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

Rilan Bai | Lin Jia | Yangyang Gao | Xu Sun | Naifei Chen | Zheng Lv | Jiuwei Cui

Cancer Center, The First Hospital of Jilin University, Changchun, China

Correspondence
Zheng Lv and Jiuwei Cui, Cancer Center, the First Hospital of Jilin University, Changchun 130021, China.
Email: lvz@jlu.edu.cn and cuijw@jlu.edu.cn

Funding information
Jilin Province Biotherapeutic Science and Technology Innovation Center Project, Grant/Award Number: 20200602032ZP; Jilin Provincial Department of Finance Project, Grant/Award Number: JLSWSRCZX2020-0023; Jilin Provincial Science and Technology Department, Grant/Award Number: 20190303146SF

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 component, 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.

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 circumscibed, 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, 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](image1.jpg)

**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](image2.jpg)

**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
E-Cadherin (+), 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).

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

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. E1299*) , 1.7%; BRCA2 c.9961C>T (p.Q3321*), 1.5%; AKT1 c.49G>A (p.E17K), 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,
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 administrated 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.

| Gene       | Base change     | Amino acid change | Functional area | 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%                        |
| IGFI1      | c.2971G>C       | p.E991Q           | EX16           | 1.10%              | 15.10%                        |
| RB1        | c.2496_2497delAG| p.L832Flk*s      | 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.V333A           | EX3            | ND                 | 5.90%                         |
| NTRK2      | c.2329G>A       | p.E777K           | EX20           | ND                 | 1.10%                         |
| BRD4       | c.1057C>A       | p.Q355K           | EX6            | ND                 | 1.00%                         |
| ELMO1      | c.1561G>A       | p.E521K           | EX17           | 1.00%              | ND                            |
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, 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. 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. 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, and β-catenin is abnormally expressed in most metaplastic cancers, 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.

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 PI3K/AKT pathway in 47% of metaplastic carcinomas, suggesting that this pathway plays an important role in the pathogenesis of metaplastic carcinomas. This is consistent with the results of AKT1 gene mutations detected in metaplastic SCC in our study.

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 metaplastic 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. In this case, in the axillary lymph node metaplastic SCC lesion, the expressions of CK5/6, CK7, CK-pan, p63 and E-cadherin, which are markers...
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. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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 approved the diagnosis of primary SCC at other sites and especially SCC of the skin primary at the breast site. Gupta et al. 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.
caused by defects in multiple pathways. 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, 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 metastatic 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. 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. Second, targeting DNA damage responses can enhance adjuvanticity by activating cytosolic immunity and immunogenic cell death. 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. 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). Therefore, many different clinical studies are currently validating the efficacy of ICIs in combination with PAPR inhibitors. 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, metastatic 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, with a 5-year overall survival rate of 51% ± 13%. 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.

**GRANT SUPPORT**

This work was supported by grants from the Jilin Provincial Science and Technology Department (20190303146SF), the Jilin Provincial Department of Finance Project (JLSWSRCZX2020-0023), and the Jilin Province Biotherapeutic Science and Technology Innovation Center Project (20200602032ZP).

**CONFLICT OF INTEREST STATEMENT**

No potential conflicts of interest are disclosed.
ETIQUETTE 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.

ORCID

Jiawei Cui https://orcid.org/0000-0001-6496-7550

REFERENCES

1. Budzik MP, Patera J, Sobol M, et al. Clinicopathological characteristics of metaplastic breast cancer – analysis of the basic immunohistochemical profile and comparison with other invasive breast cancer types. Breast. 2019;43:135–41.

2. El Zein D, Hughes M, Kumar S, et al. Metaplastic carcinoma of the breast is more aggressive than triple-negative breast cancer: a study from a single institution and review of literature. Clin Breast Cancer. 2017;17(5):382–91. https://doi.org/10.1016/j.cbc.2017.04.009

3. Sakamoto G, Inaji H, Akiyama F, et al. General rules for clinical and pathological recording of breast cancer 2005. Breast Cancer. 2005;12 (Suppl S1–27).

4. Dalla Palma P, Parenti A. Squamous breast cancer: report of two cases and review of the literature. Appl Pathol. 1983;1(1):14–24.

