Secretory Carcinoma of the Breast With Multiple Distant Metastases in Brain and Unfavorable Prognosis: a Case Report and Literature Review

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Case Report

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Abstract

Background: Secretory carcinoma of the breast is one of the rarest entities accounting for less than 0.15% of all infiltrating breast carcinomas. It has characteristic histopathological and molecular features and more favorable prognosis. In this case report, we describe a local advanced secretory carcinoma of the breast with chemo-resisted for neoadjuvant chemotherapy and unfavorable prognosis.

Case Presentation: A hard, painless and palpably bossed mass about 12 cm in diameter occupied most of the left breast of a 39-year-old woman and fixation to the overlying skin. Breast ultrasonography and magnetic resonance imaging (MRI) scan gave the same grading as BI-RADS IV. A needle biopsy was performed and pathological diagnosis was secretory carcinoma. Neoadjuvant chemotherapy (NAC) was then performed, after which ultrasonography and MRI scan revealed the tumor was partial response for EC therapy while progressive disease after the DC therapy. The tumor showed chemo-resisted for neoadjuvant chemotherapy. Left breast mastectomy and axillary lymphadenectomy were subsequently performed. Tumor cells were triple-negative and positive for S-100 and periodic acid-Schiff (PAS) staining. Fluorescence in-situ hybridization (FISH) analysis indicated the fusion arrangement of ETV6-NTRK3 gene. The patient underwent multiple distant metastases in brain, and died of these metastases 19 months after initial diagnosis.

Conclusion: Secretory carcinomas of breast have been described as a low-grade histologic subtype with a favorable prognosis. This case showed chemo-resisted for neoadjuvant chemotherapy, multiple distant metastases, and final an unfavorable prognosis. Further research is needed to better understanding of its behavior and treatment of this rare tumor.

Introduction

Secretory carcinoma is a very rare type of breast carcinoma. It was first reported in children and known as juvenile breast carcinoma [1], but now it is clear to occur in adults of both sexes. Secretory carcinoma of breast has characteristic histopathological and immunohistochemical features [2]. Recently, it has been shown that the ETS variant 6-neurotrophic tyrosine kinase receptor type 3 (ETV6-NTRK3) gene fusion is associated with secretory carcinoma [3, 4]. Secretory carcinoma of breast was generally described with a favorable prognosis and suggested that treatment should be as conservative and non-aggressive as possible [5].

Here, we report a case of a 39-year-old woman who suffered from a local advanced secretory carcinoma of the breast with chemo-resisted for neoadjuvant chemotherapy and subsequent multiple brain metastases and unfavorable prognosis. The aim of this report is to help to better understand the behavior of this rare tumor in order to develop a standard approach to treatment.

Case Presentation

Clinical history

A 39-year-old woman who noted a lump in her left breast for 13 months and which increased rapidly for 2 months. In May 2017, the patient firstly admitted to our hospital. She had no past history of malignancy and no family history of breast carcinoma.

In physical examination, a hard, painless and palpably bossed mass about 13.0 cm in diameter occupied most of the left breast and fixation to the overlying skin (Fig. 1a). There were no abnormalities in the right breast. MRI scan revealed a focal high-density mass of 11.0×12.0 cm and gave the grading as BI-RADS IV (Fig. 1b). Breast ultrasonography revealed a huge mass of size 11×11 cm, shaped regularly in the left breast and a hypoechoic mass about 2.8×1.0 cm in the left axilla. Ultrasonography examination also graded the breast mass for BI-RADS IV (Fig. 1c). The resulting pathological diagnosis for needle biopsy was secretory carcinoma and the disease in this patient was staged as T4N1M0 (Stage IIIB). Neoadjuvant chemotherapy was then performed with 4 cycles of Epirubicin/Cyclophosphamide (EC) regimens and 2 cycles of Docetaxel/Carboplatin (DC) regimens. Physical examination was routinely performed after each cycle of chemotherapy. As shown in Table 1, the tumor size gradually decreased in the first 4 cycles of EC regimens while conversely, increased in 2 cycles of DC regimens. Figures of physical examination, MRI scan and Ultrasonography during the whole course of neoadjuvant chemotherapy also revealed the tumor was partial response for EC regimens therapy while progressive for DC regimens (Fig. 1a-1i).

