

Case Report

Invasive Lobular Carcinoma with Gastric Metastasis Mimicking Linitis Plastica as the First Presentation: A Case Report

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Abstract

Invasive lobular carcinoma (ILC) can metastasize to the gastrointestinal tract and closely mimic primary gastric adenocarcinoma, especially when signet-ring cell morphology is present. Here, we report the case of a 65-year-old woman who presented with epigastric discomfort and abdominal fullness. Esophagogastroduodenoscopy showed multiple skipped mucosal lesions in the stomach, and an endoscopic biopsy revealed poorly differentiated adenocarcinoma with signet-ring cell features. She was initially diagnosed as having primary gastric cancer, with imaging showing multiple bone metastases. Later, a newly detected breast lump was diagnosed as ILC on core needle biopsy, which was positive for estrogen receptor (ER) and progesterone receptor, but negative for HER2. As no signet-ring cells were found, the initial assumption was double primary cancers of the stomach and breast. Accordingly, the multidisciplinary team discussion concluded that the breast lump represented a second primary, early-stage breast cancer, making lumpectomy and sentinel lymph node biopsy appropriate to achieve local control and prevent progression-related complications. Subsequent lumpectomy revealed ILC with signet-ring cell morphology, prompting re-evaluation of the gastric biopsy with extended immunohistochemistry, which confirmed metastatic breast origin (ER+, GATA3+, HNF4α-). Therefore, the diagnosis was revised to stage IV ILC with gastric and bone metastases. This case highlights the diagnostic challenges posed by ILC with gastric metastases exhibiting signet-ring cell morphology, and emphasizes the importance of integrating clinical history with careful, parallel pathological and immunohistochemical evaluations.

Keywords: Case report, gastric metastasis, immunohistochemical analysis, invasive lobular carcinoma, linitis plastica, metastatic breast cancer

INTRODUCTION

Invasive lobular carcinoma (ILC) accounts for 10%–15% of breast cancers and is characterized by diffuse infiltration and a discohesive growth pattern.^[1] Unlike invasive ductal

carcinoma (IDC), ILC has a predilection for metastasizing to uncommon sites, including the peritoneum, ovaries, and

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gastrointestinal (GI) tract.^[2] The presence of signet-ring cells has been reported in approximately 10%–20% of cases of ILC.^[3] Gastric metastases from ILC can mimic linitis plastica, a presentation characterized by signet-ring cell morphology and commonly associated with primary gastric cancer. Given the overlapping clinical and endoscopic features, deep biopsies and thorough immunohistochemical (IHC) analysis are crucial for accurate diagnosis and avoiding unnecessary surgery. Herein, we present a case initially diagnosed with gastric adenocarcinoma but later confirmed as metastatic ILC. This case highlights the diagnostic challenges of ILC metastases and the pivotal role of biopsies and IHC in identifying the primary site.

CASE REPORT

A 65-year-old woman with no prior history of breast cancer presented with progressive epigastric discomfort and abdominal fullness. An initial evaluation, including an esophagogastroduodenoscopy, revealed multiple skipped mucosal lesions and ulcers in the stomach [Figure 1]. Histopathology showed infiltration of gastric mucosal tissue with poorly differentiated adenocarcinoma with signet-ring cell features [Figure 2a]. IHC was positive for cytokeratin (CK) and negative (0) for HER2, which did not provide a definitive distinction between primary gastric adenocarcinoma and metastatic disease. Further investigations, including a magnetic resonance scan, revealed diffuse bone metastases over the whole spine. The patient was initially diagnosed with primary gastric cancer with bone metastases and was started on capecitabine chemotherapy.

A month later, the patient noted a right breast lump. Breast ultrasound identified a 1.2 cm irregular hypoechoic mass, which was classified as a breast imaging reporting and data system 4B lesion, indicating a moderate probability (10%–50%) of malignancy. A core needle biopsy confirmed ILC, which was positive for estrogen receptor (ER; 95%) and progesterone receptor (PR; 90%), but negative (0) for HER2, and no evident signet-ring cells were found [Figure 3]. The diagnosis was revised to double primary malignancies of the stomach and breast. Accordingly, the multidisciplinary team discussion concluded that the breast lump represented a second

primary, early-stage breast cancer, making lumpectomy and sentinel lymph node biopsy (SLNB) appropriate to achieve local control and prevent progression-related complications. The patient subsequently underwent lumpectomy and SLNB, and surgical pathology confirmed ILC with signet-ring cell morphology [Figure 2b]. The morphological overlap of signet-ring cells prompted a retrospective review of the initial gastric biopsy with additional IHC staining, which was positive for ER (90%) and GATA3, but negative for HNF4 α , indicating that the gastric lesions were metastatic from breast cancer rather than a primary gastric adenocarcinoma [Figure 4]. In addition, whole-body positron emission tomography showed diffuse fluorodeoxyglucose uptake in the stomach and diffuse gastric wall thickening with a small lumen, characteristic of linitis plastica [Figure 5]. As a result, the final diagnosis was revised to ILC, pT1cN1aM1 (bone and stomach metastasis), stage IV. Later, due to the strong ER positivity, she was started on hormonal therapy with letrozole and targeted therapy with a CDK4/6 inhibitor.

