Signet Ring Cell Carcinoma of the Breast: An Aggressive Tumor

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Background	A 66-year-old female was found to have bilateral breast cancer. After undergoing bilateral mastectomy with left axillary lymph node dissection and right sentinel lymph node biopsy, signet ring cells were found on final left breast pathology, with metastasis to the contralateral axillary lymph nodes. We present a case report of pure signet ring cell carcinoma (SRCC) of the breast with discussion of important immunohistochemical features, differential diagnosis, and prognosis.
Summary	A 66-year-old female with a rapidly enlarging left breast mass was diagnosed by core needle biopsies with inflammatory invasive ductal carcinoma with lymph node metastasis. Magnetic resonance imaging (MRI) also showed a nonpalpable right breast mass. Positron-emission tomography–computed tomography (PET-CT) was negative for distant metastasis. Despite initial tumor shrinkage with AC-Taxol, she again demonstrated rapid growth before completing 12 cycles. After left modified radical mastectomy and right simple mastectomy with right axillary sentinel lymph node biopsy, pathology revealed left breast signet ring cell carcinoma with bilateral axillary lymph node metastases. The right breast revealed a separate, well differentiated invasive ductal carcinoma. Postoperative PET-CT showed stage IV disease, including ipsilateral sub-pectoral, mediastinal, and para-aortic lymphadenopathy. The patient had rapidly progressive local recurrence of the left breast in just a few weeks postoperatively.
Conclusion	SRCC of the breast is a rare but aggressive tumor with a poor prognosis due to high incidence of lymph node involvement. When signet ring cells are found in a breast specimen, specific immunohistochemical features should be evaluated to determine whether it is a primary lesion or metastatic, usually of gastrointestinal origin. We propose a call for increased reporting of cases of SRCC of the breast to more clearly define tumor characteristics and behavior in order to guide effective treatment strategies for optimal patient outcomes.

Keywords	Signet ring cell carcinoma, breast cancer, surgical oncology

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The authors have no conflicts of interest to disclose.

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Case Description

A 66-year-old gravida one para one woman with a family history of breast and ovarian cancer (a sister with breast cancer at age 54, a paternal aunt with breast cancer at age 40 and ovarian cancer at age 45, and a maternal aunt with breast cancer in her 50s) was found to have bilateral breast masses on routine screening mammogram. Bilateral breast and axillary ultrasound examinations also showed abnormal appearing left axillary lymph nodes.

Ultrasound-guided biopsy of the left breast revealed poorly differentiated mammary carcinoma with foci suspicious for lymphovascular invasion, with associated ductal carcinoma in situ (DCIS) intermediate to high-grade with central necrosis, ER/PR/HER2/neu-negative. Ultrasound-guided biopsy of one of the abnormal left axillary lymph nodes with marker clip placement revealed metastatic ductal carcinoma of the breast.

Ultrasound-guided biopsy of the right breast demonstrated moderately differentiated invasive ductal carcinoma with associated DCIS, intermediate nuclear grade, ER/PR-positive, HER2/neu-negative. Genetic testing revealed no deleterious mutations in *BRCA1* or *BRCA2*.

Evaluation by an oncologic surgeon revealed a now palpable left breast mass, with overlying *peau d'orange*; the right breast mass was nonpalpable. At short-term follow-up, there was rapid growth and worsening of her left breast malignancy and newly palpable left axillary lymphadenopathy.

The patient was seen by medical oncology for neoadjuvant chemotherapy. A positron-emission tomography–computed tomography (PET-CT) scan showed neoplastic disease limited to the left breast, and nowhere else in the body. A Mediport was placed, and she received four cycles of AC and eight cycles of Taxol. After initial decrease in the size of her left breast mass, and improvement in the peau d'orange, the left breast mass began to grow rapidly, and the peau d'orange also worsened briskly. She began to experience progressive left breast and axillary pain. In an effort to afford her palliative locoregional pain relief, she underwent left modified radical mastectomy, including en bloc partial resection of the pectoralis muscle to grossly negative margins, left axillary dissection, and right simple mastectomy with sentinel lymph node biopsy.

