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Case Report

Breast cancer with an initial gastrointestinal presentation: a case report and literature review

Ling-Ling Zhang[1], Xiao-Cui Rong[2], Li Yuan[3], Li-Jing Cai[1], Yue-Ping Liu[1]

[1]Department of Pathology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, P. R. China; [2]Department of Radiology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, P. R. China; [3]Department of Endoscopy Room, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, P. R. China

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Abstract: The most common sites of breast cancer metastasis are the lymph nodes, lungs, bones, and liver. Gastrointestinal (GI) metastasis is relatively rare and often occurs within several years after a breast cancer diagnosis. Most patients experience abdominal pain, anorexia, bleeding, vomiting, and other digestive system symptoms, symptoms which are difficult to distinguish from primary gastric cancer. There is no characteristic change seen under a digestive tract endoscopy, and the difference in morphology under the pathological microscope from that of primary poorly differentiated gastric adenocarcinoma is so small that it can easily cause a misdiagnosis. This paper reports the case of 46-year-old female patient whose first symptom was GI discomfort. She was hospitalized for GI surgery with an unknown medical history, but, during the preoperative examination, multiple breast masses were found on both sides, which were proved by pathology to be invasive lobular cancer. According to the medical literature, bilateral breast cancer with gastric metastasis is very rare, and, so far, this is the first reported case. Despite it being a rare phenomenon, it is necessary to be aware of the possibility of metastatic lobular carcinoma in the diagnosis of poorly differentiated gastric adenocarcinoma by biopsy.

Keywords: Bilateral breast cancer, invasive lobular carcinoma of the breast, metastatic carcinoma of the digestive tract

Introduction

Worldwide, breast cancer is one of the main diseases threatening women's physical and mental health. Mainly occurring through blood and lymphatic metastasis, the common metastasis sites are the lymph nodes, lungs, bones and liver, as well as other organs [1]. Gastrointestinal (GI) metastasis is relatively rare, and since the clinical symptoms are often nonspecific, the existence of primary lesions is easily overlooked. In a small number of patients with GI metastasis, invasive lobular carcinoma (ILC) is the main histological type. It has been reported that the average time to gastric metastasis for most breast cancers is 7 years (0.12-12.5) after a diagnosis of breast cancer [2], but a more recent report suggested that it could be up to 20 years after a breast cancer diagnosis [3]. It is rare to find a case with both gastric discomfort as the first symptom and bilateral ILC of the mammary glands. This paper reports a case in which the clinician, endoscopist, and pathologist did not recognize the metastasis at first. However, subsequent examinations found that the bilateral ILC of the mammary glands was accompanied by multiple metastases throughout the whole body. We have summarized the imaging, endoscopic, histological, and immunohistochemical results of this case and reviewed the relevant literature so as to alert pathologists to the potential of such scenarios to avoid the occurrence of similar errors in the preliminary diagnosis.

Case report

A 46-year-old female patient was hospitalized in the Gastroenterology Department of the Fourth Hospital of Hebei Medical University in October 2019 for more than half a month due to epigastric discomfort. Gastroscopy showed gastric mucosal hyperemia (dilatation of 1.5-2.0 cm) and central erosion in the upper curvature of the stomach, the far anterior wall of the

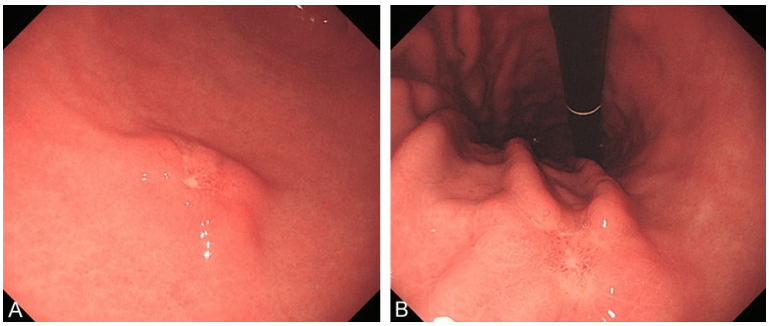

Figure 1. Gastroscopic manifestations: congestion, and swelling of the mucosa, central erosions, and depression.