This patient completed modified radical mastectomy (left breast mastectomy and left axillary lymphadenectomy) and consecutive latissimus dorsi breast reconstruction in October 2017. 4 cycles of Fluorouracil/Epirubicin/cyclophosphamide (FEC) regimens were continuously given. Radiotherapy was carried out to the chest wall and drainage areas (50Gy/25f). The patient was switched to intensive chemotherapy with oral Capecitabine for 8 cycles.

In October 2018, the patient was hospitalized again with the complaints of a headache and an ataxia. Brain MRI scan showed multiple metastases in left occipital lobe, bilateral frontal lobe and left side of the cerebellum, and the largest mass had a maximum diameter of 3.5 cm (Fig. 2a-c). Whether there were metastases in other organs was unclear. She finally gave up treatment and died in March 2019. The disease-free survival and overall survival of this patient were 10 months and 19 months, respectively.

Table 1
Tumor size by physical examination during NAC.

Chemotherapy course	☐	☐	☐	☐	☐	☐	☐	☐
Length (cm)	14.0	13.0	12.0	10.0	10.0	9.0	10.0	11.0
Width (cm)	13.0	11.0	10.5	9.5	9.5	9.0	10.0	11.0
Height (cm)	8.0	6.0	4.5	4.0	3.5	4.0	4.5	5.0

☐ Pre-chemotherapy, ☐ after 1st cycle of EC, ☐ after 2nd cycle of EC, ☐ after 3rd cycle of EC, ☐ after 4th cycle of EC, ☐ after 1rst cycle of DC, ☐ after 2nd cycle of DC, ☐ 25 days after 2nd cycle of DC

Gross features

On gross examination, the needle biopsy specimen pre-chemotherapy was strip-like, gray-red, slightly hard in texture, and nothing special. The mastectomy specimen after chemotherapy covering with skin and nipple was submitted for examination. Cut surface showed about a mass of 8×7×5 cm, with white-gray multiple nodules and obvious accompanied by bleeding and necrosis. No nipple and periareolar lesion were seen (Fig. 3). 15 lymph nodes were detected in the separate axillary tissues.

Microscopic features

Microscopic examination for biopsy specimen prechemotherapy revealed the tumor cells are arranged combinations of microcystic (Fig. 4a) and solid patterns (Fig. 4b), and characteristically contained abundant extracellular secretory material. The cells had abundant granular eosinophilic cytoplasm and round moderate grade nuclei. There was no perineural or vascular invasion. The biopsy hence suggested a secretory carcinoma of the breast. For the mastectomy specimen, the tumor also displayed the combinative structures of microcystic and solid patterns (Fig. 4c) and a pushing border near to skin (Fig. 4d), accompanied by massive necrosis and hemorrhage. Responding to neoadjuvant chemotherapy, the tumor cells showed obvious morphological changes in some areas, such as nuclear concentration and fragmentation of tumor cells and pleomorphic giant tumor cells with eosinophilic and foamy cytoplasm (Fig. 4e). Isolated tumor cell was detected in one enlarged axillary lymph node (Fig. 4f).

Immunohistochemistry of the biopsy specimen on review of paraffin embedded blocks showed tumor cells were positive cytoplasm staining for epithelial membrane antigen (EMA, Fig. 4g), S-100 (Fig. 4h), Vimentin, and positive cytomembrane staining for E-Cadherin (Fig. 4i) while triple-negative results for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2). It was also negative staining for androgen receptor (AR), gross cystic disease fluid protein 15 (GCDFP-15), and smooth muscle actin (SMA, Fig. 4j). Ki-67 proliferation index was 50%. The secretory material is positive for periodic acid-Schiff (PAS) staining (Fig. 4k).

