

# Gastric metastasis from invasive lobular breast cancer, mimicking primary gastric cancer

## A case report

Dae Hoon Kim, MD, PhD<sup>a</sup>, Seung-Myoung Son, MD<sup>b</sup>, Young Jin Choi, MD, PhD<sup>a,\*</sup>

### Abstract

**Rationale:** Gastric metastasis from invasive lobular breast cancer is relatively rare, commonly presented among multiple metastases, several years after primary diagnosis of breast cancer. Importantly, gastric cancer that is synchronously presented with lobular breast cancer can be misdiagnosed as primary gastric cancer; therefore, accurate differential diagnosis is required.

**Patient concerns:** A 39-year-old woman was visited to our hospital because of right breast mass and progressive dyspepsia.

**Diagnoses:** Invasive lobular carcinoma of breast was diagnosed on core needle biopsy. Gastroscopy revealed a diffuse scirrhous mass at the prepyloric antrum and diagnosed as poorly differentiated adenocarcinoma on biopsy. Synchronous double primary breast and gastric cancers were considered. Detailed pathological analysis focused on immunohistochemical studies of selected antibodies, including those of estrogen receptors, gross cystic disease fluid protein-15, and caudal-type homeobox transcription factor 2, were studied. As a result, gastric lesion was diagnosed as metastatic gastric cancer originating from breast.

**Interventions:** Right breast conserving surgery was performed, and duodenal stent was inserted under endoscopic guidance to relieve the patient's symptoms. Systemic chemotherapy with combined administration of paclitaxel and trastuzumab was initiated.

**Outcomes:** Forty-one months after the diagnosis, the patient is still undergoing the same therapy. No recurrent lesion has been identified in the breast and evidence of a partial remission of gastric wall thickening has been observed on follow-up studies without new metastatic lesions.

**Lessons:** Clinical suspicion, repeat endoscopic biopsy, and detailed histological analysis, including immunohistochemistry, are necessary for diagnosis of metastatic gastric cancer from the breast.

**Abbreviations:** BCS = breast conserving surgery, CDX-2 = caudal-type homeobox 2, CK = cytokeratin, CT = computed tomography, GCDPF-15 = gross cystic disease fluid protein-15, MUC-2 = mucin-2, MUC-5 = mucin-5, PET = positron emission tomography.

**Keywords:** gastric metastasis, immunohistochemistry, lobular breast carcinoma, primary gastric carcinoma, synchronous diagnosis

## 1. Introduction

Breast cancer is the most common type of cancer among women worldwide and ranks as the second most common cancer among women in Korea.<sup>[1]</sup> Owing to the advances in systemic therapies,

including intensive local treatment, chemotherapy, endocrine therapy, and targeted therapy, overall survival rates of breast cancer have increased; however, these therapies have not produced significant changes in the prognosis of patients with breast cancer accompanied by distant metastasis.

The main sites of metastasis for breast cancer are the bone, lung, and liver, whereas metastasis to the gastrointestinal tract is relatively rare; reported incidence rates are 2% to 18% of breast cancer cases. Importantly, gastric metastasis from invasive lobular breast carcinoma is reported to occur at a higher rate than the metastasis from invasive ductal carcinoma.<sup>[2]</sup> Gastric cancer has high incidence rates in Korea,<sup>[1]</sup> and differentiation between primary gastric cancer and metastatic gastric cancer based solely on clinical findings may be difficult. Inappropriate diagnosis can lead to unnecessary surgical procedures.

In the present study, we report a case of gastric metastasis from invasive lobular breast cancer, which can be misdiagnosed as primary gastric cancer. We also report the effectiveness and applications of immunohistochemical analysis in the differentiation of gastric metastasis from breast cancer and primary gastric cancer.

## 2. Case presentation

The study was approved by the institutional Review Board of Chungbuk National University Hospital, Republic of Korea. The

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<sup>a</sup> Department of Surgery, <sup>b</sup> Department of Pathology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Republic of Korea.

