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CASE REPORT

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Targeted therapy combined with immunotherapy in patients with breast infiltrating ductal carcinoma with axillary lymph node metastasis of metaplastic SCC

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Abstract

At present, the clinicopathological features, optimal treatment patterns, and prognosis of breast metaplastic squamous cell carcinoma (SCC) are not fully understood and are still controversial. Here, we report a 56-year-old female patient with breast infiltrating ductal carcinoma with axillary lymph node metastasis of metaplastic SCC admitted to our hospital. Their homology was clarified by comparing the gene mutation results of the two lesions, that is, the axillary lymph node lesion was a metastasis of breast metaplastic SCC. We treated the patient with Poly ADP-ribose Polymerase (PARP) inhibitors in combination with immune checkpoint inhibitors (ICIs) and found that she could achieve clinical benefit from the combination regimen. We reported a successful diagnosis and treatment of this rare refractory disease and reviewed the literature on the characteristics, pathogenesis, and advances in the diagnosis and treatment of breast metaplastic SCC.

KEYWORDS
breast cancer, diagnosis, metaplastic SCC, precision medicine, treatment

BACKGROUND

Breast metaplastic carcinoma is a group of carcinomas characterized by the differentiation of neoplastic epithelium into squamous cells and/or mesenchymal components, accounting for 0.2–5% of all invasive breast cancers.[1,2] Metaplastic squamous cell carcinoma (SCC) of the breast, the most common subtype of breast metaplastic carcinoma, is a rare type of invasive special carcinoma with squamous metaplasia, which shows both stratification and keratinization and/or intercellular bridges.[3] According to the presence or absence of an adenocarcinoma components, breast SCC is divided into mixed or pure types; the latter is extremely rare and accounts for 0.046–0.28% of all breast cancer cases.[4] Because breast metaplastic SCC is rare, so far reports in the literature have mainly been seen in case reports and retrospective studies with small sample data, so the clinicopathological features, optimal treatment patterns, and prognosis of this type of tumor are not fully understood and are controversial. Our study reports a patient with breast infiltrating ductal carcinoma (IDC) with axillary lymph node metastasis of metaplastic SCC admitted to the Cancer Center, the First Hospital of Jilin University. We focus on the clinical diagnosis and treatment process of developing corresponding targeted and immunotherapy strategies for this patient based on the results of gene sequencing and ultimately helping her achieve a disease response, and review the literature on the characteristics, pathogenesis, and advances in the diagnosis and treatment of breast metaplastic SCC.

Zheng Lv and Jiuwei Cui contributed equally to this work.

CASE REPORT

The patient, a 56-year-old woman, was postmenopausal. A mass in the right breast and enlargement of the right axillary lymph

nodes were found 2 months ago. On physical examination a mass measuring about 30 × 10 mm was palpable in the upper outer quadrant of the right breast, which was firm, poorly circumscribed, with a less smooth surface, poor mobility, and no tenderness. An 80 × 50 mm enlarged lymph node was palpable in the right axilla with intact local skin, no ulceration or redness, firm, fixed, and ill-defined borders. There was no abnormality of the left breast or left axillary lymph node.

Laboratory and imaging examinations

Tumor markers (20 Oct 2020): carbohydrate antigen 153 of 62.73 U/mL (<28.00 U/mL), SCC antigen of 7.18 ng/mL (<1.50 ng/mL), cytokeratin 19 fragment of 10.62 ng/mL (<5.00 ng/mL). Breast ultrasonography (20 Oct 2020): A hypoechoic mass measuring 26.8 × 8.6 mm was observed in the upper outer quadrant of the right breast, with unclear boundary and less regular shape, in which blood flow signals were observed. A hypoechoic mass measuring 79.9 × 42.4 mm was observed in the right axilla with poorly defined borders, less regular shape, and less homogeneous internal echoes, in which blood flow signals were observed. There was no abnormality of the left breast or left axillary lymph node. Conclusion: Right breast tumor BI-RADS4 class, right axillary tumor (see Figure 1). Breast mammography (22 Oct 2020): An irregular mass shadow about 18 × 14 mm in size was observed in the upper outer quadrant of the right breast, with a high-density and star-shaped margin, in which fine pleomorphic calcifications were observed. Strip high-density shadows with blurred edges were observed in the right axilla. There was no abnormality of the left breast or left axillary lymph node. Conclusion: Needle biopsy is recommended for right breast mass, BI-RADS5 class; right axillary hyperdensity, BI-RADS1 class (see Figure 2). Positron emission tomography (PET) (23 Oct 2020): Hypermetabolic nodules in the upper outer quadrant of the right breast, considering breast cancer, and it was recommended to combine with pathological examination; hypermetabolic mass in the right axilla, considering metastatic cancer. The rest showed no significant abnormalities on PET imaging. Nasopharyngoscopy and gastroscopy showed no abnormalities.

