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Neuroendocrine Carcinoma in 2 Cases of Rare Primary Small Cell Carcinoma of the Breast and its Literature Review

Bingxue Yan[1], Shifen Huang[1], Yunxia Xia[1], Fang He[1] and Xiaoling Ling[2]*

[1]*Department of Oncology, First Clinical Medical College, Lanzhou University, Lanzhou, Gansu, P.R. China*
[2]*Department of Oncology, The First Hospital of Lanzhou University, Lanzhou, Gansu, P.R. China*

Abstract

Primary Small Cell Neuroendocrine Carcinoma of the Breast (SCNCB) is rare and invasive, which lacks a standard therapy. Small cell carcinoma is a subtype of Small Cell Neuroendocrine Carcinoma (SCNC) and common in lung. It is difficult to distinguish small cell carcinoma in breast from which in the lung. Therefore, a whole-body scan is necessary to rule out metastasis from the Extra pulmonary Small Cell Carcinoma (EPSCC). This article reports two patients with SCNCB and reviews relevant literature to comprehensively discuss the diagnosis and management of this disease in these two cases.

Keywords: Primary small cell neuroendocrine carcinoma of the breast • Small cell neuroendocrine carcinoma • Diagnosis and differential diagnosis • Extra pulmonary small cell carcinoma

Introduction

Primary Small Cell Neuroendocrine Carcinoma of the Breast (SCNCB) is rare but invasive [1-8]. The incidence of SCNCB was less than 0.1% to 5% [1]. Up to now, because of its rarity, treatment has still not been standardized [1]. Here we report 2 novel cases of primary SCNCB and describe a multidisciplinary treatment approach to provide an effective therapy.

Case Series

Case 1

A 51-year-old woman (baseline characteristic as Table 1) discovered a lump in her left breast. Mammary gland light scattering revealed that the size of the mass was 1.43 × 1.06 centimeters Figure 1 and a bilateral mammogram revealed a round mass in the posterior region of the left breast (Figure 2). Emission computed tomography results showed no systemic bone metastases (Figure 3). Whole body CT scan did not reveal spread of the disease beyond the breast. This patient accepted the left breast-conserving surgery with left axillary sentinel lymph node biopsy, breast reconstruction, and fascia flap suture. Postoperative pathology Figure 4 and immunohistochemistry Table 2 confirmed the diagnosis of SCNCB, and the results have been subject to pathological consultation. Six cycles of chemotherapy (cisplatin 30 mg day 1 to 4 combined with etoposide 0.1 g day 1 to 4 every 3weeks) were given post-surgery. Thereafter, radiotherapy was administered. No recurrence happened during a 16-month follow-up period.

Case 2

A 52-year-old woman (baseline characteristic as Table 1), with a bilateral primary breast cancer was seen in our clinical. Three years ago, she was diagnosed with Her-2 positive breast cancer in her left breast. Radical surgery for left breast cancer was given, and conventional chemo radiotherapy was performed after surgery. Due to economic constraints, molecular targeted therapy was not performed. Recently, 4 × 4.5 cm mass found in her right breast. Lymph node ultrasound found several enlarged lymph nodes (Figure 5). Fine needle aspiration biopsy Figure 6 and immunohistochemistry Table 2

Table 1. Clinical summary of the cases.

Summary	Case 1	Case 2
Age (year)	51	52
Location	Left breast	Right breast
Size (centimeter)	1.43 × 1.06	4.5 × 4
Node	0/6	Multiple lymph node positive
Metastasis	No	No
Stage	pT1cN0M0 (I A)	ypT2N1M0 (II B)
Treatment	Breast-conserving surgery, chemotherapy, radiotherapy	Neoadjuvant chemotherapy, radical surgery
Outcome	16 months	22 months

