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Breast metastasis of gastric signet-ring cell carcinoma^{*}

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Metastatic breast involvement from extra-mammary neoplasms is unusual with a low incidence of 0.5% to 1.2% in clinical practice (Gupta *et al.*, 2001), 2.7% in cytological series, and 1.7% to 6.6% in autopsy series of all breast malignancies (Alva and Shetty-Alva, 1999). Nearly 500 cases have been reported in small series and case reports (Madan *et al.*, 2002). Gastric carcinoma rarely metastasizes to the breast. There are only 38 cases reported in PubMed (He *et al.*, 2015). In this study, we present a case report of a 49-year-old woman who was diagnosed with right breast metastasis from a gastric carcinoma and undertake a literature review to pay attention to the diagnosis, treatment, and the prognosis of the disease.

A 49-year-old woman complained of a lump in the right breast and the right cervical and supraclavicular lymphadenopathy. She was admitted to hospital in January 2016. Two years earlier, she had been diagnosed with gastric carcinoma and underwent a subtotal gastrectomy and splenectomy. The pathologic findings were diagnostic of gastric signet-ring carcinoma and partly poorly differentiated adenocar-

cinoma of the stomach. Metastasis was identified in 14/20 lymph nodes along the lesser curvature of the stomach, 13/15 along the greater curvature, and 2/2 along the splenic hilum region.

Physical examination revealed an approximately firm 2.0 cm×2.5 cm lump in the upper inner quadrant of the right breast without evidence of axillary lymphadenopathy. The overlaying skin and the contralateral breast and axilla were normal.

A mammography examination revealed a hyperdense shadow in the upper inner quadrant of the right breast without clusters of micro-calcified spots. The breast ultrasound showed a hypoechoic mass with irregular boundary which was 2.7 cm×1.1 cm×2.5 cm in size in the bilateral supraclavicular and axillary regions. The pelvic ultrasound showed a heterogeneous echoic mass in the left adnexal area, which was 2.1 cm×1.7 cm×2.4 cm in size.

A core needle biopsy of the lesion in the right breast revealed the cells as adenocarcinoma with signet-ring features, and the immunohistochemical features were estrogen receptor (ER), progesterone receptor (PR), C-erbB-2, and cytokeratin 20 (CK20) negative, with probably gastric origin. The cervical lymph node biopsy also showed poorly differentiated carcinoma with partly signet-ring cell carcinoma. The patient was treated with chemotherapy with paclitaxel and tegafur. Five months later, she underwent wide local excision of the right breast lump. Excision biopsy of the lump revealed poorly differentiated gastric adenocarcinoma with abundant signet-ring cells (Fig. 1). The tumor thrombus could also be seen in the capillaries (Fig. 2). Further immunohistochemistry showed that the tumor was positive for cytokeratin 7 (CK7), CK19, and CK20, but negative for ER, PR, GATA-binding protein 3 (GATA3), mammaglobin (MMG), and gross cystic disease fluid protein-15 (GCDFP-15) (Fig. 3). The patient was treated with paclitaxel-based chemotherapy and died after about 10 months.

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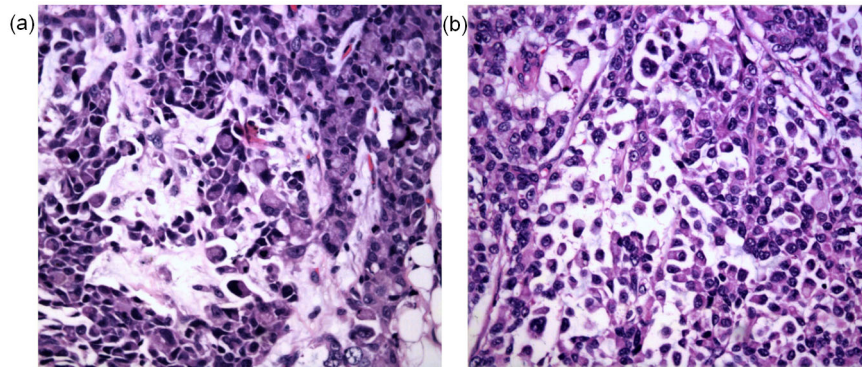


Fig. 1 Histological examination of the metastasis to the right breast

The result reveals poorly differentiated gastric adenocarcinoma with abundance of signet-ring cells in the breast parenchyma. Hematoxylin-eosin stain. (a) Magnification $\times 400$; (b) Magnification $\times 200$

