



A case report of primary squamous cell carcinoma of the breast

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Abstract: Primary squamous cell carcinoma (SCC) of the breast is a metaplastic carcinoma subtype and an especially aggressive tumor with poor prognosis. Here, we present a case of locally advanced primary SCC of the breast. We reported a case of a 32-year-old woman with a palpable lump in the inner quadrant of the right breast. Core needle biopsy was performed and revealed SCC. Immunohistochemistry staining indicated that the patient had estrogen receptor (ER)-positive immunoreactivity, but was negative for both progesterone receptor and human epidermal growth factor receptor 2 (HER2). Magnetic resonance imaging (MRI) found a mass in the right breast just 4.8 cm × 4.3 cm × 3.4 cm in size. We planned neoadjuvant chemotherapy consisting of 4 cycle of nab-paclitaxel and every 3 weeks followed by 4 cycles of epirubicin and cyclophosphamide (EC) every 2 weeks. However, after 3 cycles of EC, the disease progressed, and the chemotherapy agents were switched to nab-paclitaxel and cisplatin. Still, disease progression continued, and the chemotherapy agents were changed once more to apatinib, eribulin, and camrelizumab. As this also did not work, modified radical mastectomy was performed. Postoperative pathology revealed extensive necrosis. Our case did not achieve pathologic complete response after neoadjuvant chemotherapy. We then started local radiotherapy, and then adjuvant tamoxifen treatment of 20 mg/day followed by 6 cycles of capecitabine. No evidence of disease was detected at half-year follow-up.

Keywords: Breast cancer; neoadjuvant treatment; squamous cell carcinoma (SCC); case report

Received: 11 December 2020; Accepted: 27 April 2021; Published: 30 April 2021.

doi: 10.21037/tbcr-20-67

View this article at: <http://dx.doi.org/10.21037/tbcr-20-67>

Introduction

Primary squamous cell carcinoma (SCC) of the breast is a metaplastic carcinoma subtype. The etiology and pathogenesis of primary SCC of breast still remains unclear. It is a particularly aggressive tumor with poor prognosis and is seen in fewer than 0.1% (0.04–0.075%) of all breast malignancies (1). Here, we present a case of locally advanced primary SCC of the breast. We present the following case in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/tbcr-20-67>).

Case presentation

We report a case of a 32-year-old woman with a palpable lump in the inner quadrant of the right breast in

December 2019, which had been untreated. The mass increased rapidly without redness or swelling on the surface of the skin. In March 2020, she went to a local hospital for examination. In the hospital, color Doppler ultrasonography showed a tumor 4 cm × 3 cm in size. The patient was diagnosed as metaplastic carcinoma with squamous cell component (MCSC) of the right breast by hollow needle puncture pathological examination which was delayed to April 28, 2020 due to the COVID-19 epidemic. Immunohistochemistry revealed the following: MCSC of the right breast, composed of SCC. Immunohistochemistry indicators were as follows: estrogen receptor (ER) 20%, progesterone receptor (PR) negative, human epidermal growth factor receptor 2 (HER2) 0–1+, and Ki67 50%. On May 2020, she was transferred to our hospital (Renmin Hospital of Wuhan University) for treatment. The patient