Breast ultrasonography (26 Jan 2021): A hypoechoic mass measuring 12.7 × 7.7 mm was observed in the upper outer quadrant of the right breast at nearly 12 o'clock position, with ill-defined borders, less regular shape, calcification, and a few blood flow signals in and around it. A hypoechoic mass measuring 21.3 × 10.5 mm was observed in the right axilla with poorly defined borders, less regular shape, and less homogeneous internal echoes, in which blood flow signals were observed. There was no abnormality of the left breast or left axillary lymph node (see Figure 3).

Biopsy and immunohistochemical staining

Pathology of the right breast mass revealed IDC with moderate-grade intraductal carcinoma, grade 2. Immunohistochemical staining: ER (estrogen receptor) (+90%, strong positive), PR (progesterone receptor) (+5%, moderate-strong positive), HER-2 (human epidermal growth factor receptor 2) (4B5) (1 +), Ki-67 (+ 5%), GATA3 (+), CK7 (+), CK5/6 (−),

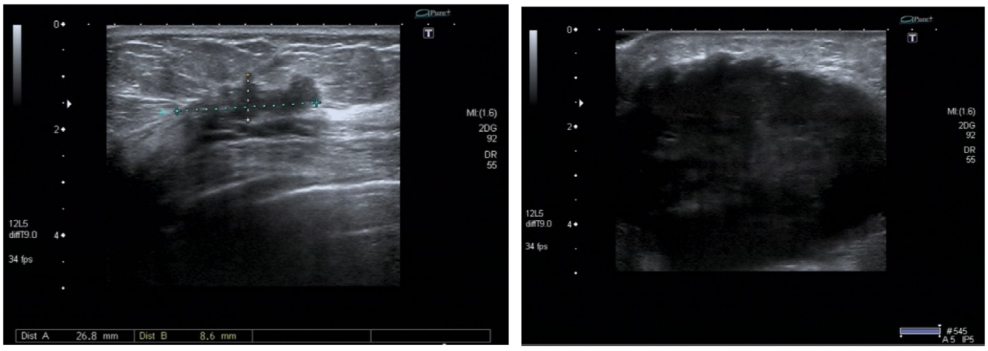

FIGURE 1 Breast ultrasonography (20 Oct 2020). Left, right breast, with a hypoechoic mass measuring 26.8 × 8.6 mm in the upper outer quadrant; right, the right axillary lymph node, with a hypoechoic mass measuring 79.9 × 42.4 mm

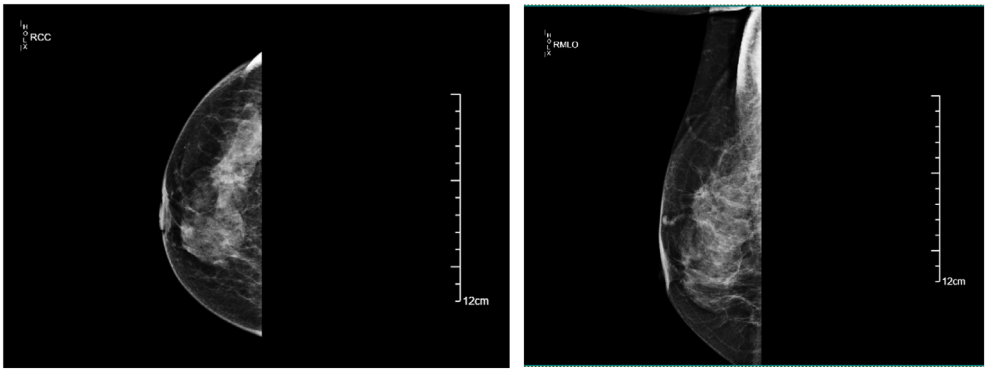

FIGURE 2 Breast mammography of the right breast (22 Oct 2020). Left, axial; right, oblique lateral position. An irregular mass shadow about 18 × 14 mm in size was observed in the upper outer quadrant of the right breast