Final pathology of the left breast and axillary contents revealed multifocal invasive carcinoma with signet ring histology, lymphovascular invasion, positive deep and superficial margins, and eight of nine lymph nodes positive with macrometastases. Histology showed invasive carcinoma with the presence of signet ring cells (SRCs). The majority of tumor cells (greater than 50 percent) showed features of SRCs, with large mucin filled vacuoles, displacing the nucleus to the periphery, and the tumor was diagnosed as signet ring cell carcinoma (Figure 1).

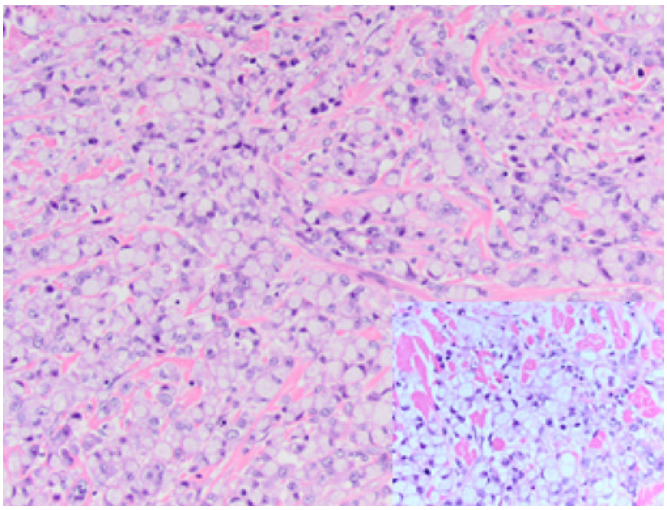

Figure 1. The majority of tumor is composed of signet ring cells, with abundant intracytoplasmic mucin and peripheral displacement of the nuclei. Inset showing high-powered magnification of signet ring cells.

High mitotic activity, moderate nuclear pleomorphism, and high nuclear atypia were seen. Lymphovascular invasion was present, and the tumor extended to the nipple and underlying muscle (Figure 2, Figure 3, and Figure 4).