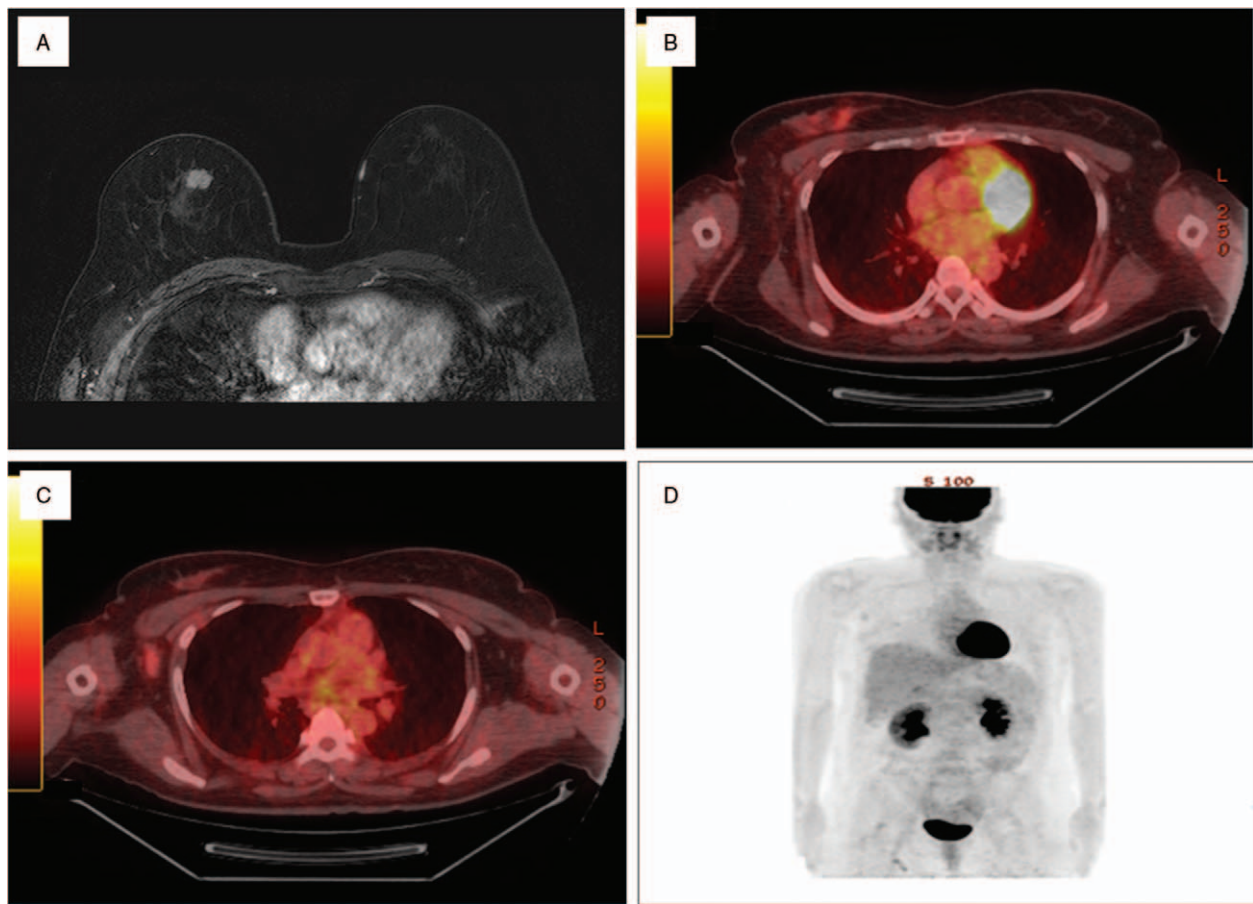
\* Correspondence: Young Jin Choi, Department of Surgery, Chungbuk National University Hospital, Chungbuk National University College of Medicine, 1 Chungdae-ro, Seowon-gu, Cheongju-si, Chungcheongbuk-do 28644, Republic of Korea (e-mails: choijj@chungbuk.ac.kr; yj0139@naver.com).

