Secretory Carcinoma of the Breast Mimicking Invasive Ductal Carcinoma: A Case Report

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Patient: Female, 40-year-old
Final Diagnosis: Secretory breast carcinoma
Symptoms: Breast mass
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare disease
Background: Secretory breast carcinoma (SBC), an extremely rare malignancy, is related to a chromosomal translocation which leads to an ETV6-NTRK3 fusion mutation. SBC is characterized by eosinophilic secretions and is usually triple-negative, with a small number of patients demonstrating ER-positivity of the tumors. Diagnosis can be challenging and requires genomic testing for confirmation.

Case Report: A 40-year-old woman presented with a breast mass found on mammography. She underwent an ultrasound-guided biopsy of the tumor. Initial pathology evaluation revealed features consistent with invasive ductal carcinoma. The immunochemistry report described an ER-positive, PR-negative, and HER2-negative tumor. The specimen was sent for oncotype scoring, which was not performed due to the specimen not meeting the criteria for invasive ductal carcinoma and displaying pathological features of SBC. A fluorescent in situ hybridization (FISH) study revealed ETV6 translocation, consistent with the diagnosis of SBC. The patient underwent lumpectomy followed by adjuvant radiotherapy and endocrine therapy. She remains in complete remission 3 years after treatment.

Conclusions: Accurately diagnosing SBC is of extreme importance as it has an indolent clinical course, but has a favorable prognosis if detected early. Due to nonspecific imaging findings, pathology evaluation with immunohistochemical staining followed by genomic testing is required. Our case highlights the challenges associated with SBC diagnosis requiring genomic testing due to equivocal pathological findings, along with increasing incidence of SBT in adults. There are no established guidelines for SBC management. The mainstay of treatment is partial or total mastectomy. Data on the benefits of adjuvant endocrine therapy, chemotherapy, and radiotherapy are inconclusive.

Keywords: Breast Neoplasms • Chemotherapy, Adjuvant • Radiotherapy • Secretory Breast Carcinoma

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Background

Secretory breast carcinoma (SBC) is an extremely rare malignancy, accounting for less than 0.15% of breast cancer cases [1]. SBC was initially identified in children, with an average age of 9 years old, and was previously known as juvenile breast carcinoma [2]. SBC is related to a balanced t (12;15) translocation, which leads to \textit{ETV6-NTRK3} gene fusion, driving abnormal cell proliferation [3]. This breast cancer type is characterized by abundant eosinophilic secretions and is usually triple-negative on immunohistochemical staining [4]. SBC has a favorable prognosis and, in most cases, requires surgical excision and sentinel node biopsy, with no adjuvant chemotherapy [4]. We present an elusive and challenging diagnosis of estrogen receptor (ER)-positive secretory breast carcinoma.

Case Report

A 40-year-old woman with no significant past medical history was found on a screening mammogram to have a 10-mm, oval, high-density mass in the upper outer quadrant of the left breast. The patient reported no constitutional symptoms and denied acute pain, recent weight loss, or fatigue. Targeted left breast ultrasound revealed an 11×12×11 mm hypoechoic solid mass with angular margins located at middle depth and associated with a small area of increased vascularity. The mass was associated with an architectural distortion of the breast parenchyma. Targeted sonographic interrogation over the left axilla was normal. Excision biopsy revealed a moderately differentiated tumor forming tubules, which was interpreted as invasive ductal carcinoma (Figure 1). The tumor was ER-positive with an expression of 20%, progesterone receptor (PR)-negative, and HER2-negative (Figures 2-4). Repeat

Figure 1. Microscopic examination of the tumor shows tumor cells with predominantly microcystic and tubular patterns (arrows) separated by sclerotic stroma mimicking invasive ductal carcinoma (H&E ×40).

Figure 2. Benign breast ducts at the bottom of the picture show strong positive ER staining, while the tumor cells show weak patchy staining.

Figure 3. Benign breast ducts at the bottom of the picture show strong positive PR staining, while tumor cells are negative.

Figure 4. Tumor cells lack membranous HER2/neu staining.
biomarker testing confirmed the receptor expression profile of the tumor. The patient elected lumpectomy after reviewing multiple management options with the breast surgeon and oncologist. Mass excision was performed, with the pathology report describing the tumor as invasive ductal carcinoma with cell nests interpreted as poorly formed tubules (Figure 5). The tumor was graded with a glandular differentiation score of 3, nuclear polymorphism score of 2, and mitotic rate score of 1, with an overall grade of 2. The tumor specimen was sent for oncotype scoring (Oncotype DX, Genomic Health, Inc., Redwood City, CA). Prior to oncotype scoring, the specimen was reviewed by a breast pathologist, who reported that the sample was not processed, as it demonstrated features of secretory breast carcinoma. This subtype was not included in the validation studies of the Oncotype DX and resubmission of the sample was not recommended. The specimen was then sent for a second pathology opinion in the academic institution and the SBC diagnosis was confirmed (Figure 6). Fluorescence in situ hybridization (FISH) revealed ETV6 translocation, which is the criterion standard for diagnosis of SBC. The potential benefits of adjuvant endocrine therapy in the setting of weak ER-positivity of the tumor were discussed and the patient elected to proceed with radiotherapy and endocrine therapy with tamoxifen. The patient remains in complete remission 3 years after treatment completion.