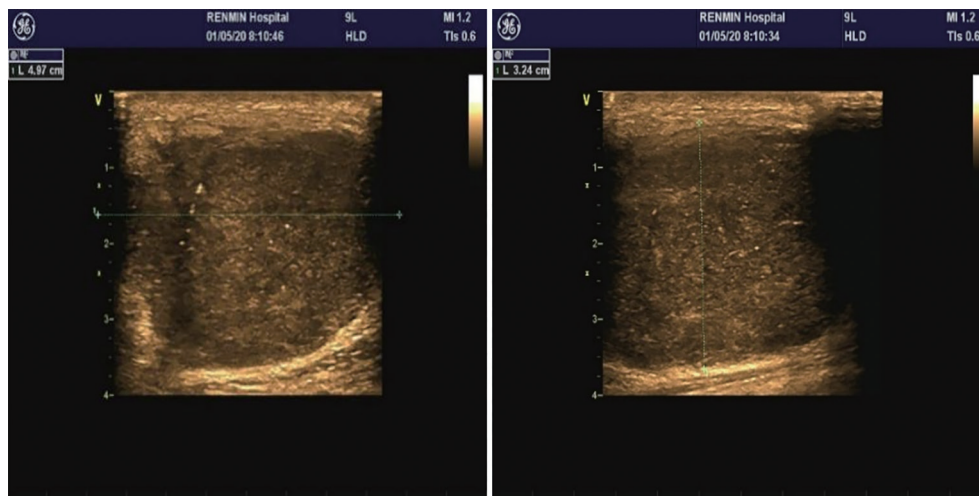


Figure 1 Color Doppler ultrasonography of the breast. Tumor size 5 cm × 3.3 cm.

had no history of tumor or relevant family history, and no other underlying diseases. A physical examination found a 5.0 cm × 4.0 cm palpable mass in the upper right breast, which was hard, and had poor mobility and an unclear boundary. Color Doppler ultrasonography in our hospital showed a tumor 5 cm × 3.3 cm in size (*Figure 1*). Auxiliary examinations in our hospital showed normal routine blood test results, and normal liver, kidney, and heart functions. Tumor marker CA153 was elevated to 55.6 U/mL. Whole-body positron emission tomography-computed tomography (PET-CT) examination showed no distant metastasis. On May 2, 2020, a consultation on her pathological section conducted in our hospital confirmed the patient as MCSC of the breast. Immunohistochemistry revealed the following: ER20%, PR negative, HER2 negative, Ki67 50% (*Figure 2*), GATA-3 positive, GCDPF-15 negative, and myoglobin negative (*Figure 3*). Fine needle aspiration of the right axillary lymph node found cancer cells. The final diagnosis was the following: MCSC of the right breast, cT3N1M0 stage IIIA, luminal B, and HER2 negative. Neoadjuvant chemotherapy and intensive sequential epirubicin/cyclophosphamide (EC) regimen were administered. The ovarian function was protected by subcutaneous injection of leuprorelin during chemotherapy. According to the plan, color ultrasonography evaluation was conducted once every 2 cycles, and breast magnetic resonance imaging (MRI) evaluation was conducted once every 4 cycles (*Figure 4*). According to the Response Evaluation Criteria in Solid Tumors (RECIST), the disease progressed. The baseline tumor diameter was 4.8 cm

before chemotherapy. After 3 cycles of neoadjuvant chemotherapy (May 1, 2020; May 15, 2020; May 29, 2020) using an intensive epirubicin dose (160 mg, 100 mg/m²) and cyclophosphamide (960 mg, 600 mg/m²), the tumor diameter was 6.5 cm (*Figure 4*). A pathological examination using core needle biopsy was performed. The results were as follows: ER20%, PR negative, HER2 negative, Ki67 50% (*Figure 5*), and disease progress. As there was no change in the pathological indicators, the chemotherapy regimen was changed. On June 14, the nab-paclitaxel (400 mg, 260 mg/m²) + cisplatin (120 mg, 75 mg/m²) regimen was started for 1 cycle of treatment. From July 1, apatinib (250 mg, qd, po), eribulin (2 mg, 1.2 mg/m², d1, 8) and camrelizumab (200 mg) were used. The tumor diameter was 7.5 cm, indicating further disease progression (*Figure 6*). On August 2, 2020, a modified radical mastectomy of the right breast was performed (*Figure 7*). Postoperative pathological examination revealed the following: high grade MCSC of the right breast, with vessel carcinoma embolus positive, a tumor size of 6.5 cm × 6 cm, ER5%, PR negative, HER2 negative, Ki67 70% (*Figure 8*), and 1/24 metastasis of the right axillary lymph node. Neoadjuvant therapy response by pathological examination was determined to be Miller-Payne (MP) class 2 and residual cancer burden (RCB) level III. American Joint Committee on Cancer (AJCC) ypTN stage was ypT3N1a. The SP142 test indicated the patient was programmed death-ligand 1 (PD-L1) positive. Postoperative gross examination revealed a massive necrotic hematoma in the tumor capsule (*Figure 9*), which was consistent with the breast MRI evaluation (*Figure 4*). The