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**Figure 1.** Breast magnetic resonance imaging (MRI) (A) and positron emission tomography-computed tomography (PET-CT) (B–D) findings showing irregular enhancing mass in the right breast with axillary lymph node metastasis. There was no evidence of distant metastasis.

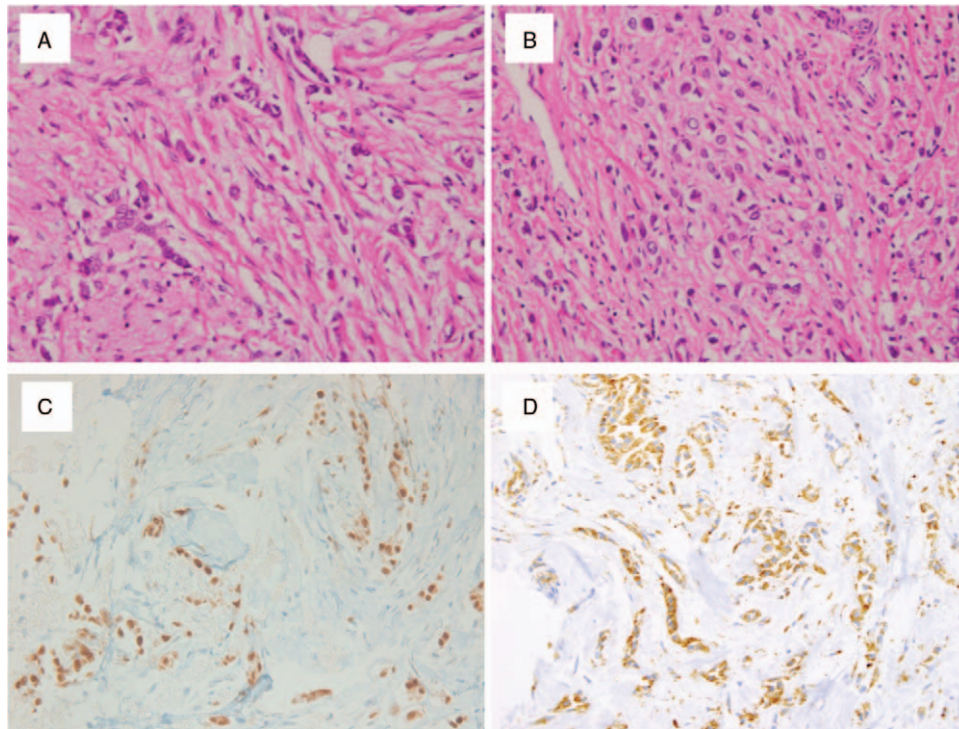
patient agreed to authorize us to share the figures and the experiences during her treatment procedure in our department. Informed consent was obtained.

A 39-year-old woman visited the clinic because of the presence of a palpable mass in the right breast that had developed 2 months ago, and discomfort in the upper abdomen. The patient was on medication with antacid for chronic gastritis that she had been diagnosed with at a private hospital based on her upper gastrointestinal endoscopy results. A solid mass in the upper outer region of the right breast and enlarged ipsilateral axillary lymph nodes could be palpated on physical examination. Ultrasonography and breast magnetic resonance imaging (MRI) results showed single masses on the upper outer quadrant of the right breast, as well as multiple axillary lymphadenopathy (Fig. 1A). The patient was diagnosed with invasive lobular breast carcinoma after a core needle biopsy. Blood test results, including liver function measurements, were all normal. The hemoglobin, carcinoembryonic antigen, and carbohydrate antigen 15-3 levels were 12 g/dL, 4.36 ng/mL, and 34.59  $\mu$ mL, respectively. No abnormal finding was observed on abdominal ultrasonography other than bilateral hydronephrosis. Positron emission tomography (PET) results showed lesions in the right breast and axilla, and no evidence of distant metastases (Fig. 1B–D).