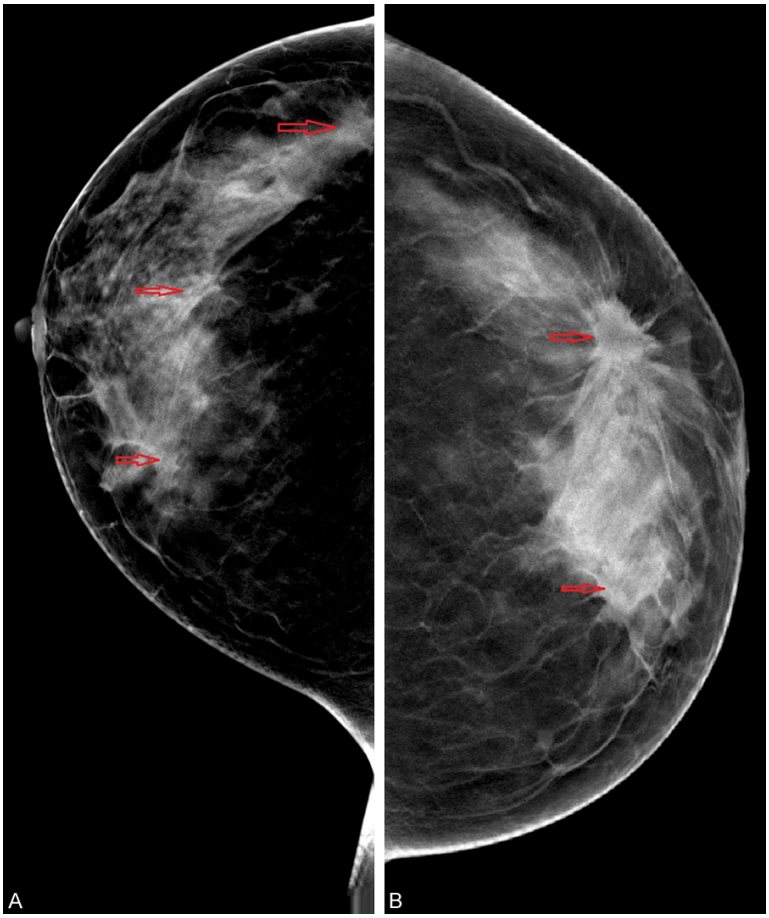

Figure 2. Molybdenum-based imaging showed multiple diffuse, irregular masses and non-mass-like lesions in both breasts with clear nonhomogeneous enhancement, and some lesions had sharp or burred edges (Red arrows).

body, the junction of the body and the antrum, and the proximal curvature of the antrum. A diagnosis of gastric multifocal lesions (with a suspicion of cancer) was made (**Figure 1A**, **1B**). No obvious abnormality was found in the laboratory examination. After admission, the patient underwent further examinations. An abdominal computed tomography (CT) scan showed that the wall of the gastric antrum was thickened, which is consistent with gastric cancer. At the same time, the left axillary lymph nodes were enlarged, and the ribs, vertebrae, and ilium of the whole body were occupied. A color Doppler examination of the bilateral axillary lymph nodes showed that there were no enlarged lymph nodes in the right axilla. In the left armpit, 2.6×1.2 cm hypoechoic nodules could be seen, but no normal hilar structure was seen, suggesting a fusion of the two nodules. A diagnosis of left axillary lymph node enlargement was made, so a lymph node puncture was performed. Molybdenum-based imaging was used, and multiple diffuse irregular mass-like and non-mass-like enhancements, which were significant and nonhomogeneous, were found in both breasts. Some of the lesions had blurred edges, indicating a malignancy, so a diagnosis of Breast Imaging, Reporting and Data System (BI-RADS) category 5 was made (**Figure 2**), and a bilateral breast biopsy was performed.

