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Original Article

Breast cancer metastasis to the stomach may misdiagnose as primary gastric cancer: report of one case and review of literature

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Abstract: Background: Breast cancer metastasis to the stomach is rare. It may prove very difficult to distinguish a breast cancer metastasis to the stomach from a primary gastric cancer on the basis of clinical, endoscopic, radiological and histopathological features. It is important to make this distinction in order to administer the appropriate treatment. Case presentations: A 39-year-old woman, accepting treatment for invasive breast cancer 13 years age, showed gastrointestinal symptoms with persistent in indigestion, lack of appetite, and epigastric pain. The patient required radical curative surgery in view of an apparent localized primary gastric cancer. Postoperative histology revealed a poorly differentiated adenocarcinoma and immunohistochemistry (IHC) for gross cystic disease fluid protein-15 (GCDFP-15) was positive, hepatocyte nuclear factor 4a (HNF4a) was negative and caudal type homeobox transcription factor 2 (CDX2) was negative, suggesting metastatic breast cancer. Conclusion: In patients with a history of breast cancer, a high index of suspicion for potential breast cancer metastasis to the stomach should be considered when new gastrointestinal symptoms develop. For a differential diagnosis, IHC is recommended, and when the final diagnosis of metastatic breast cancer is confirmed, systemic treatment is preferred.

Keywords: Breast cancer, metastasis, gastrointestinal symptoms, immunohistochemistry

Introduction

Breast cancer is the most common tumor and the leading cause of death among females worldwide [1]. It is a heterogeneous group of tumors with variable morphology, behavior, and response to therapy. The two most common histologic types of invasive breast cancer are ductal and lobular carcinomas, accounting for approximately 71% and 5% of all cases in the China, respectively [2]. Although pathologically distinct, invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) have similar clinical outcomes and prognosis [3]. Common sites of breast cancer metastasis include lungs, liver, bones, brain, and adrenal glands. Gastrointestinal (GI) tract metastasis from breast origin is considered rare in clinical practice [4]; and reports on this subject in the literature are poor and mostly limited to case reports [4-9]. Most series report a greater propensity for lobular carcinoma to metastasize to the GI tract [4, 8, 9], while the ductal carcinomas most frequently relapse in the liver, the lungs and the brain. Metastatic spread to the stomach may occur many years after the initial treatment for breast cancer. It may prove very difficult to distinguish from a primary gastric cancer. Moreover, the clinical presentation of gastric metastases from breast cancer mimics a primary gastric tumor. The radiological and endoscopic findings will also be similar to those of a primary GI tumor. However, it is important to make this distinction as the basis of treatment for breast cancer metastasis to the stomach is usually with systemic therapies rather than surgery.

In this study we present a case of breast cancer metastasis to the stomach, which is initially considered to represent a primary gastric cancer, and we also review the related literature.

Presentation of case

A 39-year-old woman underwent a right modified radical mastectomy in April 2002. Pathology

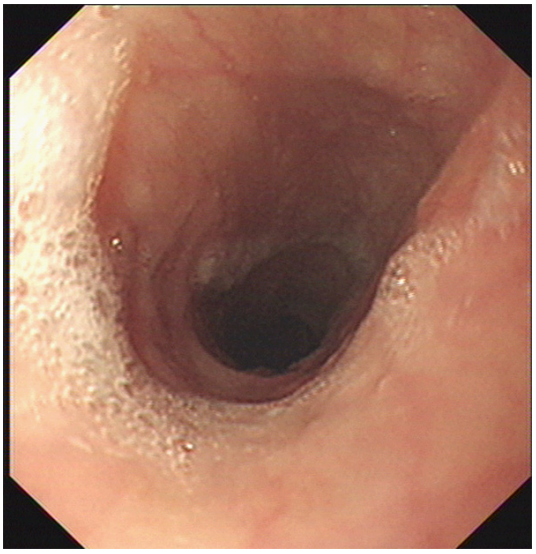

Figure 1. Gastric ulceration was found under gastroscopy.

