Secretory breast carcinoma: a clinicopathological and immunohistochemical study of 7 cases

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Abstract: Secretory breast carcinoma (SBC) is a rare distinct subtype of invasive breast cancer with good prognosis. Due to the limited reported SBC cases, our aim was to discuss the clinicopathological features of a series of SBC cases. We accepted 7 cases of SBC from the First Affiliated Hospital of China Medical University between 2011 and 2015. Seven respective tissue slides were stained with hematoxylin and eosin and performed immunohistochemistry with antibodies against ER, PR, HER-2 and Ki-67. The age of the patients (all women) ranged from 25 to 61 years (median age, 50). The tumor sizes ranged from 1.70 cm to 3.04 cm in diameter (median size, 2.0 cm). None had positive axillary lymph nodes. Histologically, most cases showed mixed microcystic, solid and tubular patterns. All tumor cells showed intracellular and extracellular secretory materials and mild to moderate dysplasia. Immunohistochemically, most cases were negative for ER, PR, and HER2 and had a low Ki-67 LI. The median follow-up period was 39 months, and they did not have recurrence after surgery. One patient was not available for follow-up. One patient developed recurrence and metastasis 18 months after the initial surgery and died within 42 months of the surgery. This case had mixed patterns, moderate nucleus atypia, a prominent nucleolus, and high Ki-67 LI. We suggested that solid and nested invasive growth patterns, higher nucleus grade, and high Ki-67 LI may be related to poor prognosis. However, the number of cases was not enough and more studies need to be researched in the future.

Keywords: Secretory breast carcinoma, breast cancer, immunohistochemistry

Introduction

Secretory breast carcinoma (SBC) is a rare type of breast cancer (less than 0.15% of all cases) [1]. SBC was first termed as “juvenile carcinoma” by McDivitt and Stewart in 1966, based on the fact that the average age of the seven female children was nine, with the ages ranging from three to fifteen years old [2]. Though subsequent research reported that this carcinoma was not limited to young adolescents and could occur in any age, the use of the term “juvenile carcinoma” lasted for ten more years. In 1980, Tavassoli and Norris proposed this disease could be renamed “secretory carcinoma” (2/3 of about 100 published SBC cases have been adults) [3]. SBC can occur both in females and males. SBC is a distinct variant of breast cancer and is distinguished by the characteristic of abundant extracellular and intracellular secretory materials, which is usually periodic acid-Schiff (PAS) positive eosinophilic secretions. In 1981, the World Health Organization officially listed SBC as a type of breast cancer [4]. SBC always occurs in the subareola but it may occur in any region of the breast. It usually presents as a mobile and well-described mass, sometimes resembling fibroadenoma [5]. In histology, SBC mainly includes solid, microcystic, and tubular patterns. Generally, SBC is negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER)-2/neu, and has a low proliferation index. This tumor has favorable prognosis and rare axillary lymph node metastases [6].
Secretory breast carcinoma of 7 cases

Recently, studies have found that SBC has a characteristic balanced chromosome translocation t(12;15), which creates an ETV6-NTRK3 fusion gene that encodes a chimeric tyrosine kinase [7].

Nevertheless, there are very few case series that report this rare aggressive neoplasia. In this paper, we reported 7 cases of SBC in Chinese women and investigated a clinicopathological characteristic of SBC.

Materials and methods

Case selection

We reviewed the slides of SBC patients between 2011 and 2015 retrospectively from the First Affiliated Hospital of China Medical University. After a second diagnosis confirmed by two pathologists, 7 cases of SBC were accepted. Additional clinical and pathological information was obtained from pathological reports and hospital records. In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants.