The study was conducted in accordance with the Declaration of Helsinki (2013 revision). The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. A written consent was obtained from the patient.

Pathological findings

Under a low-power microscope, a large number of cells with the same shape were found gathered in the local gastric mucosa, and the cells were arranged in cords or diffusely located. At high magnification, the nuclei were round or

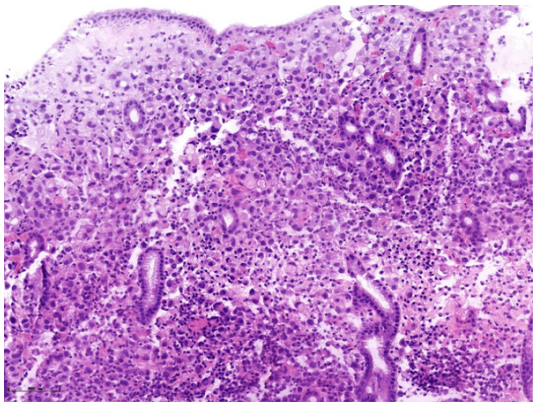

Figure 3. Gastric body mucosa biopsy. The microscopy findings were as follows: cancer cells in the gastric mucosa were arranged in sheets, infiltrating the gastric mucosa glands (HE ×100).

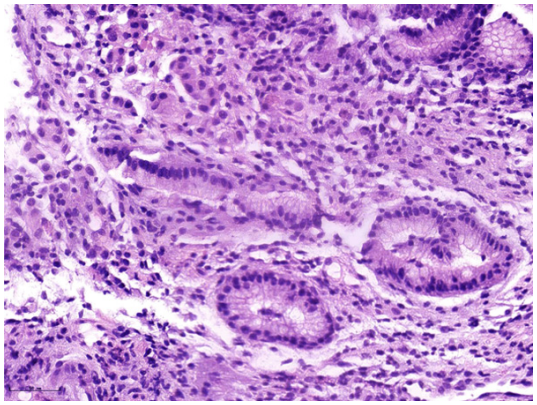

Figure 4. Gastric antrum mucosa biopsy. The cells were moderately heteromorphic, some nuclei were eccentric, the cells had rich cytoplasms, and intracellular mucus could be seen (HE ×200).

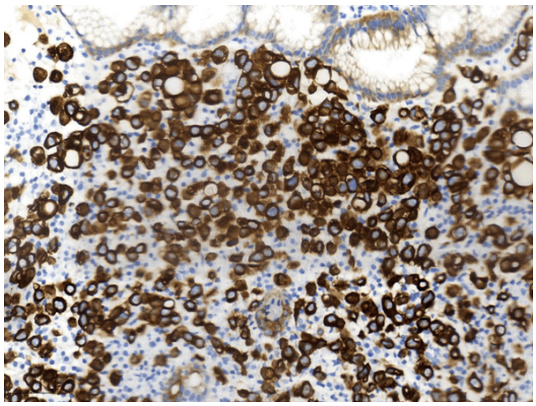

Figure 5. The CK7 was diffusely strongly positive (IHC EnVision, ×400).

oval and hyperchromatic, with abundant cytoplasms and red staining. Some cells were rich

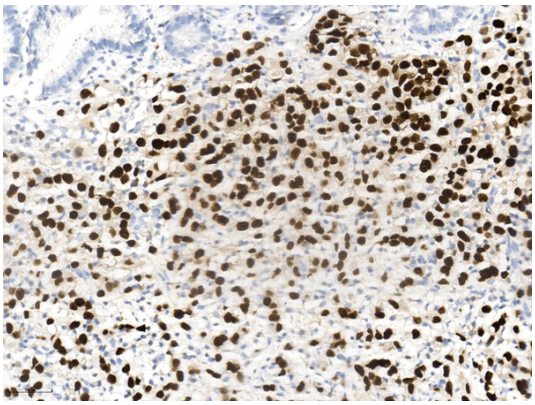

Figure 6. The ER was strongly positive (IHC EnVision ×400).

