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Case Report

Pathological Complete Response to Neoadjuvant Chemotherapy in a Patient with HER2-Positive Squamous Cell Carcinoma of the Breast

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Keywords
Pathological complete response · Breast cancer · Squamous cell carcinoma

Abstract
Squamous cell carcinoma (SCC) of the breast is a rare malignancy that usually has a triple-negative phenotype and poor clinical outcomes. Because HER2-positive SCC of the breast is extremely rare, its clinicopathologic features are understudied, and the effects of neoadjuvant chemotherapy including anti-HER2-targeted therapy on the tumor are unclear, although treatment resistance was described in some reports. In this study, we reported a case of HER2-positive SCC of the breast in which a pathological complete response to neoadjuvant chemotherapy was observed.

Introduction

Squamous cell carcinoma (SCC) of the breast is a rare malignancy that accounts for <0.2% of all breast cancers [1]. SCC can be diagnosed when >90% of the malignant cells are of the squamous type [2]. The origin of the SCC component remains unclear. Some authors hypothesized that SCC of the breast arises as an extensive and prominent squamous metaplasia in invasive duct carcinoma [3, 4], whereas others suspected that SCC initially presents as benign

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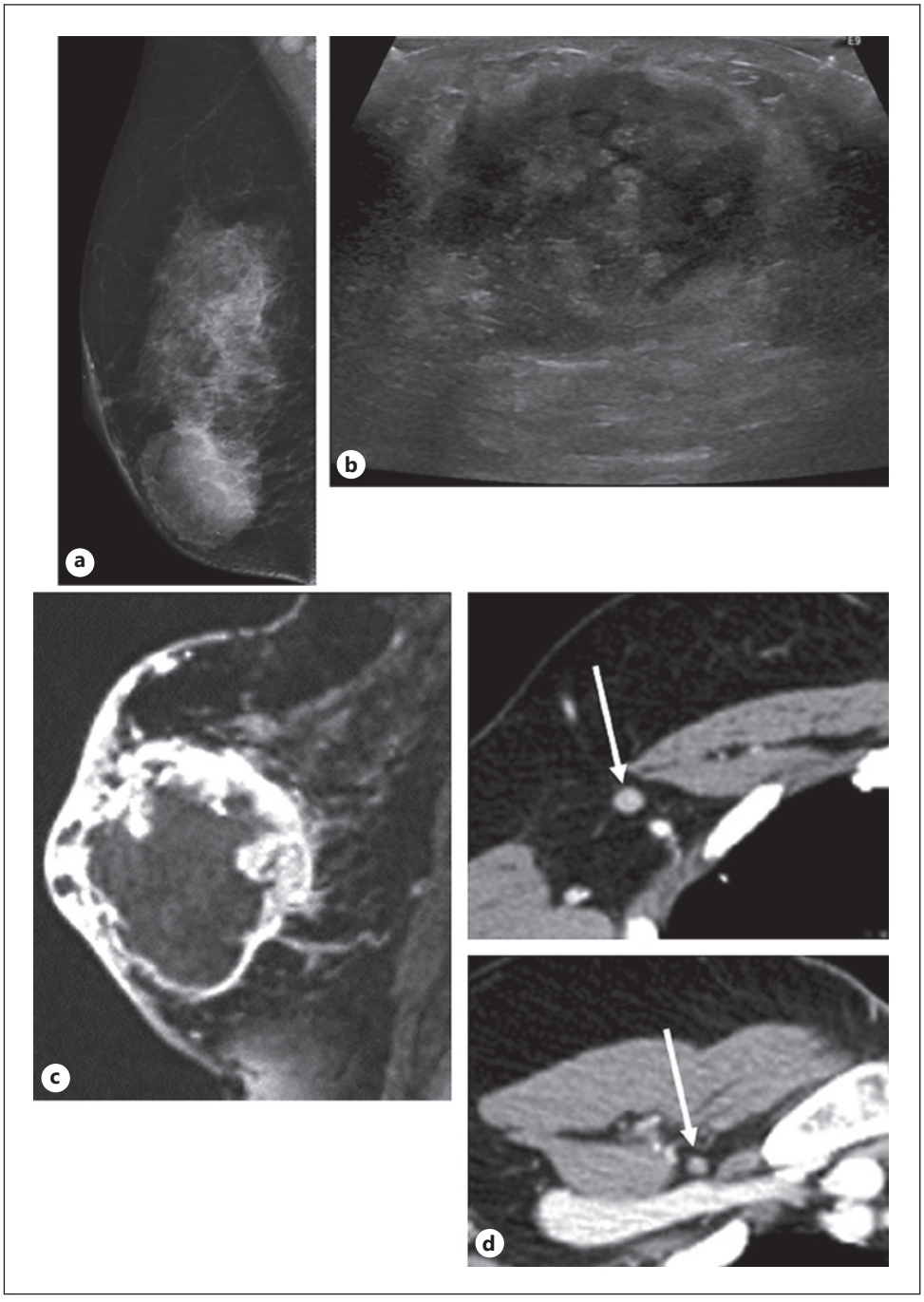

