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Case Report and Review of the Literature

Small Cell Carcinoma of the Breast: A Report of 2 Cases and Literature Review

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ABSTRACT

Two female patients were diagnosed with primary small cell carcinoma of the breast that was estrogen receptor, progesterone receptor, and Her-2 Neu negative. Diagnosis was made by ultrasound-guided core needle biopsy. They both underwent neoadjuvant chemotherapy. The first patient had negative sentinel lymph node biopsy and underwent postoperative whole breast radiation. She has remained disease-free. The second patient underwent preoperative radiation only, had one positive sentinel lymph node, and declined postoperative radiation. The second patient had metastasis to the axillary lymph nodes as well as recurrence. She was treated with chemotherapy, surgery, and radiation, but ultimately developed more diffuse metastasis. We discuss current literature regarding diagnosis, treatment, and prognosis in small cell carcinoma of the breast.

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Introduction

Small cell carcinoma is a poorly differentiated neuroendocrine tumor that most commonly arises in the lung. Primary small cell carcinoma of the breast is rare. Hence, initial evaluation should be to exclude metastasis from extramammary sites [1, 2]. Overall survival for primary extra-pulmonary small cell carcinoma is poor [1, 3, 4]. Although there is limited data given the rarity of this entity, the most common treatment modality appears to be a combination of local treatment and chemotherapy [4]. We present two cases of triple-negative small cell carcinoma of the breast from our institution over the past 6 years.

Case 1

A female in her 50's with a past medical history significant only for tuberculosis as an infant presented to her primary care physician with left breast pain and a lump in the upper outer quadrant. She was premenopausal at presentation and had not had a recent mammogram. Her family history was negative for any malignancy. She was a nonsmoker. A diagnostic mammogram demonstrated an irregular mixed echogenic mass ($4 \times 3.8 \times 2.4$ cm) at the site of palpable concern as well

as a mildly enlarged left axillary lymph node. Ultrasound (US) guided core needle biopsy revealed small cell carcinoma that was estrogen and progesterone receptor-negative and Her-2 Neu negative. Preoperative molecular profiling demonstrated no actionable mutations. The left axillary node was also biopsied and showed only benign lymphoid tissue. A positron emission tomography (PET) scan showed no evidence of a separate primary tumor or distant metastasis.

She was started on neoadjuvant chemotherapy with carboplatin and etoposide and completed 6 cycles with good response. Repeat imaging demonstrated that the mass had decreased in size to $1.9 \times 1.2 \times 1.7$ cm. The patient then underwent left partial mastectomy and sentinel lymph node biopsy. Pathology revealed poorly differentiated carcinoma, small cell type. Pathologically, the tumor was 1.7 cm in its greatest dimension with negative margins. Ductal carcinoma *in situ* (DCIS) was not seen in the specimen. Immunostain for CD 56 was diffusely positive. Immunostain for synaptophysin was focally positive. Immunostains for AE1/AE3 and CAM 5.2 were positive in dot like pattern. The sentinel node was negative for metastatic carcinoma.

The patient completed whole breast and axillary radiation therapy without significant side effects. No adjuvant chemotherapy was given.

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She underwent a follow-up PET scan six months after surgery. The PET scan demonstrated no evidence of 18-fluoro-2-deoxyglucose (FDG) avid malignancy. She will have a follow-up PET scan in another six months. She will then undergo annual breast imaging unless new issues prompt earlier assessment.

Case 2

A female in her 60's presented with the complaint of a mass in the right upper outer quadrant of her breast in July of 2015. Her past medical history was significant for hypertension, hyperlipidemia, cataracts, arthritis, and a distant history of pericarditis. She had a 15-pack-year history of smoking until age 30. A mammogram and an US showed a 2.8 cm spiculated mass. A core biopsy returned triple-negative small cell carcinoma. Immunohistochemical stains were positive for CD56, synaptophysin, and focally positive for chromogranin, cytokeratin and TTF-1. Staging studies revealed this to be the only site of disease.

She underwent neoadjuvant chemotherapy starting with cisplatin and etoposide. Radiation therapy was given with the second cycle of chemotherapy. The patient developed renal failure and her chemotherapy regimen was changed to carboplatin and etoposide. She completed 4 total cycles of treatment then underwent a partial mastectomy and sentinel node biopsy. She had a residual 2 mm small cell cancer with 1 of 2 sentinel nodes with individual small cell tumor cells. She declined adjuvant radiation therapy.

Surveillance computed tomography (CT) scan in August 2019 showed right axillary and supraclavicular lymphadenopathy, and core biopsy confirmed recurrence of small cell cancer. She was treated with carboplatin, etoposide, and atezolizumab for 4 cycles, and atezolizumab for 6 additional cycles.

In May 2020, she underwent excision of what was thought to be a symptomatic hypertrophic scar at her previous lumpectomy site, but this proved to be recurrent small cell cancer. Atezolizumab was discontinued because of continuing progression in the axilla and supraclavicular nodes, with extension to jugular nodes. She underwent radiation therapy, which was discontinued after 25 of planned 35 treatments because of blistering and subsequent skin infection. Carboplatin and paclitaxel were recommended to be given concurrently with radiation, but the patient declined. By November 2020 she had developed multiple suspicious areas in the lungs as well as liver metastasis. She had also developed bone metastasis. She was started on lurbinectedin (received 5 cycles) and denosumab in March 2021. In August 2021, the patient was found to have brain metastasis with vasogenic edema and she was transitioned to hospice.