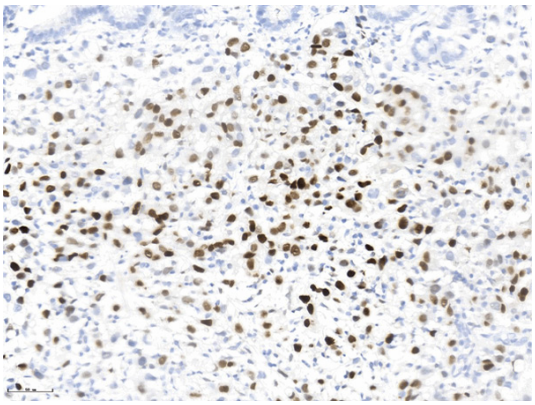

Figure 7. The PR was strongly positive (IHC EnVision ×400).

in intracellular mucus, showing an atypical signet ring shape. Small and uniform cell infiltrative growth, destroying the gastric mucosa epithelium, could be seen in the gastric mucosa, which is similar to the findings in primary poorly differentiated adenocarcinoma of the stomach (**Figures 3**, **4**). The pathological diagnosis was poorly differentiated adenocarcinoma. After the space-occupying lesions in the breast were found, the subsequent immunohistochemistry results (**Figures 5**-**8**) showed cytokeratin markers AE1/AE3 (+), cytokeratin 7 (CK7) (+), estrogen receptor (ER) (80% positive), progestogen receptor (PR) (80% positive), and GATA binding protein 3 (GATA3) (+) in the antrum and body of the stomach. A pathological diagnosis was made of metastatic poorly differentiated adenocarcinoma from primary breast cancer.

The left axillary lymph node biopsy showed that the infiltration of the heteromorphic tumor cells in the fibrous tissue was consistent with the

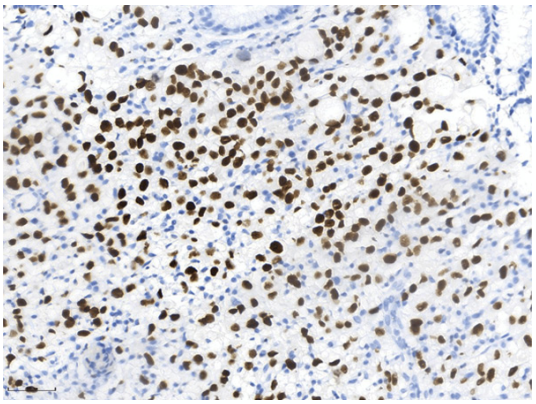

Figure 8. The GATA3 staining (IHC EnVision, ×400).

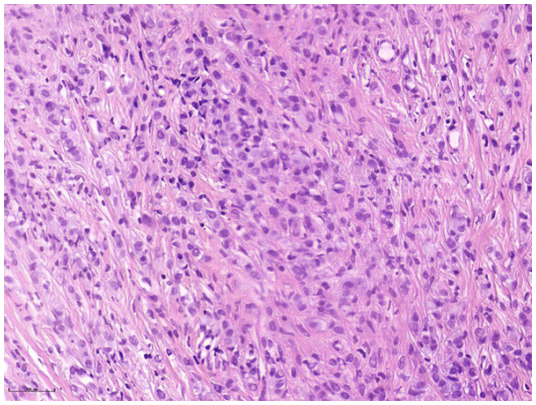

Figure 9. The histology of the left axillary mass (HE ×400).

growth pattern of cancer, and the tumor cells were small and monotonous (**Figure 9**). The immunohistochemistry results were as follows: AE1/AE3 (+), estrogen receptor (ER) (80% positive), progestogen receptor (PR) (80% positive), HER2 (1+), mammaglobin (±), GATA3 (+), the human hematopoietic progenitor cell antigen (CD34) (vessel+), phosphoprotein of 120 kDa (p120) (cytoplasm+), and epithelial cadherin (E-cadherin) (-). A pathological diagnosis of poorly differentiated adenocarcinoma originating in the breast was made.