Right breast conserving surgery and axillary lymphadenectomy were performed. A biopsy performed after surgery confirmed the presence of invasive lobular breast carcinoma, measuring 2 cm in the right breast (Fig. 2A). Metastasis was observed in 5 out of 20 dissected axillary lymph nodes (Fig. 2B). The breast

carcinoma was immunohistochemically positive for estrogen receptor (2+, 90%) and progesterone receptor (2+, 60%), and negative for E-cadherin and C-erb-B2 (Fig. 2C and D). An additional immunohistochemical analysis identified the breast carcinoma was positive for gross cystic disease fluid protein-15 (GCDFP-15), and negative for caudal-type homeobox 2 (CDX-2) transcription factor, mucin-2 (MUC-2), and mucin-5 (MUC-5).

Two weeks after the surgery, gastroscopy was performed again because discomfort and pain in the upper abdomen were persistent; a diffuse scirrhous mass was identified at the prepyloric antrum with pyloric obstruction (Fig. 3A). Abdominal computed tomography (CT) scans showed hypertrophy of the gastric wall of the pyloric region accompanied by pyloric obstruction (Fig. 3B). No evidence of lymphadenopathy or metastasis was found, whereas bilateral hydronephrosis was observed. Based on these findings, the patient was diagnosed with T3N0M0 gastric cancer according to the 7th edition of the AJCC staging system. Poorly differentiated adenocarcinoma partially resembling the morphology of signet ring cell carcinoma was observed on gastroscopic biopsy. The aforementioned lesion was positive for estrogen receptor (2+), progesterone receptor (1+), and GCDFP-15, and negative for CDX-2, cytokeratin (CK) 5, CK14, MUC-2, MUC-5, and E-cadherin. Finally, the lesion was diagnosed as metastatic gastric cancer originating from invasive lobular carcinoma. A difference in the level of C-erb-B2 expression was found between the gastric lesion and the primary breast carcinoma; overexpression of C-erb-B2 was observed in the metastatic gastric cancer (Fig. 4).

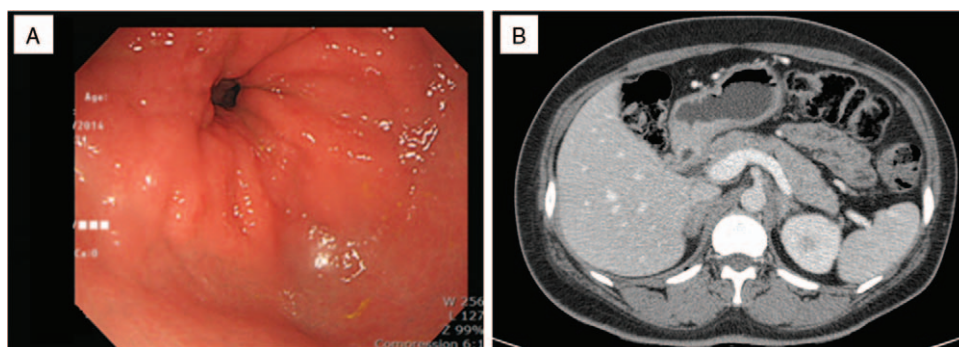


**Figure 2.** Histopathology of breast at the invasive front showed invasive lobular carcinoma, morphologically resembling signet ring cell carcinoma with poorly adhesive cancer cells (hematoxylin and eosin staining  $\times 400$ ) (A). Single-cell invasive pattern was prominent in metastatic lymph nodes (hematoxylin and eosin staining  $\times 400$ ) (B). The primary breast carcinoma was immunohistochemically positive for estrogen receptor (C) and negative for C-erb-B2 (D).