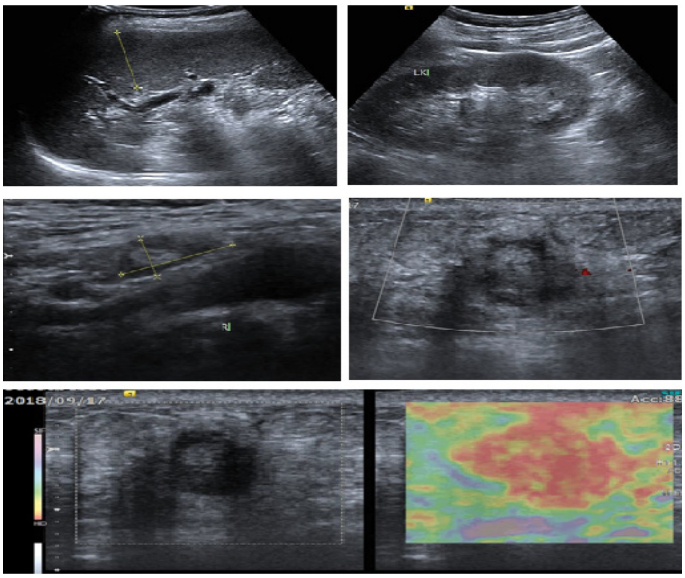

Figure 1. Bilateral breast gland structure disorder, echo distribution is uneven, about 5 cm from the left breast and about 7 cm from the nipple to explore a low echo region about 11.2 × 11.3 mm, the boundary is not clear, irregular shape, uneven internal echo The aspect ratio is slightly larger than 1, CDFI: A little blood flow signal can be seen around, and the arterial spectrum is detected. The RI is about 0.6, and the elastic score is 4 points.

***Address for Correspondence:** Ling X, Department of Oncology, The First Hospital of Lanzhou University, Lanzhou, Gansu, P.R. China, E-mail: lzdxdyyyybx@163.com*

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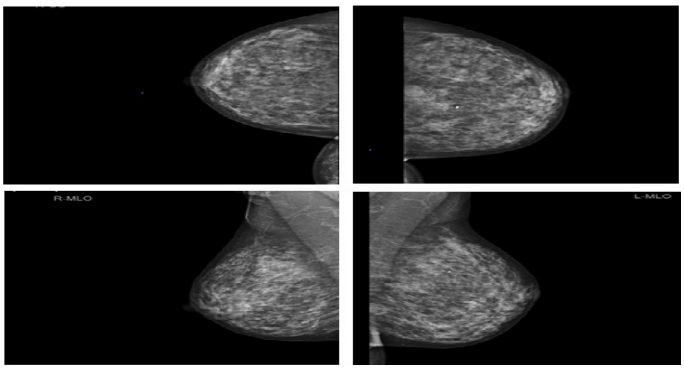

Figure 2. In the posterior region of the left lower lobe, a circular isobaric mass with a diameter of about 15 mm can be seen, and the edge is clear; the asymmetrical shadow is visible in the posterior region of the right upper lobe, and the double breast is scattered in a dot shape, the center is translucent, coarse calcification, and the skin and nipple are not seen exception.

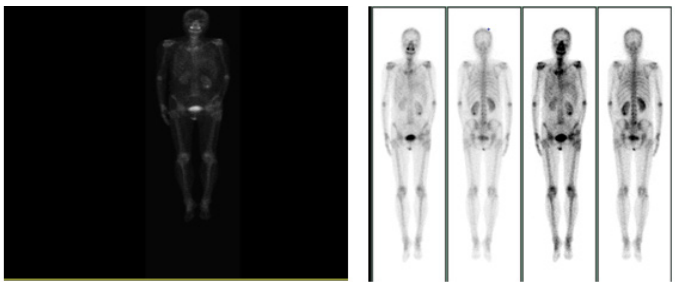

Figure 3. After the intravenous tracer 99 mTc-MDP, the systemic and local bone imaging was delayed before and after the whole body: the whole body bone development was clear, the bilateral sides were basically symmetrical, and the local tracer showed no obvious abnormal increase or decrease. Physiological development of both kidneys and bladder. No obvious metastatic lesions in the whole body.

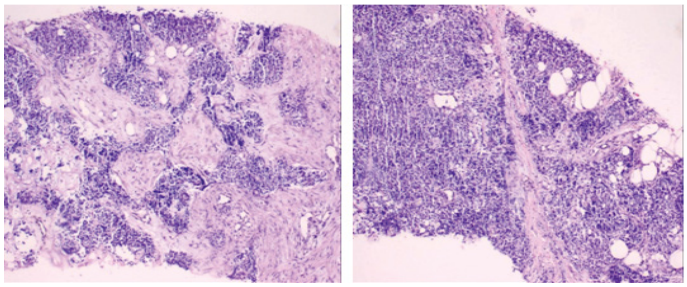

Figure 4. Left breast after surgery HE staining (HE: 200x).

confirmed the diagnosis of SCNCB, while no metastatic lesions were detected in CT scan of the craniocerebral chest and total abdomen. The patient received three cycles of neoadjuvant chemotherapy in our hospital (cisplatin 60 mg day 1 to 2 combined with etoposide 0.1 g day 1 to 5 every 3 weeks). The mass has shrunk significantly. Then she received the radical surgery in local hospital. After the operation, continued to give EP regimen of chemotherapy to the local hospital for 3 cycles (specific dose unknown), and given local radiation therapy, the total dose was 5500 cGy. No progression occurred during a 22-month follow-up period.