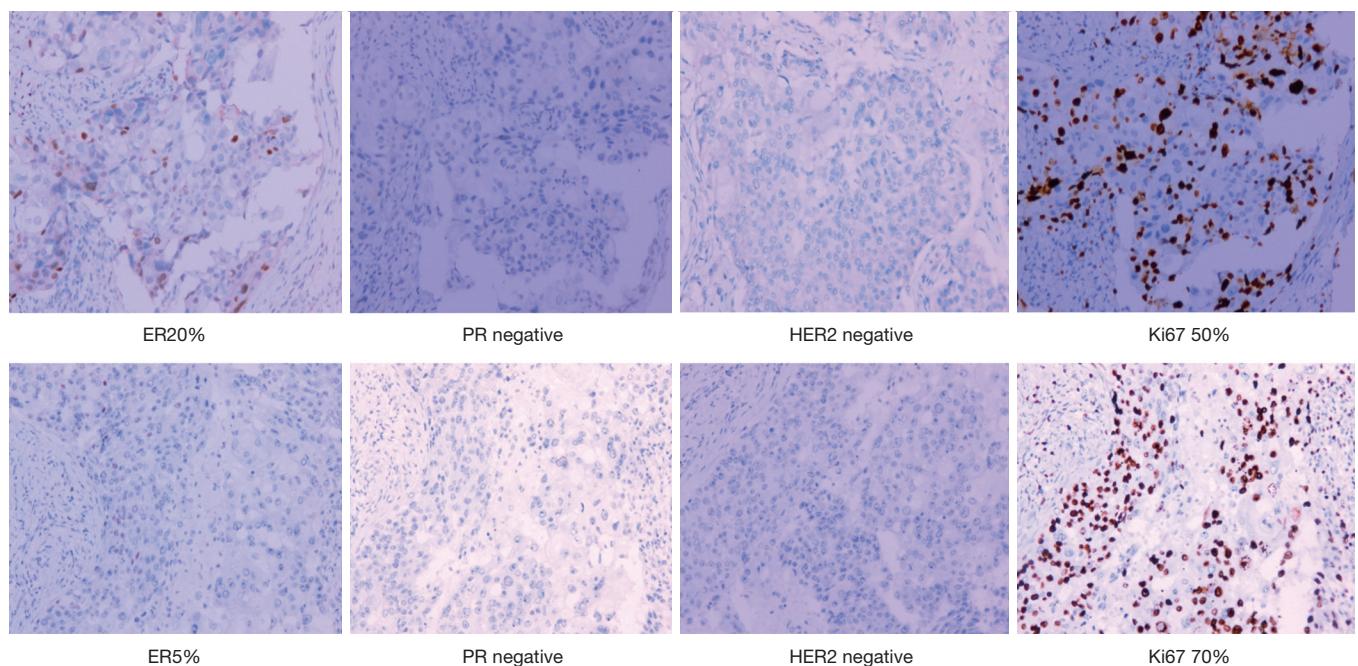


Figure 2 Above: before chemotherapy, ER, PR, HER2, Ki67 status, HE $\times 100$. Below: after five cycles of chemotherapy ER, PR, HER2, Ki67 status, HE $\times 100$. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HE, hematoxylin-eosin staining.