During a medical examination, the patient stated that she had no family history of breast or gastric cancer, had never been diagnosed with lobular carcinoma in situ, and had never undergone hormone replacement therapy in the past. After a multidisciplinary team meeting, it was determined that no additional surgery would be performed for the metastatic gastric cancer, and a duodenal stent was inserted under the guidance of endoscopy to relieve the patient's symptoms (Fig. 5A and B). Systemic chemotherapy with combined administration of paclitaxel ( $80\text{ mg/m}^2$ ) and trastuzumab ( $2\text{ mg/kg}$ ) at 1-week intervals was initiated. Pyloric obstruction was moderately reduced and evidence of reflux was found on gastroscopy performed 6 months after the diagnosis (Fig. 5C). Moreover, 7

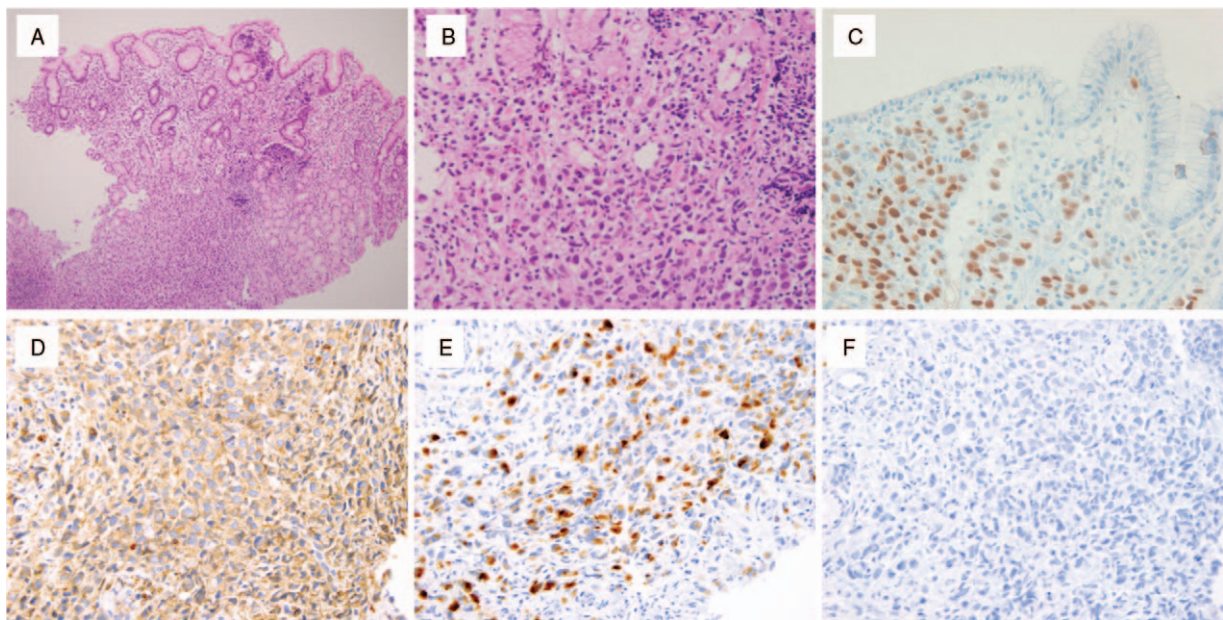
months after the diagnosis, small bowel obstruction occurred as a result of stent displacement. A laparotomy for stent removal, and resection and anastomosis of the small bowel were performed.

Currently, 41 months after the diagnosis, the patient is still undergoing the same therapy and has been experiencing tolerable grade 1 peripheral neuropathy and changes in the nails. Gastrointestinal symptoms, including discomfort in the upper abdomen, have mostly been relieved. No recurrent lesion has been identified in the breast and evidence of a partial remission of gastric wall thickening has been observed on follow-up abdominal CT scans (Fig. 5D). Lastly, no evidence of new metastasis has been observed.



**Figure 3.** A diffuse, scirrhous mass at the prepyloric antrum with pyloric obstruction was identified on gastroduodenoscopy (A). Abdominal CT scan with contrast demonstrating pyloric obstruction with diffuse gastric wall thickening (B).