Discussion

The vast majority (95%) of small cell neuroendocrine cancers occur primarily in the lungs and are associated with a poor prognosis [1, 5, 6]. Standard treatment regimens include cisplatin or carboplatin and etoposide with radiation and surgical resection when possible. Extrapulmonary small cell cancers are rare, and treatment regimens have generally followed lung treatment plans. Other primary sites for small cell cancers include the GI tract, gallbladder, bladder, prostate, larynx, salivary glands, cervix, and skin [7]. Extrapulmonary small cell

carcinoma treated with chemotherapy has better outcomes than no treatment or radiotherapy alone, and chemoradiation provided improved overall survival compared to chemotherapy or radiotherapy alone [4].

Breast cancers with neuroendocrine differentiation are common, as a significant proportion of papillary or mucinous cancers will have neuroendocrine features including chromogranin and synaptophysin staining [1]. These tumors are usually of indolent luminal A type, hormone positive and Her2 negative [1, 2, 8, 9]. Previous WHO classification determined that tumors expressing <50% neuroendocrine features should be classified as breast cancer with neuroendocrine differentiation versus neuroendocrine tumor [10].

In contrast, pure primary neuroendocrine tumors of the breast are extremely rare and are classified as well differentiated or poorly differentiated. Well differentiated neuroendocrine tumors are considered carcinoid tumors, whereas poorly differentiated neuroendocrine tumors have cell morphology similar to small cell carcinoma of the lung. Histologic diagnosis is made by cell morphology as well as the presence of markers such as chromogranin and synaptophysin.

Extrapulmonary small cell carcinoma has displayed heterogeneous immunoreactivity for neuroendocrine markers [8]. The diagnosis of small cell carcinoma of the breast can be supported by detecting immunohistochemical evidence of neuroendocrine differentiation. The expression of neuroendocrine markers is inconsistent and there is no one pattern of neuroendocrine marker expression, but the presence of chromogranin and synaptophysin appears to be common [8, 9, 11, 12]. Our patients had focally positive synaptophysin and chromogranin tissue staining. Small cell carcinoma of the breast is histologically similar to small cell carcinoma of the lung [1]. It can be diagnosed as having primary origin in the breast if an in-situ component (usually DCIS) is identified, or if staging studies do not reveal any other sites of disease [2, 5, 8]. The majority of small cell cancers in the breast will be hormone receptor positive and Her2Neu negative [13]. The patients we present had tumors that were triple-negative. This has been reported in previous cases and has not been an indicator of prognosis [12]. Both patients were classified as high grade, with accordingly poor prognosis, as observed in the second patient.

Most patients with small cell carcinoma of the breast present with a palpable breast mass and/or axillary lymphadenopathy [2]. Previous studies report that axillary lymph node involvement is often present at presentation [8, 9]. When diagnosing small cell carcinoma of the breast, it is critical to rule out primary small cell cancer elsewhere [11]. Diagnosis usually requires a core needle biopsy because the tumors have nonspecific imaging findings on mammography, US, and magnetic resonance imaging (MRI) [14]. Our patients had core biopsy-proven diagnosis and underwent a PET scan that revealed no alternative primary tumor and no metastasis.

Due to a lack of clinical trials, there is no standard recommendation for treatment of neuroendocrine carcinoma of the breast [11]. According to recent WHO classification, neuroendocrine carcinoma of the breast is treated based on standard breast cancer parameters [5]. Of note, Mandish *et al.* demonstrated that small cell carcinoma of the breast has improved overall survival compared to other extrapulmonary small cell carcinomas [4].

The recommended systemic therapy for small cell lung cancer is four cycles of cisplatin/etoposide, but patients who tolerate this well may receive up to 6 cycles [15]. Previous case reports have reported successful use of systemic therapy consisting of cisplatin/etoposide regimen in treating small cell carcinoma of the breast [9, 16, 17]. Both of our patients responded to neoadjuvant cisplatin/etoposide, although the patient in case two did not have a lasting response.

Surgical intervention has also shown an overall survival benefit in small cell breast carcinoma [4]. A large retrospective study examining prognostic factors in extrapulmonary small cell carcinomas found that the combination of local therapy (defined as radiation or surgery) combined with chemotherapy as well as female gender provided a favourable prognosis [18]. The best outcomes for small cell carcinoma of the breast appear to result from a combination of surgical treatment, chemotherapy, and radiation. [4, 9, 17]. Both of our patients received combination therapies. The patient in the second case had a poorer outcome. It is unclear if omission of radiotherapy initially may have played a role in this, as there is conflicting data about the benefits of radiotherapy, with a SEER based analysis showing no survival benefit to radiotherapy [19].

The prognosis of small cell carcinoma of the breast is variable and heavily influenced by the stage of disease at time of diagnosis and tumor size [8, 9, 12]. Breast primaries appear to have much better outcomes than lung. The SEER study showed median survival of 150 months for localized breast disease, compared to 16 months for localized small cell lung cancer. Regional disease also compared favourably, at 56 months for breast versus 13 months for pulmonary small cell cancer. The median survival for distant metastatic disease at presentation, however, was equally poor at 7 months for both disease sites. The majority of the medical literature about breast small cell carcinoma is individual case reports. Continuing collection of information about these rare tumors may help guide treatment in the future.

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