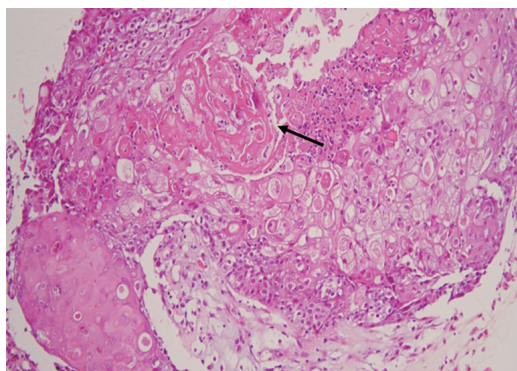


Figure 3 Baseline pathological results for consultation before chemotherapy. The infiltrating carcinoma was characterized by nests of infiltrating stroma, and the cancer cells had characteristics of squamous-cell carcinoma, with abundant cytoplasm, visible intercellular bridges, keratinization, and inflammatory cell infiltrates observed in the stroma. HE $\times 200$ (with arrow indicating keratinization).

MRI T2 signal diagram and diffusion-weighted imaging (DWI) signal diagram showed that the area with high signals was gradually shrinking; meanwhile, the breast MRI

indicated that the tumor component was also shrinking, the necrotic bleeding range was increasing, and a large hematoma had formed. In combination with the above treatment and postoperative pathological examination, it was clear that the chemotherapy had limited efficacy on MCSC of the breast and was creating difficulties in postoperative treatment. Therefore, a polygenic test for guiding the follow-up treatment was recommended. Foundation-1 polygenic test results showed microsatellite (MS)-stable and no tumor mutation burden (TMB) related to immunotherapy, which was consistent with the negative PD-L1 finding from by postoperative pathological immunohistochemistry. *PIK3CA*, *PTEN*, and *FGFR1* mutations related to drug resistance were also found, while *BRCA1* and *BRCA2* were not mutated (Figure 10). The genetic test results showed drug resistance, which was consistent with the results of the previous treatment period. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The patient has given the consent for the case report to be published.