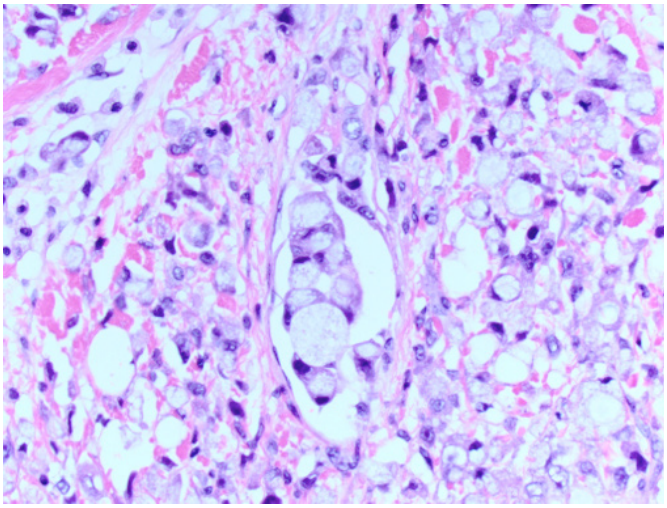

Figure 2. Intravascular invasion

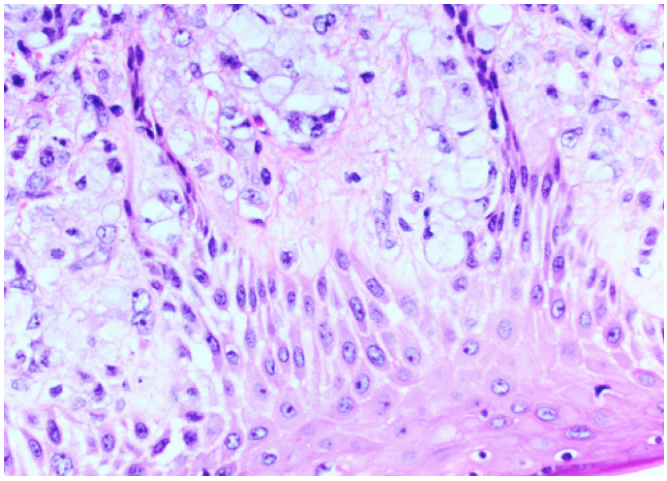

Figure 3. Tumor cells extending to the nipple

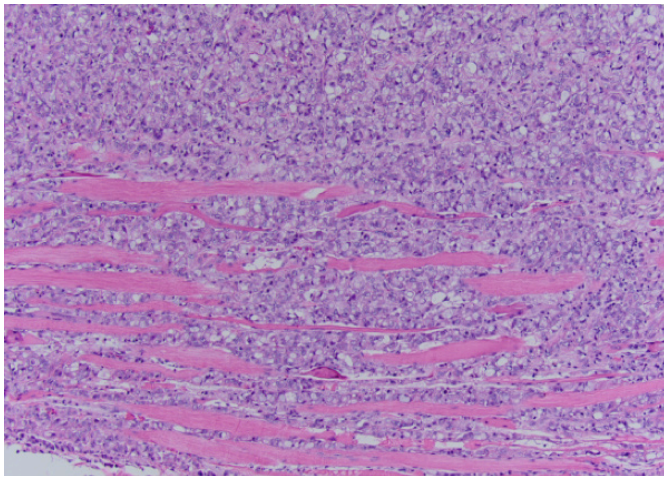

Figure 4. Tumor cells extending into the muscle

Additionally, SRCs were seen in the contralateral sentinel lymph node specimen (Figure 5). The tumor was positive for E-cadherin, cytokeratin (CK) 7, and negative for CK 20.

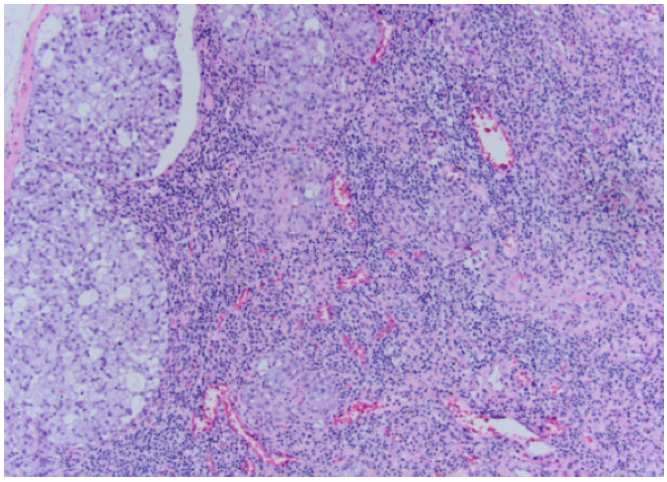

Figure 5. SRCs in the right lymph node, representing M1 disease

Final pathology of the right breast revealed low grade invasive ductal carcinoma with associated DCIS. Margins were negative, but two lymph nodes from the right axilla were positive with morphology consistent with metastasis from the contralateral breast. Postoperative PET-CT showed stage IV disease, including ipsilateral sub-pectoral, mediastinal, and para-aortic lymphadenopathy.

The patient unfortunately had a rapidly progressive local recurrence with significant tumor burden only a few weeks postoperatively. Aggressive tumor recurrence is depicted at four weeks and again at 11 weeks postoperatively (Figure 6 and Figure 7). The patient expired 12 weeks postoperatively.