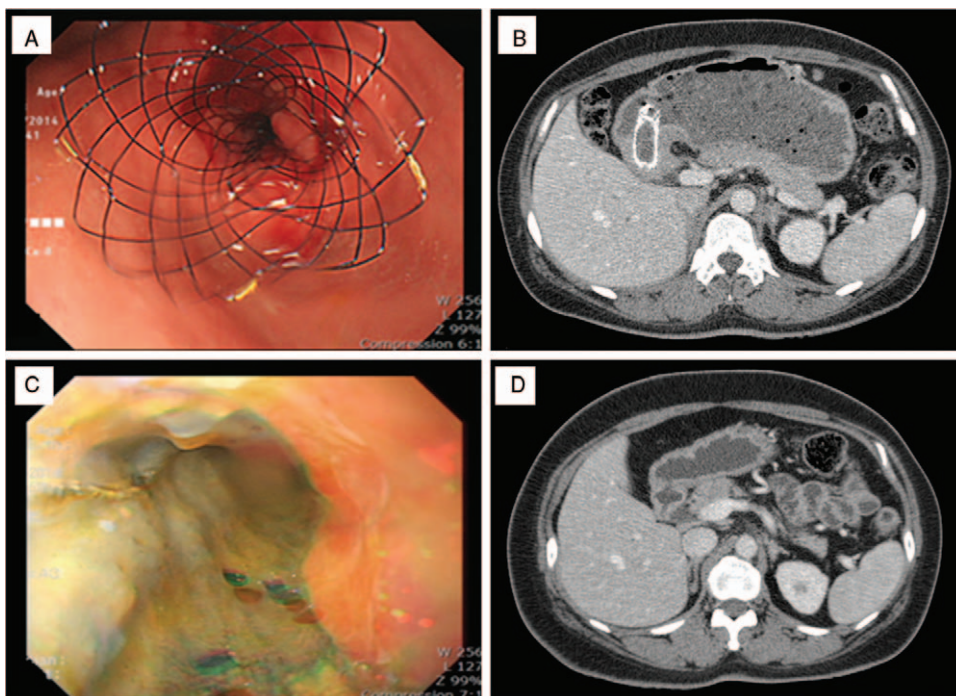


**Figure 4.** Histopathology of gastric lesions. Gastric biopsy showed poorly differentiated adenocarcinoma with signet ring cell morphology and intact normal gastric mucosa resembling the primary breast lesion (hematoxylin and eosin staining  $\times 100$ ) (A) and (hematoxylin and eosin staining  $\times 400$ ) (B); immunohistochemistry was positive for estrogen receptor (C), C-erb-B2 (D), and GCDFP-15 (E), and negative for CDX-2 (F). These findings demonstrated that the gastric lesion was metastatic from breast carcinoma.

### 3. Discussion and Conclusion

Gastric metastasis of malignant breast carcinoma is relatively rare. Clinical symptoms include loss of appetite, feeling bloated soon after eating, upper abdominal pain, bleeding, and

vomiting.<sup>[2]</sup> In the present case, the main symptoms were indigestion and upper abdominal pain resulting from pyloric obstruction caused by the mass. As observed in this case, metastatic gastric cancer is often presented as linitis plastica, which spreads to the muscular layers of the stomach and gastric



**Figure 5.** A duodenal stent was inserted to relieve pyloric obstruction (A, B). Pyloric obstruction was moderately reduced and evidence of reflux was found on gastroscopy performed 6 months after the diagnosis (C). Forty-one months after initial diagnosis, gastric wall thickening was improved without any new lesions (D).

mucosa, whereas it is rarely accompanied by external pressure or separate nodules. According to Taal et al, invasive lobular carcinoma accounts for 83% of all the metastases from malignant breast tumors and it often spreads throughout the stomach.<sup>[2]</sup> The most common site of metastasis from invasive lobular carcinoma is the stomach; gastric metastases are observed at rates of 6% to 18% during a biopsy. Most gastrointestinal metastases present as one among multiple distant metastases several years after breast cancer surgery, and the mean time from the primary diagnosis of breast cancer to metastasis is reported to be 6 to 7 years.<sup>[3]</sup> Therefore, the case observed in this study, in which a metastasis occurred only in the stomach at the time of primary diagnosis of breast cancer, is extremely rare.