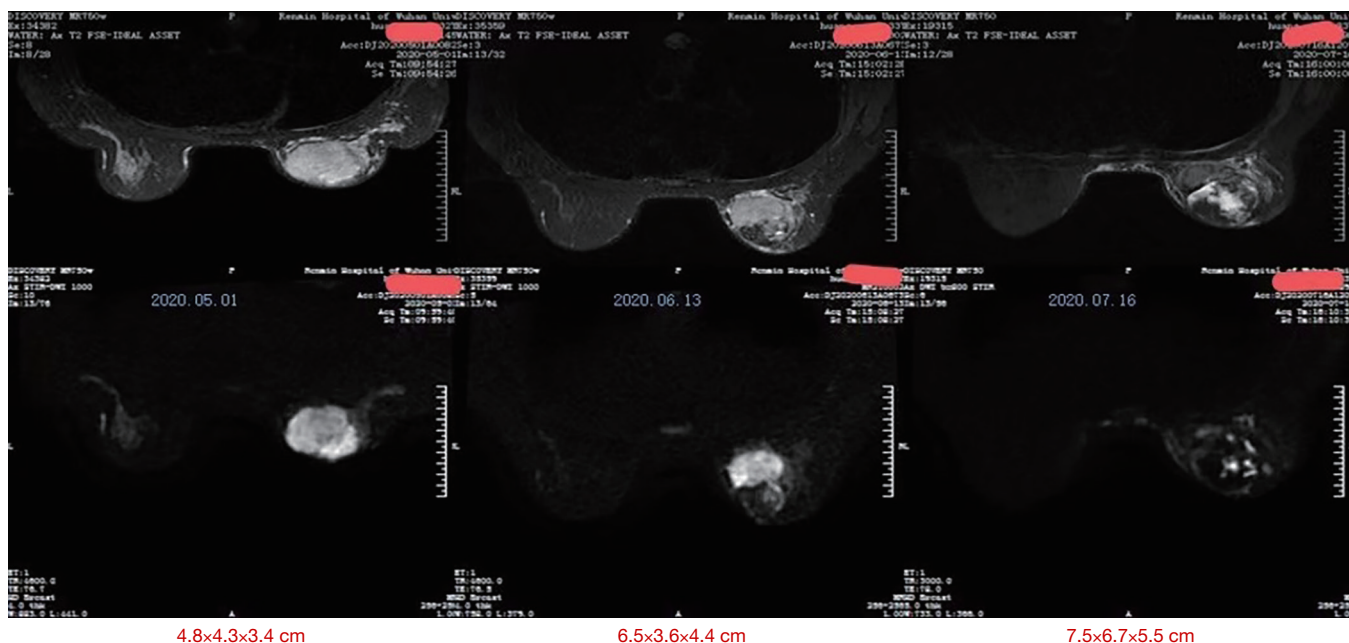


Figure 4 Breast MRI The maximum size of the tumor was assessed on MRI before chemotherapy, 3 cycles after chemotherapy and 5 cycles after chemotherapy, Above: T2 signal. Below: DWI. Left: baseline tumor diameter 4.8 cm before chemotherapy; middle: 6.5 cm after 3-cycle EC chemotherapy, and 7.5 cm after 5-cycle EC chemotherapy. MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.

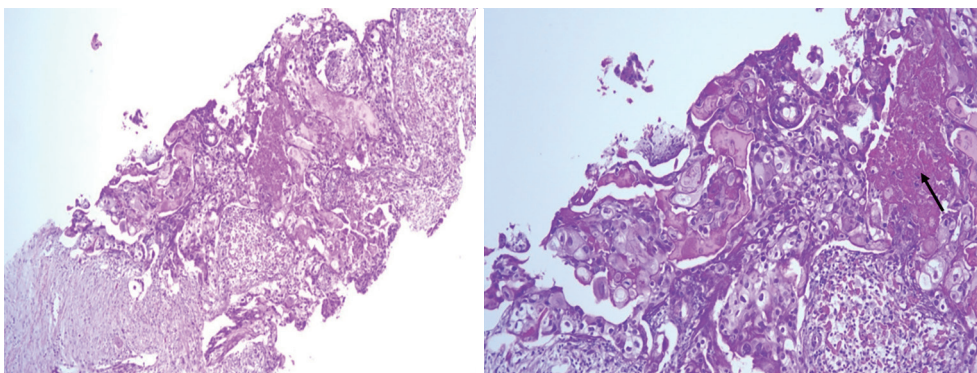


Figure 5 Pathological assessment. Biopsy after 3 cycles of EC chemotherapy. Left: microscopic necrosis in the nests, HE $\times 100$. Right: microscopically, the cancer cells varied in size, with some nuclei shrunken, accompanied by keratinization and necrosis, HE $\times 200$ (with arrow indicating necrosis). EC, epirubicin and cyclophosphamide.

Discussion

The patient was diagnosed with MCSC, which is a type of bio-SCC, known as metaplastic breast carcinoma (MPBC). The incidence rate of MPBC is very low, accounting for just 0.2–5% of breast carcinoma (2) cases, and thus the incidence rate of MCSC is even lower. MPBC consists of ductal epithelial cells, squamous cells and/or chondroid

cells, and spindle cells, with SCC being the most common histologic subtype (3). MPBC usually occurs among women above 50 years old, and presents as a rapidly growing breast mass (4) as compared to invasive ductal carcinoma (IDC). Locally advanced metaplasia may be found in about 90% of the patients, 50% of whom will have secondary distant metastasis. The risk of metastasis is twice that of triple-negative breast cancer (TNBC) (5,6). About 10% of MPBC