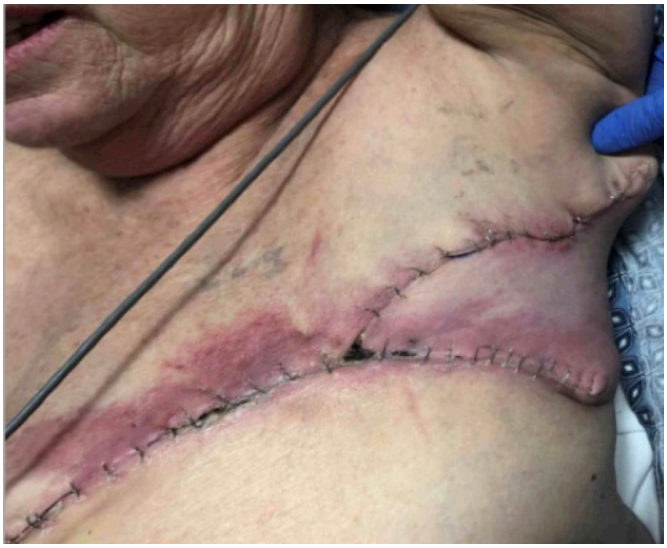

Figure 6. Recurrence at four weeks postoperatively

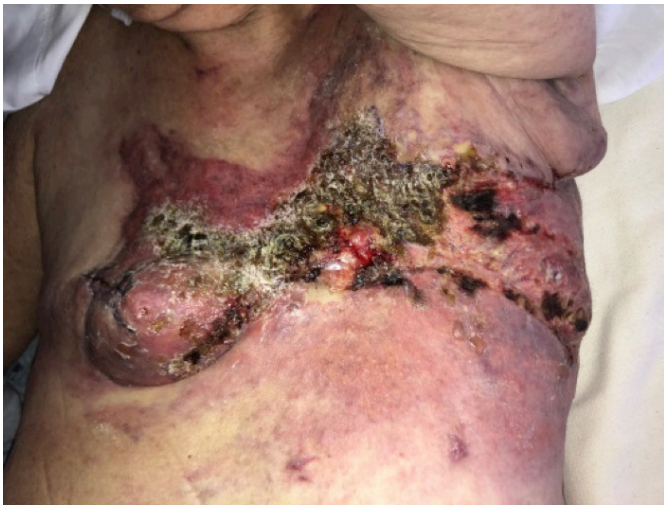

Figure 7. Recurrence at 11 weeks postoperatively

Discussion

Signet ring cell carcinomas (SRCCs) of the breast are extremely rare, especially in pure form.[1,2] SRCCs can be associated with either lobular or ductal carcinoma. Prevalence of signet ring features varies, reported in 2 to 4.5 percent of all breast cancers.[3] The first report of SRCC of the breast was described by Saphir in 1941.[4] Currently, in the World Health Organization (WHO) Classification of Tumors of the Breast (fourth edition), SRCC is listed as an invasive breast carcinoma, but is not regarded as a tumor type of its own; rather, it can be observed with either invasive lobular carcinoma or with invasive carcinomas, no specific type (NST) as well as mucinous carcinomas.[5] SRCC was previously classified as a distinct subset of mucinous carcinoma in the third edition.[3] The American Joint Committee on Cancer (eight edition) does not list signet ring cell carcinoma as a histology code.[6] Historically, SRCC was thought to be related specifically to lobular carcinoma.[7] The reported cases of SRCC of the breast in the literature have varied in association with mucinous, lobular, ductal, and metaplastic carcinoma.

