

# Carcinoma with signet ring cell differentiation associated with invasive breast cancer: A case report

WEI YANG<sup>1</sup>, SHUN DING<sup>2</sup>, LITAO WANG<sup>3</sup>, FUPENG REN<sup>4</sup>, YUNYING LAI<sup>5</sup>,  
HONGFANG WANG<sup>6</sup>, HUAN WANG<sup>3</sup>, GUODAI HONG<sup>1</sup> and WENBIN GAO<sup>1</sup>

Departments of <sup>1</sup>Oncology and <sup>2</sup>Pathology, The Third Affiliated Hospital of Shenzhen University, Shenzhen, Guangdong 518000; <sup>3</sup>Department of Emergency Surgery, The First Clinical College, Qingdao University, Qingdao, Shandong 266000; <sup>4</sup>Department of Hematology and Oncology, Hwa Mei Hospital, University of Chinese Academy of Sciences, Ningbo, Zhejiang 315000; Departments of <sup>5</sup>Radiology and <sup>6</sup>Gastroenterology, The Third Affiliated Hospital of Shenzhen University, Shenzhen, Guangdong 518000, P.R. China

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**Abstract.** Carcinoma with signet ring cell differentiation is uncommon in patients with invasive breast cancer. Clinical evidence has suggested that the prognosis of this tumor is usually poor if the stage is advanced. The case of a 40-year-old female patient with primary cancer in the right breast accompanied by bilateral neck, axillary, right subclavian and mediastinal lymph node metastases, and left breast metastasis is presented in the current study. The patient developed superior vena cava syndrome and was restricted in lifting the upper right limb when presenting at the Third Affiliated Hospital of Shenzhen University, Shenzhen. The histopathological and immunohistochemical features included ~80% of the tumor cell area having a signet ring cell pattern, exhibiting the phenotype of lobular carcinoma, and ~20% of the tumor cell area exhibiting a ductal carcinoma immunophenotype with neuroendocrine expression. The patient received chemotherapy with paclitaxel liposomes and doxorubicin hydrochloride liposomes according to the general guidelines for the treatment of stage IV breast carcinoma. The patient achieved a partial response after 4 cycles of treatment, and then experienced progressive disease in the form of brain metastasis after 6 cycles. Owing to the rarity of carcinoma with signet ring cell differentiation in invasive breast carcinoma, this case report discusses the patient's clinical and histopathological characteristics, and the treatment prognosis.

## Introduction

According to global cancer statistics from GLOBOCAN 2020, the number of cases of breast cancer in women exceeded that of lung cancer to make it the most frequently diagnosed cancer, with an estimated 2.3 million new cases (11.7%) compared with 2.24 million cases of lung cancer (11.4%) (1). In China, researchers performed a descriptive secondary analysis of the GLOBOCAN 2020 data and when the incidence was stratified by sex, breast cancer was also the most common type of cancer among women (2). Signet ring cell breast carcinoma (SRCBC), a rare variation on invasive lobular carcinoma, was first described in 1976 (3). The carcinoma is histologically defined by the presence of intracytoplasmic, mucin-rich vacuoles that cause nuclear displacement toward one cell pole, forming a crescent or signet ring shape, in >20% of its tumor cells (4,5). In previous years, carcinoma with signet ring cell differentiation has been categorized as invasive breast carcinoma, and to date, only a few cases have been reported (6-8). The prevalence of SRCBC is postulated to be as high as 2-4.5% of all breast carcinoma cases (9,10). The prognosis is mainly associated with the stage. Patients with SRCBC exhibit a more advanced disease stage, with higher mortality rates, compared with other histological subtypes of breast cancer. In a previous study, stage-based survival analyses found 5- and 10-year survival rates of 26.9 and 8.8%, respectively, for stage IV SRCBC. Patients in a lower stage had higher rates of locoregional therapy using surgery and radiation, while patients in a higher stage were more likely to receive systemic chemotherapy (5). Cases of brain metastasis of carcinoma with signet ring cell differentiation in invasive breast cancer are rare, as previously noted (9,10). In the present study, the case of a patient diagnosed with carcinoma with signet ring cell differentiation for advanced invasive breast cancer is reported.

## Case report

A 40 years-old female patient was referred to the Third Affiliated Hospital of Shenzhen University in January 2018. In January 2015, she had presented with a nodule 1x1 cm in

*Correspondence to:* Mr. Wei Yang or Professor Wenbin Gao, Department of Oncology, The Third Affiliated Hospital of Shenzhen University, 47 Youyi Road, Shenzhen, Guangdong 518000, P.R. China

E-mail: junweiyang@163.com

E-mail: drwenbingao@163.com

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size in the upper quadrant of the right breast. In June 2017, the breast nodule raised the skin surface and was ~3x3 cm in size. In that year, the patient went to the hospital for treatment, and the doctor recommended surgery; however, the patient refused the proposed treatment. In October 2017, the right breast mass had rapidly increased to ~110x110 mm in size and occupied the right breast. At the same time, due to metastasis to the right axillary lymph node, the right upper limb blood circulation of the patient was restricted, right upper limb swelling was observed and pain appeared. In December 2017, the patient suffered from slight facial puffiness and chest tightness, as well as difficulty swallowing when eating dry food. Therefore, soft and liquid diets were advised. The patient had no past history or family history of breast disease.