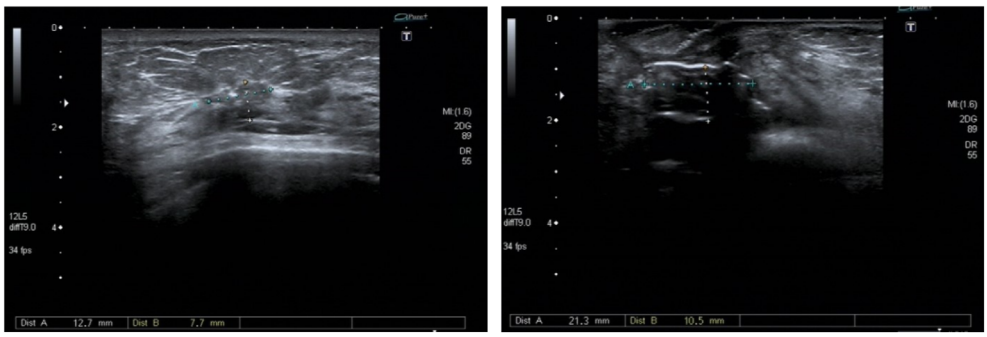

FIGURE 3 Breast ultrasonography (26 Jan 2021). Left, right breast, with a hypoechoic mass measuring 12.7 × 7.7 mm in the upper outer quadrant of the right breast at nearly 12 o'clock position; right, the right axillary lymph node, with a hypoechoic mass measuring 21.3 × 10.5 mm

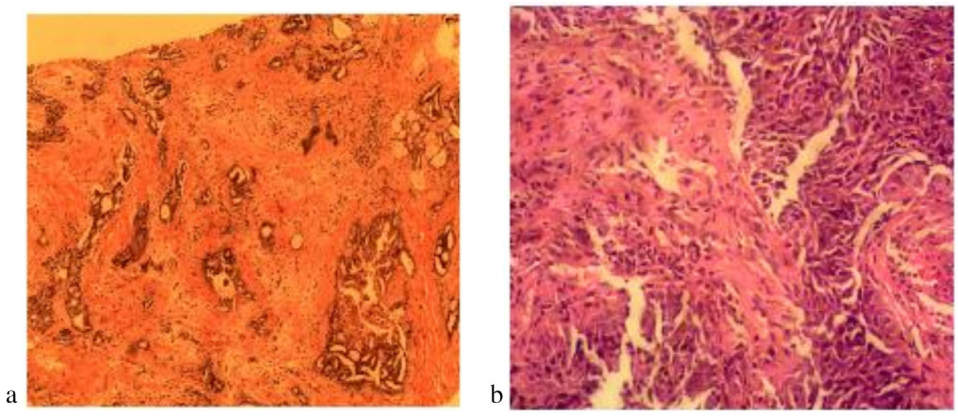

FIGURE 4 Immunohistochemical staining (HE staining, × 400): (a) right breast and (b) right axillary lymph node

E-Cadhein (+), P63 (partial +), Calponin (partial −) (see Figure 4a). Pathology of the right axillary lymph node revealed poorly differentiated carcinoma infiltration in the puncture tissue, which was supported as SCC. Immunohistochemistry staining: ER (−), PR (−), HER-2 (4B5) (0), Ki-67 (+ 80%), GATA3 (−), CK5/6 (+), CK-pan (+), E-Cadherin (+), P63 (+), P40 (+), P120 (membrane +), Vimentin (a little +), Calponin (−), AR (−), SOX10 (−), TTF-1 (−), CgA (−), Syn (−), CD68 (−), TPS and combined positive score (CPS) of PD-L1 (22C3) is 70%, 70, respectively (see Figure 4b).

Gene mutation detection

Whole exome sequencing (WES) was performed for the breast lesion and the lymph node lesion in this patient, and the details of the mutation results are listed in Table 1. The relatively significant mutation types are as follows: Breast lesion: (a) somatic variation, frequency: CASP8 c.466C>G (p.Q156E), 3.1%; NFE2L2 c.235G>A(p.E79K), 2.5%; BRCA2 c.3895G>T (p. E1299c *), 1.7%; BRCA2 c.9961C>T (p.Q3321*), 1.5%; AKT1 c.49G>A (p.EI7K), 1.2%; ELMO1 c.1561G>A, 1.0%; (b) genomic mutation: tumor mutation burden-low (TMB-L, 0.96 Muts/Mb) and HLA-A homozygote; (c) no germline mutation detected. Axillary lymph node SCC: (a) somatic variants, frequency: NFE2L2, 34.2%; CASP8, 30.6%; AKT1 p.E17K, 17.8%; RB1 p. L832Ffs*5, 14.5%; BRCA2 p.E1299*, 9.4%; BRCA2 p.Q3321*, 9.3%; (b) genomic mutation: TMB-H, 19.2Muts/Mb, microsatellite stable (MSS), and HLA-A homozygous; (c) no germline mutations were detected.

