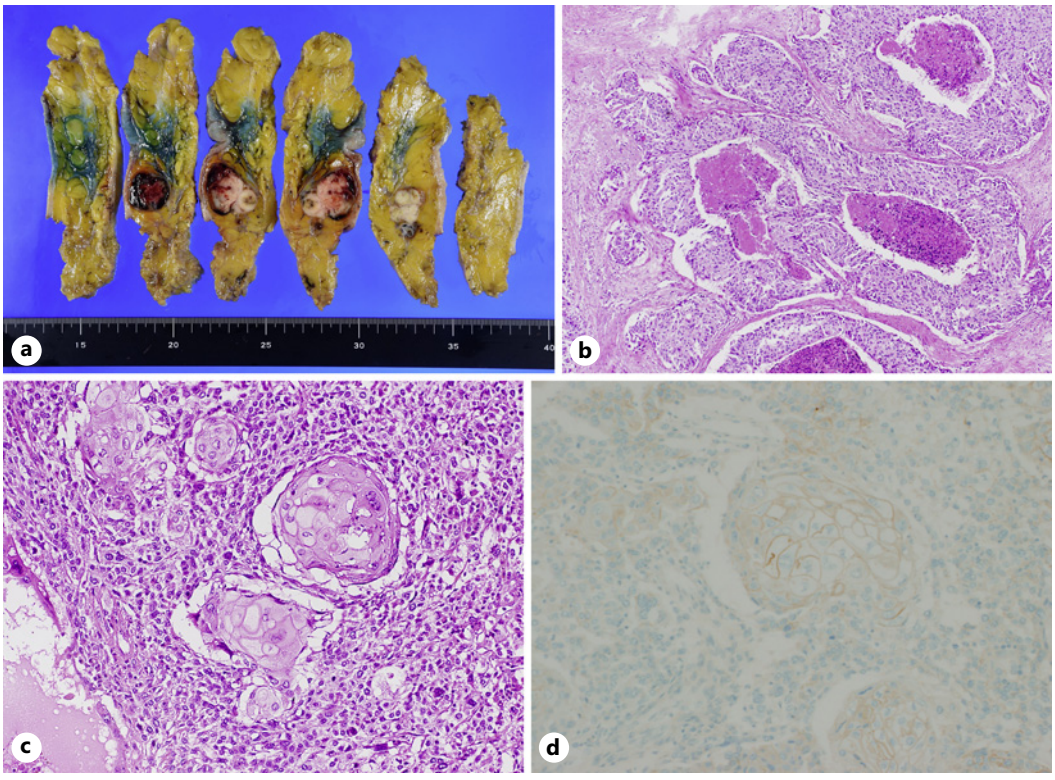

Fig. 3. a Surgical specimen showed fibrosis and hemorrhage around the tumor. **b**, **c** The postoperative pathological results suggest that the tumor cells were pleomorphic and proliferated in sheets with necrosis and keratinization. **d** HER2 was weekly expressed on the surface of the cancer cells (score of 2+).

advanced stage at initial presentation than conventional breast cancer, so NAC is often considered as a treatment for patients with MBC. MBC has been shown to have poor response to NAC compared with conventional triple-negative breast cancer [5–7]. Therefore, there is another argument that immediate surgery without NAC should be recommended in patients with MBC with operable tumors [7]. Paclitaxel + carboplatin has been shown in previous studies to be effective against squamous cell carcinoma, similar to in the current patient [10]. Leibl et al. [11] reported that many MBCs were positive for HER1 and targeted protein kinase inhibitors, such as gefitinib, might be effective. However, these studies each had small sample sizes with various limitations, so no effective treatments for MBC have been established.

HER2-positive MBC is extremely rare, reportedly accounting for just 5–7% of MBC [2, 3, 5]. In some studies, patients with HER2-positive MBC received HER2-targeted NAC, which led to pathological complete response [5, 12]. Wu et al. [13] reported MBC with subtype converted from triple-negative to HER2-positive and the patient achieved a long progression-free survival time through chemotherapy and trastuzumab-targeted therapy after the subtype change. On the other hand, our patient had resistance to NAC with HER2-targeted drugs and anthracycline antibiotics. However, there are few reports related to the treatment for HER2-positive MBC, and the effect of NAC for HER2-positive MBC and the role of HER2 in MBC remain unclear.

Some HER2-positive breast cancers have resistance to HER2-targeted therapy. The subgroup termed “basal-like HER2-positive breast cancer” has resistance to HER2-targeted therapy and a poor prognosis [9, 14, 15]. Basal-like HER2-positive breast cancer is defined immunohistochemically as ER negative, HER2 positive, and any basal marker (CK5/6, CK14,

EGFR1) positive at any level. Hui et al. [15] reported that basal-HER2 phenotype needs more attention and that it might require a different treatment strategy. Chung et al. [9] reported on that the basal phenotype and its link to Akt signaling as one clinically relevant pathway of trastuzumab resistance. However, further studies are needed to characterize the role of Akt in this phenomenon. In our patient, some atypical cells were CK5 positive, which suggests the possibility of predicting resistance to HER2-targeted therapy in advance.

Diagnosing metaplastic carcinoma appropriately by preoperative needle biopsy is often difficult [16]. In the present case, core needle biopsy before the operation led to the diagnosis of IDC of no special type. However, the postoperative pathological result of the surgical specimen led to the diagnosis of metaplastic carcinoma (squamous cell carcinoma). In core needle biopsy before the operation, there were a few metaplastic components, but it was difficult to be diagnosed as metaplastic carcinoma because the number of metaplastic components was small. We believe that NAC has a significant effect on IDC components, but metaplastic components that were resistant to NAC grew. The difference in diagnosis before and after the operation therefore seems to be due to the small amount of biopsy material rather than due to histological changes. We suggest that it would have been beneficial to perform vacuum-assisted breast biopsy after three courses of Tmab+Pmab+DTX.

Diagnosis by core needle biopsy can be inaccurate, so it is important to consider the possibility of MBCs by imaging findings. However, the mammographic, sonographic, and MRI imaging characteristics of MBCs can be similar to IDC as well as probably benign features [17]. On the other hand, Inoue et al. [18] showed that the cystic degeneration and capsular enhancement that form during the NAC could indicate squamous cell carcinoma. The significant effect of preoperative chemotherapy on tumor necrosis was hypothesized to result in the formation of a coat around the tumor, and that the survival and proliferation of drug-resistant cells along the coat is the cause of this change. In the present case, the tumor enlarged and there was cystic degeneration and capsular enhancement after NAC. The possibility of MBC components should have been considered, even after the diagnosis of IDC.

In conclusion, when HER2-positive breast cancers have poor response to HER2-targeted NAC, there should be consultation with pathologists on the diagnosis by biopsy, with consideration of the possibility of special types breast cancers, performance of vacuum-assisted breast biopsy, or cessation of NAC and conversion to surgery. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534847).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

Funding Sources

The authors declare that they have received no financial support in relation to this report.

Author Contributions

All authors were involved in the preparation of this manuscript. K. Tateishi collected the data and wrote the manuscript. M. Kiyoi summarized the data and revised the manuscript. M. Miyasaka, M. Kawaji, H. Nakanishi, Y. Furuta, and M. Nishimatsu treated this patient. Y. Nishimura made substantial contributions to the study design and revised the manuscript. Y. Takahashi and M. Nishikawa gave a pathological diagnosis. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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