Physical examination revealed the patient's face and right upper limb were significantly swollen, and restriction in lifting the upper right limb was observed. Multiple enlarged lymph nodes were observed in the right neck, and the right supraclavicular and axillary lymph nodes, measuring 50x30 mm, were fused. Irregularly shaped multiple fused lumps of ~110x110 mm in size occupied the entire right breast and were mainly solid and partially cystic with tenderness. Varicose veins were observed on the chest wall, the skin on the right breast was red and swollen, and redness and swelling had invaded the left chest wall. The skin of the right breast, sternum and upper quadrant of the left breast was hard (Fig. 1A). Satellite nodules could be palpated subcutaneously in the right upper quadrant and left upper quadrant of the left breast. The patient's laboratory study results revealed elevated carcinoembryonic antigen (CEA) and carbohydrate antigen 153 (CA153) levels of 189.2 (0-5) ng/ml and 272.8 (0-25) U/ml, respectively (Fig. 1).

MRI of the breast showed a large mass in the right breast with an irregular shape and a size of ~116x113x69 mm. The skin of the right breast was significantly thickened, with involvement of the right pectoralis major. Irregular signals could be observed past the left areola and the upper left quadrant of the left breast, which were attributed to nodules (Fig. 2A). A contrast-enhanced CT scan of the chest showed multiple soft-tissue shadows on the right breast area, and some lesions had fused and become unevenly strengthened. The third anterior right rib was invaded, and the bone was broken. Numerous swollen lymph node metastases were observed around the lesions in the breast area, on both sides of the armpit, on the right subclavian lymph node, on both sides of the neck and on the mediastinum (Fig. 2D). At this time, MRI of the head (Fig. 2H) and contrast-enhanced CT of the lung did not show evidence of metastatic disease (Fig. 2D). Contrast-enhanced CT scanning of the abdomen and gastroscopy were performed, and no organ-derived lesions other than the breast-occupying lesions were identified. Based on the patient's symptoms, signs and imaging examination, it was hypothesized that the primary disease originated from the breast. According to the 8th American Joint Committee on Cancer staging system for breast cancer, the Tumor-Node-Metastasis classification was T4bN3cM1 stage IV (11).

Pathological examination by ultrasound-guided core-needle biopsy with three biopsies revealed carcinoma with signet ring cell differentiation. The biopsy tissue was fixed using 10% neutral formaldehyde solution at room temperature for 1-2 h. The tissue was dehydrated and embedded in paraffin

and sectioned at 4  $\mu$ m. Hematoxylin and eosin staining was at room temperature for 5-10 min and 30 sec respectively. Then 3% H<sub>2</sub>O<sub>2</sub> was used for blocking at room temperature for 4 min. An Olympus optical microscope (Olympus Corporation) was used to observe, and magnification or scale bar was shown in the figures (Figs. 3 and 4). Microscopically, tumor cells were arranged in a solid nest-like or pawn-like arrangement, in which ~80% of the tumor cell cytoplasm was translucent and contained mucin that was signet ring cell-like, and some tumor cell cytoplasm was eosinophilic (Fig. 3B). Immunohistochemical (IHC) staining employed ready-to-use primary antibodies including ER (cat. no. 790-4325; Roche Diagnostics), PR (cat. no. 790-4296; Roche Diagnostics), Her-2 (cat. no. 790-4493; Roche Diagnostics), Ki67 (cat. no. 790-4286; Roche Diagnostics), p63 (cat. no. 790-4509; Roche Diagnostics), E-cad (cat. no. MAB-0738; Fuzhou Maixin Biotechnology Development Co., Ltd.), p120 (cat. no. MAB-0621; Fuzhou Maixin Biotechnology Development Co., Ltd.), GATA3 (cat. no. MAB-0695; Fuzhou Maixin Biotechnology Development Co., Ltd.), SYN (cat. no. MAB-0742; Fuzhou Maixin Biotechnology Development Co., Ltd.), CgA (cat. no. MAB-0707; Fuzhou Maixin Biotechnology Development Co., Ltd.), SMMHC (cat. no. MAB-0121; Fuzhou Maixin Biotechnology Development Co., Ltd.), (cat. no. CK)7 (cat. no. Kit-0021; Fuzhou Maixin Biotechnology Development Co., Ltd.), CK20 (cat. no. Kit-0025; Fuzhou Maixin Biotechnology Development Co., Ltd.), 34 $\beta$ E12 (cat. no. Kit-0020; Fuzhou Maixin Biotechnology Development Co., Ltd.), CDX-2 (cat. no. RMA-0631; Fuzhou Maixin Biotechnology Development Co., Ltd.), CK5/6 (cat. no. ZM-0313; OriGene Technologies, Inc.) were used at 37°C for 32 min. Ready-to-use secondary antibodies (cat. no. 760-500; Roche Diagnostics) and conjugated peroxidase were used at 37°C for 8 min. HRP/DAB was also used and chromogen detection performed with an Ultra View Universal DAB Detection kit (cat. no. 760-500; Roche Diagnostics GmbH). IHC staining results were positive for cytokeratin (CK)7, CK20 (section), tumor protein p120 (cytoplasm), 34 $\beta$ E12 and Ki67 (70%) (Fig. 3) and negative for E-cadherin (E-cad), p63, GATA-binding factor 3 (GATA3), CK5/6, homeobox protein CDX-2 (CDX-2), estrogen receptor (ER), progesterone receptor (PR), receptor tyrosine-protein kinase erbB-2 (Her-2), smooth muscle myosin heavy chain (SMMHC), synaptophysin (SYN) and chromogranin A (CgA). Approximately 20% of the tumor cell area had a ductal carcinoma immunophenotype with neuroendocrine expression (Fig. 3A). The IHC staining results of this area were positive for E-cad, p120 (membrane), GATA3, CK7, ER, PR, SYN, CgA and Ki67 (Fig. 4), and negative for CK20, CK5/6, CDX-2, p63, Her-2, 34 $\beta$ E12 and SMMHC.