The left breast biopsy showed that the tumor cells were denser than the cells in the right biopsy sample and were arranged in nests or sheets; the cell heteromorphism was clear, and the cells had hyperchromatic nuclei and eosinophilic cytoplasms (**Figure 10**). The right breast biopsy showed that the tumor cells were arranged in cords or rows. The tumor cells were small and monotonous, and the degree of heteromorphism was small (**Figure 11**). The immu-

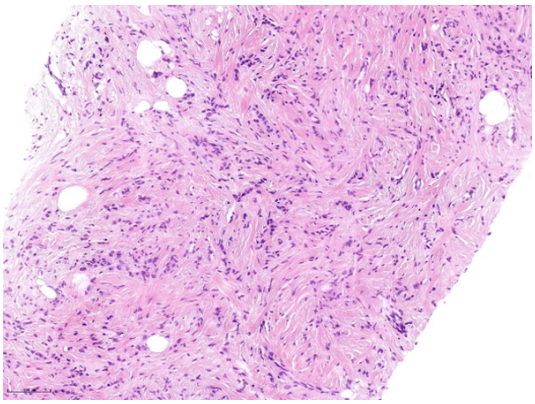

Figure 10. The histological examination of the right breast tumor showed that the tumor cells were dense and moderately heteromorphic and had slightly hyperchromatic cytoplasms (HE ×200).

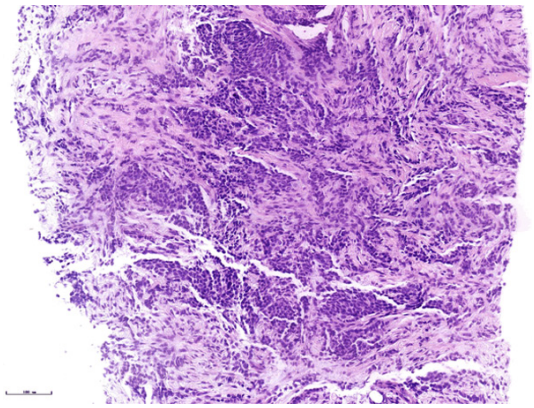

Figure 11. In the left breast biopsy sample, the tumor cells were sparse, arranged in cords, with a beaded structure in some parts, and had less heteromorphism than the cells in the right breast biopsy sample (HE ×200).

nohistochemistry results were as follows: ER (80% positive), progesterone receptor (PR) (80% positive), human epidermal growth factor receptor 2 (HER-2) (1+), E-cadherin (-), and p120 (cytoplasm+) (**Figures 12**, **13**). A pathological diagnosis of ILC of the breast was made.

The patient was confirmed to have clinical stage IV bilateral invasive lobular breast cancer with gastric and multiple bone metastases, so she was transferred to the oncology department for further treatment.

Discussion

Gastrointestinal metastasis of primary invasive breast cancer is rare. The Mayo Clinic reviewed 12,000 cases of metastatic breast cancer;

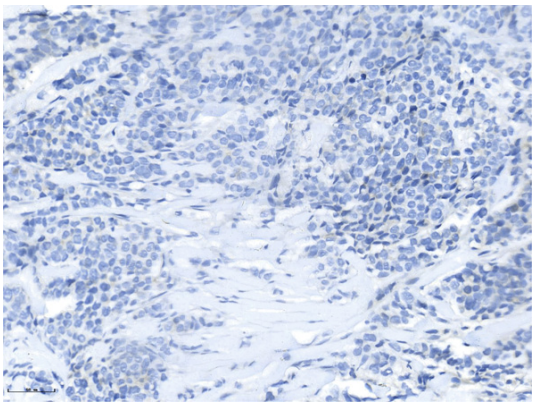

Figure 12. The E-cadherin protein was absent (IHC EnVision, ×200).