Immunohistochemical evaluation

Two independent and blinded investigators randomly evaluated all the slides. ER and PR are considered positive if positive nuclear staining is at least 1% [8]. HER2 staining was defined as follows [9]: IHC staining of 3+ (>30% uniform, intense membrane staining of tumor cells); 2+ (at least 10% complete membranous staining, either weak or uniform staining of tumor cells); 1+ (<10% weak incomplete membranous staining of tumor cells); 0 (no immunostaining). IHC staining of 0 to 1+ were deemed as negative. S-100 protein was considered positive if the antigen was expressed in the nucleus or the cytoplasm, with nuclear expression being more dominant. Ki-67 was considered positive when nuclear staining presented with any intensity. The Ki-67 labeling index (LI) was determined by counting the number of Ki-67-positive tumor cell nuclei in 1000 invasive tumor cells in the hot spots. At least three high-power (>40 objective) fields were selected randomly, including the most densely Ki-67 staining areas, which were called “hot spots”.

Table 1. Summary of clinical features of 7 patients with SBC

<table>
<thead>
<tr>
<th>Case no</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Site</th>
<th>Tumor size (cm)</th>
<th>Duration (mo)</th>
<th>Treatment</th>
<th>ALN involved</th>
<th>Recurrence (mo)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>F</td>
<td>R</td>
<td>1.8×1.5×1</td>
<td>1</td>
<td>LE</td>
<td>NE</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>F</td>
<td>L</td>
<td>2×2×2</td>
<td>24</td>
<td>MRM + CT</td>
<td>None</td>
<td>None</td>
<td>Well, 23</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>F</td>
<td>R</td>
<td>2×2</td>
<td>12</td>
<td>MRM + CT</td>
<td>None</td>
<td>None</td>
<td>Well, 52</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>F</td>
<td>R</td>
<td>2.2×2×1.5</td>
<td>6</td>
<td>MRM + CT + RT</td>
<td>None</td>
<td>Yes, 18</td>
<td>Died, 42</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>F</td>
<td>L</td>
<td>2.6</td>
<td>1</td>
<td>SM + CT</td>
<td>NE</td>
<td>None</td>
<td>Well, 52</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>F</td>
<td>R</td>
<td>3.04×1.1</td>
<td>12</td>
<td>MRM + CT</td>
<td>None</td>
<td>None</td>
<td>Well, 39</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>F</td>
<td>R</td>
<td>1.7×1.5×1</td>
<td>3</td>
<td>NAC + MRM + CT + ET</td>
<td>None</td>
<td>None</td>
<td>Well, 39</td>
</tr>
</tbody>
</table>

Abbreviations: ALN, Axillary lymph nodes; CT, chemotherapy; ET, endocrinotherapy; F, female; L, left; LE, local excision; mo, months; MRM, modified radical mastectomy; NA, not available; NE, not examined; R, right; RT, radiotherapy; SM, simple mastectomy; y, years old; NAC, neoadjuvant chemotherapy.
Results

Clinical findings

The clinical features of the 7 patients with SBC are summarized in Table 1. The ages of the 7 patients (all women) ranged from 25 to 61 years (median age, 50). The tumor size ranged from 1.70 cm to 3.04 cm in diameter (median size, 2.0 cm). Of the 7 cases, 5 (71.4%) were in the right breast and 2 (28.6%) were in the left breast. All the patients went for clinical consultation after discovering a painless mass in the breast either by routine physical examination or by accidental self-examination. None had bleeding discharge from the nipple. The tumors had been growing slowly, and the mean duration from detection of the mass to treatment ranged from 1 to 24 months (median months, 6). In most of the cases, ultrasonography (Figure 1) and mammography (Figure 2) revealed a small, well-circumscribed, and solitary mass. No case suffered axillary lymph node infiltration. All 7 patients received surgery: 5 radical mastectomies, 1 simple excision, and 1 local excision. Excluding the patient who had local excision (case 1), the other six
cases received postoperative chemotherapy, with one (case 4) receiving radiotherapy and one (case 7) receiving neoadjuvant therapy and endocrinotherapy. Clinical follow-up was available in 6 cases, and one patient (case 4) developed the evidence of recurrence and metastasis 18 months after the initial surgery and died after 42 months of the surgery. The follow-up period after the surgery of the 5 living cases ranged from 23 to 52 months (median months, 39), and they did not have recurrence after surgery.

