Case Report

Gastrointestinal metastatic signet ring cell breast cancer in young females: a case report

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Background: Signet ring cell carcinoma (SRCC) is characterized by strong invasiveness and rapid progression. It occurs mostly in young and middle-aged patients, and early patients may have no clinical symptoms. Gastric SRCC with breast cancer metastasis is relatively rare. It often presents challenges for clinicians and pathologists and may lead to an absolutely different therapeutic strategy.

Case Description: In this paper, we report on a 37-year-old woman who was admitted to the hospital with a left breast mass discovered 5 days earlier, the mass was occasionally painful, and there was no skin swelling, skin depression, or other abnormalities. The initial diagnosis considered her to have a left breast tumor. The patient was previously healthy with no family history of tumor. Considering the possibility of malignant lesions, she underwent resection of the left breast tumor and surrounding tissue. Postoperative pathological findings suggested SRCC (left breast mass). Although the patient had no history of gastrointestinal tumors, considering that SRCC can also appear in the gastrointestinal tract and other organs. We performed gastroscopy on the patient, showed an ulcerative mass in the greater curvature of the gastric body, with irregular nodular uplift of the surrounding mucosa. The excised breast lesions were analyzed by immunohistochemistry, and the pathological result showed SRCC (left breast tumor). Combined with the results of immunohistochemistry, it was consistent with gastrointestinal metastasis. Through our multi-faceted differential diagnosis, the final diagnosis of the patient was clear, which not only bought time for the patient's subsequent treatment, but also avoided misdiagnosis and blind treatment due to the particularity and rarity of the case.

Conclusions: Gastric cancer should be considered when breast tumors show SRCC without *in situ* lesion. Signet ring cell gastric cancer (occult) should be excluded even if the patient has no family history of gastric cancer. It is important to distinguish metastatic cancer from primary breast cancer to avoid misdiagnosis and blind treatment due to the particularity of the case, at which point an early recognition can be made and an optimal treatment plan can be chosen.

Keywords: Signet ring cell carcinoma (SRCC); breast cancer; gastrointestinal metastatic; case report

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Introduction

Signet ring cell carcinoma (SRCC) is a poorly differentiated and weakly cohesive cancer characterized by a large amount of mucus within the cell that pushes the nucleus to one side, creating a crescent shape or signet ring cell morphology (1,2). SRCC is a type of gastric cancer with a high degree of malignancy, which has a low incidence rate. Patients with early stage gastric cancer may not have clinical symptoms,

and are typically in the advanced stage when they are discovered. Gastric SRCC with breast cancer metastasis is relatively rare.

We reviewed previously published articles on signet ring cell breast cancer combined with gastric cancer. Simple gastric SRCC is more common in young and middle-aged women, while gastric SRCC with breast cancer metastasis is more common in perimenopausal women. Gastrointestinal discomfort is the first symptom in most cases when found. There have also been reports of breast masses and calcified microfocals as the first symptoms, but they were misdiagnosed as inflammatory breast cancer, and received breast cancer treatment (3). The pathological results of this case report suggest that the patient had gastrointestinal metastatic signet ring cell breast cancer. This case is the first of its kind in Shandong Provincial Maternal and Child Health Care Hospital. We report this case to improve the diagnostic experience and reduce the misdiagnosis rate of such special cases, so as to provide a reference experience for clinical diagnosis and treatment. We present the following article in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-242/rc).

Case presentation

A 37-year-old female presented with a left breast mass during physical examination, and was admitted to the Department of Breast and Thyroid Surgery of Shandong Provincial Maternal and Child Health Care Hospital in May 2021. This study was approved by the institutional ethics board of Shandong Provincial Maternal and Child Health Care Hospital (approval No. 2021-097). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

