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Primary Small Cell Carcinoma of the Breast Combined with Invasive Ductal Carcinoma 1

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Abstract

Primary small cell carcinoma of the breast (SmCC) is a rare type of breast cancer and a histological subtype of neuroendocrine breast cancer. There is no standard treatment method, and the prognosis is unknown. It needs to be differentiated from lung metastases. A case of a 52-year-old woman is reported here who was diagnosed with small cell carcinoma combined with invasive ductal carcinoma. Whole-body PET-CT and enhanced MRI of the adrenal glands excluded any other primary disease. The patient received an adjuvant chemotherapy regimen of anthracycline combined with cyclophosphamide, sequential cisplatin, and paclitaxel. The patient was kept under close observation for any changes. This case report reviews the literature on SmCC to better understand its pathology characteristics and therapy. Due to the particularity of the patient's tumour composition, we referred to the treatment plan for small-cell lung cancer and adopted a treatment plan based on cisplatin.

Keywords: Small cell carcinoma, invasive ductal carcinoma, breast cancer, pathology, therapy.

INTRODUCTION

Neuroendocrine breast cancer (NEBC) is a rare subtype of breast cancer, accounting for approximately 0.3% to 1% of all breast cancers [1]. Despite being first described more than 40 years ago, WHO did not classify NEBC as a distinct subtype of breast cancer until 2003 [2]. This manuscript reports a case of primary breast small cell carcinoma (SmCC) in combination with invasive ductal carcinoma (IDC) along with the discussion on pertinent literature.

1. CASE DESCRIPTION

A 52 years old female patient, in a postmenopausal state, chief complaint: "Right breast mass found for one month". Physical examination revealed a palpable mass with a 1.5 cm × 3.0 cm diameter, firm, ill-defined, poorly mobile mass located in the inner of the right breast. Imaging findings (Fig. 1): (1) A breast ultrasound examination showed that there was a hypoechoic nodule next to the nipple in the 3-4 o'clock position of the right breast, with an echoless dark area inside and multiple hypoechoic masses in the right axilla. (2) Double mammography showed a lump in the lower quadrant of the right breast with a clear margin. A hollow-core needle was used to perform a biopsy of the right breast lump, but intraoperative frozen pathology could not determine the nature of the tumour. Subsequently, a minimally invasive excision biopsy was performed. Based on the appearance and texture of the resected tissue, we considered the possibility of malignancy. The postoperative paraffin sections also verified our judgment, suggesting small-cell carcinoma. After communicating with the patient's family, we conducted a radical mastectomy with sentinel-node biopsy on the right breast. Pathology: Invasive ductal carcinoma (15%) and small cell carcinoma (85%) were detected from the composition of the tumour. Small cell carcinoma cells are relatively uniform in morphology, with little plasma, a high nuclear-to-plasma ratio, and a lamellar or nested distribution. More cancer thrombus was seen in the vasculature, and no signs of cancer metastasis seen in lymph nodes (0/5). Immunohistochemical staining (Fig. 2-3): Both invasive ductal carcinoma and small cell carcinoma showed estrogen receptor (ER) (-), progesterone receptor (PR) (-), HER-2(-), Ki-67(approximately 90% +), neuron-specific enolase（NSE）(-), Chromogranin A (CgA) (-), synaptophysin（Syn）(-), thyroid transcription factor-1 (TTF-1) (-), CD56 (focal lesions +) and GATA3(-) in invasive ductal carcinoma and CD56 (+) and GATA3(+) in small cell carcinoma. To rule out metastatic small cell carcinoma, Positron emission tomography-computed tomography whole-body fusion image (Fig. 4) was performed, which showed a high possibility of adrenal metastases. Subsequently, an enhanced MR scan of the

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adrenal glands was performed (Fig. 4). After a discussion between the imaging and interventional specialists, they believed that there were no abnormalities in the bilateral adrenal glands. The results of the 21-gene test on the blood of the patient were (for more information, see the Appendix): (1) somatic variants, with one somatic variation discovered; (2) *RB1* deletion and *TP53* gene variation. Staging: pT2N0M0. Treatment strategy: EC sequential TCb chemotherapy as adjuvant treatment. The patient is being observed very carefully.

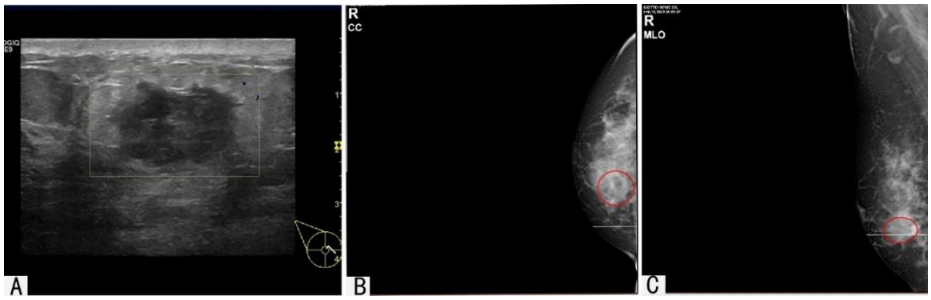

Figure 1: Ultrasound of the right breast (**A**): hypoechoic nodule with an echoless dark area visible within; Mammogram of the right breast: right CC-view (**B**) and MLO-view (**C**) showing a tissue mass (circle) in the right breast.