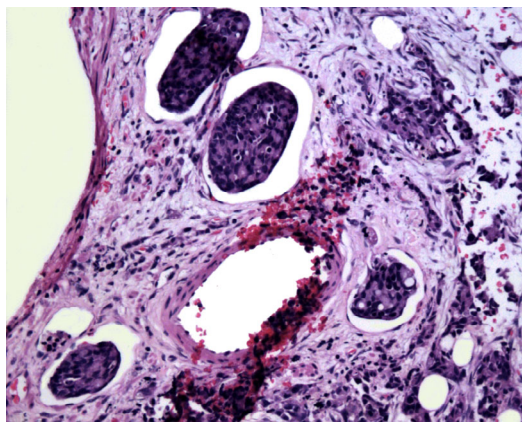


Fig. 2 Tumor thrombus seen in the capillaries

Hematoxylin-eosin stain. Original magnification $\times 100$

Breast cancer is the commonest malignancy in women. However, metastatic tumors to the breast are relatively rare. The commonest cause is contralateral breast carcinoma. The most common solid tumors metastasizing to the breast from other sites are malignant melanoma, lymphoma, rhabdomyosarcoma, lung tumors, ovarian tumors, renal cell carcinoma, leukemia, thyroid carcinoma, cervical carcinoma, gastrointestinal carcinoma, genitourinary tumors, and soft tissue sarcoma (Parrell Soler *et al.*, 2011). Therefore, the prognosis of metastases of the breast is important.

The average age of the patients is 47 years and premenopausal women are more commonly affected (Parrell Soler *et al.*, 2011).

Clinically, most metastatic tumors to the breast are freely mobile, well-defined, round, and solitary, and some of them are multiple or have diffuse involvement without overlying skin changes (Shiraishi

et al., 2001). They are more likely to be encapsulated within the subcutaneous tissue adjacent to the mammary stroma so can be palpated (Akçay, 2002). The breast invasion is the initial manifestation of metastatic disease in 25%–40% of cases (Boutis *et al.*, 2006). Approximately two-thirds of the invasions present in the upper outer quadrant of the breast (Tian *et al.*, 2016). Nipple retraction and nipple discharge are rare while bilateral axillary lymph node involvement can be frequently observed (Akçay, 2002).

Radiologic features of breast metastases on both mammography and sonography are nonspecific. On mammography, the metastatic lesions are usually diffuse and show ill-defined changes such as skin thickening or increased consistency. The masses are generally round with fairly well-defined margins appearing as benign lesions and are superficially located in the upper outer quadrant. They tend to have the same size as they are palpated (Boutis *et al.*, 2006). Microcalcifications and the occurrence of multiple tumor nodules are rare (Parrell Soler *et al.*, 2011). On sonography, the focal lesions are almost the same as the presentation of the mammography. They are usually hypoechoic lesions with a homogeneous internal structure and can be mobile (Canda *et al.*, 2007).

The immunoprofile of breast metastases from stomach adenocarcinomas is positive for adenocarcinoma markers such as CK7, CK20, and carcinoembryonic antigen (CEA) while negative for ER, PR, GCDFF-15, as well as for C-erbB-2 (in up to 20% it can be positive) (Boutis *et al.*, 2006; Parrell Soler *et al.*, 2011). It has been demonstrated that immunohistochemical staining for CK alone cannot

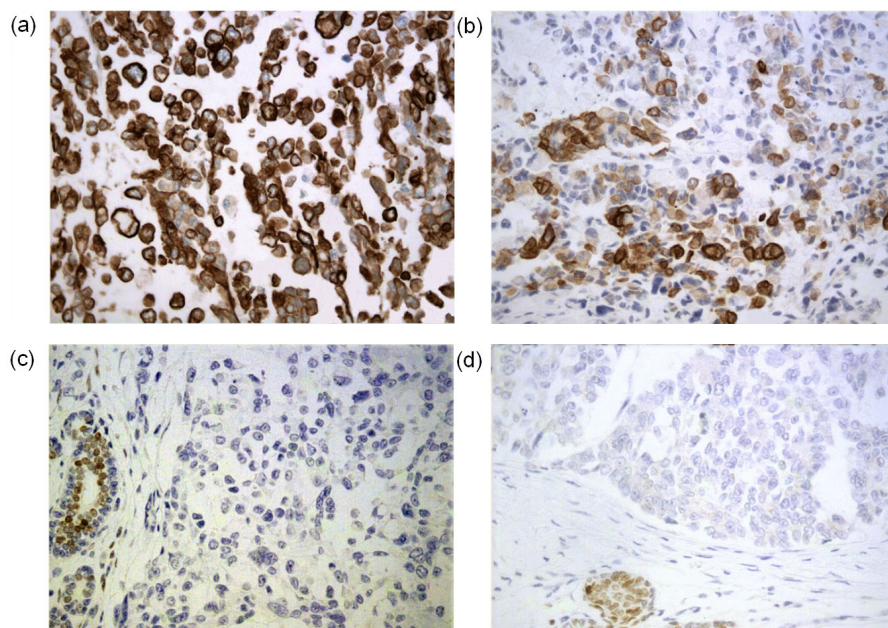


Fig. 3 Immunohistochemistry showing that the tumor was positive for CK19 (a) and CK20 (b), while negative for ER (c) and GATA3 (d)

Original magnification $\times 400$

distinguish primary breast cancer and metastatic breast carcinoma from gastric cancer (Sato *et al.*, 2008). Staining for ER, PR, and GCDFF-15 is specific for metastatic breast carcinomas while CK20 is highly specific for primary gastric carcinomas (O'Connell *et al.*, 2005). Therefore, biopsy of the breast lesions and histopathologic examination should be performed to distinguish a primary breast cancer from a metastatic tumor (Parrell Soler *et al.*, 2011).