**Histopathological findings**

The histological findings of the 7 patients with SBC are summarized in Table 2. H&E staining and immunohistochemical pictures of two cases are displayed in Figures 1 and 2. The border of tumors displayed pushed or infiltrated and tumor cells showed several histological patterns, such as microcystic (Figures 1A and 2A), solid, and tubular patterns. Microcystic patterns were most frequent, but all three patterns can be mixed with varied proportions.
Table 2. Histopathological and immunohistological findings of 7 cases of SBC

<table>
<thead>
<tr>
<th>Case</th>
<th>Morphological patterns</th>
<th>Mitosis (/10 HPF)</th>
<th>Grade</th>
<th>ER</th>
<th>PR</th>
<th>HER2</th>
<th>Ki-67</th>
<th>S-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Microcystic + solid</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10%</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Microcystic</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1+</td>
<td>1%</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Microcystic</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>NE</td>
<td>3%</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Microcystic + nested + solid</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40%</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Microcystic + tubular</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>90%+</td>
<td>1+</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>Microcystic + solid + tubular</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20%</td>
<td>NE</td>
</tr>
<tr>
<td>7</td>
<td>Microcystic + solid + tubular (calcification)</td>
<td>1</td>
<td>1</td>
<td>50%+</td>
<td>-</td>
<td>2+</td>
<td>40%</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor-2/neu; NE, not examined; PR, progesterone receptor.

among the cells. One case also displayed nested patterns (Figure 2B) mixed with microcystic (Figure 2A) and solid patterns. Most tumor cells had mild atypia without a prominent nucleus, but one case presented a prominent nucleus (Figure 2B). Mitotic activity was rare: two cases were in 2/10 HPF, and others were in 1/10 HPF. Two cases were grade 2, and other cases were grade 1. All tumor cells were round to polygonal in shape and observed secretory materials within tumor cells and extracellular lumens (Figure 1B) or a granular or vacuolated cytoplasm (Figure 2B).

**Immunohistochemical findings**

The immunohistochemical findings of the 7 patients with SBC are summarized in Table 2. The rate of negative expression of ER, PR, HER2 was 85.7% (6 of 7), 85.7% (6 of 7), and 83.3% (5 of 6, one not examined) respectively. The Ki-67 LI had a mean value of 17.71% and ranged from 1% to 40%.

**Discussion**

This SBC occurs mostly in young females, but middle-aged and older women can also be affected [10, 11]. In our cases, the median age of the patients was 50. This held that SBC could occur in older females. Additionally, occasional cases have been reported in men [12]. The tumor is usually a single mass and occurs in any quadrant of the breast, mostly under the mammary areola. SBC typically presents as a painless, mobile, well-circumscribed and slow-growing small mass. Bloody nipple discharge may manifest in some cases [13]. Breast ultrasound typically shows a solitary hypoechogenic mass that resembles a benign lesion of the breast [14]. In our report, all patients were female with ages ranging between 25 to 61 years, and the tumor locations coincided with that of typical breast carcinomas. The tumor sizes were small, with most being less than 2.0 cm in diameter.

**Pathomorphology**

According to the arrangement of tumor cells of SBC, Akhtar et al revealed that SBC mainly had solid, microcystic, and ductal histological patterns [15]. The solid pattern is characterized by the nodular structure of dense tumor cells, and the large clusters of the tumor cells are separated by variable thickness fibrous septa. Within the cytoplasm of the tumor cells, amounts of eosinophilic granules and small secretory vacuoles are present. In microcystic patterns, tumor cells consist of small cystic spaces which can combine into macro-cystic spaces. Among the tumor cells, there are unequal sizes of gland-like or cyst-like spaces containing eosinophilic secretions and lined by cuboidal epithelium cells. The ductal pattern consists of duct-like spaces with secretions [16]. Some tumor cells proliferate in the form of papillary projections [17]. In our cases, most cases were mixed with several usual patterns. We also found a patient (case 4) with nested growth pattern that had poor prognosis. SBC tumor cells consist with two subtypes and Tavassoli et al classified the SBC tumor cells into Type A and B according to the variations in the tumor cell cytoplasm and distribution of secretions [3]. Whether the SBC constituted mainly of Type A or Type B cells had no prognostic value. Our cases presented a mixture of these two types of cells with minimal cellular pleomorphism and mitoses.
Immunophenotype and molecular genetics

