A case report of primary small cell carcinoma of the breast and review of the literature

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Abstract

Primary small cell carcinoma (SCC) of the breast, an exceedingly rare and aggressive tumor, is often characterized by rapid progression and poor prognosis. We report a case of primary SCC of the breast that was diagnosed through pathologic and immunohistochemical examinations. Computed tomography (CT) scans failed to reveal a non-mammary primary site. Due to the scant number of relevant case summaries, this type of tumor is proved to be a diagnostic and therapeutic challenge. Therefore, we also reviewed relevant literature to share expertise in diagnosis, clinicopathologic characteristics, treatment, and prognosis of this type of tumor. Future studies with more cases are required to define more appropriate treatment indications for this disease.

Key words: Small cell carcinoma, breast, neuroendocrine

Case Report

In October 2011, a 39-year-old woman presented a painless mass in her left breast for 3 months. There were no accompanying symptoms such as nipple retraction, dimpling, or palpable axillary lymph nodes. Physical examination revealed a 2 cm × 2 cm, elastic, firm, ill-defined suspicious mass in the upper outer quadrant of her left breast. On the mammography, the mass appeared round with indistinct margins with lots of punctates and scattered calcifications along the duct (Figure 1A).

Additionally, an ultrasound scan revealed two solid and low heterogeneous echoes in the left breast: one was in the 3 o’clock position, 35 mm away from the nipple (Figure 1B); the other was also in the 3 o’clock position, 65 mm away from the nipple (Figure 1C). Both were poorly defined with irregular borders. However, the levels of serum tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), CA15-3, and CA19-9 were all within normal limits.

The patient did not undergo a fine needle biopsy. An intraoperative biopsy confirmed the pathologic diagnosis of SCC with the component of ductal carcinoma in situ (DCIS). As a result, she underwent modified radical mastectomy with axillary lymph node dissection. Microscopically, the mass (in the 3 o’clock position, 35 mm away from the nipple) was about 0.8 cm × 0.5 cm × 0.5 cm, which was diagnosed histologically as an intermediate grade DCIS, whereas the second mass (in the 3 o’clock position, 65 mm away from the nipple) was about 1.4 cm × 1.2 cm × 0.6 cm and was comprised...
Figure 1. Imaging examinations of a 39-year-old woman with primary small cell carcinoma (SCC) of the breast. A, mammography reveals a round mass with obscure margins and lots of punctates and scattered calcifications along the duct. B and C, ultrasound scan shows two solid and low heterogeneous echoes in the left breast. One is in the 3 o’clock position, 65 mm away from the nipple (B); the other is also in the 3 o’clock position, 35 mm away from the nipple (C). Two lesions are both poorly defined with irregular borders.

of intermediate grade DCIS (30%) and SCC (70%). Histological examination showed that the tumor was composed of small round or oval cells with a high nucleocytoplasmic ratio, small hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm, which were arranged diffusely and patchily. Widespread necrosis was present (Figure 2A). Immunohistochemically, tumor cells of the DCIS component were positive for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). However, the tumor cells of the SCC component were negative for these markers, whereas the Ki67 proliferation index (percentage of Ki67-positive cancer nuclei) was 70%. Furthermore, the SCC tumor cells were highly positive for neuroendocrine differentiation markers including synaptophysin (Figure 2B), neuron specific enolase (NSE) (Figure 2C), thyroid transcription factor-1 (TTF1) (Figure 2D), and CD56 (Figure 2E), but they were negative for chromogranin A (CgA) (Figure 2F). Histological examination also demonstrated 1 positive lymph node out of 13 level I axillary lymph nodes.

Therefore, a search for a non-mammary primary site was carried out, especially focusing on pathologic changes in the lungs. The result of computed tomography (CT) scans of the neck, chest, and upper abdomen were all within normal limits, and bone scintigraphy was negative for metastatic disease. As a result, we concluded that the breast was the primary site, and primary SCC of the breast was diagnosed.