Discussion

In the two female patients reported in this article, the local mass was within 2 cm and whole-body scan showed that patient did not have distant metastases. Both patients were confirmed have SCNCB by pathological biopsy and immunohistochemistry. Both two patients received etoposide and cisplatin therapy. Neither patient has been diagnosed with recurrence or metastasis so far. The second patient had a history of HER-2 positive breast cancer of left five years ago. She received six cycles of "TAC" chemotherapy after modified

Table 2. Immunohistochemistry of the cases.

Summary	Case 1	Case 2
ER	-	-
PR (%)	-	10%
Her-2	-	-
KI-67 (%)	70%	80%
TTF-1	-	++
CD56	++	-
CK7	-	+
CK20	-	-
Syn	++	+
CD8/18	plot+	++

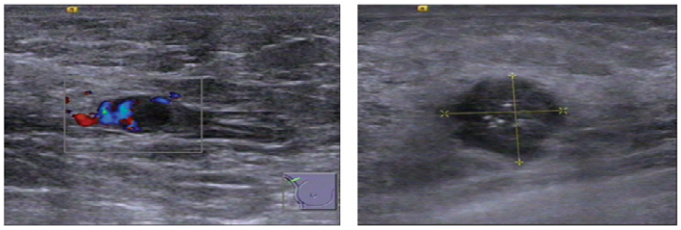

Figure 5. The structure of the right gland is disordered, and the echo distribution is uneven. It is about 3.5 cm away from the nipple at 1 o'clock, and 13 mm away from the skin. A low echo zone with a size of about 14.0 × 13.7 mm is detected. The boundary is clear and the shape is regular. There are several strong echogenic spots visible in the CDFI: No obvious blood flow signal in the nodules.

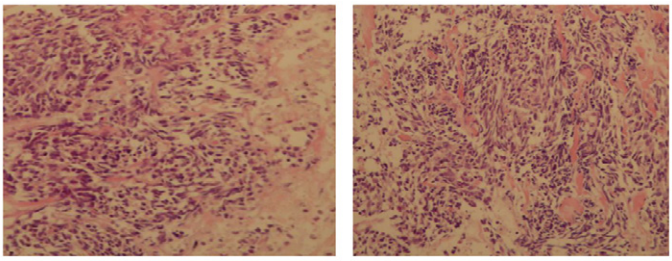

Figure 6. HE staining of right breast lymph node puncture tissue (HE: 200x).

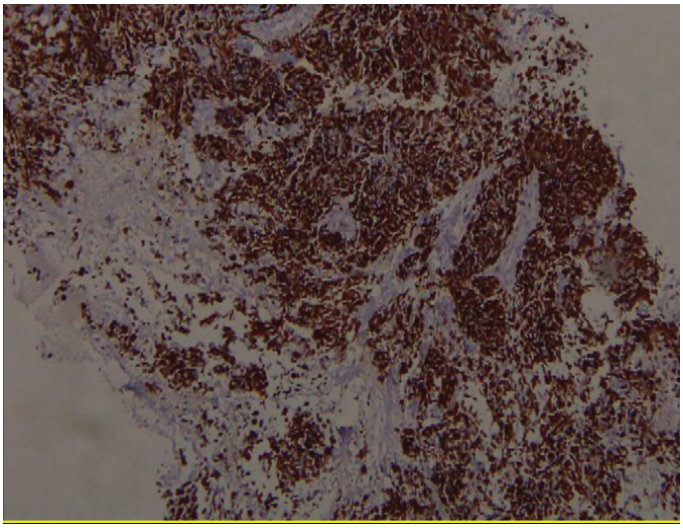

Figure 7. Section showing positive staining for Synaptophysin in the invasive component.

radical mastectomy (cyclophosphamide 0.6 g once, epirubicin 60 mg once and docetaxel 60 mg twice every 3 weeks). The clinical baseline characteristics of both patients are reported in Table 1 and the immunohistochemical results are reported in Table 2. Primary SCNCB is uncommon [1,3-9], and a form of small cell neuroendocrine carcinoma [3-6]. While SCNC is mostly seen in lung

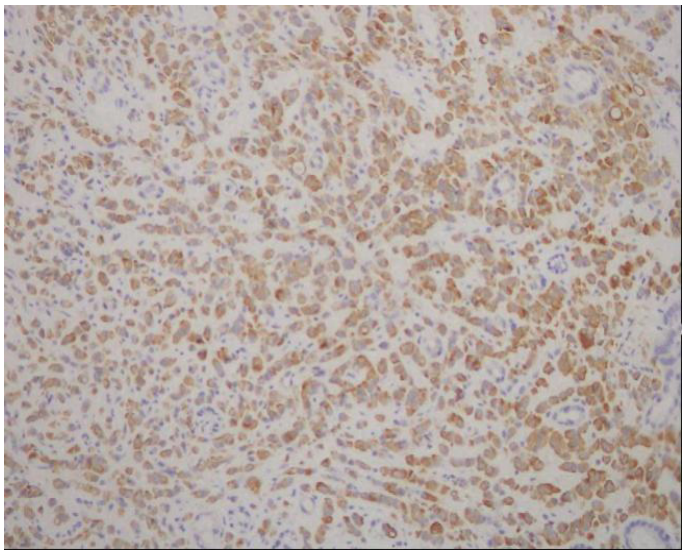

Figure 8. Section showing positive staining for CK7 in the invasive component.