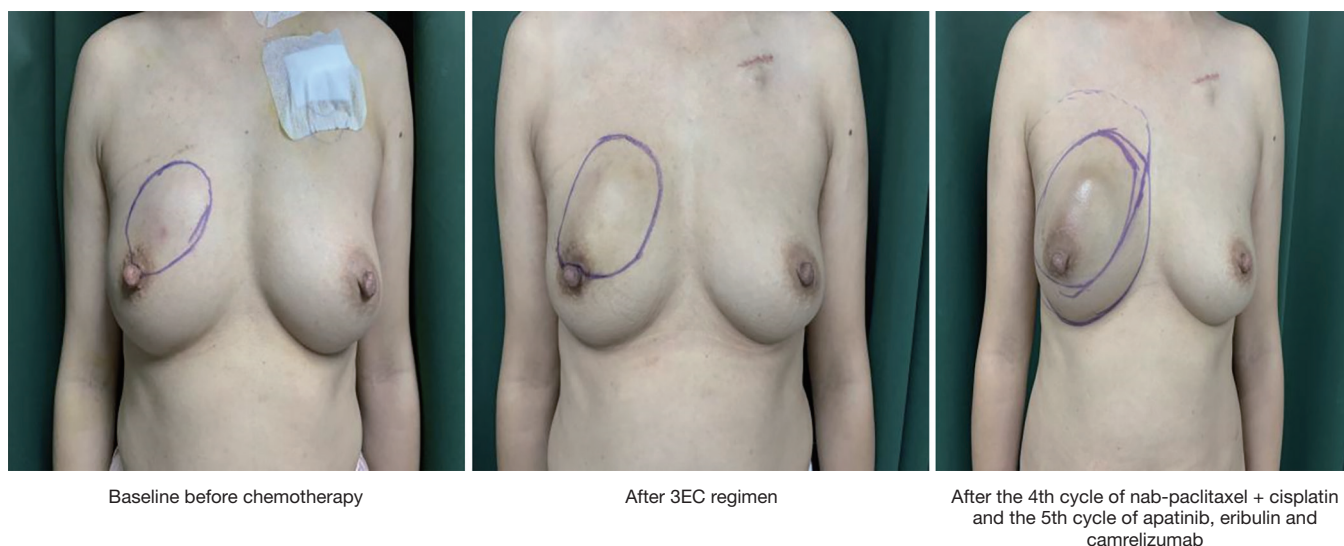


Figure 6 Before and after treatment.

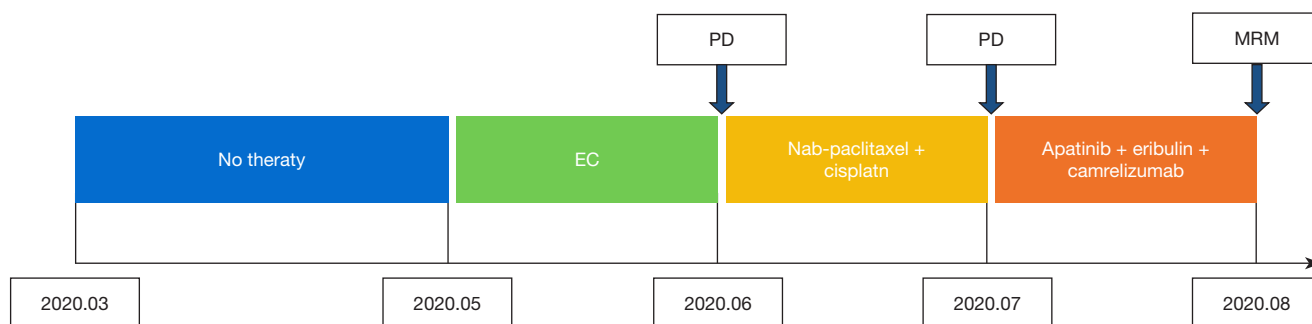


Figure 7 Timeline of the patient’s treatments. EC, epirubicin and cyclophosphamide; PD, progression disease; MRM, modified radical mastectomy.

patients have distant metastasis at initial diagnosis, but the probability of axillary lymph node metastasis is low compared with that of other types of breast cancer, and about 15–20% of cases show axillary lymph node metastasis (7,8). MPBC has a high incidence rate of lung metastasis as compared to TNBC (42% *vs.* 18%) (9). MPBC tends to have a worse outcome than TNBC, with an average overall survival (OS) less than 1 year if metastasis occurs. The OS was as low as 3.4 months in some studies (10-12), while the 5-year OS was found to be 89% for IDC, 73% for TNBC, and 54–69% for MPBC (6,13,14). For MPBC, a tumor size greater than 5 cm, lymph node metastasis, and high Ki-67 are high risk factors, which indicate poor 5-year OS and progression-free survival (PFS) (6).