Clinical diagnosis and treatment

Based on the medical history, physical signs, and the results of PET, endoscopy, biopsy, and gene sequencing of this patient, it was considered that the axillary lymph node metastasis was breast metaplastic SCC. The patient was clinically diagnosed with "right breast IDC (cT2NxM0) with axillary lymph node metastasis of metaplastic SCC".

Our hospital carried out multidisciplinary treatment (MDT), including pathology, imaging, interventional ultrasound, breast surgery, gynecology, and medical oncology, and agreed with the current diagnosis. In terms of treatment strategies, considering the large size of the lesion and the difficulty of surgery, neoadjuvant therapy could be performed first followed by surgical treatment. The patient received two courses of chemotherapy of liposomal doxorubicin plus cyclophosphamide from October 2020 to December 2020, with the right breast lesion enlarged by 10.4% and the right axillary lymph node lesion enlarged by 40.8%. The efficacy was evaluated as progressive disease (PD). On December 20, 2020 another course chemotherapy of docetaxel plus cisplatin was given, with the right breast lesion reduced by 6.7% and the right axillary lymph node lesion enlarged by 65.3%. The patient experienced disease progression again. Considering that the axillary lesion continued to enlarge,

TABLE 1 Details of mutation results in the breast lesion and the lymph node lesion

Gene	Base change	Amino acid change	Functional area	Mutant frequency/copy number	
				Right breast lesion	Right axillary lymph node lesion
NFE2L2	c.235G>A	p.E79K	EX2	2.50%	34.20%
CASP8	c.466C>G	p.Q156E	EX2	3.10%	30.60%
LRP1B	c.1996G>A	p.E666K	EX13	1.10%	18.90%
AKT1	c.49G>A	p.E17K	EX3	1.20%	17.80%
ROS1	c.4191G>T	p.W1397C	EX26	1.70%	16.60%
ROS1	c.1319C>T	p.S440F	EX12	1.60%	16.40%
HRAS	c.468C>G	p.F156L	EX5	1.70%	16.40%
CARD11	c.3385G>C	p.E1129Q	EX25	2.30%	15.90%
ZFHX3	c.9482C>T	p.S3161F	EX10	1.70%	15.80%
IGF1R	c.2971G>C	p.E991Q	EX16	1.10%	15.10%
RB1	c.2496_2497delAG	p.L832Ffs*5	EX24	ND	14.50%
BTK	c.544C>T	p.R182W	EX7	ND	13.70%
ERBB2	c.3616C>T	p.Q1206*	EX27	1.40%	13.60%
ELF3	c.1109G>C	p.R370P	EX9	1.80%	11.30%
BRCA2	c.3417_3419delGAGinsAAT	p.S1140I	EX11	ND	10.30%
BRCA2	c.3376G>C	p.E1126Q	EX11	1.30%	10.20%
BRCA2	c.3895G>T	p.E1299*	EX11	1.70%	9.40%
BRCA2	c.9961C>T	p.Q3321*	EX27	1.50%	9.30%
SCUBE2	c.1891C>T	p.H631Y	EX16	ND	8.90%
BRCA2	c.3444G>C	p.Q1148H	EX11	1.40%	8.40%
AXL	c.398T>C	p.V133A	EX3	ND	5.90%
NTRK2	c.2329G>A	p.E777K	EX20	ND	1.10%
BRD4	c.1057C>A	p.Q353K	EX6	ND	1.00%
ELMO1	c.1561G>A	p.E521K	EX17	1.00%	ND

which affected the quality of life of the patient, subsequently she underwent a radiotherapy (RT) of the axillary lymph node lesion. Fortunately, the right breast lesion was enlarged by 2.4% and the right axillary lymph node lesion was reduced by 60.1%, with the efficacy evaluation of partial response (PR). Based on the physical condition of the patient, she was considered not suitable for surgery and chemotherapy was continued. From February to April 2021 the patient received two courses chemotherapy of capecitabine plus vinorelbine. The right breast lesion was enlarged by 5.6% and the right axillary lymph node lesion was reduced by 3.2%, which was assessed as stable disease (SD).