Fig. 1. a Mammography revealed a mass with branching-type calcifications and enlarged nodes. **b** Ultrasonography disclosed a hypoechoic and heterogeneous solid mass in the right breast. **c** MRI revealed a rim-enhancing mass, localized skin thickening, and enhancement overlying the tumor consistent with skin invasion. **d** Computed tomography identified axillary lymph node metastasis (upper) and subclavicular lymph node metastasis (lower).

breast conditions such as abscesses or develops in association with implants [5–7]. Recently, some reports stated that SCC and its adjacent invasive ductal carcinoma component shared the same origin, but their transcription landscape and driven pathways differed [8–10].

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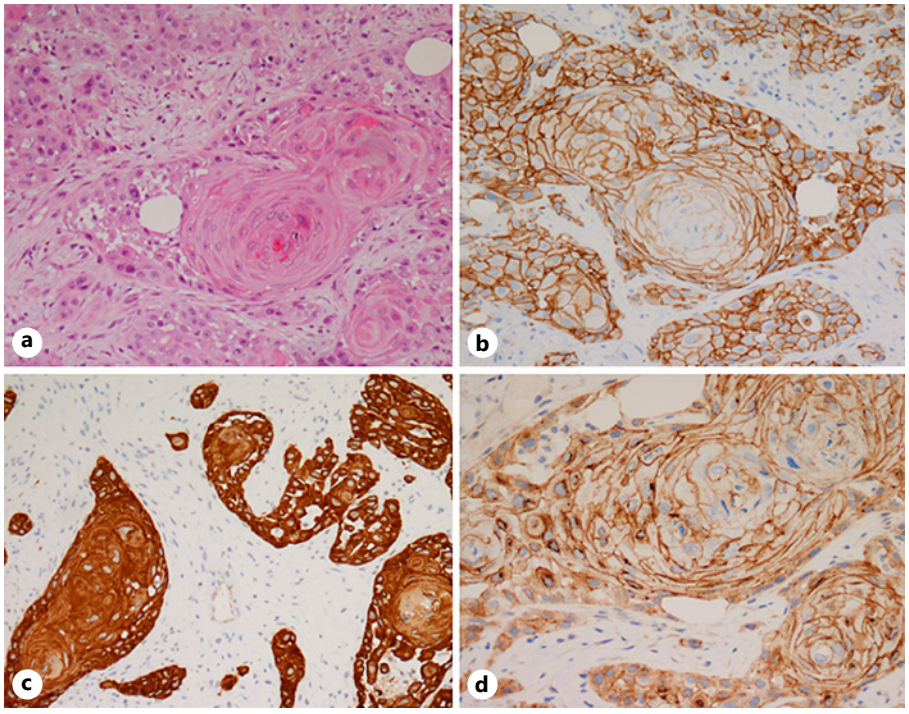

Fig. 2. a Histological findings in SCC of the breast (hematoxylin and eosin staining). Atypical cornified squamous cells were proliferating, suggesting SCC. **b** HER2 was overexpressed on the surface of the cancer cells. **c** Cytokeratin 5 and 6 was overexpressed in the cancer cells, suggesting the basal-like subtype. **d** EGFR expression was enhanced on the surface of cancer cells. SCC, squamous cell carcinoma.