In our case, the patient was positive for CK7, CK19, and CK20 while negative for ER, PR, GATA3, MMG, and GCDFF-15. Considering the patient's medical history of gastric signet-ring carcinoma two years before, the immunohistochemistry may suggest that the breast mass was most likely metastatic adenocarcinoma from gastric cancer rather than breast cancer. The clinical manifestations of the breast lump with right cervical and supraclavicular lymphadenopathy, without microcalcifications, and with the lack of hormone receptor may suggest an extramammary primary and metastatic carcinoma. The presence of a heterogeneous echoic mass in the left adnexal area may suggest metastatic ovarian involvement while more persuasive proof was lacking. Although the metastatic involvements of breast and ovary are extremely rare and there are only five cases

that have been reported, the selective invasion of hormone-dependent organs may explain why breast and ovary are involved (Boutis *et al.*, 2006).

The mechanism of how the gastric malignancy metastasizes to the breast is still unknown. There are two distinct routes proposed, lymphatic and blood-borne. The most common lymphatic source of breast metastasis is contralateral primary breast cancer. Boutis *et al.* (2006) thought that increased blood supply of the breast was proposed as the mechanism for breast metastasis in premenopausal women. Premenopausal women are more commonly affected. The younger age of women suggested that the breast is a favorite site for metastasis because of a relatively rich blood supply (Vergier *et al.*, 1991; Shiraishi *et al.*, 2001). On the other hand, Vergier *et al.* (1991) also hypothesized that estrogen may promote extramammary tumorigenesis. Gastric cancer seems to be more aggressive in younger people with hormonal factors implicated. The growth of gastric cancer may be affected by their hormonal circumstances (Maeta *et al.*, 1995). It has been demonstrated that estrogen receptor β was found in stomach adenocarcinomas. The effects of estrogen may be mediated by ER- β , specifically in signet-ring cell adenocarcinoma (Matsuyama *et al.*, 2002). Therefore, we think the

mechanism of breast metastases from gastric cancer may be determined by hormonal factors. How the gastric malignancy metastasizes to the breast will need more research.

As for treatment, most patients survive less than one year after the diagnosis of metastatic breast cancer. Systemic treatments include neoadjuvant chemotherapy appropriate to the primary tumor and curative surgery of the primary cancer or metastatic breast cancer can be helpful (Shiraishi *et al.*, 2001). Sato *et al.* (2008) thought that breast surgery cannot prolong the patients' survival but just relieves the symptoms due to the metastatic breast lesions. The treatment is now controversial.

In conclusion, for the metastasis to the breast from gastric carcinoma, the immunoprofile may help in early diagnosis. The patient underwent subtotal gastrectomy, chemotherapy treatment with paclitaxel and tegafur, and local excision of right breast lump, but died after about 10-month chemotherapy. Therefore, more research on the mechanism and the clinical features of the metastasis disease is needed. Besides, the found of cancer stem cells (CSCs) recently may also explain the metastatic mechanism (Liu *et al.*, 2015). In future, with the application of circulating tumor cells and DNA, a better understanding of the tumor heterogeneity may help improve the therapy.

Compliance with ethics guidelines

Li-yuan WEI, Mei KONG, Zhen ZHANG, and Xiao-chen ZHANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from the patient for being included in the report.

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中文概要

题 目：胃印戒细胞癌转移至乳腺病例分析

概 要：乳腺外来源的转移性乳腺癌在所有乳腺癌中所占比例较低，约为 0.5%~1.2%，胃印戒细胞癌转移至乳腺更为罕见。本文报道了一例由胃印戒细胞

癌转移至乳腺的女性患者，结合相关文献回顾，探讨并总结转移性乳腺癌与原发乳腺癌在发病机制、临床表现、影像学特点及病理组织和免疫组化中的不同点。本报告旨在提示临床医师在乳腺肿瘤的诊断中，应详细结合患者病史，考虑到乳腺外转移可能，结合病理结果及免疫组化等手段以明确诊断，早期开展后续治疗。此外，随着循环肿瘤细胞和 DNA 技术的不断发展，对转移性乳腺癌机制的研究更加深入，可能会为此类疾病提供更好的治疗方案。

关键词：转移性乳腺癌；胃印戒细胞癌；乳腺外转移