The patient had unintentionally discovered a left breast mass 5 days prior to hospitalization. The mass was occasionally painful, and there was no skin swelling, skin depression, or other abnormalities. The patient was otherwise healthy and had no history of other diseases. There was no family history of cancer, no history of genetic and infectious diseases. Her occupation is in legal consulting, and she has no bad eating habits such as high fat, no history of smoking, and no history of drinking. She had no abnormal mental status, diet, urine and feces, and no recent change in weight. Specialist physical examination showed that the bilateral breasts were symmetrical, and there was no redness, ulcers, hyperpigmentation, or scarring. Also, the bilateral nipples were symmetrical, and there was no retraction and retraction. A mass (approximately 3.5 cm × 2.5 cm in size) was palpated in the upper outer quadrant of the left breast; it was hard, with unclear borders, and poor mobility. There was no palpable mass in the right breast and no abnormal discharge. Abnormally enlarged lymph nodes were not palpated in the bilateral axillae and supraclavicular fossa.

In the outpatient department, breast ultrasound examination showed the following: (I) a patchy low echo area was detected in the gland layer of the upper quadrant of the left outer breast, with a range of about 3.9 cm × 2.6 cm × 1.8 cm, unclear boundary, irregular shape, uneven internal echo, and multiple mildly dilated catheter echoes Breast Imaging Reporting and Data System category 4A (BI-RADS category 4A); (II) bilateral mammary hyperplasia and left breast duct dilation; and (III) the echo of a lymph node was detected in the left axilla, about 1.7 cm × 0.8 cm in size, with thickened cortex and clear portal structure. After admission, relevant tests were carried out and mammography was performed, which suggested focal asymmetry of the left breast and catheter dilation (BI-RADS category 4A), suggesting a high possibility of inflammatory lesions. Carcinoembryonic Antigen (CEA), Carbohydrate Antigen 199 (CA199), and Carbohydrate Antigen 724 (CA724) were significantly increased in the serum tumor markers, of which CA724 was significantly increased by 99.77 U/mL (reference value: 0–6.9 U/mL).

Other examinations, such as abdominal ultrasound, routine blood, and biochemical tests, showed no obvious abnormalities. Considering the large volume of the left breast mass, the possibility of malignant lesions, clear indications of surgery, communication of the disease, and consent of the patient, resection of the left breast mass and some surrounding tissues was performed. Rapid intraoperative pathological diagnosis suggested that clumps and cords of signet ring cells could be seen in the fibrous stroma of the breast (left breast mass), and malignant or metastatic lesions could not be ruled out. The intraoperative rapid frozen pathological diagnosis is shown in *Figure 1*.

We then inquired again about whether the patient had gastrointestinal-related symptoms and family history, and she denied them all. In order to further confirm

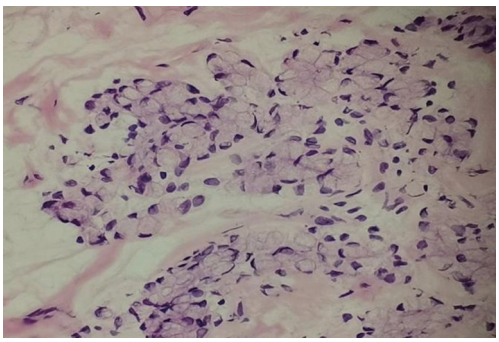

Figure 1 Rapid pathological diagnosis results of frozen breast tissue (hematoxylin and eosin staining) showed clusters and cord-shaped signet ring cells (×200).

the diagnosis, under our recommendation, the patients underwent electronic gastroscopy. Gastroscopy showed an ulcerative mass of about 3.0 cm × 4.0 cm in size in the greater curvature of the gastric body, with irregular nodular uplift of the surrounding mucosa, as well as yellow and white fur on the bottom. Six biopsies were taken, which were tough and bled easily. We considered the possibility of gastric malignancy. At the same time, the pathological results of the patient's breast lesions showed SRCC (left breast tumor), which, combined with the immunohistochemical results, were consistent with gastrointestinal metastasis.