Considering that the tumor lesion remained large after chemotherapy and the patient was temporarily inoperable, it was recommended that the patient should take a biopsy again for gene sequencing to identify the type of gene mutation. Based on the results, we administered Poly ADP-ribose Polymerase (PARP) inhibitors, fluzoparib capsules, in combination with the immune checkpoint inhibitor camrelizumab (anti-PD-1 monoclonal antibody) in July 2021. After two courses of treatment, the right breast lesion remained stable and its size numerically decreased (13.1 × 7.4 mm) compared with before treatment, while the axillary lymph node lesion was significantly reduced by 25.6% (31.6 × 16.6 mm), with an overall efficacy evaluation of SD. After four courses, the overall response remained SD. Although PR was not achieved, the size of axillary SCC lesions was significantly reduced and breast lesions remained stable, suggesting that the patient could benefit from the combination regimen of immunotherapy and targeted therapy. It is recommended to continue treatment for several courses, and surgical treatment may be considered when the lesion is appropriate. By January 26, 2022, the patient had undergone 12 courses of immunotherapy combined with targeted therapy and the breast color ultrasound showed that the size of the right breast lesion was 12.7 × 7.7 mm, which is further reduced compared to before. Surprisingly, the size of the axillary lymph node lesion was 21.3 × 10.5 mm, which was reduced by 49.85%. Overall, this patient was evaluated as having a PR for treatment efficacy. After multidisciplinary consultation, the patient was advised that surgical treatment was currently feasible. On February 17, 2022, the patient underwent surgical treatment at the Department of Breast Surgery,

Changchun Cancer Hospital, and the tumor lesion of the breast and axillary lymph node lesion were removed. Postoperative pathology was consistent with the previous diagnosis of IDC of the breast and SCC of the axillary lymph nodes. Close attention will need to be paid to changes in the patient's condition, appropriate postoperative adjuvant therapy, and active postoperative prognosis follow-up.

DISCUSSION

Clinical and pathological characteristics

Breast metaplastic SCC is usually a poorly differentiated, high histological grade tumor,[5–7] and the incidence of such diseases is extremely low, with fewer than 100 cases reported in the literature (PubMed/Medline). In our case, the patient's age of onset was 56 years and the axillary metastatic lesion was 79.9 × 42.4 mm. Biopsy pathology showed that the axillary metastatic lesion was a triple-negative, poorly differentiated SCC with high histological grade and rapid disease progression. These signs are consistent with previously reported clinical manifestations and pathological features. In addition, these tumors are often accompanied by foci of necrosis, hemorrhage, cyst formation, and inflammatory changes.[8] In this case, the local skin of the axillary SCC lesion was initially intact, and the tumor was not accompanied by a liquefaction, but as the disease progressed local skin invasion gradually occurred. These features are consistent with the clinical manifestations and pathological features of metaplastic SCC.

Pathogenesis and gene mutation characteristics

The pathogenesis of metaplastic carcinoma of the breast is not clear, and one possible mechanism is the epithelial to mesenchymal transition (EMT) theory, e.g. the expression of Snail, Twist, TGF-β, and Goosecoid, which are core markers of EMT, is found to be upregulated in metaplastic carcinoma.[9] Gene profiling of metaplastic carcinoma showed features of EMT. Unlike nonspecific types of invasive breast cancer, genes related to cell motility, migration, and extracellular matrix production are highly expressed in metaplastic cancer, while genes related to cell junctions are poorly expressed. Animal model studies have found that endogenous β-catenin mutation, a signaling molecule in the WNT (Wingless-Type MMTV Integration Site Family) signaling pathway, can lead to squamous metaplasia of breast epithelium,[10] and β-catenin is abnormally expressed in most metaplastic cancers,[11] while the activation of the WNT pathway plays an important role in EMT. Another possible mechanism is the myoepithelial cell theory, which can highly express mammary myoepithelial genes such as p-cadherin, p63, and calponin.[12]