The immunohistochemistry profile of SCC often indicates a triple-negative subtype, suggesting aggressive histological features and poor outcomes [11].

HER2-positive breast cancer is rather unusual in SCC, and all available data regarding HER2-positive SCC of the breast were generated by case reports and small retrospective studies [1, 12–16], and the clinicopathologic features of this rare subtype of SCC have not been described in detail. In this study, we reported a case of HER2-positive SCC of the breast, an extremely rare breast cancer, which exhibited a pathological complete response to neoadjuvant chemotherapy.

Case Report

A 48-year-old woman presented with a right breast lump in May 2019. Physical examination revealed a 5-cm lump with redness on her right lower breast and the absence of axillary lymphadenopathy. Diagnostic mammography detected a mass with branching-type calcifications. Breast ultrasonography revealed a 42-mm hypoechoic and heterogeneous solid mass, and contrast-enhanced MRI disclosed a 47-mm round, centrally necrotic mass with rim enhancement and invasion-suggesting enhancement into the overlying skin in the right breast. Additionally, thoracic and abdominal CT revealed the absence of distant organ metastases and axillary and subclavicular lymph node metastases (i.e., stage IIIC [T4bN3aM0]; Fig. 1). Biopsy of the breast mass revealed SCC. Immunohistochemistry confirmed that the lesion was positive for HER2, cytokeratin 5/6 (CK5/6), and EGFR and negative for ER and PgR (Fig. 2). The patient completed 4 cycles of dose-dense doxorubicin and cyclophosphamide every 2 weeks, followed by 4 cycles of trastuzumab plus pertuzumab and docetaxel every 3 weeks as neoadjuvant chemotherapy. Contrast-enhanced MRI