The pathological immunohistochemical results showed the following: estrogen receptor (ER)(–), progesterone receptor (PR)(–), Human epidermal growth factor receptor 2 (HER-2)(2+), Ki67 (30% hot spot area), GATA-binding protein 3 (GATA3)(–), Cytokeratin 7 (CK7)(+), Cytokeratin 20 (CK20)(+), villin(+) and CDX-2(+). Among these, we were interested in CK7(+), CK20(+), and villin(+), which, combined with other immunohistochemical indicators, proved that the first breast lesions found in this patient were metastatic cancer, and were considered to be gastric cancer metastasis. The immunohistochemical results of the breast tumor are shown in *Figure 2*. Finally, the histopathological diagnosis of gastroscopic biopsy was as follows: poorly differentiated carcinoma, some of which were SRCC [HER-2(2+)]. The immunohistochemical results of the gastroscopic biopsy tissue are shown in *Figure 3*, which confirmed our previous diagnosis.

Through our multi-faceted differential diagnosis, the final diagnosis of the patient was clear, which not only bought time for the patient's subsequent treatment, but also avoided misdiagnosis and blind treatment due to the particularity and rarity of the case. Considering that the latter treatment in this case was mainly chemotherapy and radiotherapy, the patient was transferred to the medical oncology department for follow-up treatment. HER-2 gene fluorescence *in situ* hybridization test was negative, and the patient received XELOX (capecitabine + oxaliplatin) for 6 cycles. The efficacy evaluation after treatment was stable disease (SD).

Discussion

According to the Classification of Tumors by the World Health Organization (WHO), SRCC is a poorly differentiated and weakly cohesive carcinoma characterized by a large amount of mucus in the cells that pushes the nucleus to one side, forming a crescent shape or signet ring cell morphology (1,2). Primary SRCC can originate in many organs, most commonly in the stomach, followed by the colon, esophagus, rectum, lung, pancreas, breast, bladder, small intestine, and gallbladder. Primary SRCC in the breast accounts for only 1.5% (4-6).

SRCC is a type of gastric cancer with a high degree of malignancy. It is characterized by strong invasion and rapid disease progression, and is more common in middle-aged and young people, especially young women (7-9). Patients without a family history of gastric cancer may also have a high incidence of occult signet ring cell gastric cancer if they carry mutant reproductive genes (10). In the present case, the pathological findings suggested SRCC (left breast mass). Considering that SRCC may also appear in other organs, the primary lesion should be further identified for differential diagnosis.

Signet ring cell breast cancer with gastric cancer is rare, with fewer than 60 cases having been reported so far. We performed a literature search of the PubMed, MEDLINE, Embase, Google Scholar databases using keywords such as "stomach or gastric cancer"; "tumor or cancer or carcinoma or adenocarcinoma"; "breast cancer or breast"; and "transfer". As of December 2021, a total of 33 cases of SRCC had been diagnosed with either the stomach or breast as the primary site, including 22 cases of primary gastric cancer and 11 cases of primary breast cancer. Breast mass and calcification microfoci were the first symptoms in 15 cases, and gastrointestinal discomfort was the first symptom in 14 cases. Also, three patients with ovarian cancer as the first symptom were diagnosed as primary SRCC of the stomach with breast and ovarian cancer metastasis, and another case was diagnosed as primary SRCC of the