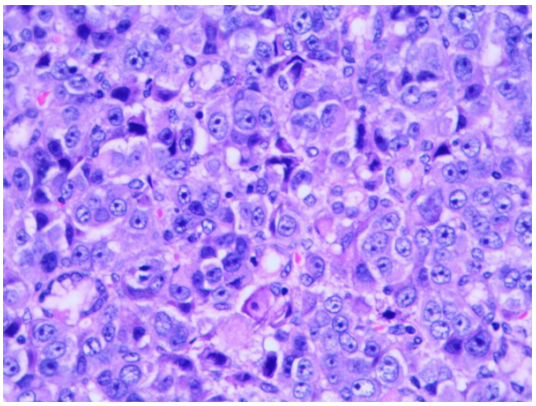

Figure 2. A poorly differentiated carcinoma was presented in the gastric biopsy specimen (hematoxylin and eosin stain, ×400).

at that time was found to be IDC G2 pT2 N14/24 M0. Immunohistochemistry (IHC) results were as follows: estrogen receptor (ER) positive, progesterone receptor (PR) positive, human epidermal growth factor receptor-2 (Her-2) negative, Ki-67 positive (20%). A complete staging was performed, with abdominal ultrasound, chest radiography, and bone scan; no metastases were found. After surgery, she was treated with cyclophosphamide (500 mg/m^2), adriamycin (50 mg/m^2) and fluorouracil (500 mg/m^2) days 1-21, 6 cycles. Subsequently, radiotherapy on the right chest and supraclavicular area was completed, and meanwhile endocrine therapy with tamoxifen (20 mg/day) was started for five years.

In September 2009, the patient was admitted to our department, since she had a solid mass and pain in the right chest. A bone scan was performed, and multiple bone metastases were detected. The solid mass was then resected and pathology revealed the presence in the chest of metastasis from breast cancer (ER positive, PR positive, HER2 negative). In November 2009, the patient received the laparoscopic oophorectomy. After that, she was treated with capecitabine (2500 mg/m^2, day 1-14) and paclitaxel (175 mg/m^2, day 2) days 1-21, 6 cycles. At the same time, she was treated with zoledronic acid for 3 years. In April 2010, endocrine therapy with anastrozole (1 mg/day) was started. In December 2012, the patient showed disease progression, then anastrozole was stopped and endocrine therapy with exemestane (25 mg/day) was initiated.

In April 2015, she showed persistent indigestion, lack of appetite, and epigastric pain. A gastroscopy found some ulceration (**Figure 1**) in the gastric antrum and biopsies revealed the presence of poorly differentiated cancer (**Figure 2**). Subsequently, a computed-tomography (CT) scan was performed, demonstrating no evidence of metastasis in the abdomen. At the demand of the patient, a laparoscopic-assisted radical distal gastrectomy (Billroth I) was performed. Postoperative histology revealed a poorly differentiated adenocarcinoma of the stomach with 7 out of 17 lymph nodes involved. IHC of the surgical specimen showed gross cystic disease fluid protein-15 (GCDFP-15) positive, hepatocyte nuclear factor 4a (HNF4a) negative, caudal type homeobox transcription factor 2 (CDX2) negative, ER negative, PR negative, and Her-2 negative (**Figure 3**). Therefore, pathologists believed that it was metastasis from breast carcinoma. Then systemic therapy with chemotherapy was performed. The patient died 9 months later with other multiple metastases.

Discussion

Metastatic tumors of the GI tract are rare, but are more common than clinically suspected, as documented by autoptic evaluations [10]. Breast cancer is the most common primary malignancy to metastasize to the GI tract along with melanoma, ovarian and bladder cancer [10]. The metastatic patterns of lobular and ductal carcinoma have been reported to be dif-