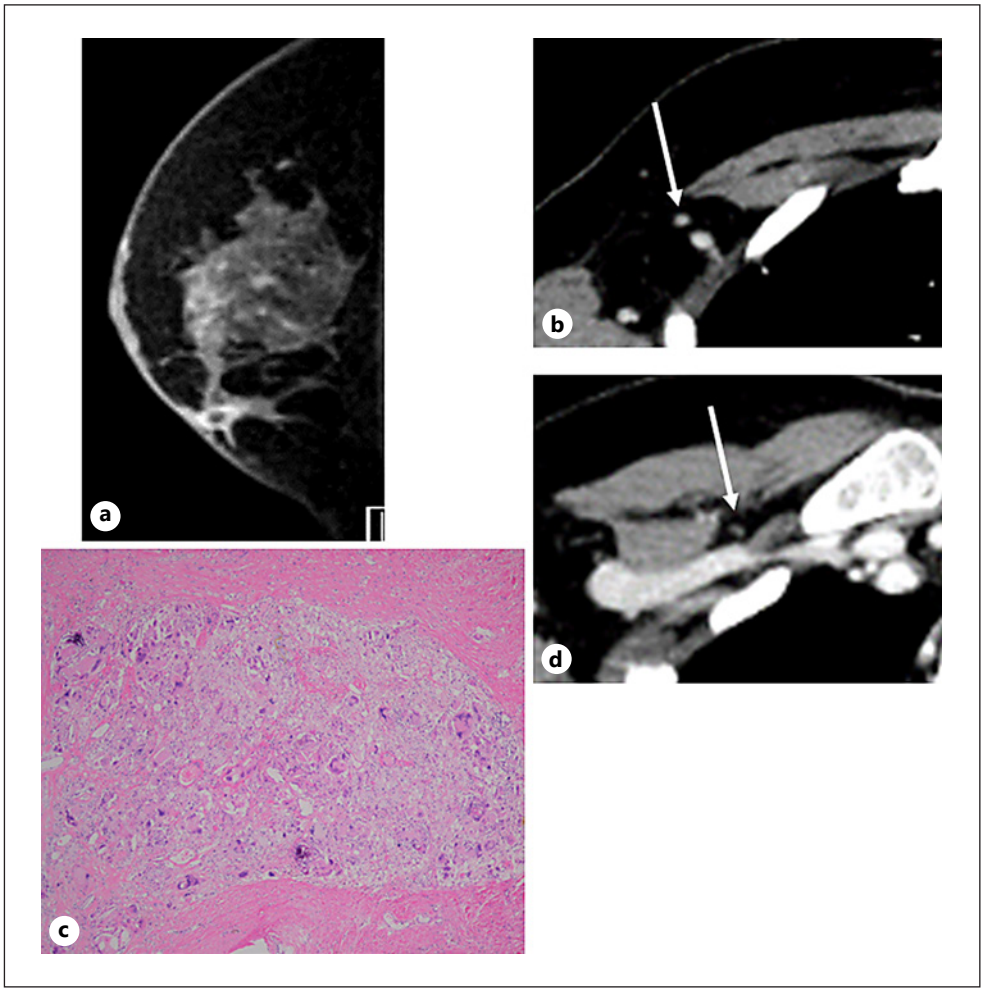

Fig. 3. a Magnetic resonance imaging after neoadjuvant chemotherapy demonstrated a shrinking tumor without skin invasion. **b** Computed tomography revealed shrinkage of the axillary (upper) and subclavicular lymph nodes (lower) after neoadjuvant treatment. **c** The histological findings after neoadjuvant treatment demonstrated the complete absence of viable tumor cells. Clusters of foamy macrophages, cholesterol clefts, fibrosis, and multinucleated giant cells were observed.

after neoadjuvant chemotherapy revealed that the tumor was considerably decreased in size to an 18-mm irregular mass without skin invasion, and CT revealed regression of the axillary and subclavicular lymph nodes, indicating a partial response (Fig. 3a–b). Subsequently, mastectomy and axillary dissection were performed. The histological therapeutic effect was pathological complete response in the both tumor and lymph nodes (Fig. 3c). Postmastectomy radiotherapy and 14 cycles of trastuzumab plus pertuzumab were provided as adjuvant treatment. The patient has not experienced recurrence as of 22 months after the surgery.

Discussion

There are limited data from studies with small sample sizes regarding HER2-positive SCC of the breast. Barnes et al. [17] reported that 1 of 26 patients with adenosquamous carcinoma (4%) displayed HER2/neu overexpression. Shui et al. [15] reported that 3 of 30 cases of SCC

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(10%) were HER2 positive. Lei et al. [16] reported that 13 of 58 cases of metaplastic SCC (22%) were HER2 positive. Additionally, because few clinicopathologic and therapeutic studies have examined HER2-positive SCC because of the rarity of the disease, the effect of neoadjuvant chemotherapy is unclear. Because SCC is generally considered an aggressive, treatment-refractory disease with a poor prognosis, some physicians believe that HER2-positive SCC of the breast is likely to display primary resistance to HER2-targeted therapies. Furthermore, 1 report indicated that combined overexpression of EGFR and CK5/6 was the only independent prognostic factor for SCC of the breast [18].

Some reports based on immunohistochemical assessment suggested that a subtype of SCC of the breast coexpresses basal CKs and HER2 protein, which is the so-called basal-HER2 subtype (ER negative and basal CK positive) [19–21]. They considered that the basal-HER2 subtype is linked to resistance to anti-HER2 agents and chemotherapy because this subtype was associated with poorer survival than basal-like and HER2-positive breast cancers [20, 22].

In the present case, the immunohistochemistry profile of SCC of the breast disclosed HER2-positive breast cancer that was ER negative, CK5/6 positive, and EGFR positive on immunohistochemistry, suggestive of the basal-HER2 subtype. Although this breast cancer might be a treatment-refractory disease according to some previous reports, a pathological complete response was obtained via neoadjuvant chemotherapy with dose-dense doxorubicin and cyclophosphamide, followed by pertuzumab and trastuzumab plus docetaxel, with both therapies contributing to substantial tumor regression, and the patient has not experienced recurrence within 2 years after surgery.

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Statement of Ethics

The patient provided written informed consent for publication of this case, including images. The study was exempt from ethics committee approval since maximum measures were taken to eliminate any patient identifiers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R. Matsunuma and Y. Usui wrote the main manuscript. All authors critically reviewed the manuscript for content.

Data Availability Statement

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

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