In the present case, gastric metastasis was not detected during a systemic examination performed at the time of breast cancer diagnosis. PET scans obtained before surgery did not show any evidence of gastric tumors; tumors were observed only in breast and axillary lesions. The sensitivity of PET is reported to be relatively lower for the diagnosis of gastric cancer compared with that of other cancer types, and this is attributed to issues associated with physiological absorption of F-18 fluorodeoxyglucose and involuntary movements by the gastric wall. Gastric cancer morphology is also associated with sensitivity of PET. Although the sensitivity of PET is high for papillary or ductal carcinoma and poorly differentiated solid adenocarcinoma, high false-negative rates are reported for signet ring cell carcinoma and poorly differentiated nonsolid adenocarcinoma.<sup>[4]</sup>

In general, it is difficult to differentially diagnose primary gastric cancer and metastatic gastric cancer based on gross endoscopy results alone. Because gastric metastases are mostly localized to the submucosal and seromuscular layers, endoscopy results may present as normal in 50% of the cases.<sup>[5]</sup> In the present case, the patient was not appropriately diagnosed even after multiple rounds of endoscopy and biopsies, possibly because a biopsy of the deeper gastric layers, including the submucosa, was not performed.

Although diffuse gastric adenocarcinoma and metastatic gastric cancer from invasive lobular carcinoma may exhibit a single-cell invasive pattern or morphologically resemble signet ring cells, they have different methods of treatment and prognoses.<sup>[6]</sup> In such a case, a detailed immunohistochemical analysis can be of great help. Connel et al compared immunohistochemical results between gastric metastases from breast cancer and primary gastric cancer.<sup>[7]</sup> The results demonstrated increased expression levels of estrogen and progesterone receptors, GCDFP, and CK5/6 in gastric tumors metastasized from breast cancer, compared with those in primary gastric cancer; 72% for estrogen receptor, 33% for progesterone receptor, 78% for GCDFP-15, and 61% for CK5/6 in metastatic cancer, whereas zero expression levels were observed for estrogen receptor, progesterone receptor, and GCDFP, and 14% for CK5/6 in gastric metastases from primary gastric cancer. Estrogen receptor, progesterone receptor, and GCDFP-15 were characteristics pertaining solely to gastric metastasis from breast cancer.

Various markers whose primary origin is the breast have been used in clinical practice. Among these, estrogen receptor is the most influential and sensitive marker for differentiating metastatic breast cancer. However, they have low sensitivity (~50%) for other metastatic cancers, as well as low specificity because they can be expressed by other types of cancer aside from endometrial, ovarian, and breast cancer. Although there are rare reports on expression of estrogen or progesterone receptors in

gastric adenocarcinoma, estrogen receptors are reported to be almost never expressed in gastrointestinal adenocarcinoma, especially in colorectal cancer. A gross cystic disease fluid is a pathological secretion released by the breast and is characterized by increased levels of the GCDFP-15. This protein has been used as a breast-specific marker with sensitivity of 11% to 73% and specificity of 93% to 100%. GCDFP-15 is known to be expressed in not only breasts, but also malignant tumors originating from the salivary gland, external genitals, eyelid, and apocrine duct of the bronchial tubes, and in certain instances of gynecologic adenocarcinoma (5%–10%); however, it is almost never expressed in gastrointestinal cancer. Other breast-specific markers include mammaglobin and GATA-binding protein, with sensitivity of 26% to 84% and 32% to 95%, respectively.<sup>[8]</sup>

CK7 and CK20 are useful cytokeratin markers that can differentiate distant and metastatic gastric tumors. Although CK7+/CK20– are usually expressed in adenocarcinoma of the breast, lung, and ovary, CK7–/CK20+ is more commonly expressed in intestinal adenocarcinoma. In addition, homeobox protein CDX-2, which is necessary for intestinal formation and encodes transcription factors that are involved in the differentiation and proliferation of intestinal epithelial cells, is mostly expressed by malignant gastrointestinal tumors, specifically at a rate of 61% for gastric cancer and 96% for colorectal cancer.<sup>[9]</sup> Although the levels of expression of CK7 and CK20 were not measured in the present case, GCDFP-15, estrogen receptor, and progesterone receptor positive, and CDX-2 negative results alone suffice in the differentiation of metastatic gastric cancer from primary gastric cancer.