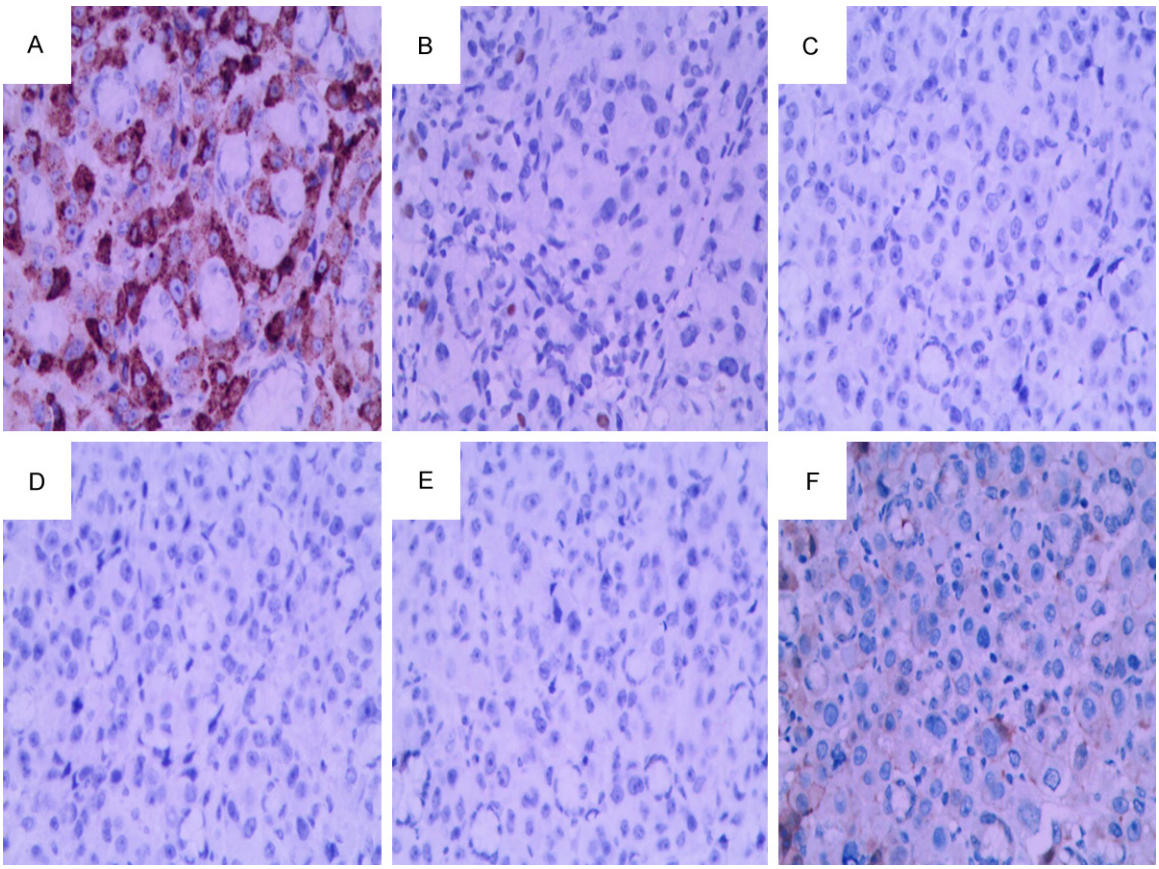

Figure 3. Immunohistochemistry scan of gastrectomy specimen. Notes: A. GCDFP-15 (+), ×400; B. HNF4a (-), ×400; C. CDX2 (-), ×400; D. ER (-), ×400; E. PR (-), ×400; F. Her-2 (-), ×400. Abbreviations: GCDFP-15: gross cystic disease fluid protein-15; HNF4a: hepatocyte nuclear factor 4a; CDX2: caudal type homeobox transcription factor 2; ER: estrogen receptor; PR: progesterone receptor; Her-2: human epidermal growth factor receptor-2.

ferent significantly. Compared to ILC, IDC seems to spread less frequently to the GI tract. In a study of 2,605 patients, the metastatic rate of IDC to the GI tract was considerably lower than that of ILC (0.2% versus 4.5%; $P<0.05$) [11]. The mechanism behind this correlation has been exploring and requires further studies.

From our review of the literature, gastric metastases from mammary carcinomas frequently develop many years after the primary tumor, raising suspicions about a new primary cancer within the stomach. This interval could often be more than 4 years, and even as long as 28 years [12]. The time interval between primary breast cancer and GI tract involvement is 13 years in this case. The most common type of gastric involvement is as "linitis plastica" appearance with diffuse infiltration of the submucosa and muscularis propria. Other appearances of gastric metastases include nodular or polypoid lesions and ulcerated lesions, as reported in our case. The clinical presentation of a breast cancer metastasis to the stomach is often indistinguishable from primary gastric cancer, as the symptoms are nonspecific, including dyspepsia, anorexia, epigastric pain, early satiety, vomiting and bleeding. In general, endoscopic, radiological and histological evaluation is essential to discriminate primary gastric cancer from breast cancer metastasis to the stomach. However, radiological and endoscopic findings are often nonspecific, and may be hard to distinguish from primary gastric cancer. Radiological findings on CT or barium studies include encasement of the whole stomach as seen in linitis plastica, multiple lesions of the stomach or extrinsic lesions of the gastric wall [13]. Endoscopic evaluation only shows discrete mucosal abnormalities indistinguishable from other tumors. As a result, many cases are not diagnosed as breast cancer metastasis

to the stomach until surgery is performed. The patient in this report was also initially diagnosed with an apparent primary gastric cancer. Ultimately this diagnosis was revised to metastatic breast cancer, but only after surgery.