5. Gupta C, Malani AK, Weigand RT, Rangineni G. Pure primary squamous cell carcinoma of the breast: a rare presentation and clinicopathologic comparison with usual ductal carcinoma of the breast. Pathol Res Pract. 2006;202(6):465–9. https://doi.org/10.1016/j.prp.2006.01.006

6. Siegelmann-Danieli N, Murphy TJ, Meschter SC, Stein ME, Prichard J. Primary pure squamous cell carcinoma of the breast. Clin Breast Cancer. 2005;5(3):270–2. https://doi.org/10.3816/CBC.2005. n.030

7. Kato K, Yamamoto S, Hato S, et al. Breast-conserving surgery for squamous cell carcinoma of the breast-report of a case. J Jpn Pract Surg Soc. 2009;58(2):338–40.

8. Murialdo R, Boy D, Musizzano Y, et al. Squamous cell carcinoma of the breast-report of a case. Jpn J Cancer Res. 2006;97(10):1577–1582.

9. Taube JH, Herschkowitz JI, Komurov K, Zhou AY, Gupta S, Yang J, et al. Core epithelial-to-mesenchymal transition interactome gene-expression signature is associated with claudin-low and metaplastic breast cancer subtypes. Proc Natl Acad Sci USA. 2010;107(35):15449–54. https://doi.org/10.1073/pnas.1004900107

10. Miyoshi K, Shillingford JM, Provost FL. Activation of β-catenin signaling in differentiated mammary secretory cells induces transdifferentiation into epidermis and squamous metaplasias. Proc Natl Acad Sci USA. 2002;99(1):219–24.

11. Hayes MJ, Thomas D, Emmons A, Giordano TJ, Kleer CG. Genetic changes of Wnt pathway genes are common events in metaplastic carcinomas of the breast. Clin Cancer Res. 2008;14(13):4038–44.

12. Tse GM, Tan PH, Putti TC, Lui PCW, Chaiwun B, Law BKB. Metaplastic carcinoma of the breast: a clinicopathological review. J Clin Pathol. 2006;59(10):1079–83. https://doi.org/10.1136/jcp.2005.030536

13. Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee JS, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. Cancer Res. 2009;69(10):4116–24. https://doi.org/10.1158/0008-5472.Can-08-3441

14. Zhang Y, Toy KA, Kleer CG. Metaplastic breast carcinomas are enriched in markers of tumor-initiating cells and epithelial to mesenchymal transition. Mod Pathol. 2012;25(2):178–84. https://doi.org/10.1038/modpathol.2011.167

15. Van Hoeven KH, Drudis T, Cranor ML, et al. Low-grade adenosquamous carcinoma of the breast. A clinicopathologic study of 32 cases with ultrastructural analysis. Am J Surg Pathol. 1993;17(3):248–58. https://doi.org/10.1002/1097-0047.19930300-00005

16. Shui R, Li A, Yang F, Zhou X, Yu B, Xu X, et al. Primary squamous cell carcinoma of the breast with unusual basal-HER2 phenotype. Int J Clin Exp Pathol. 2014;7(8):5203–9.

17. Rostock RA, Bauer TW, Eggleton JC. Primary squamous carcinoma of the breast: a review. Breast Dis. 1984;10(3):27–31.

18. Hennessy BT, Krishnamurthy S, Giordano S, Buchholz TA, Kau SW, Duan Z, et al. Squamous cell carcinoma of the breast. J Clin Oncol. 2005;23(31):7827–35. https://doi.org/10.1200/jco.2004.00.9589

19. Zhang X, Zhang R, Zang F, Zhao L, Yuan Z, Wang P. Clinical features and treatment of squamous cell carcinoma of the breast. Oncol Targets Ther. 2016;9:3181–5. https://doi.org/10.2147/ott.2016.95128

20. Bhatt L, Fernando I. Primary squamous cell carcinoma of the breast: achieving long-term control with cisplatin-based chemotherapy. Clin Breast Cancer. 2009;9(3):187–8. https://doi.org/10.3816/CBC.2009. n.031

21. Dejager D, Redlich PN, Dayer AM, Davis HL, Komorowski RA. Primary squamous cell carcinoma of the breast: sensitivity to cisplatin-based chemotherapy. J Surg Oncol. 1995;59(3):199–203. https://doi.org/10.1002/jso.2930590313

22. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. IV. Squamous cell carcinoma of ductal origin. Cancer. 1990;65(2):272–6. https://doi.org/10.1002/1097-0142(19900115)65:2<272::aid-cncr280650215>3.0.co;2-6

23. De Vos M, Schreiber V, Dantzer F. The diverse roles and clinical relevance of PARPs in DNA damage repair: current state of the art. Biochem Pharmacol. 2012;84(2):137–46. https://doi.org/10.1016/j.bcp.2012.03.018

24. Tung NM, Robson ME, Ventz S, Santa-Maria CA, Nanda R, Marcom PK, et al. TBCRC 048: phase II study of Olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. J Clin Oncol. 2020;38(36):4274–82. https://doi.org/10.1200.jco.2020.02151

25. Pantelidou C, Sonzogni O, De Oliveria TM, et al. PARP inhibitor efficacy depends on CDB+ T-cell recruitment via intratumoral STING pathway activation in BRCA-deficient models of triple-negative breast cancer. Cancer Discov. 2019;9(6):722–37. https://doi.org/10.1158/2159-8290.Cd-18-1218

26. Sen T, Rodriguez BL, Chen L, Corte CMD, Morikawa N, Fujimoto J, et al. Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. Cancer Discov. 2019;9(5):646–61. https://doi.org/10.1158/2159-8290.Cd-18-1020

27. Maio M, Covre A, Fratta E, di Giacomo AM, Taverna P, Natali PG, et al. Molecular pathways: at the crossroads of cancer epigenetics and immunotherapy. Clin Cancer Res. 2015;21(18):4040–7. https://doi.org/10.1158/1078-0432.Ccr-14-2914

28. Chabanon RM, Rouanne M, Lord CJ, Soria JC, Pasero P, Postel-Vinay S. Targeting the DNA damage response in immuno-oncology: developments and opportunities. Nat Rev Cancer. 2021;21:701–17. https://doi.org/10.1038/s41568-021-00386-6

29. Vikas P, Borcherdng N, Chennamadhavuni A, Garje R. Therapeutic potential of combining PARP inhibitor and immunotherapy in solid tumors. Front Oncol. 2020;10:570. https://doi.org/10.3389/fonc.2020. 00570

30. Vikas P, Borcherdng N, Zhang W. The clinical promise of immunotherapy in triple-negative breast cancer. Cancer Manage Res. 2018;10:6823–33. https://doi.org/10.2147/cmar.2018.64502

31. Vinayak S, Tolaney SM, Schwartzberg L, Mita M, McCann G, Vinayak S. Targeting the DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. Cancer Discov. 2019;9(5):646–61. https://doi.org/10.1158/2159-8290.Cd-18-1020

32. Domchek SM, Postel-Vinay S, Im SA, Park YH, Delord JP, Italiano A, et al. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. Lancet Oncol. 2020;21(9):1155–64. https://doi.org/10.1016/s1470-2045(20)30024-7
33. Moisidis E, Ahmed S, Carmalt H, Gillett D. Primary squamous cell carcinoma of the breast. ANZ J Surg. 2002;72(1):65–7. https://doi.org/10.1046/j.1445-2197.2002.02298.x
34. Behranwala KA, Nasiri N, Abdullah N, Trott PA, Gui GPH. Squamous cell carcinoma of the breast: clinico-pathologic implications and outcome. Eur J Surg Oncol. 2003;29(4):386–9. https://doi.org/10.1053/ejso.2002.1422
35. Cardoso F, Leal C, Meira A, Azevedo R, Maurício MJ, Leal da Silva JM, et al. Squamous cell carcinoma of the breast. Breast. 2000;9(6):315–9. https://doi.org/10.1054/brst.1999.0145
36. Nayak A, Wu Y, Gilcrease MZ. Primary squamous cell carcinoma of the breast: predictors of locoregional recurrence and overall survival. Am J Surg Pathol. 2013;37(6):867–73. https://doi.org/10.1097/PAS.0b013e3182877569

How to cite this article: Bai R, Jia L, Gao Y, Sun X, Chen N, Lv Z, et al. Targeted therapy combined with immunotherapy in patients with breast infiltrating ductal carcinoma with axillary lymph node metastasis of metaplastic SCC. Thorac Cancer. 2022;13(19):2799–807. https://doi.org/10.1111/1759-7714.14602