Fluorescence in-situ hybridization (FISH) analysis indicated the fusion translocation t (12;15) of ETV6-NTRK3 gene. As shown in Fig. 4l, the red signal represented ETV6 gene, and the green signal represented NTRK3 gene, and there were number of ETV6-NTRK3 fusion signals detected by FISH.

Discussion

Secretory carcinoma of breast is one of the rarest entities accounting for less than 0.15% of all infiltrating breast carcinomas [2]. It was first described in 1966 by McDivitt and Stewart as a rare breast neoplasia identified in female children and adolescents, at the average age of nine [1]. But now it was clear to occur in adults of both sexes [6–8]. The typical clinical presentation of secretory carcinoma of breast is a slow-growing, painless, well-circumscribed, palpable mass occurring anywhere but more common in the outer upper quadrant of breast [9]. Microscopically, secretory carcinoma of breast is arranged with a solid, microcystic and tubular structure, composed of cells that produce abundant intracellular and extracellular

milk-like secretory material, intensively positive for alcian blue or PAS. The tumor cells have low-grade features with small to medium sized, oval to round nucleus, scant mitotic activity and abundant granular eosinophilic cytoplasm. Occasionally, the papillary growth area can also be the dominant structure. Immunohistochemically, tumors cells were positive for S100 staining and triple-negative for ER, PR and HER2 [2, 9, 10]. Tognon et al firstly reported in 2002 that secretory carcinoma of breast harbored a recurrent balanced chromosomal translocation, t (12;15) (p13; q25), which leads to the formation of the ETV6-NTRK3 fusion [11].

In addition to breast, secretory cancer can also occur in other organs which containing secretory glands, such as parotid gland, salivary gland, sweat gland, lacrimal gland and thyroid [12–17]. Secretory carcinoma occurs in other organs shows the same combinative structures of cribriform patterns, solid patterns, and microcystic patterns, and extracellular secretion positive for Alcian blue or PAS. The ETV6-NTRK3 gene fusion are also showed in secretory carcinomas occurring in the breast and other organs. Recently, some novel gene mutations of secretory carcinomas occurring in the salivary glands were reported. Sasaki et al found a case with CTNNA1-ALK fusion [18] and Black et al reported another case harboring two gene fusions, ETV6-RET and EGFR-SEPT14 [19], expanding the molecular characterization of secretory carcinoma beyond the ETV6-NTRK3 gene mutation.

Secretory carcinoma of breast was generally described with a favorable prognosis, but there were still a few cases presenting distant metastases. According to literatures till date, 12 cases of secretory carcinoma of breast with distant metastasis were reported (6 cases with multiple organ metastases), the most common metastatic organs were lung (9 cases), liver (4 cases), bone (4 cases) and skin (2 cases), and other metastatic organs were kidney (1case), mediastinum (1case), pancreas (1case) and serous (1 case). 8 cases of mortality due to metastatic secretory carcinoma was reported, from 6-240 months after initial diagnosis (mean survival was 74.6 months) [5, 20–29].

Due to scarcity of reported cases, there are no consensus guidelines for treatment. Surgery is considered the mainstay of treatment of secretory carcinoma. The demonstration of late local recurrence has led many to propose mastectomy for the patients with this disease [30]. In adults, a simple mastectomy, at minimum, is recommended. Modified radical mastectomy has been favored by some authors in cases with tumor sizes greater than 2 cm and poor gross circumscription [31]. Adjuvant chemotherapy and radiation have been tried for the disease without much success [23].