When referred to the Third Affiliated Hospital of Shenzhen University in January 2018, the patient had a Karnofsky performance status (KPS) score of 90 (12). Considering the status of advanced breast cancer, the tumor stage and the pathology, and in accordance with current guidelines and specifications, the clinician first sought to administer rescue chemotherapy with the patient's consent. The doxorubicin hydrochloride and paclitaxel liposomes (AT) regimen was selected for the reason that the tumor should be shrunk rapidly, to relieve the patient's symptoms quickly. On the other hand, paclitaxel is usually combined with salvage chemotherapy for breast cancer

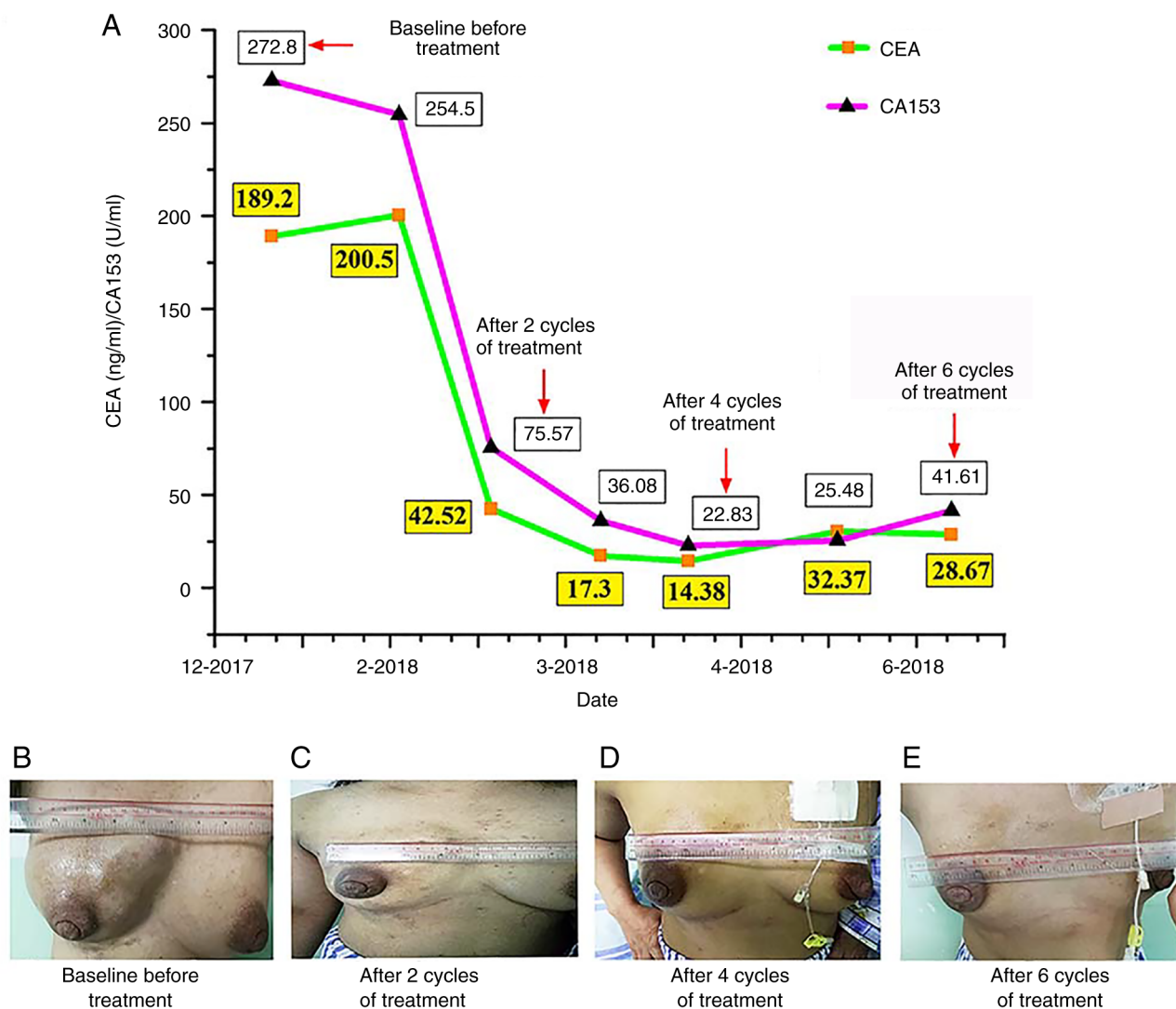


Figure 1. Post-treatment changes of breast masses and tumor markers in patient. (A) CEA (ng/ml) and CA153 (U/ml) levels are shown at different treatment time points. Clinical response of the right breast mass at (B) baseline before chemotherapy and after (C) 2, (D) 4 and (E) 6 cycles. CEA, carcinoembryonic antigen; CA153, carbohydrate antigen 153.