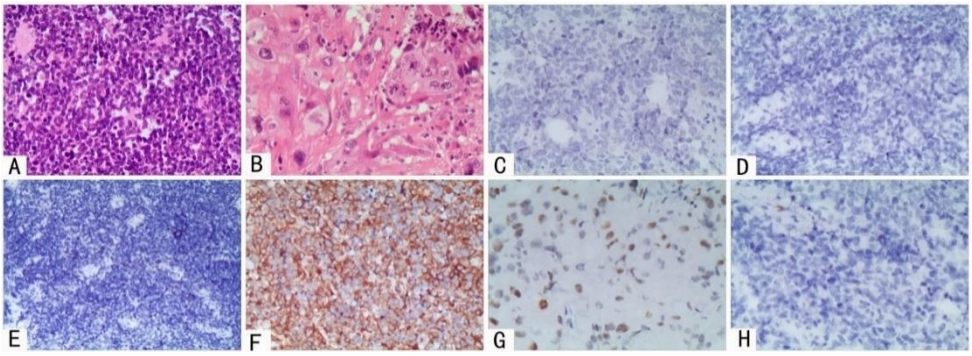

Figure 2: (A) Small cell carcinoma cells are relatively uniform in morphology, with little plasma, a high nuclear-to-plasma ratio, and a lamellar or nested distribution（B）The microscope observed the presence of an invasive ductal carcinoma component（HE）; Immunohistochemical staining of small cell carcinoma cells was seen to be negative for NSE（C）, CgA（D）, Syn（E） and TTF-1（H） and positive for CD56（F） and GATA3（G）.（×200）

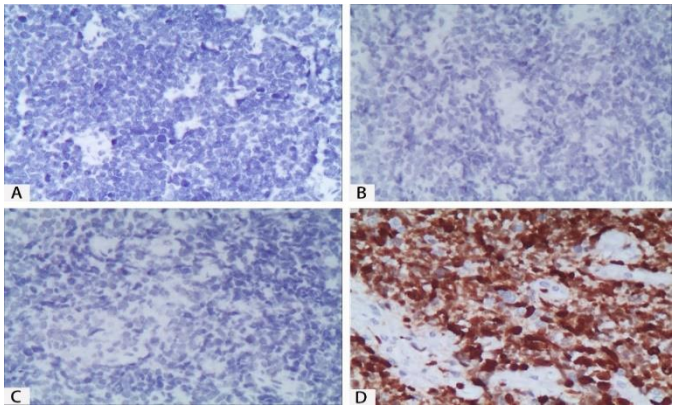

Figure 3: Small cell carcinoma cells stained negative for ER (A), PR (B), and HER-2 (C) immunohistochemically and positive for Ki-67 (D) immunohistochemically (×200).

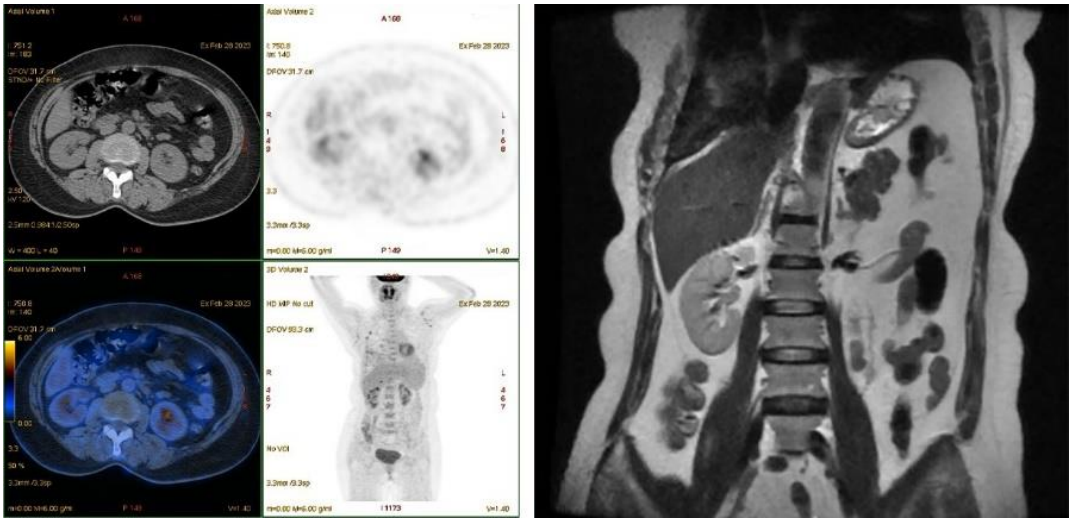

Figure 4: Positron emission tomography-computed tomography whole-body fusion image showing nodular foci in the medial limb of the right adrenal gland; MR scan of the renal region + adrenal glands + angiography enhancement scan suggesting no abnormalities in the adrenal glands bilaterally.