Notably, the patient in this case also had an AKT1 gene mutation in the axillary lesion, which was not seen in the primary breast lesion. Querying the clinvar database revealed that the AKT1 c.49G>A (p. Glu17Lys) mutation was associated with squamous differentiation variants, lung SCC, and head and neck SCC, suggesting that the AKT1 gene may be associated with the squamous metaplasia process of the axillary lymph node metastasis of this patient. Previous researchers have detected an abnormal P13K/AKT pathway in 47% of metaplastic carcinomas, suggesting that this pathway plays an important role in the pathogenesis of metaplastic carcinomas.[13] This is consistent with the results of AKT1 gene mutations detected in metaplastic SCC in our study, further suggesting that the axillary lymph node lesion may be mediated by the P13K/AKT pathway during metaplasia. In addition, it has also been reported that the occurrence of breast SCC may be related to the cancer stem cell (CSC) theory, e.g. increased expression of cancer stem cell markers $CD44^{+}/CD24^{-}$, $CD29^{+}CD24^{-}$, and ALDH1 was found in breast SCC,[14] but no relevant evidence was found in this case.

In this study, we identified the simultaneous occurrence of breast IDC and metaplastic SCC of the axillary lymph node, but it was difficult to identify the primary site of metastatic carcinoma of the axillary lymph nodes initially based on pathological and immunohistochemical findings alone. The results of WES showed that the mutant genes of the two lesions were basically similar, with somatic mutations of BRCA2 gene, while no germline mutations were detected, suggesting that the two were highly likely to have the same origin, and further analysis confirmed the diagnosis of metaplastic SCC. In addition, we mapped the clonal evolution process based on the primary tumor and metastasis gene cloning data, simulating the change process of gene mutation from primary lesion to metastasis (see Figure 5). Given that the BRAC genes and AKT1 genes we focused on belong to the same level of genes in the clonal analysis, and that NFE2L2 and CASP8 also belong to the same level of master clones, we therefore delineated the clonal evolution process in the Figure 5. It can be seen that NFE2L2, CASP8, AKT1, and BRCA2 are clones that gradually increase during metaplastic metastasis, while the cloning of the ELMO1 gene gradually disappeared and RB1 is an emerging clone in the metastatic lesion. In the past, most cases reported primary metaplastic SCC of the breast with lymph node SCC or non-SCC metastasis, while in this case the primary lesion of the breast showed a common type of IDC, but the axillary lymph node showed a change of metaplastic SCC, which is a rare situation that has never been reported in previous studies.

Characteristics of immunohistochemical staining

Most breast SCC expresses broad-spectrum and high molecular weight cytokeratin (CK), overexpression of p63, high positive rates of EGFR, and almost negative expression of ER/PR and HER-2.[15,16] In this case, in the axillary lymph node metaplastic SCC lesion, the expressions of CK5/6, CK7, CK-pan, p63 and E-cadheren, which are markers

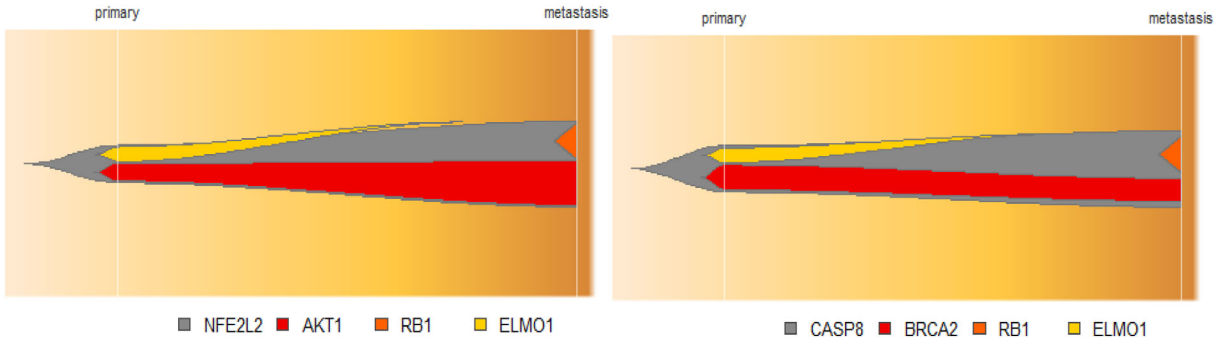

FIGURE 5 Clonal evolution process from primary tumor to metastasis

associated with squamous cell carcinoma, were positive, while the common markers of breast cancer, ER/PR and HER-2, were negative. The breast cancer lesion was IDC type with positive expression of hormone receptors and HER-2. Interestingly, some of the markers associated with SCC, E-Cadhein, CK7, and p63 (partial +), were positively expressed in the breast cancer lesion, suggesting that the origin of the breast lesion and the axillary metaplastic SCC might be the same.