Curtit et al compared immunohistochemical results of primary and metastasis sites of breast cancer before and after treatment, and found differences in the levels of expression of the estrogen and progesterone receptors at 17% and 29% of the sites, respectively. A significant change in the level of expression of the estrogen receptor was found at metastasis sites after chemotherapy, and specifically anthracycline-based chemotherapy.<sup>[10]</sup> In the present case, although estrogen and progesterone receptors were expressed at both the primary and metastasis sites of breast cancer, C-erb-B2 was only expressed at the metastasis sites. The level of C-erb-B2 expression may differ between primary and metastasis sites of breast cancer in 5% to 10% of the cases, rates that are lower than those of estrogen or progesterone receptors.<sup>[11]</sup> The expression of C-erb-B2 in the metastatic gastric tumor observed in the present case demonstrated the potential for C-erb-B2-targeted therapy as an addition to chemotherapy and endocrine therapy. The present study is also meaningful in that a patient was maintained in partial remission through prolonged targeted therapy that was planned based on the immunohistochemical results, and in doing so, demonstrated the usefulness of long-term targeted therapy.

Chemotherapy, endocrine therapy, or combined therapy, which are treatment options for gastric metastasis from invasive lobular carcinoma, have remission rates of 32% to 53%, and can prolong survival time by 2 to 3 years.<sup>[12]</sup> Treatment decisions can be made based on clinical symptoms of an individual patient, and the role of multidisciplinary teams, including those in charge of the gastrointestinal tract, is crucial in the decision-making process. Although resection of liver or pulmonary metastases is reported to increase survival rates in selected patients, reports of resection resulting in a significant increase in survival rates for gastric metastases are rare. In limited cases, prolonged survival has been reported for patients in complete remission from

primary breast cancer with solitary gastric metastases, who underwent gastric resection, relative to those that did not undergo resection; survival time of 38 months versus 14.38 months, respectively.<sup>[12]</sup> However, because gastric metastases are accompanied by metastases of the gastric wall and other regions of the gastrointestinal tract in most cases, surgical treatment of gastric tumors is not recommended as a primary treatment option. Surgical treatment, such as bypass surgery, may be used in cases of complete intestinal obstruction or in emergencies, such as perforation of the gastric wall. McLemore et al treated some patients with gastric metastasis using conventional surgical procedures for symptom relief, and reported no increase in survival rates after surgery. Specifically, they reported that the patient's history of undergoing chemotherapy or hormone therapy is an important prognostic factor, whereas old age and the presence of gastric metastasis are poor prognostic factors.<sup>[13]</sup>

In conclusion, we have reported a case of invasive lobular carcinoma with gastric metastasis, which can be misdiagnosed as primary gastric cancer. Accurate diagnosis and patient-tailored treatment can be achieved through clinical suspicion, repeated endoscopy, and accurate histological examination including disease-specific immunohistochemical analysis.

#### Author contribution

**Data curation:** D.H. Kim, S.-M. Son, Y.J. Choi.

**Formal analysis:** S.-M. Son, Y.J. Choi.

**Investigation:** D.H. Kim.

**Methodology:** Y.J. Choi.

**Project administration:** Y.J. Choi.

**Supervision:** S.-M. Son.

**Visualization:** D.H. Kim, Y.J. Choi.

**Writing – original draft:** Y.J. Choi.

**Writing – review & editing:** S.-M. Son, Y.J. Choi.

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