2. DISCUSSION

Small cell carcinoma (SmCC), while commonly occurring in the lung, is a highly aggressive tumour that can also develop in the breast, larynx, trachea, and other locations [1].

Concerning the pathological features of SmCC, the WHO defines NEBC as having three criteria [2]. One of these features is the presence of markers of neuroendocrine signatures, such as Syn, NSE, and CgA in immunohistochemistry. However, these markers are not always positive in SmCC [3]. Immune markers play an adjunctive role in the differential diagnosis of primary and metastatic NEBC. Positive expression of TTF-1 indicates a metastatic tumour, and positive expression of GATA3 indicates a mammary origin [2]. In the case of excluding other primary cancers, the diagnosis of SmCC can be made by combining the microscopic morphology of the cancer cells with immunohistochemical staining.

To date, the postoperative primary therapy for SmCC is chemotherapy, endocrine therapy, and radiotherapy. There is no standard approach for selecting a chemotherapy regimen to treat SmCC. The 2022 NCCN Clinical Practice Guidelines for SCLC recommend chemotherapy regimens for SCLC, including Irinotecan + Cisplatin or Carboplatin and Cisplatin or Carboplatin+Etoposide [4]. The chemotherapy treatment for SmCC refers to the chemotherapy regimen recommended by the aforementioned clinical practice guidelines for SCLC. According to some reports, chemotherapy drugs are based on the expression of Ki-67 protein. When SmCC expresses approximately 10% Ki-67, anthracycline therapy is generally recommended [5]. In the absence of robust data on the role of platinum compounds and etoposide in the adjuvant therapy of SmCC, Inno et al. [3] recommended treatment according to the same regimen as for ductal carcinoma. Therefore, if necessary, anthracyclines and/or taxanes chemotherapy regimens should be prioritized. 15% of this patient's pathological tissue was invasive ductal carcinoma, so the chemotherapy regimen of anthracycline combined with cyclophosphamide followed by cisplatin combined with paclitaxel was used.

The condition of the hormone receptors determines whether to administer hormone therapy as adjuvant therapy. According to one study, ER and PR were positive in 33% to 50% of the diseased tissues in SmCC [6]. No HER-2-positive primary breast small cell carcinomas (SmCC) are currently documented [1]. Furthermore, the role of HER-2 in primary small cell breast cancer (SmCC) is uncertain [7]. Targeted HER-2 therapy may be an option for HER-2-positive SmCC, assuming that its function is comparable to that in other invasive breast cancers [7]. The role of radiotherapy in the therapy of primary small cell breast cancer (SmCC) is controversial. It has been proposed that the therapy strategy might be personalized. Kanat et al. [8] proposed that adjuvant chemotherapy and radiotherapy may be avoided in older postmenopausal individuals with well-characterized malignancies. They reported seven cases of primary small cell carcinoma of the breast in females, one of whom was 75 years old, had no lymph node metastases, tested positive for ER and PR, was treated with tamoxifen alone, and had no evidence of recurrence at 20 months follow-up.

SmCC is a rare and specific type of breast cancer that has morphological and immunohistochemical characteristics

similar to those of SCLC, and the diagnosis is mainly based on pathology. Although there is currently no standard therapy, it can be based on the molecular expression characteristics of breast cancer, thus using chemotherapy, endocrine therapy, radiotherapy, targeted therapy and other suitable multi-modal adjuvant therapy. However, its efficacy needs to be confirmed by data from retrospective studies with large samples.

PATIENT'S CONSENT

Informed consent was taken from the patient.

CONFLICT OF INTEREST

The author declare no competing interests.

ACKNOWLEDGEMENTS

None.

AUTHOR'S CONTRIBUTION

Not Applicable.

SUPPLEMENTARY APPENDIX

1. An explanation of the breast cancer gene 21 detection method

In this study, a high-throughput gene sequencing platform was used to capture high-depth sequencing of all 18 genes' coding regions, specific exons of two genes, intron regions connected to the breakpoints of one fusion gene, and specific variants of one gene. Four different types of tumor gene variants, including point mutations, small fragment insertions, copy number variations, and known fusion genes, were also identified.

2. List of breast cancer genes identified by 21 gene testing

2.1 ***List of somatic gene testing for variants***

2.1.1 Contains all 18 genes' coding areas

ATM	*BRAF*	*BRCA1*	*BRCA2*	*CCND1*	*CDK4*
CDK6	*CDKN2A*	*ERBB2*	*FBXW7*	*KRAS*	*NF1*
NTRK1	*PIK3CA*	*PTEN*	*RB1*	*STK11*	*TP53*

2.1.2 ***Contains two genes' partial coding region***

AKT	*ESR*

2.1.3 ***Contains the promoter, fusion breakpoint region, and intron of one gene***

NTRK

2.1 ***List of assays for germline variant genes***

2.1.1 ***Contains the entire code for 2 genes.***

BRCA1	*BRCA2*

2.2 ***Contains a certain gene variation***

CYP2D6

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