The patient was treated with six cycles of docetaxel (75 mg/m²) and carboplatin (350 mg/m²) in combination once every three weeks. After the initial treatment, the patient was clinically monitored for disease relapse and metastasis.
Discussion

Small cell neuroendocrine carcinoma has been described in many extra-pulmonary sites, including the breast, larynx, gastrointestinal tract, prostate, bladder, ovary, and cervix\(^{[4,5]}\). In particular, primary SCC of the breast is considerably rare. To our knowledge, 56 cases have been reported in the literature\(^{[1-2,6-38]}\). In summarizing the clinicopathologic characteristics of these cases, most of them are found in women; only two male cases have been reported\(^{[6,26]}\). The median age of the patients at presentation was 52 years (range, 29 to 81 years). Tumor size ranged from 1 to 18 cm (mean, 4.63 cm), and about 62.8% of the tumors (2 to 5 cm in size) were in T2 stage according to the National Comprehensive Cancer Network (NCCN) guidelines. Approximately 60.4% (32/53) of the patients exhibited axillary lymph node metastasis. Most of them were accompanied by vascular invasion and intraductal lesion. Primary SCC of the breast can be diagnosed if there is no evidence for an extra-mammary primary site or if an in situ component can be demonstrated histopathologically within the breast. It is important that the DCIS component is truly a precursor lesion of SCC and supports a primary breast origin\(^{[15]}\). The presence of an in situ component is useful, though not indispensable, toward the diagnosis of primary breast tumors.

We also reviewed previous immunohistochemical reports\(^{[12,6-36]}\). The tumor cells from approximately 28.8% (15/52) of reported patients were positive for either ER or PR. However, HER2 overexpression has never been reported in these cases. In general, the positive rates of ER, PR, and HER2 were about 60%–70%, 50%–60%, and 20%–30%, respectively, displaying a common phenotype of invasive ductal carcinoma\(^{[39,40]}\). Moreover, positive neuroendocrine markers could provide strong support for diagnosis. The positive rates of NSE and synaptophysin were 88.2% (45/51) and 63.8% (30/47), respectively, and some of the tumor cells were positive for CD56, TTF1, CgA, and other markers.

This type of breast carcinoma is rare and has generally been considered to be extremely aggressive. As a result, no standard treatment for this disease exists\(^{[17,21]}\). The most effective option seems to be modified radical mastectomy with axillary lymph node dissection followed by adjuvant chemotherapy. Considering that the biological characteristics of this type of breast carcinoma are similar to SCC of the lung, effective drugs for SCC, such as platinum compounds and etoposide, were selected to treat these patients; drugs for common types
of breast cancer were not selected. Paclitaxel has been found safe and effective as first-line therapy for small cell lung carcinoma [43]. In addition, paclitaxel-containing regimens have also been used for patients with breast cancer as a standard adjuvant therapy. In the case of SCC with a DCIS component, we prefer a docetaxel and carboplatin combination rather than other ordinary regimens such as cyclophosphamide, epirubicin, and 5-fluorouracil (CEF). Individual treatment strategy, including chemotherapy, radiotherapy, and endocrine therapy alone or in combination, should be determined according to patient's age, tumor size, axillary lymph node status, and molecular phenotype.

The prognosis for this type of tumor is generally believed to be as poor as its pulmonary counterparts [58]. However, previous reports show that the prognosis can be better if such tumors are detected at an earlier stage. According to previous reports [12], the mean follow-up time was 21 months (range, 3 to 60 months), the metastasis or relapse rate was 35.7% (20/56), and the mortality was 19.6% (11/56). The most common sites of metastasis were the liver, brain, bone, lungs, and lymph nodes. The treatment of disease relapse, however, remains poorly characterized. As for our 39-year-old patient, tumor cells of the SCC component were negative for ER, PR, and HER2. In addition, the high Ki67 index and the presence of metastases in 4 axillary lymph nodes may result in a high risk of disease relapse and metastasis. Thus, after her systemic and individual treatments, a rigorous clinical monitoring of disease relapse and metastasis is necessary.

Conclusions

In summary, primary SCC of the breast is a new challenge. Due to the rarity of cases, no standard treatment exists. According to previous reports, earlier detection and multidisciplinary therapies may be relevant to improved prognosis. Further studies with more cases will enhance our understanding of the clinicopathologic characteristics of this tumor and may result in the development of new therapeutic modalities, thus improving the outcome of these patients.

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