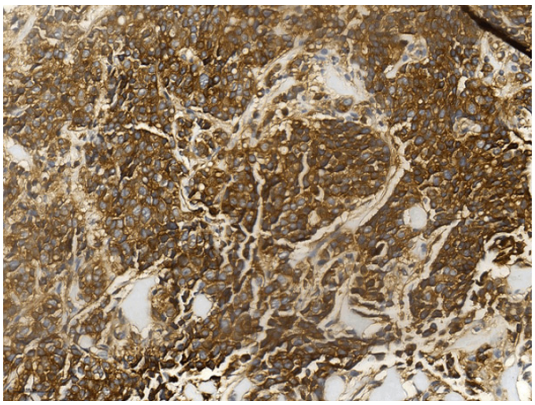

Figure 13. P120 was positive in the cytoplasm (IHC EnVision, ×200).

only 73 cases had gastrointestinal metastasis, and the metastasis rate was 8%-35% [2]. Different histological types of primary breast cancer tend to have different metastasis sites. Compared with invasive ductal cancer, ILC is more likely to have distant metastases, especially those located in the gastrointestinal tract, peritoneum, ovaries, and uterus [4-6]. Taal et al. reported that of 8,215 patients with metastatic breast cancer, 51 had gastric metastases, 36 of which were ILC [7]. Almubarak's study showed that 34 out of 35 breast cancer patients with gastric metastases had ILC [8], and Xu et al. [4] reviewed 78 cases of breast cancer with gastric metastasis, and 65.4% (51/78) of the cases were the histological type ILC.

Since the onset of ILC is insidious, very few cases of gastrointestinal metastasis are treated with gastrointestinal discomfort presenting as the first symptom. We retrieved seven articles reporting this rare phenomenon (**Table 1**) [9-15]. All the eight cases, including the one reported in this article, were female patients, aged 46-78 years, and the first major clinical manifestations were mainly abdominal discomfort, ascites with nausea and vomiting, persistent abdominal pain, anemia, upper gastrointestinal bleeding, and constipation, and four of the patients experienced weight loss. The main transfer sites were the stomach, colon, rectum, and peritoneum. The histological type of breast lesion was ILC in seven cases, one of which was signet ring cell carcinoma, which is considered to be a special subtype of breast cancer [16].

Of the eight patients, those with metastases to the stomach showed mucosal erosions and polyps; those with metastases to the intestines were more likely to form submucosal masses due to hidden clinical symptoms, leading to intestinal stenosis. According to reports in the medical literature, breast cancer metastasized to the stomach can also be endoscopically manifested as volcanic ulcer-like new organisms; the stomach wall is diffusely affected, showing a "leather pouch", and some patients even show normal gastric mucosa with lesions located under the mucosa [17]. Therefore, it is difficult to distinguish primary gastrointestinal tumors or other benign lesions using endoscopy. Imaging is also lacking in specificity, often only showing a thickening of the gastrointestinal wall, very similar to a primary gastrointestinal tumor [18]. In this group of eight patients, seven of them showed a thickening of the stomach or intestinal wall. This is why these patients were initially treated for gastrointestinal tumors.

However, the morphology under the biopsy pathology microscope is also lacking in characteristics. In this case, the tumor cells are infiltrated in the mucosal layer and the mucosal muscle layer. The tumor cells are round and oval with clear atypia and abundant cytoplasms. Eosinophilic, red-stained mitotic figures with large nuclei are discernible. Metastatic ICL cells have poor adhesion, and signet ring-like cells often appear, which can easily be confused with primary gastrointestinal cancer with low adhesion.