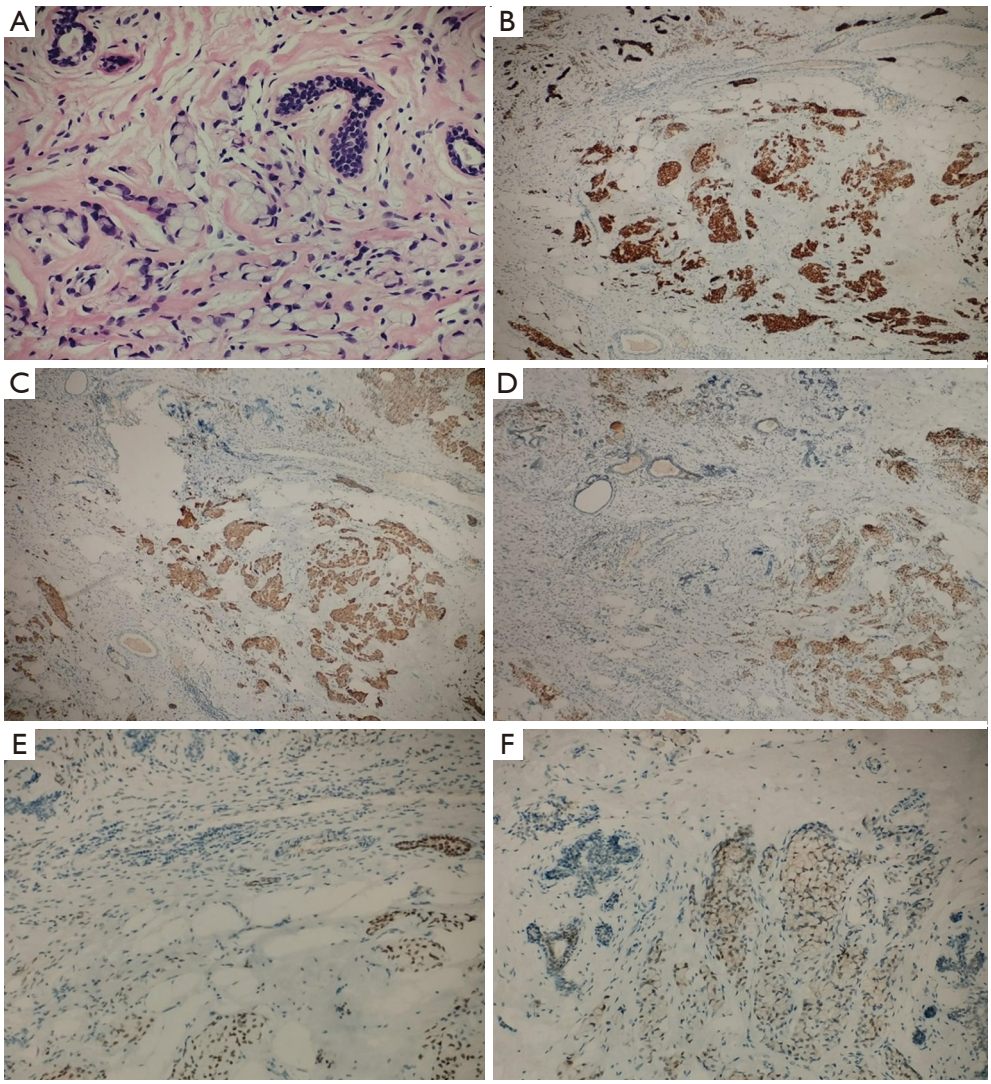

Figure 2 Pathological diagnosis results of the breast tissue in this case. (A) Signet ring cell infiltration beside the milk duct (hematoxylin and eosin staining, ×100); (B) CK7 staining positive (immunohistochemical staining, ×40); (C) CK20 staining positive (immunohistochemical staining, ×40); (D) positive for Villin staining (immunohistochemical staining, ×40); (E) positive for CDX-2 staining (immunohistochemical staining, ×40); and (F) positive for HER-2 staining (immunohistochemical staining, ×40).

stomach with breast and cervical cancer metastases. The ages of the patients ranged from 23 to 67 years, with a mean of 45.16±11.25 years. The retrieved cases and statistics are shown in *Table 1*.

It has been reported that simple SRCC of the stomach is more likely to occur in young and middle-aged women, while SRCC of the stomach with breast cancer metastasis is more likely to occur in perimenopausal women (40-42). In this case, the age of onset was 37 years old, which was relatively young and consistent with the age characteristics of SRCC of the stomach with breast cancer metastasis. Therefore, for young breast disease patients, especially those with BI-RADS 4A imaging diagnosis, professional surgeons cannot ignore detailed medical history collection and related professional examinations, such as mammography, breast Magnetic Resonance Imaging, serum tumor-related markers, etc. Single tumor marker detection has limited application value in the early diagnosis of breast cancer. Combined detection of serum tumor markers significantly improves the sensitivity of tumor diagnosis,