and is considered if the patient has not received anthracycline therapy. Therapy with paclitaxel liposomes and doxorubicin hydrochloride liposomes (135 and 35 mg/m<sup>2</sup>, respectively, on day 1 of a 21-day cycle) was initiated in January 2018. The patient tolerated chemotherapy well, and after two cycles of treatment, the symptoms of facial and right upper limb swelling were significantly reduced, and the patient achieved a partial response (PR) with an obvious decrease in the size of the target lesion (Figs. 1B, 2B and E). CEA and CA153 levels were also decreased (Fig. 1). After four cycles of treatment, the swelling of the right breast was further reduced (Fig. 1C), and repeated MRI and CT scans showed a PR with a slight decrease in the target lesion compared with that after 2 cycles of treatment (Fig. 2C and F). Tumor marker levels were also further decreased; however, a slight increase was noted after the 5th cycle of treatment (Fig. 1). Considering that the patient's previous clinical symptoms had improved significantly (Fig. 1D), and the imaging evaluation revealed a PR, the original treatment was considered for the 6th cycle, and the patient was prepared for radiotherapy five times a week with a dose of 2 Gy for ~5-6 min, 25 times (5 weeks).

During preparation for radiotherapy, the patient suddenly developed symptoms of headache and dizziness that were paroxysmal, accompanied by nausea and vomiting. Later, the patient developed a walking disorder, gradually became unresponsive and had one seizure (KPS score of 20). On physical examination, the patient's vital signs were stable, and consciousness was lethargic, arousable and responsive to painful stimuli. The patient was sensitive to light reflexes, had cognitive impairment, could not answer simple questions and did not cooperate with the physical examination. Although neck stiffness was suspected in this patient, pathological signs were negative. Routine blood, liver and kidney function, ion tests and other laboratory tests showed no apparent abnormalities, while the CA153 level was increased. Enhanced MRI examination showed new lesions under the left parietal cortex (Fig. 2I) compared with the baseline examination before chemotherapy (Fig. 2H). Although the single brain metastasis detected by imaging was small, the patient exhibited obvious symptoms of central nervous system (CNS) pathology. The patient's family did not consent to breast MRI examination which was attributed to the patient's inability to cooperate with