Table 1. Literature summary of the breast cancer cases with gastrointestinal symptoms as the first manifestation

Year	Authors	Patient gender	Age	Clinical symptoms	Metastatic lesion	Endoscopy performance	Imaging performance	Breast lesions	Histological type	Immunohistochemical phenotype	Treatment	survival status
2003	Chow [9]	F	78	Ascites, nausea, vomiting, weight loss	Colon, liver, kidney, double ovaries	-	Colon thickening liver metastatic nodules	Upper left quadrant of breast	Invasive lobular carcinoma	ER (+) PR (+)	-	-
2011	Arrangoiz [10]	F	70	Abdominal pain; diarrhea, constipation alternate, decreased bowel movements, flatulence, weight loss	Stomach, rectum, peritoneum, left axillary lymph node, lung nodule, bone, sickle ligament	Colonoscopy showed a mass 3 cm-7 cm from the anal margin of the rectum with obstruction. Gastroscopy biopsy shows thickening of the mucosa	Repeated CT scans of the abdomen and pelvis show thickening around the rectum	Upper left quadrant of left breast. size 7.4 cm ×1.8 cm ×6.6 cm	Invasive lobular carcinoma	ER (+) PR (-) HER2 (1+)	Paclitaxel + bevacizumab sequential zoledronic acid	12 m, survive
2015	Dória. MT [11]	F	60	Upper abdominal pain, vomiting, weight loss	Stomach, liver, peritoneum	Mucosa around the stomach and antrum is fragile and partially necrotic	Irregular thickening of the stomach wall	Middle and lower quadrant of left breast, maximum diameter 4 cm	Invasive lobular carcinoma	ER (+), PR (-) HER2 (-), ki-67 (10%)	Gastrectomy, peritoneal biopsy + liver nodule resection. Anti-estrogen therapy (letrozole)	-
2015	Osaku. T [12]	F	69	Constipation	Rectum, sigmoid colon, peritoneum	Normal colon and rectal mucosa	Thickness and narrowing of rectum and sigmoid colon	Right breast area C about 5×6 mm	Invasive lobular carcinoma	ER (+), PR (-) HER2 (-)	Laparotomy Hormone therapy + taxanes and anthracyclines. Paclitaxel, docetaxel and anthracycline outpatient treatment for one year, hormone treatment for three years	48 m, dead
2017	Khan I [13]	F	56	Anemia, upper gastrointestinal bleeding	Swollen stomach, colon, bone, bladder, pancreas	Multiple ulcerative nodules and polypoid folds in the gastric mucosa, cecum and proximal ascending colon	-	Extensive lesions of the right breast	Signet ring cell carcinoma	-	Chemotherapy	Died during treatment
2018	Mantiero M [14]	F	53	Upper abdominal pain, indigestion, nausea and vomiting after meals, weight loss	Stomach, peritoneum	Pyloric mucosa thickening and narrowing	Thickened pyloric sinus wall, enlarged mesenteric lymph nodes (20 mm) and peritoneal mass	No lesions in the breast. Enlarged lymph nodes in both armpits	Invasive lobular carcinoma	ER (90%), PR (35%+) HER2 (1+), Ki-67 (<5%)	Antihormonal therapy	2 y, survive
2018	Woo J [15]	F	51	Epigastric pain	Stomach, bone	an elevated mucosal lesion with central depression in the greater curvature of lower body	suspicious focal wall thickening in the greater curvature of the lower corpus	Tumor presenting with diffuse and multifocal involvement of both breasts measured >7 cm	Invasive lobular carcinoma	ER (+), PR (+), Her-2 (-)	Chemotherapy Radiotherapy, And Endocrine therapy	66 m, survive