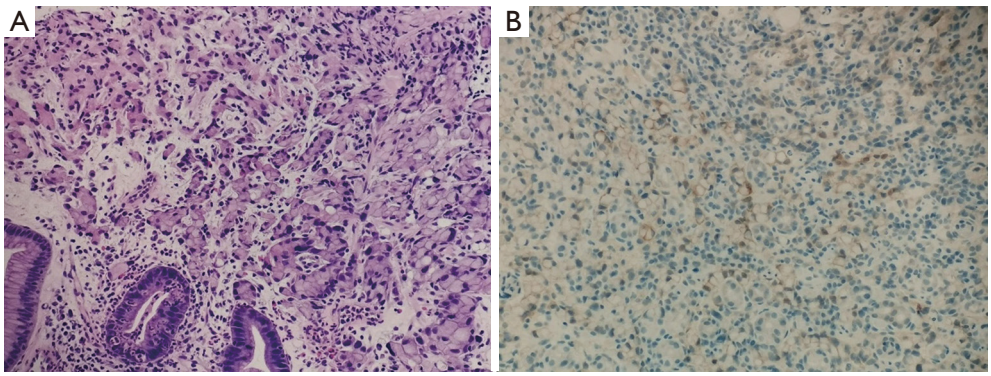

Figure 3 Histopathological results of gastroscopic biopsy in this case. (A) Signet ring cell infiltration (hematoxylin and eosin staining, ×100); (B) positive for HER-2(2+) staining (immunohistochemical staining, ×100).

especially for liver, biliary, pancreatic tumors, lung cancer, breast cancer, gastric cancer, colorectal cancer, and other digestive tract tumors. Moreover, the combined detection of CA15-3, CA125, and CEA can complement each other and effectively improve the performance indicators of breast cancer diagnosis (43,44), which is of certain value for the early diagnosis and treatment of breast cancer.

Breast cancer diagnosis relies on histopathological examination, and pathological specimens can be obtained through a variety of surgical methods, including core needle biopsy (CNB) and open surgical biopsy. In this case, the patient underwent excision of the left breast mass and some surrounding tissue, considering the possibility of malignant lesions of the left breast mass. Signet ring cells can be seen locally in the fibrous stroma of the breast as indicated by pathological diagnosis. The choice of complete tumor resection here can avoid misdiagnosis due to the particularity of the case.

Pathological diagnosis based on histopathological features has always been the "gold standard" of tumor diagnosis and the basis of clinical treatment. It plays an important role in the pathological diagnosis of special types of malignant tumors, such as breast SRCC. SRCC of the breast needs to be differentiated from mucinous cystadenocarcinoma, metastatic mucinous carcinoma, and metastatic SRCC, which can be combined with clinical history and immunohistochemical results (45-48). According to the literatures we searched, CK20+ and CDX2+ were indicative of gastric cancer as the primary focus, while ER+, PR+, and gross cystic disease fluid protein-15 (GCDFP-15)+ were supported by breast cancer as the primary focus. GATA3 has only been used as the main differential indicator in recent years to differentiate primary breast cancers from gastrointestinal tumors. The study by Hui *et al.* reported that ER and GATA-3 are effective methods for differentiating signet ring tumors of the breast and gastrointestinal tract (49). In this case, the immunohistochemical results of ER, PR and GATA-3 were negative, which suggested that breast SRCC was not the primary lesion. Meanwhile, CK20 and CDX2 also helped to support the gastrointestinal origin of the signet ring tumors. This case report is consistent with the findings of Hui. It is important to differentiate between metastatic and primary breast cancer at pathological diagnosis.

SRCC is a type of gastric cancer with a high degree of malignancy, which has a low incidence rate. Patients with SRCC early stage may not have clinical symptoms, and are typically in the advanced stage when they are discovered. Through our multi-faceted differential diagnosis, the final diagnosis of the patient was clarified earlier, which not only bought time for the patient's subsequent treatment, but also avoided misdiagnosis and blind treatment due to the particularity and rarity of the case.