Detailed immunohistochemical analysis may be the only reliable method to differentiate between metastatic and secondary primary gastric carcinoma. There are many breast-associated and GI-associated marks to assist in evaluating these metastatic carcinomas for which a primary breast carcinoma is entertained. Metastatic breast carcinoma is usually positive for ER, PR and GCDFP-15, while the primary gastric carcinoma is generally positive for HNF4a and CDX2. ER and PR can be present occasionally in a primary gastric tumor, but a high level favors a breast cancer metastasis. Van Velthuysen et al. [14] reported that second-generation estrogen receptors are not observed in the expression of gastric cancer and are useful in diagnosing breast cancer metastases to the stomach. Although ER and PR have been used as reliable markers to determine the breast origin, it is worth noting that ER and PR negativity has been reported in patient with breast cancer metastasis [15]. Previous reports have demonstrated that the discordance of ER and PR status between primary breast cancer and those metastases is 15-40%, and most of the discordances included loss of ER and PR expression [16, 17]. A possible explanation can be represented by the dedifferentiation of tumor cells during disease progression. As in the present case, the IHC for ER and PR were negative in the gastric metastatic breast carcinoma, while ER and PR were positive in the primary breast carcinoma. Therefore, hormone receptors are not useful and may result in misdiagnosis for some patients. However, GCDFP-15 is highly specific for mammary differentiation in females, and is frequently used as an immunohistochemical marker for the evaluation of a potential mammary origin of metastatic carcinoma of unknown primary site. An excellent correlation between GCDFP-15 positivity and the origin of a metastatic breast carcinoma has been demonstrated [18]. According to some reports, their sensitivity is 55-76% and their specificity is 95-100% [19, 20]. HNF4a is expressing in epithelial cells of endodermal tissues, including the stomach, gut, liver, and pancreas, but not in most other organs including mammary glands and ovaries [21]. It is a highly useful marker in discriminating primary and metastatic stomach from breast carcinomas with a sensitivity of 99-100% and specificity of 100% [22, 23]. CDX2 is a homeobox gene that encodes a transcription factor believed to play an important role in the regulation of proliferation and differentiation in the GI tract. It proves to be particularly positive in a subset of adenocarcinomas arising in the stomach, esophagus and colorectum, while it is not observed in any carcinomas of the breast [24]. Therefore, the positivity for GCDFP-15 and in contrast, the negativity for HNF4a and CDX2 were of great value in diagnosing an unsuspected gastric metastasis from breast cancer in the present case.

Data on treatment are scarce. As breast cancer metastasis to the stomach represents evidence of systemic disease, systemic treatment is recommended as the first line treatment. However, surgery is reserved only for palliative surgical resection for obstruction and bleeding. McLemore et al. [25] reported that chemotherapy and hormone treatment were effective, while surgical intervention did not have a significant effect on survival. However, Wang et al. [26] reported that surgery combined with systemic treatment to treat the GI metastasis gave a satisfactory result, especially for patients with significant clinical manifestations. Therefore, the decision-making process for surgical intervention should be based on the clinical presentation and symptoms, the availability of chemotherapeutic options and a quality of life discussion. In the present case, surgical treatment was performed in consideration of secondary primary gastric carcinoma only based on biopsy pathology and the demand of the patient. Unfortunately, the final diagnosis was revised to metastatic breast cancer after surgical intervention. Then systemic therapy with chemotherapy was performed. However, In this case, surgery combined with systemic treatment gave a dissatisfactory result.

Conclusion

In conclusion, GI tract metastasis from breast carcinoma is very rare, and accurate and definite diagnosis is difficult due to nonspecific clinical presentations and long intervals between manifestations. The history of breast can-

cer and IHC can help with correct diagnosis. Surgery combined with systemic treatment may be not effective, especially for patients without significant clinical manifestations.

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Disclosure of conflict of interest

None.

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