SRCC of the breast can be a primary or metastatic tumor. The high incidence of GI metastasis in patients with SRCC in a study by Merino et al[7] posed a valid question: could the breast lesions be metastases from the GI tract? Differentiating between breast and gastric cancers may be difficult, but literature review indicates that each has distinct immunophenotype[8]. In a case series study by Tot,[9] immunohistochemical features of both primary invasive lobular breast carcinomas and gastrointestinal (GI) SRCCs were evaluated. In this study, all metastatic GI lesions were CK 20+/ER-. Primary SRCC of the breast is typically CK 7+/CK 20- while GI SRCCs are typically CK 20+/CK 7-.[10,11] In the case report by Mahmud et al,[8] use of immunohistochemical results correctly diagnosed a metastatic breast carcinoma of the stomach instead of a primary breast lesion. Recent publication by Hui et al[12] supported the previous results by Tot: primary GI lesions with signet ring features exhibited CK 20 positivity while primary breast lesions with signet ring features exhibited ER positivity. E-cadherin positivity favors ductal origin of breast tumors, as seen in this case. While ER and GCDFP-15 are generally positive in primary SRCC of the breast, their negativity does not exclude breast origin.[10] High-grade breast tumors with poor differentiation are less likely to be estrogen receptor positive, and triple negative breast tumors are less likely to be GCDFP-15 positive. In this case, ER/GCDFP-15 negativity did not rule out a breast primary, but CK 20 negativity discouraged gastrointestinal origin. Breast origin was further implied by a second, postoperative, PET-CT scan showing distant metastases to various nodal basins consistent with primary breast cancer, without presence of activity within any intraabdominal organs. Furthermore, while it would have been academically satisfying for the patient to undergo panendoscopy to confirm lack of gastrointestinal malignancy, she was never felt to be well enough to undergo such a procedure.

Signet cell appearance is due to large mucin filled vacuoles, displacing the nucleus to the periphery.[2,3] When >20 percent signet ring cells are present, the carcinoma is labeled SRCC.[7] Pure SRCC requires the majority of the neoplastic cells to show signet ring features.[13]

The prognosis for SRCC remains poor,[14] with higher incidence and extent of lymph node involvement, especially in cases of ductal carcinoma with associated signet ring cells.[1] SRCCs frequently metastasize to regional lymph nodes, peritoneal surfaces, ovaries, and lungs.[11] In pure form, as in this report, SRCCs are more aggressive than mucinous, ductal, or lobular invasive carcinomas.[13] Bilateral involvement is typically associated with lobular carcinoma,[13] but in this report, the patient had two separate primary lesions, both ductal in origin. The hormonal receptors may carry a better prognosis for disease-free survival,[15] but unfortunately this patient's left breast pathology was ER/PR/HER2-negative. SRCCs are more likely to demonstrate lymphovascular invasion,[16] indicating a more aggressive behavior of these tumors, including high incidence of lymph node metastasis.[14] Hull et al demonstrated an association of axillary lymph nodal involvement in cases of ductal carcinoma with associated signet ring cell carcinoma as well as a higher mortality rate.[1] Because of this aggressive nature, some authors advocate SRCC as a subtype due to distinct clinical and pathologic features.[1,7,17] Quantification of the percentage of SRCs could be useful in determining more aggressive behavior. Bartosch et al[16] determined a higher SRC percentage correlated to a higher incidence of lymphovascular invasion and lymph node metastases.

Conclusion

SRCC of the breast remains a rare diagnosis. Due to its aggressive nature, it is important to report, regardless of histological subtype.[16] Though it may originate from either lobular or ductal origin, classification as its own entity may be beneficial for future diagnosis and treatment,[13] especially given the aggressive nature of this malignancy. Prognosis

of SRCCs remains poor. Additionally, despite controversy over its classification, SRCC must be considered when differentiating between breast and GI primary lesions, with special attention to immunohistochemical features.

Lessons Learned

SRCC of the breast is a rare, aggressive tumor that must be differentiated from metastatic gastrointestinal cancer based on specific immunohistochemical features. Increased reporting of cases of SRCC of the breast is necessary to more clearly define tumor characteristics and behavior and guide effective treatment strategies for optimal outcomes.

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