Conclusions

Gastric cancer should be considered when breast tumors show SRCC without *in situ* lesion. Signet ring cell gastric cancer (occult) should be excluded even if the patient has no family history of gastric cancer. It is important to distinguish between metastatic carcinoma and primary breast cancer, also can avoided misdiagnosis and blind treatment due to the particularity and rarity of the case. For patients with advanced metastatic breast cancer patients, the optimal treatment option involves making an appropriate and early diagnosis, and prolonging the patient's life with tumor control, while at

Table 1 Thirty-three cases of SRCC with stomach or breast as primary site

Case	Age/ gender	Initial symptom	Primary carcinoma	Histologic type	Immunohistochemistry	Treatment
Arifa Abid *et al.*, 2013 (11)	59/F	Stomach	Breast	Lobular carcinoma	CK7+, AE3+, AE–, ER+, PR+, CK20–, CDX2–, HER2–	Endocrine therapy
Tetsuji Kudo *et al.*, 2005 (12)	59/F	Stomach	Breast	Signet ring-cell carcinoma	GCDFP15+	Chemotherapy, 2 years
Idrees Khan *et al.*, 2017 (13)	56/F	Stomach	Breast	Signet cell carcinoma	–	Chemotherapy
S. Di Cosimo *et al.*, 2003 (14)	39/F	Ovarian	Stomach	Signet cell carcinoma	GCDFP15–, ER–, c-erbB-2–	Chemotherapy
Yoichiro Kondo *et al.*, 1984 (15)	51/F	Stomach	Breast	Signet cell carcinoma	–	Bilateral mastectomy and partial gastrectomy
Tomoi Sato *et al.*, 2008 (16)	67/F	Breast	Stomach	Poorly differentiated adenocarcinoma with signet ring cells inside the lymphatics	ER–, PR–, HER2–, CK20–, MUC 5AC–, GCDFP15+, CK7+, MUC2+	Chemotherapy
Hyunee Yim *et al.*, 1997 (17)	48/F	Stomach	Breast	Signet cell carcinoma	GCDFP15+, ER–	Chemotherapy
Sibel K. Cetintas *et al.*, 2006 (18)	48/F	Breast	Breast	Signet cell carcinoma	ER+, PR+, CK+, CD20–, CR-A–	Chemotherapy
Kwangil Yim *et al.*, 2017 (19)	65/F	Stomach	Breast	Signet ring cell carcinoma	GCDFP15–, GATA3+, ER–, PR–, c-erbB-2+	Chemotherapy
Oya Kayacan *et al.*, 2008 (20)	28/F	Left breast	Stomach	Signet ring cell carcinoma	–	–
Huanhuan Yan *et al.*, 2017 (21)	39/F	Left breast	Stomach	Signet ring cell carcinoma	CK7–, CK20–, villin++, CAM5.2+, Ki-67 (50%), P53+, c-erbB-2–	Chemotherapy
Qiuhong Tian *et al.*, 2016 (22)	37/F	Breast	Stomach	Signet ring cell carcinoma	CK7+, CK20–, villin++, ER–, PR–, HER2–	Chemotherapy
Qiuhong Tian *et al.*, 2016 (22)	31/F	Right breast	Stomach	Signet ring cell carcinoma	CK7(–), CK20(3+), villin(3+), PR(–), S100(–), Vim(–), ER(–), Ki-67(+), c-Erb-B2(–), CD34(–), E-cadherin(2+)	Chemotherapy
Audrius Dulskas *et al.*, 2019 (23)	34/F	Stomach	Stomach	Signet ring cell type of adenocarcinoma	CDX-2+, CK20+, ER–, CK7–, GATA 3–	Chemotherapy, Radiation therapy
Gregory E. Jones *et al.*, 2007 (24)	51/F	Stomach	Breast	Adenocarcinoma of a signet-ring pattern	ER+, PR+, CK7+, GCDFP15+, CK20–, HER2–	Palliative care
Gregory E. Jones *et al.*, 2007 (24)	61/F	Stomach	Breast	Poorly differentiated adenocarcinoma of signet ring cell type	ER+, PR+, CK7+, CK20–, HER2–	Chemotherapy and radiotherapy to her brain
CH Park, *et al.*, 1996 (25)	48/F	Right Breast	Breast	Signet ring cell carcinoma	–	Chemotherapy