Tavassoli and Norris [6] suggested three features that indicated a favorable prognosis in secretory carcinoma of the breast: (1) tumor size less than 2 cm; (2) age of less than 20 years at diagnosis; and (3) circumscribed margins. Unfortunately, none of these three features was present in our case. After completing the medical inspection, 4 cycles of EC regimens and 2 cycles of DC regimens neoadjuvant chemotherapy was firstly used because of its large tumor size (12 cm) and late clinical stage (T4N1M0/IIIB). The tumor was partial response for EC regimens therapy while progressive for DC regimens. Avoided losing the opportunity of surgical treatment, modified radical mastectomy was performed immediately. 4 cycles of FEC regimens and 8 cycles intensive chemotherapy were continuously given. Radiotherapy was

carried out to the chest wall and drainage areas. The patient was then switched to intensive chemotherapy with oral Capecitabine for 8 cycles. But regrettably, multiple brain metastases were found 10 months later and the overall survival of this patient was 19 months.

Conclusion

In this paper, we report a case of secretory breast carcinoma of a 39-year-old female on the basis of imaging, histopathological pattern, immunophenotype and molecular alteration. Different from this rare subtype of breast cancer as described with a low-grade histologic and favorable prognosis, our case showed chemo-resisted for neoadjuvant chemotherapy and multiple distant metastases in brain, and final an unfavorable prognosis. To the best of our knowledge, this is the first report of secretory carcinoma of breast with multiple metastases in brain and died of these metastases.

Abbreviations

AR: androgen receptor; DC: Docetaxel/Carboplatin; EC: Epirubicin/Cyclophosphamide; ER: estrogen receptor; FEC: Fluorouracil/Epirubicin/cyclophosphamide; GCDFP-15: gross cystic disease fluid protein 15; HER2: human epidermal growth factor receptor 2; FISH: Fluorescence in-situ hybridization; MRI: magnetic resonance imaging; PAS: periodic acid-Schiff; PR: progesterone receptor; SMA: smooth muscle actin

Declarations

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Authors' contributions

HPT conceptualized the case report, performed the histopathologic evaluation and largely contributed to writing. LHZ conceptualized the case report and collected clinical data. HBJ collected imagological data. GEX supervised throughout the study and approved the final manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This case study was approved by the Institutional Review Board for ethical committee of Shenzhen Maternity & Child Healthcare Hospital.

Consent for publication

Written informed consent was obtained from the patient for publication of the case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no conflicts of interest.

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Figures

Figure 1

Physical, imaging and ultrasound examination of tumor during NAC. a, b, c: pre-Chemotherapy; d, e, f: after 4th cycle of EC; g, h, i: 25 days after 2nd cycle of DC

Figure 2

Multiple metastases (white arrows) in brain scanned by MRI. a. metastases in left cerebellar hemisphere in horizontal plane; b. metastases in left frontal lobe in horizontal plane; c. metastases in bilateral frontal lobe in coronal plane.

Figure 3

Gross finding appearance of the mastectomy specimen showed a solid-cystic mass with clear margin and white nodules in the cut surface

Figure 4

Microscopic features. a. microcystic pattern with of the tumor per chemotherapy (HE, $\times 100$); b. Solid pattern of the tumor per chemotherapy (HE, $\times 100$); c. solid pattern of the tumor in the mastectomy specimen (HE, $\times 100$); d. the pushing border near to skin showed in the mastectomy specimen (HE, $\times 40$); e. morphological changes of tumor cells after chemotherapy (HE, $\times 100$); f. isolated tumor cell was detected in axillary lymph node (HE, $\times 100$); g. positive cytoplasm staining for EMA by IHC (Envision, $\times 100$); h. Positive cytoplasm staining for S100 by IHC (Envision, $\times 100$); i. Positive cytomembrane staining for E-Cadherin by IHC (Envision, $\times 100$); j. Negative staining for SMA by IHC (Envision, $\times 100$); k. The extracellular secretory material was positive on staining with periodic acid-Schiff (PAS, $\times 100$); l. Fluorescence in-situ hybridization (FISH) analysis indicating the presence of ETV6-NTRK3 fusion arrangement ($\times 1000$).

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