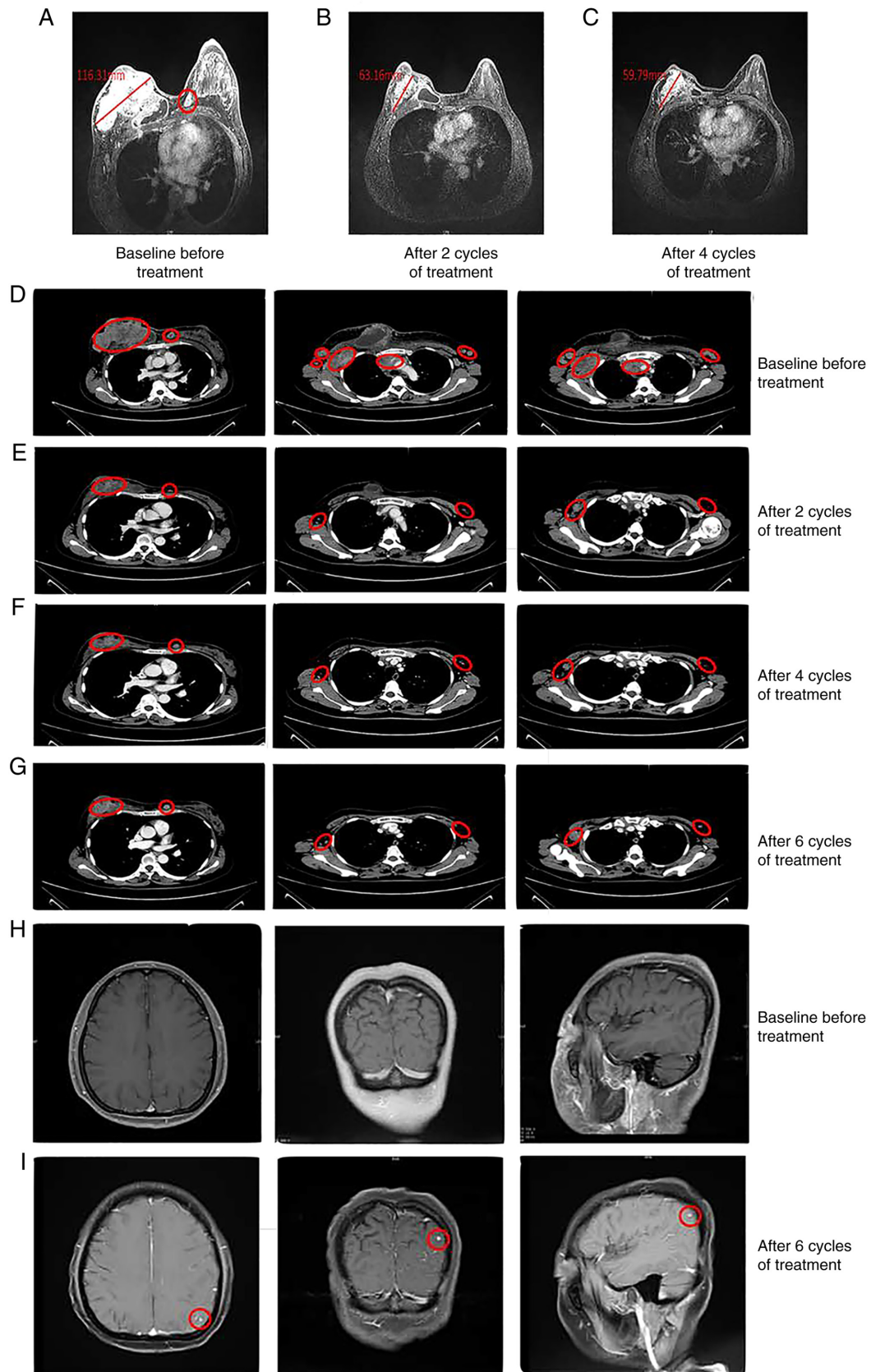


Figure 2. (A) The maximum measured diameter of the lesion was 116.31 mm at baseline before chemotherapy. (B) After 2 cycles of paclitaxel liposomes and doxorubicin hydrochloride liposomes chemotherapy, the diameter of the lesion was markedly reduced to 63.16 mm. (C) After 4 cycles of chemotherapy, the diameter of the lesion was 59.79 mm. A 4th breast MRI assessment was not performed. Contrast-enhanced CT scans of the chest at (D) baseline and after (E) 2 and (F) 4 of chemotherapy revealed significantly shrinkage in the masses in the right breast area and a large number of enlarged lymph nodes on both sides of the axilla and the mediastinum; however, according to enhanced CT and, the right breast mass and bilateral metastatic lymph nodes were slightly enlarged after (G) 6 cycles of treatment compared with those after (F) 4 cycles of treatment. An enhanced MRI examination was performed (H) before chemotherapy and (I) new lesions were observed under the left parietal cortex after 6 cycles of chemotherapy. The content shown in the red circled areas refers to the breast mass and metastatic lymph nodes. Fig. 2A-C, H and I) are MRI scans and Fig. 2D-G) are CT scans.