Table 1 (*continued*)

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Case	Age/ gender	Initial symptom	Primary carcinoma	Histologic type	Immunohistochemistry	Treatment
SS Qureshi *et al.*, 2005 (26)	34/F	Stomach	Stomach	Signet ring cell carcinoma	Ck20+, GCDFP–, ck7–, S-100–, ER–, PR–	Gastrectomy, chemotherapy
C. Gregoire *et al.*, 2014 (27)	66/F	Stomach	Breast	Signet ring cell adenocarcinoma	ER+, PR+, E-cadherin–	Stop chemotherapy, Hormonal therapy
Anastasios L Boutis *et al.*, 2006 (28)	37/F	Left breast	Stomach	Signet ring cell carcinoma	ER–, PR–, c-erbB-2–, CK7+, CK20+,	Chemotherapy
HH Buerba-Vieregge *et al.*, 2021 (29)	38/F	Stomach	Stomach	Signet ring cell carcinoma	HER2–, GATA3–, ER–, ACE+, CK7+, CK20+	Chemotherapy
S. Krichen Makni *et al.*, 2007 (30)	40/F	Stomach	Stomach	Signet ring cell carcinoma	ACE–, CK20–, CK7+, ER–, PR–	Chemotherapy
Doval *et al.*, 2009 (31)	34/F	Ovarian	Stomach	Signet ring cell carcinoma	GCDFP-15–, ER–, PR–, HER-2/neu (ERBB2)–, CA125–	Chemotherapy
Li-Yuan Wei *et al.*, 2017 (32)	49/F	Breast	Stomach	Signet ring cell carcinoma	ER–, PR–, c-erbB-2–, CK20–, CK7+, CK19+, CK20+, GATA3–, GCDFP-15–, MMG–	Chemotherapy
Asumi Iesato *et al.*, 2015 (33)	41/F	Pelvic and breast	Stomach	Signet ring cell carcinoma	MUC5AC+, HIK1083+	Chemotherapy
Asumi Iesato *et al.*, 2015 (33)	34/F	Cervical polyp	Stomach	Signet ring cell carcinoma	HER2–, ER–, PR–, HIK1083+, GCDFP15+, MUC6+	Chemotherapy
Chun-Lan He *et al.*, 2015 (34)	48/F	Left breast	Stomach	Signet ring cell breast carcinoma	CK7+, CK20+, villin+, EGFR+, ErbB2/HER2+, ER–, PR–, GCDFP-15–, CEA–, (CA) 153–, CA125–, CA199–	Chemotherapy
Susanne Briest *et al.*, 1999 (35)	46/F	Both breasts	Stomach	Signet ring cell carcinoma	ER–, PR–, CK7+, CK20+, CEA+	Chemotherapy
Jin-Young Kwak *et al.*, 2000 (36)	41/F	Left breast	Stomach	Signet ring cell carcinoma	ER–, GCDFP–	–
Jin-Young Kwak *et al.*, 2000 (36)	23/F	Right breast	Stomach	Signet ring cell carcinoma	ER–, GCDFP–	–
Yiu Shiobhon Luk *et al.*, 2012 (37)	54/F	Right breast	Stomach	Signet ring cell carcinoma	ER–, c-erbB-2–, AE1/AE3+, PAS-D+, E-cadherin+, CK7+, CK20+	Chemotherapy
Atul K Madan *et al.*, 2002 (38)	39/F	Abdomen	Stomach	Signet ring cell carcinoma	GCDFP-15–, c-erg–, ER–, PR–, BRST-2–, CK20+, CK7+	Palliative surgery
Karl J. Schmutzer *et al.*, 1973 (39)	22/F	Stomach	Stomach	Krukenberg tumors	–	Gastrectomy, oophorectomy, mastectomy, chemotherapy

SRCC, signet ring cell carcinoma; F, female.

the same time improving their quality of life.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-242/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-242/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the institutional ethics board of Shandong Provincial Maternal and Child Health Care Hospital (approval No. 2021-097). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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