In the previous studies of IHC, most cases of SBC were ER, PR, and HER-2 negative (triple-negative), especially in children and adolescents [18-20], although a few cases have reported hormone receptors were positive [21]. Diallo et al reported 13 cases of SBC, the expression of ER, PR and HER-2 are low, and immune-positive rates were 31% (4/13), 15% (2/13) and 15% (2/13) respectively [22]. Our cases also showed low expression of hormone receptors and HER-2. Recently, studies have demonstrated that the immunohistological features of SBC belonged to the basal-like breast cancer phenotypic spectrum, including cytokeratins 5/6 (CK5/6), CK14, and KIT expression [23]. Initial gene spectrum analysis showed that all basal-like tumors have bad prognosis, but now researchers think the prognosis is different within variant subtypes. SBC is one of the basal-like tumors that has good prognosis and has significant heterogeneity with basal cell like carcinoma [23]. In molecular genetics, studies have found that SBC has a characteristic balanced chromosome translocation t (12; 15), which creates an ETV6-NTRK3 fusion gene that encodes a chimeric tyrosine kinase [7]. In 2002, Tong et al first reported expression of the ETV6-NTRK3 fusion gene in SBC, and the fusion gene was confirmed in 12 of 13 (92%) SBC cases, but it was not expressed in other ductal cancers [7]. Nikita et al also confirmed that the ETV6-NTRK3 fusion gene is a characteristic genetic alteration in SBC [24].

Treatment and prognosis

SBC does not have consensus treatment guidelines, surgery is the primary treatment of SBC, but the method and extend of surgery remains controversial [25]. There is insufficient evidence to recommendation in chemotherapy and a metastatic SBC had been reported that it had no response to chemotherapy [26]. However, adjuvant chemotherapy is usually used, especially in patients with positive axillary lymph nodes [27]. Radiotherapy after the conservative surgery can be advised in adults, however it is not advised in children because of some negative effects such as pulmonary fibrosis, damage of the rib and asymmetry of the rib cage [28]. Recent research suggested PKC412, also named midostaurin, to be an inhibitor of the ETV6-NTRK3 fusion gene; this means it could serve as a therapeutic drug for SBC [29]. SBC has excellent prognosis, and axillary lymph node metastases or distant metastases events were rarely reported. Poor prognostic factors previously reported were masses greater than 2 cm in diameter and poor gross circumscription [30].

In our case, a 26-year-old woman (case 4) developed the evidence of recurrence and metastasis 18 months after the initial surgery and died after 42 months of the surgery. The tumor size was 2.2×2.0×1.5 cm, and she was treated with modified radical mastectomy in combination with chemotherapy and radiotherapy. In microscopy, the tumor patterns were mixed microcystic, nested and solid patterns, mitosis was 2/10 HPF, nucleus grade was 2, and the Ki-67 LI was 40%. The recurrence and poor prognosis in this patient suggested that solid and nested invasive growth patterns, higher nucleus grade, and high Ki-67 LI may be correlated with poor prognosis.

SBC is a rare type of breast cancer with indolent behavior and good prognosis. In our reports, we suggested that high grade tumors with a prominent nucleus and high Ki-67 LI may be related with poor prognosis. However, the number of cases was not enough to confirm this, and more studies are needed for further research.

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Disclosure of conflict of interest

None.

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