The study of Tray *et al.* included the largest MPBC dataset by far (15). They confirmed that most MPBCs have a low TMB, are MS-stable, are enriched with *TP53* and *PIK3CA* mutations, and have a 65% *TP53* mutation rate and a 35% *PIK3CA* mutation rate. In a single-center study, patients with *PIK3CA*-mutated tumors had a poorer prognosis than those with *PIK3CA* wild-type tumors (16). However, when treated with liposome doxorubicin, bevacizumab, and mTOR inhibitors (everolimus), patients with *PIK3CA* mutation had a significantly higher objective response rate compared with those without the mutation (17). In MPBC, the *Tp53* mutation indicates a better clinical prognosis than that of the *Tp53* wild type (18). It is speculated that the *Tp53* mutation can predict the sensitivity

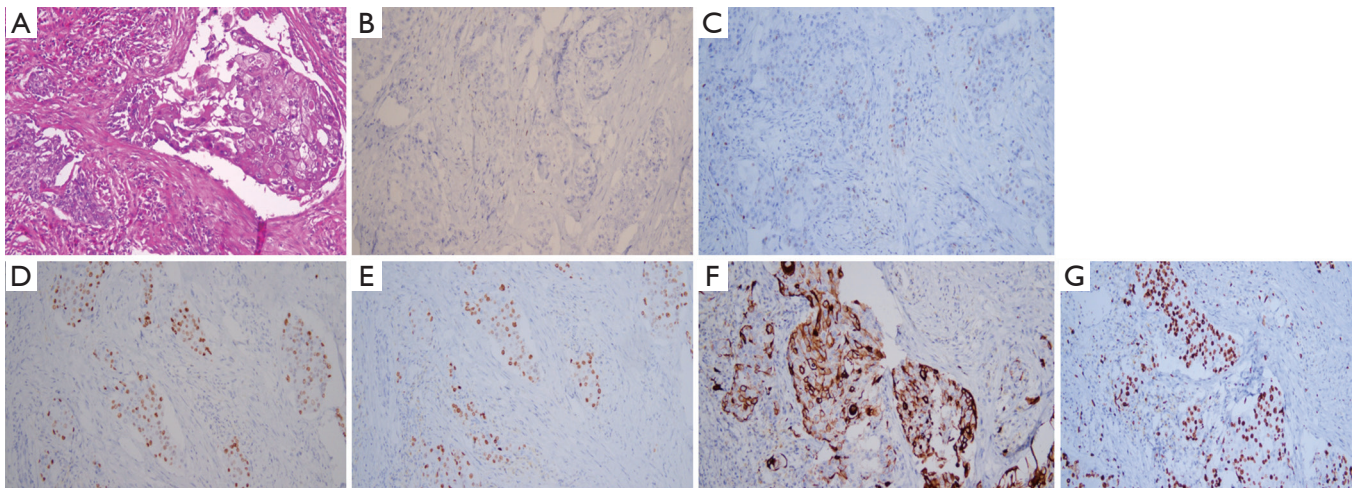


Figure 8 Pathology after radical mastectomy. (A) The nests of carcinoma showed squamous cell differentiation, with keratinization, HE $\times 200$; (B) AR and PR negative; (C) moderate ER, with a positive rate of approximately 5%; (D) P40 positive, IHC $\times 200$; (E) P63 positive, IHC $\times 200$; (F) CK5/6 positive IHC $\times 200$; (G) Ki67 positive rate: about 70%, IHC $\times 200$.