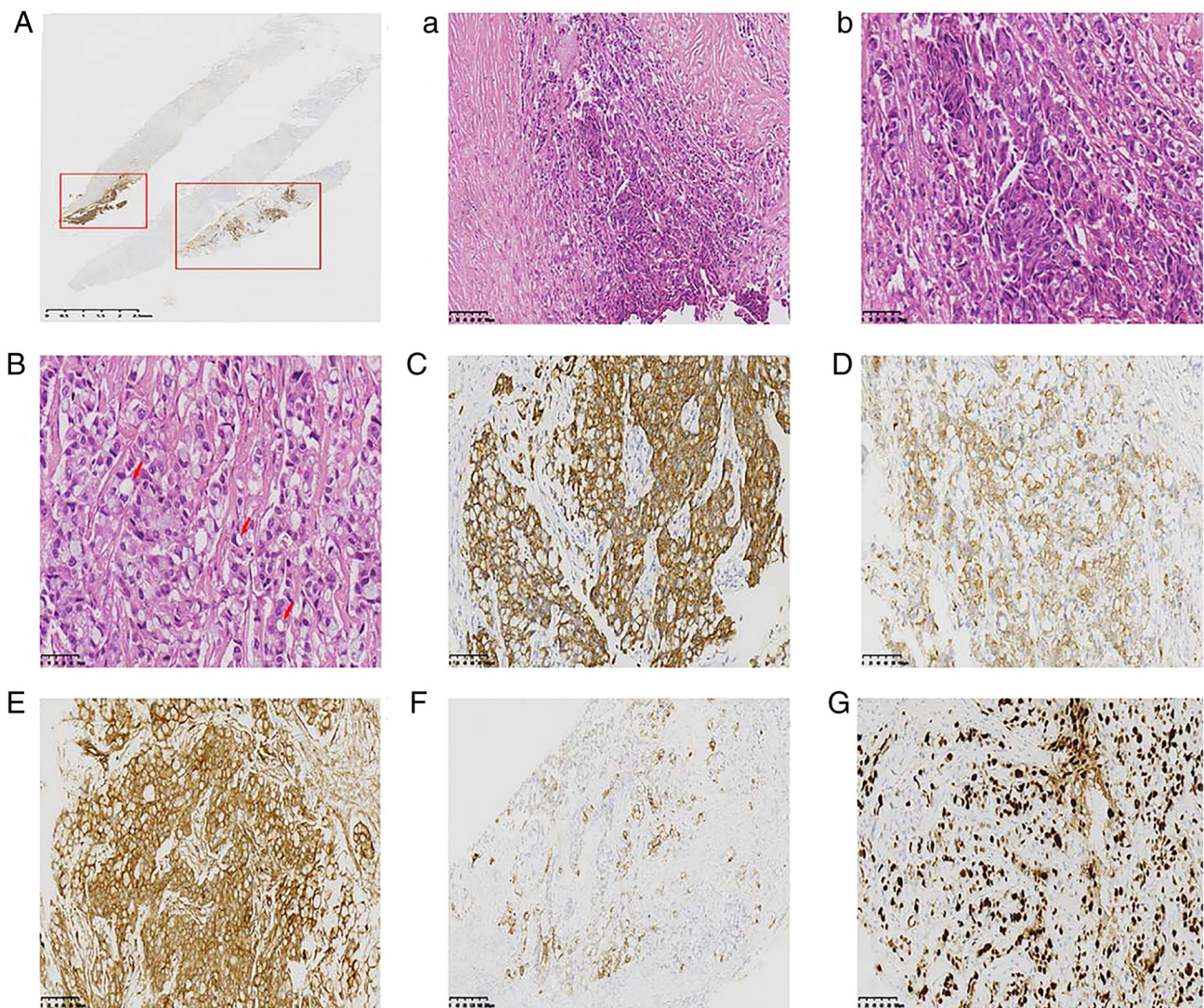


Figure 3. (A) Microscopically, ~20% of the tumor cell area had a ductal carcinoma immunophenotype that was positive for E-cad. Tumor cells were arranged in (A-a) solid nest-like (H&E staining; magnification, x200; scale bar is 100  $\mu$ m) or (A-b) pawn-like (H&E staining; magnification, x400; scale bar, 50  $\mu$ m) arrangements, in which (B) ~80% of the tumor cell cytoplasm was translucent and contained mucin, which was signet ring cell-like (H&E staining; magnification, x400; scale bar, 50  $\mu$ m). Immunohistochemistry findings of the tumor showed that the signet ring cell carcinoma component was positive for (C) CK7, (D) CK20 (section), (E) tumor protein p120 (cytoplasm) (magnification, x200), (F) 34 $\beta$ E12 and (G) Ki67 (70%) (magnification, x100; scale bar, 200  $\mu$ m). CK, cytokeratin.

the long-term MRI examination under the current conditions, so only a chest enhanced CT examination was performed (Fig. 2G). Since the patient could not be placed in the lateral lying position, the family considered the patient's condition to be significantly more severe, and so did not consider further vertebral puncture to detect cerebrospinal fluid pathology and refused radiotherapy. The patient returned to Huizhou Central People's Hospital for supportive treatment and died in July 2018.

## Discussion

Primary signet ring cell carcinoma (SRCC) of the breast is a rare disease that originates from both invasive lobular carcinoma and ductal carcinoma (13). Only a few cases of SRCC of the breast have been reported, and its prevalence ranges from 2 to 4.5% of total breast cancer cases (9,10). In the 2012 classification of breast carcinomas by the World Health Organization, carcinoma

with signet ring cell differentiation was classified as invasive breast carcinoma (14). Breast metastases of gastric SRCC may be difficult to distinguish from primary breast carcinoma. New antibodies for immunohistochemistry have been revealed to be useful for the differential diagnosis of such cases. For example, research has shown that primary breast SRCC is usually CK7-positive but CK20-negative, whereas gastrointestinal SRCC is typically CK20-positive but CK7-negative. Together with ER staining results, the expression patterns for CK7 and CK20 can be used for distinguishing between gastrointestinal SRCC and breast SRCC (15).

In the present case report, the IHC staining results were positive for CK7 (section) and negative for ER. Considering that the specimen was obtained from a puncture biopsy and that there were tissue limitations such as size and location, these findings do not fully reflect the actual histological type. The microscopic appearance of the patient's puncture specimen largely conformed to the main components