Diagnosis and differential diagnosis

Definite diagnosis mainly depends on pathological biopsy (such as needle biopsy and aspiration biopsy cytology), combined with medical history and accessory examination. It is relatively easy to diagnose breast cancer as primary when adenocarcinoma cells are present together with SCC. In breast cancer cases with only a pure SCC component, it is important to distinguish this from metastatic breast cancer at other sites and especially SCC of the skin primary at the breast site. Gupta et al.[5] proposed four principles for the diagnosis of primary SCC of the breast: (i) more than 90% of the tumors (components) are SCC; (ii) tumor-like ductal or stromal components are seen in the specimens; (iii) the tumors do not originate from the breast skin surface, nipple skin, or skin appendages; and (iv) the metastasis of SCC at nonbreast sites is excluded.

Unlike previous cases, the primary breast lesion in this case was a common type of IDC, while the pathological and immunohistochemical results of the axillary lymph node lesion suggested SCC, making it more difficult to confirm the diagnosis, especially to differentiate it from SCC at the axillary skin and metastasis of SCC at other sites. A previous study assisted assessment of the origin of metaplastic carcinoma of the breast by WES. WES sequencing of metaplastic carcinoma tissue samples and adjacent conventional invasive ductal carcinoma tissue samples from eight patients was performed to evaluate single nucleotide variants, indels, copy number variants, and subclonal structure in the two tissues, respectively, and it was found that in each case the two tumor components had almost the same somatic mutation profile and were presumably of the same origin. In this case, the diagnosis of tumors at other sites was first excluded by systematic PET examination, head MRI, nasopharyngoscopy, and gastroscopy. The patient then underwent a WES, which showed that there were multiple common gene mutation types in both the breast lesion and the axillary metaplastic SCC lesion (see Table 1), confirming the possibility of the same origin for both.

Treatment strategies and prognosis

At present, the treatment of breast SCC, like other common types of breast cancer, is based on radical mastectomy, which can be combined with adjuvant or neoadjuvant RT, chemotherapy, and other therapies. Breast SCC is resistant to chemotherapy regimens routinely used for breast IDC (including anthracyclines, methotrexate, 5-fluorouracil, and cyclophosphamide).[17–19] In our case report, the patient received multiple regimens of chemotherapy after initial diagnosis, but the axillary SCC lesion showed significant drug resistance. However, there are also individual case reports[20,21] suggesting that cisplatin-based chemotherapy is able to achieve long-term disease control, but these results need to be further validated. Currently, evidence supporting the use of RT for SCC of the breast is lacking. Although SCC at other sites is often sensitive to RT, the effectiveness of RT in this rare disease has been questioned.[18,22] Primary SCC of the breast is usually a hormone receptor-negative tumor,[16] implying that hormone-based endocrine therapy may not be effective for this tumor. In this case, the axillary lymph node SCC lesion was negative for ER, PR, and HER-2, suggesting that endocrine therapy and trastuzumab therapy were ineffective.

In recent years, high-throughput sequencing technology has developed rapidly and can find specific targets by extensive sequencing of the whole genome of individual patients. Our reported patient received whole genome sequencing, which showed the presence of a BRCA2 mutation. BRCA2 is a tumor suppressor gene that plays a role in the repair process of DNA double-strand damage, and its mutation can lead to homologous recombination deficiency (HRD). PARP inhibition can lead to synthetic lethality in cancer cells with those mutations, which are combinatorial effects