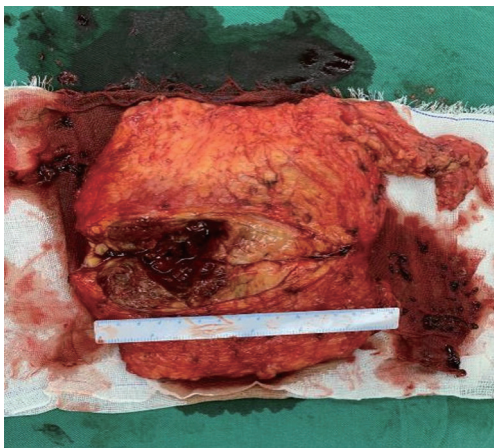


Figure 9 Postoperative gross examination: a mass of necrotic blood clots can be seen in the center of the tumor.

to antiangiogenic drug therapy (19) although these findings need to be verified by a further large-sample studies. In addition, most MPBC patients have low TMB and MS-stable indicators. The above studies are consistent with the genetic test results of this patient.

MPBC has a poor response to neoadjuvant chemotherapy, and the pathologic complete response rate is only 11%, which is lower than that of TNBC. Patients with MPBC should be included in relevant clinical trials for new neoadjuvant regimens. In the absence of clinical trials, if MPBC lesions can be removed, an operation may be

Biomarker Findings

Microsatellite status-MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

PIK3CA H1047R
PTEN T319fs*1
FGFR1 amplification
MYC amplification
KEL E239*
NSD3 (WHSC1L1) amplification
RAD21 amplification
TP53 R209fs*6
ZNF703 amplification

3 Disease relevant genes with no reportable alterations: *BRCA1*, *BRCA2*, *ERBB2*

Figure 10 FICDX test: the patient had zero TMB and are microsatellite stable and was enriched with *PIK3CA* and *PTEN* and *FGFR1* mutations. *, premature translation termination codons. TMB, tumor mutation burden.

performed directly (20). The results of the largest scale MPBC study thus far, conducted in the United States, indicated that adjuvant radiotherapy should be given to patients with pT3-4 or lymph node positive after lumpectomy (21).

Based on the above analysis, as with IDC, surgery,

Table 1 Selected trials for consideration of MPBC

Trial (Clinicaltrials.gov NCT)	Treatment setting	Therapeutic agents	MPBC or TNBC
ARTEMIS (NCT02456857)	Neoadjuvant	Liposomal Doxorubicin, Bevacizumab, and Everolimus	Selected locally advanced TNBC predicted insensitive to standard chemotherapy (progressed or did not tolerate anthracycline-based NAC), based on molecular profiling/mesenchymal gene signatures
SWOG S1418 (NCT02954874)	Adjuvant	Pembrolizumab	TNBC with residual disease following (≥ 1 cm or positive lymph nodes)
DART Trial (NCT02834013)	Metastatic	Nivolumab and Ipilimumab	MPBC
Morpheus-TNBC (NCT03424005)	Metastatic	Multiple immunotherapy-based treatment combinations	TNBC
Several immunotherapy trials (Phase I or pilot studies)	Neoadjuvant adjuvant metastatic	PD-1 or PD-L1 agents	TNBC

Little data is available regarding the efficacy of neoadjuvant regimens in MPBC. MPBC, metaplastic breast cancer; NAC, neoadjuvant chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TNBC, triple negative breast cancer.

chemotherapy and radiotherapy are still the main means of MPBC treatment, but the survival rate is relatively low, indicating that there are still no effective treatment methods. At present, several MPBC-related clinical trials are ongoing (*Table 1*). For MPBC patients, the effect of neoadjuvant therapy is poor; their conditions progress rapidly, and are usually accompanied by multiple genetic changes of poor prognosis. For these patients, surgery should be performed as soon as possible if their conditions still progress during neoadjuvant chemotherapy. Further clinical studies need to be conducted to improve treatment efficacy.

Conclusions

Primary SCC of the breast is a very rare disease with no standard treatment approach. If disease progression continues under neoadjuvant chemotherapy, timely surgery should be strongly considered.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/tbcr-20-67>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tbcr-20-67>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The patient has given the consent for the case report to be published.

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- (English Language Editor: J. Gray)

doi: 10.21037/tbcr-20-67

Cite this article as: Yao X, He H, Yuan J, Yao F. A case report of primary squamous cell carcinoma of the breast. *Transl Breast Cancer Res* 2021;2:16.