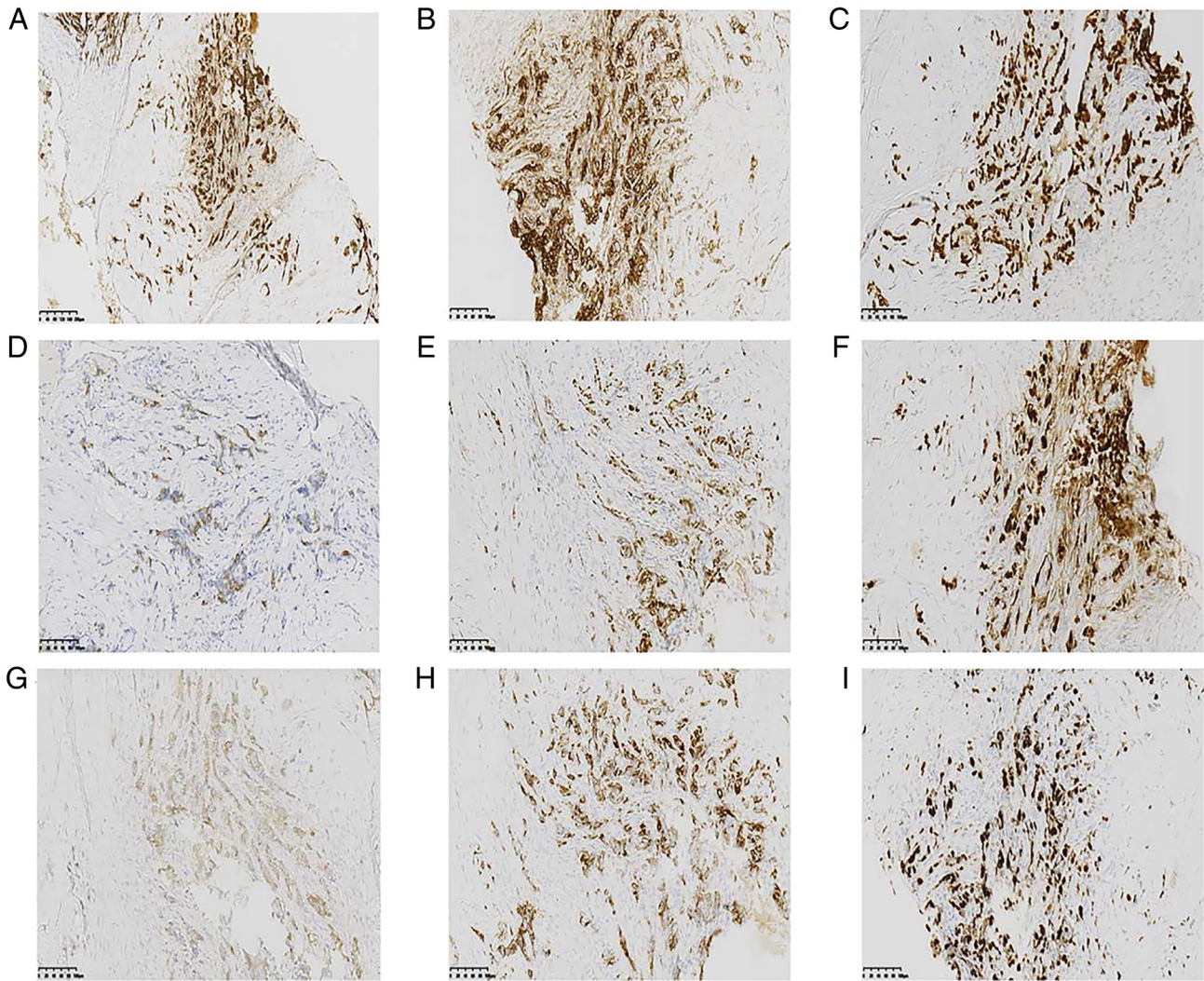


Figure 4. Immunohistochemical staining results for the ductal carcinoma immunophenotype with neuroendocrine expression, which was positive for (A) E-cadherin (magnification, x100), (B) tumor protein p120 (cytoplasm), (C) GATA-binding factor 3, (D) cytokeratin 7, (E) estrogen receptor, (F) progesterone receptor (70%), (G) synaptophysin, (H) chromogranin A, and (I) Ki67 (magnification, x200; scale bar, 100  $\mu$ m).

of SRCC. Notably, ~80% of the tumor cell cytoplasm in the pathological tissue was translucent and contained mucin, which appeared signet ring cell-like, and ~20% of the tumor cell area exhibited a ductal carcinoma immunophenotype with neuroendocrine expression. Research has shown that patients with multifocal breast cancer who have heterogeneous tumors in terms of the molecular phenotype have significantly shorter disease-free survival times (16). Carcinoma with signet ring cell differentiation associated with invasive breast cancer often presents with lymphatic metastasis and is associated with a high Ki67 index (3). In addition, the mortality rate is higher for SRCC than that for other forms of mammary carcinoma without signet ring cells (9). The aforementioned tumor biological behavior and molecular pathology are in line with the findings of the present case.

Recent studies have shown that a large tumor burden (17,18), axillary lymph involvement, high tumor number (18,19), high histological grade (17), triple-negative breast cancer (18,20), high Ki67 index (21), BRCA1 mutation (22) and breast cancer metastasis to the CNS (20) are associated with reduced survival time in breast cancer. The present case was consistent

with these findings, although the BRCA gene was not tested for in this case.

With regard to the treatment process of this disease, after the fifth cycle of treatment, although the patient's imaging evaluation resulted in a PR, the CEA and CA153 tumor markers were slightly elevated, indicating that the tumor might have begun to exhibit drug resistance. The elevated levels also suggested a poor prognosis. The onset of neurological symptoms in this case was sudden. Although the brain metastasis was small, the patient exhibited clinical symptoms such as unresponsiveness, headache, dizziness, neck pain, walking disorder and epilepsy, which were accompanied by nausea and vomiting. The symptoms led to a significant decrease in the patient's physical strength and quality of life, which seriously affected the patient's willingness to receive further treatment.

In conclusion, carcinoma with signet ring cell differentiation associated with invasive breast cancer is a rare malignant tumor that should be distinguished from metastases of signet ring cells to the breast. Pathological and clinical characteristics should be used for the diagnosis of this type of carcinoma. The prognosis of this tumor type is usually poor (3). Therefore,

early detection and timely and standardized treatment are the keys to successfully treating this disease.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Authors' contributions

WY and WBG designed the case report. SD, YYL, LTW, FPR and HFW made substantial contributions to acquisition of data, and analysis and interpretation of data. HW and GDH advised on patient treatment or analyzed patient data. WY drafted the manuscript. FPR and WBG revised it critically for important intellectual content and gave final approval of the version to be published. WY and SD confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

The husband of the patient provided written informed consent for the use of the patient information for research purposes, including the publication of case details and accompanying images.