**Discussion**

In 1980, Tavassoli and Norris proposed the name “secretory breast cancer” for this very rare breast carcinoma. While the cancer’s exaggerated secretory features had previously been found almost exclusively in juveniles, their review of 19 patients identified the cancer in patients up to 69 years of age [4]. Since then, multiple case reports have confirmed the occurrence of SBC in adults [5,6]. SBC has been reported in patients from 3 to 83 years old, with a median age of 25 [5]. Our 40-year-old patient presented with SBC at a later age, which made the diagnosis challenging even for experienced pathologists.

The defining mutation in SBC is a balanced translocation between chromosomes 12 and 15, resulting in an ETS variant 6-neurotrophic tyrosine kinase receptor type 3 (ETV6-NTRK3) fusion gene encoding a chimeric tyrosine kinase [7]. The ETV6-NTRK3 gene fusion has previously been detected in pediatric malignant mesenchymal tumors, including congenital fibrosarcoma and congenital cellular mesoblastic nephroma, and is responsible for excessive cell proliferation [8]. Detection of this mutation has provided a key tool for the diagnosis of these challenging cases.

SBC usually presents as a painless, firm mass in the breast, which may move when palpated. Some people with SBC also have nipple discharge. Most tumors are localized in the upper outer quadrants [5]. Our patient presented with a lesion in the upper outer quadrant without other symptoms.

SBC can be initially suspected on ultrasonography or diagnostic mammography with subsequent ultrasound-guided biopsy. The diagnostic value of the mammogram is limited as SBC usually presents as a discrete solitary mass favoring fibroadenoma rather than a malignant tumor [9]. Typical ultrasound findings show an oval, round, or tubular mass that can be hypoechoic or isoechoic, usually benign-appearing, and seen as a single mass or a group of nodules [10]. In rare cases, T2-weighted MRI images can show a complex cystic mass that has an early washout enhancement [10]. Sentinel lymph node biopsy is used as...
a diagnostic and prognostic tool for the staging of SBC. The involvement of 3 or more lymph nodes is associated with an increased risk of metastases [10].

Although classic pathologic findings of SBC demonstrate abundant eosinophilic secretions in intracellular vacuoles and intercellular spaces, it may have overlapping histologic features with invasive ductal carcinoma such as tubular structures formation, desmoplastic tumor stroma, and blood vessel elastosis. The most characteristic histologic feature of SBC is the presence of intracellular and extracellular secretions that are PAS-positive (periodic acid-Schiff). However, the small glands of invasive ductal carcinoma may also produce mucus, which can be misleading. The latter underlies the challenges associated with differential diagnosis of these tumors on core biopsy. SBC has microcystic, solid, or tubular architecture, or a mixture of all 3 patterns. The SBC tumor cells have uniform nuclei with low-grade cytologic atypia and a low mitotic rate [11]. Most tumors stain positive for S100 and negative for ER, PR, and HER2/neu [5,6]. ER-positivity has been reported in a limited patient population [12]. ER-positive SBC was described in a 9-year-old patient with weakly ER-positive, PR-negative secretory breast carcinoma [13]. Separately, in a case series of 44 SBC patients, 21 patients had ER-positivity, although the characteristics of the patients in the less prevalent group were not clearly defined in the paper [14]. Therefore, the hormone expression may not always be consistent despite the classic triple-negative profile described in the literature [1]. In challenging cases, such as our patient with equivocal pathologic findings and rare receptor expression profile, the FISH study is performed to confirm the diagnosis.

Due to the paucity of cases, there is no consensus on the treatment of SBC. Treatment varies from case to case, depending on the age of the patient, their preference, size of the tumor, hormone-positivity, and lymph node involvement [13]. The primary option for treatment is a total or partial mastectomy, depending on tumor size and patient preference. There are no established guidelines dictating the extent of surgical excision. Due to the reduced metastatic capacity of the tumor, total axillary lymphadenectomy is under debate and the extent of lymph node dissection varies depending on the clinical presentation [15].

Adjuvant radiation therapy may be considered, especially in those who, like our patient, undergo breast-conserving surgery. Although some data suggest that adjuvant radiation can induce a sustainable disease-free period, there is no conclusive evidence of its benefits in SBC [10,16-18]. The use of adjuvant chemotherapy has not been widely investigated. Adjuvant therapy with doxorubicin and cyclophosphamide was used in a young patient due to her age-related risk of recurrence [10]. There is emerging research on the use of tropomyosin receptor kinase inhibitors (TRK) for the treatment of NTRK fusion cancers like SBC [19]. TRK inhibitors may be a promising treatment modality in the future. To date, there are no ongoing clinical trials on secretory breast carcinoma.

Although the possibility of SBC extension to the axillary lymph nodes exists, as well as the possibility of distant metastases, the overall tumor prognosis is excellent [5]. There are no data suggesting that a positive hormone receptor expression profile affects survival or prognosis [6,14].

Conclusions

The diagnosis of SBC remains radiologically and pathologically challenging, especially in older patients. The nature of pathologic findings may initially be misleading and require a second opinion. In addition, the hormone expression of this cancer may not be consistent with expectations. Pathologic findings may mimic those observed in invasive ductal carcinoma, but the prognosis is dramatically different. Our case emphasizes the need to maintain high suspicion of SBC in older patients with equivocal pathologic findings. In such cases, FISH becomes a diagnostic test of choice, with the ETV6-NTRK mutation being a pathognomonic abnormality for SBC.

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