tissue [1-6], but also occurs in breast, larynx, trachea, gastrointestinal tract and other tissues [1-9]. Due to its rare occurrence, there currently lacks of standard therapy [1]. In fact, up to now, less than 70 cases have been reported worldwide [7]. In the 2016, McCullar et al. described 19 SCNCB patients; the median age was 58 years, range 37 to 79 years [2]. Moreover, the vast majority of cases involved postmenopausal women over 60 [1-10]. In many cases, regional lymph node involvement had already occurred at the first visit (50% to 67% of patients) [1]. However, in the two cases we reported, no distant metastasis was found, and only the second case found regional lymph node metastasis.

SCNCB has no specific appearance on radiological images [11,12]. A large number of patients had breast mass and/or lymph node metastasis [9], but there still were certain cases where no masses [3]. SCNCB can't distinguish from other tumors by breast X-ray mammography, ultrasound, or magnetic resonance imaging [11], and also requires a biopsy to confirm diagnosis to exclude metastasis form a different primary tumor [7,13]. Histopathological images of SCNCB are most similar to those of small cell lung cancer [6-13], including small nuclei, dark stained cytoplasm, fine granules, evenly distributed chromatin, absent or not obvious nucleoli, and more common mitosis [9-15]. Carcinoma *in situ* can reveal the breast primary [1-12]. Immunohistochemistry is an efficient method to distinguish SCNCB from other breast tumors [13]. The positive rate of Estrogen Receptor (ER), Progesterone Receptor (PR), NSE and synaptophysin (syn) are 60% to 70%, 50% to 60%, 88.2% and 63.8% respectively [5]. Others have reported the positive expression of CD56, TTF-1, and chromogranin A in SCNCB [3-15]. About these two cases the syn Figure 7 and CK7 Figure 8 expression was positive. Her-2 expression was negative in almost patients. In 2016, next-generation gene sequencing revealed that both small cell cancers of the breast and of the lung displayed a mutation of TP53 in 75% of cases. In the case of breast, 33% of cases displayed a mutation in PIK3CA while PIK3CA mutations were completely absent in small cell cancer of the lung [2,8]. It is still unclear how SCNCB arises, but it has been suggested that it may arise from regular lobular or ductal carcinoma [16], or from cells which have multipotent capability of differentiation [17].

There currently has no standard treatment method for SCNCB [1], and recently a multi-disciplinary approach has been proposed [1,7]. Compared with lung cancer, surgical intervention is more important for extrapulmonary small cell carcinoma (EPSCC) [9-18], especially for small cell cancer of the breast [11]. Chemotherapy and radiotherapy are needed as adjuvant therapies post-surgery [5,19]. Chemotherapy usually includes platinum compounds combined with etoposide, anthracycline and docetaxel [1,18]. For tumors with *in situ* characteristics, docetaxel combined with carboplatin is a more preferred option. Neoadjuvant therapy is also important. It has been reported that the curative effect of neoadjuvant chemotherapy can be evaluated by measuring changes in tumor-mass. However, another report revealed that surgery had no positive effect on the outcome of EPSCC, and that preventive craniocerebral irradiation was a factor for positive outcome for EPSCC [18,20]. Reports on the prognosis of SCNCB varies widely according to the literatures [4-8], and depends on tumor stage [2-21]. A high Ki-67 index and involvement of four regional lymph nodes could be a risk factor for recurrence and metastasis [5,22]. The rate of one year recurrence-free-survival varied from 13% to 64% with the multi-disciplinary treatment [18]. The most common sites of metastasis were liver, brain, lung and lymph nodes, similar to other forms of breast cancer [5]. It has been reported that, the prognosis of early stage was better than later stage [9]. According to a report from 2013, the three-year survival for localized and extensive EPSCC tumors was 28% and 9% respectively. The prognosis of small cell cancer of the breast was often better, with a 3-year survival.

Conclusion

Small cell neuroendocrine cancer of breast is a rare disease. A number of small cell cancer of breast patients had the swelling mass, also had no-mass reports. It was crucial to exclude the metastasis tumor from other tissue or organic when diagnosis of small cell carcinoma of breast, especially from the lung. Recently, a multi-disciplinary approach of surgery, chemotherapy, and radiotherapy has been used to treat patients with SCNCB. The prognosis for small cell carcinoma of the breast varies widely, and the early disease is the most optimistic in all EPSCCs.

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