As a result of the atypical clinical, imaging, and pathology findings, immunohistochemistry plays an important role in the diagnosis of this disease. Most gastric metastatic breast cancers are ER-positive, PR-positive/negative, and HER2-negative. However, in primary gastric adenocarcinoma, ER and PR can be positively expressed by 20%-28% of patients [19]. In a few cases, metastatic breast cancer is negative for ER and PR, so a diagnosis cannot be made based on these two items alone [20]. Cytokeratin 7 (CK7) and cytokeratin 20 (CK20) combined with gastric adenocarcinoma and breast cancer markers are generally recommended. CK7 and CK20 are expressed in gastric adenocarcinoma but not in breast cancer. Both carcinoembryonic antigen and caudal type homeobox transcription factor 2 are positive in primary gastric adenocarcinoma, while gross cystic disease fluid protein-15, mammary globulin, and GATA3 are breast-derived markers, but their sensitivity and specificity are quite different. Therefore, it is necessary to detect the related antibodies [21]. In this case, GATA3 and CK7 were diffusely positive, and the finding of CK20 negative was consistent with breast tumors. Another study has shown that forkhead box protein A1 is also helpful in identifying breast tumors. Its positive rate in hormone receptor-positive breast cancer is as high as 96.2% [22]. The reason why ILC easily transfers to the gastrointestinal tract can be explained by its different biological and histological characteristics. Berx et al. [23] found that most ILCs lack E-cadherin expression, which leads to a loss of adhesion between cells. Transfer and diffusion can occur in the early stage of the disease. This may also explain the first symptom of our case being stomach discomfort, and ILC was found to be the cause of multiple metastases throughout the body. In the eight patients we reviewed, the breast lesions were almost all extensive, and they manifested as irregular and homogeneous areas of imaging, which in one case were occult. In addition, the breast lesions were not palpable but were found through imaging. This is also one of the reasons why breast lesions are often ignored. In our case, bilateral ICL of the breast was also found, which was the only case among the eight cases.

Multifocal carcinoma found on both sides is more common in ICL [24-26]. In the patient we reported on, ICL was found at the same time in both breasts. From an imaging point of view, the bilateral mammary glands were all multiple masses. However, there were axillary and intramammary lymph nodes on the left side, so it is possible that ICL of the left breast may have metastasized to the right side and multiple parts of the body. However, histopathology showed that the morphologic features of the two mammary glands were not exactly the same. The left breast cancer cells were denser and more heteromorphic than the right breast cancer cells. Therefore, we believe that bilateral primary breast cancer is likely.

The treatment for metastatic breast cancer in the gastrointestinal tract is mainly chemotherapy, endocrine therapy, and targeted therapy. Only a few patients can undergo palliative surgical resection if they have symptoms such as gastrointestinal obstruction. The effective rate of systemic treatment is about 46% [27]. The treatment of this group of patients is typically chemotherapy and antihormonal therapy, but individual cases have undergone gastrectomies. One of the eight patients in this group died during her treatment, and the longest survivor died during the 4-year follow-up. At present, the patient we reported on has received six cycles of TX chemotherapy (Paclitaxel liposome 240 mg D1; Capecitabine 1.5 g, 2/day, q21d). At the same time, she was given comprehensive treatment of acid suppression and antiemetics. After eight months of follow-up, her current situation is stable.

ICL of breast patients with extramammary symptoms has also been reported in the case literature [28], but this phenomenon is rare. In the case we reported on, it was rare to find bilateral breast spaces at the same time. The initial diagnosis of gastroscopy did not recognize it. Therefore, for patients with gastrointestinal discomfort, and a biopsy showing poorly differentiated adenocarcinoma, especially signet ring cell carcinoma, one should be alert to the possibility of metastasis, regardless of whether there is a history of breast cancer. It is important to ask for a detailed medical history, or to take one if necessary, and to carry out immunohistochemical identification, and make an early diagnosis to avoid unnecessary surgical treatment.

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Disclosure of conflict of interest

None.

Address correspondence to: Yue-Ping Liu, Department of Pathology, The Fourth Hospital of Hebei Medical University, No. 12 Jiankang Road, Chang'an District, Shijiazhuang 050011, P. R. China. Tel: +86-0311-86095374; E-mail: liuyp_dr@163.com

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