caused by defects in multiple pathways.[23] Currently, the PARP inhibitors olaparib and talazoparib are recommended by the United States. Food and Drug Administration (FDA) and National Comprehensive Cancer Network (NCCN) guidelines for patients with germline BRCA1/2 mutations, HER2-negative, metastatic breast cancer. Recently, in the TBCRC048 trial,[24] olaparib achieved an objective response rate of 50% in patients with somatic breast cancer susceptibility gene (BRCA) gene mutations, suggesting that in addition to germline BRCA mutations, breast cancer patients with somatic BRCA mutations are also a potential benefit population for PARP inhibitors. However, this requires further studies to confirm, and there are no efficacy data for these drugs in patients with metaplastic squamous cell carcinoma. In addition to novel targeted therapies, immune checkpoint inhibitors (ICIs) have been continuously explored and tried in the treatment of a variety of tumors in recent years and made a breakthrough. Our report showed that the axillary metaplastic SCC lesion of this patient had higher TMB-H. The TPS and CPS of programmed death ligand 1 (PD-L1) (22C3) are 70% and 70, respectively, suggesting that the patient had higher PD-L1 expression levels in tumor cells and the tumor microenvironment, and may benefit from ICIs. In addition, the latest reports showed that PARP inhibitors may exert pro-immune efficacy through multiple mechanisms and have a synergistic effect with ICIs.[25–28] These synergistic effects include: First, long-term PARP inhibition leads to sustained DNA damage, genomic instability, and epigenetic changes in tumor cells, leading to neoantigen production and increased tumor immunogenicity.[27] Second, targeting DNA damage responses can enhance adjuvanticity by activating cytosolic immunity and immunogenic cell death.[28] Furthermore, PARP inhibitor-induced DNA double-strand breaks produce double-stranded DNA fragments in tumor cells, which activate stimulators or interferon genes (STING) and produce a type I interferon response through cyclic GMP-AMP lyase (cGAS) binding, thereby upregulating chemokines CCL5 and CXCL10, leading to T cell recruitment followed by increased tumor lymphocytes infiltration to enhance immunotherapeutic effects.[25,26,29] Finally, PARP inhibition can also mediate potential synergy with ICIs through interferon-independent mechanisms, such as upregulation of immune blocking targets (e.g., PD-L1).[26] Therefore, many different clinical studies are currently validating the efficacy of ICIs in combination with PAPR inhibitors.[29–32]

The immunohistochemical and WES results showed that the patient had BRCA2 mutation, high TMB, and high expression of PD-L1 protein in the axillary lymph node lesion, thus it was thought that this patient may benefit from PARP inhibitors in combination with ICIs. We therefore treated the patient with fluzoparib capsules in combination with camrelizumab. After 12 courses of treatment, metaplastic SCC of the primary breast lesion and axillary lymph nodes decreased significantly, and the overall efficacy evaluation achieved PR. Subsequently, the patient underwent surgery and complete resection of the two lesions, and postoperative pathology confirmed that the previous diagnosis was correct. Close postoperative follow-up was recommended. During the whole course of PARP inhibitor combined with ICIs, the patient developed tolerable drug-related adverse events, including asthenia grade 1, hypothyroidism (TSH:17.894 [0.35–4.94] uIU/ml; FT3 < 1.64 [2.43–6.01] pmol/L; thyroglobulin antibody 12.79 [0–4.11] IU/mL; thyroid peroxidase antibody >1000 [0–5.61] IU/mL), and diabetes grade 2 (fasting blood glucose 11.56 mmol/L), which all improved with symptomatic management. Overall, the safety of the combination was generally tolerable. At present, in the absence of sufficient and accurate data, the most suitable treatment options for this rare disease, metaplastic SCC of the breast, cannot be determined. Management decisions need to be individualized, focusing on a combination of multidisciplinary treatments to improve patient survival.

Due to its rarity, the optimal treatment and prognosis of patients with metaplastic breast SCC remain controversial. Overall, breast SCC has a poor prognosis and most authors believe that it is characterized by local recurrence, progressive invasion, and easier distant metastasis,[18,33–35] with a 5-year overall survival rate of 51% ± 13%.[36] Therefore, special attention should be paid to the follow-up of patients after treatment and tumor recurrence should be closely monitored. In the future, close clinical follow-up, larger and prospective data collection, and further multidisciplinary multicenter studies are recommended to investigate the demographic, pathological, imaging, and molecular characteristics, and optimal treatment options and prognosis of metaplastic breast SCC, and ultimately optimize its clinical care.

SUMMARY

This study reported a case of primary breast IDC with metastatic metaplastic SCC of the axillary lymph node. Combined with the results of genetic testing and multidisciplinary consultation of the patient in this case, we confirmed the clinical diagnosis and the patient eventually achieved clinical benefit after received PARP inhibitors combined with ICI treatment. Our successful case provides a new strategy and direction for the diagnostic process and treatment options of such rare and refractory diseases, suggesting that precision medicine will bring more clinical benefits to breast metaplastic SCC patients.

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CONFLICT OF INTEREST STATEMENT

No potential conflicts of interest are disclosed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study recorded and analyzed the clinical data of a patient who underwent routine diagnosis and treatment in the First Hospital of Jilin University, so it did not involve ethical approval.

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