### Competing interests

The authors declare that they have no competing interests.

### References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
- Cao W, Chen HD, Yu YW, Li N and Chen WQ: Changing profiles of cancer burden worldwide and in China: A secondary analysis of the global cancer statistics 2020. *Chin Med J (Engl)* 134: 783-791, 2021.
- Wu X, Zhang Z, Li X, Lin Q, Chen G, Lu J, Zeng Y, Hu D, Huang K, Lin Z and Yan J: Poorer prognosis of primary signet-ring cell carcinoma of the breast compared with mucinous carcinoma. *PLoS One* 11: e0162088, 2016.
- Frost AR, Terahata S, Yeh IT, Siegel RS, Overmoyer B and Silverberg SG: The significance of signet ring cells in infiltrating lobular carcinoma of the breast. *Arch Pathol Lab Med* 119: 64-68, 1995.
- Mehdi M, Kong AL, Frebault J, Huang S, Huang CC and Cortina CS: Prognostic outcomes of signet ring cell carcinoma of the breast. *J Surg Res* 264: 138-148, 2021.
- Li X, Feng YF, Wei WD, Liu P, Xie ZM, Wang J and Xie XM: Signet-ring cell carcinoma of the breast: A case report. *World J Surg Oncol* 11: 183, 2013.
- Kuroda N, Fujishima N, Ohara M, Hirouchi T, Mizuno K and Lee GH: Invasive ductal carcinoma of the breast with signet-ring cell and mucinous carcinoma components: Diagnostic utility of immunocytochemistry of signet-ring cells in aspiration cytology materials. *Diagn Cytopathol* 35: 171-173, 2007.
- Chatterjee D, Bal A, Das A, Kohli PS, Singh G and Mittal BR: Invasive duct carcinoma of the breast with dominant signet-ring cell differentiation: A microsatellite stable tumor with aggressive behavior. *Appl Immunohistochem Mol Morphol* 25: 720-724, 2017.
- Hull MT, Seo IS, Battersby JS and Csicsko JF: Signet-ring cell carcinoma of the breast: A clinicopathologic study of 24 cases. *Am J Clin Pathol* 73: 31-35, 1980.
- Merino MJ and Livolsi VA: Signet ring carcinoma of the female breast: A clinicopathologic analysis of 24 cases. *Cancer* 48: 1830-1837, 1981.
- Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, Weaver DL, Winchester DJ and Hortobagyi GN: Breast cancer-major changes in the American joint committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin* 67: 290-303, 2017.
- Mor V, Laliberte L, Morris JN and Wiemann M: The karnofsky performance status scale. An examination of its reliability and validity in a research setting. *Cancer* 53: 2002-2007, 1984.
- Karabagli P and Kilic H: Primary pure signet cell carcinoma of the breast: A case report and review of the literature. *Breast Cancer* 20: 363-366, 2013.
- Sinn HP and Kreipe H: A brief overview of the WHO classification of breast tumors, 4th edition, focusing on issues and updates from the 3rd edition. *Breast Care (Basel)* 8: 149-154, 2013.
- Tot T: The role of cytokeratins 20 and 7 and estrogen receptor analysis in separation of metastatic lobular carcinoma of the breast and metastatic signet ring cell carcinoma of the gastrointestinal tract. *APMIS* 108: 467-472, 2000.
- Duan YS, Mao QX, Li LF, Sun YD, Wang L and Cui SD: Intertumoral heterogeneity of molecular phenotype and analysis of prognosis in multifocal and multicentric breast cancer. *Zhonghua Zhong Liu Za Zhi* 38: 833-838, 2016 (In Chinese).
- Nguyen D, Yu J, Reinhold WC and Yang SX: Association of independent prognostic factors and treatment modality with survival and recurrence outcomes in breast cancer. *JAMA Netw Open* 3: e207213, 2020.
- Deniz M, DeGregorio A, DeGregorio N, Bekes I, Widschwendter P, Schochter F, Ernst K, Scholz C, Bauer EC, Aivazova-Fuchs V, *et al*: Differential prognostic relevance of patho-anatomical factors among different tumor-biological subsets of breast cancer: Results from the adjuvant SUCCESS A study. *Breast* 44: 81-89, 2019.
- Evcimik T, Degerli MS and Bilgic T: The effect of prognostic factors on long-term protection in breast cancer. *Cureus* 12: e8878, 2020.
- Mohar-Betancourt A, Alvarado-Miranda A, Torres-Dominguez JA, Cabrera P, Lara-Medina F, Villarreal-Gómez YS and Reynoso-Noverón N: Prognostic factors in patients with breast cancer and brain metastasis as the first site of recurrence. *Salud Publica Mex* 60: 141-150, 2018 (In Spanish).
- Kanyilmaz G, Yavuz BB, Aktan M, Karaağaç M, Uyar M and Findik S: Prognostic importance of Ki-67 in breast cancer and its relationship with other prognostic factors. *Eur J Breast Health* 15: 256-261, 2019.
- Huszno J, Kolosza Z and Grzybowska E: BRCA1 mutation in breast cancer patients: Analysis of prognostic factors and survival. *Oncol Lett* 17: 1986-1995, 2019.



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