DISCUSSION

ILC metastasizing to the GI tract has been reported in 2%–18% of cases,^[4] with the stomach being the most affected site, accounting for 60% of GI metastases in patients with ILC.^[5] The metastatic pattern is often diffuse and infiltrative, presenting as multiple erosions or changes resembling linitis plastica in the stomach.^[6] Compared with IDC, ILC is significantly more likely to metastasize to the GI tract (4.5% vs. 0.2%, $P < 0.05$).^[7] IDC generally forms discrete nodules, while ILC typically causes diffuse gastric wall thickening

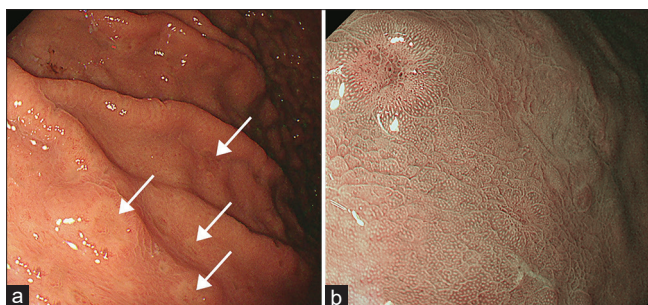


Figure 1: Endoscopic image showing (a) multiple skipped mucosal lesions and ulcers in the stomach (arrows), (b) malignant-looking appearance of cell infiltration in mucosal tissue

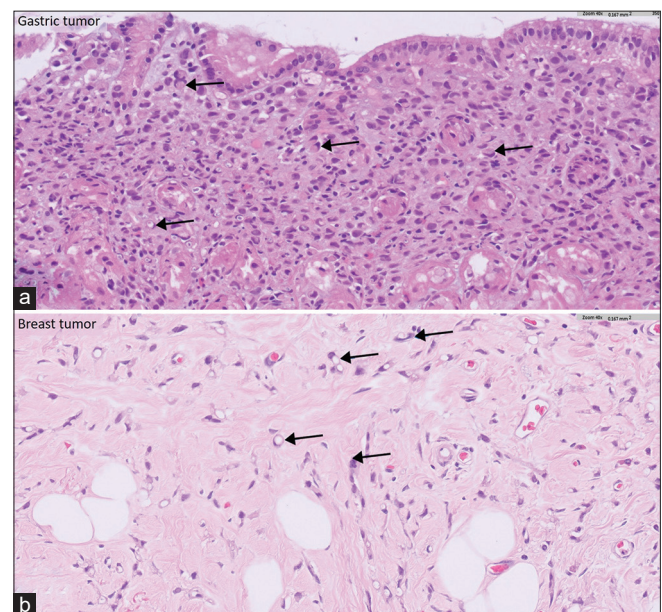


Figure 2: (a) Initial histopathology of tissue from an endoscopic biopsy showing infiltration of gastric mucosal tissue with poorly differentiated adenocarcinoma with signet-ring cell features (arrows) (H and E, $\times 40$), (b) Surgical specimen from lumpectomy showing invasive lobular carcinoma with signet-ring cell morphology (arrows) (H and E, $\times 40$)

and rigidity, mimicking primary diffuse gastric carcinoma.^[6] Importantly, almost all cases of gastric metastasis mimicking linitis plastica are derived from ILC, highlighting the need for heightened clinical suspicion in patients presenting with gastric linitis plastica, especially those with a history of breast cancer.^[8]

Gastric metastases from ILC often present with nonspecific GI symptoms such as epigastric pain, weight loss, nausea, vomiting, early satiety, anemia, or GI bleeding.^[9] These symptoms closely resemble those of primary gastric cancer, making the diagnosis challenging. Moreover, such symptoms can develop many years and even over a decade after the initial diagnosis and treatment of breast cancer, particularly ILC.^[10] Endoscopic findings may be unremarkable or demonstrate features such as diffuse gastric wall thickening, rigidity, or a classic linitis plastica appearance. Histologically, ILC is characterized by a unique discohesive growth pattern, driven by the loss of E-cadherin due to CDH1 mutations, which promotes single-file infiltration of tumor cells and explains the tumor's propensity for metastasis to the GI tract, peritoneum, and bone.^[11] Molecular overlap between ILC and diffuse-type gastric carcinoma is further underscored by the association of

germline CDH1 mutations with both hereditary diffuse gastric cancer and lobular breast cancer.^[11]

Signet-ring cell morphology, resulting from cytoplasmic mucin accumulation and nuclear displacement, is another feature shared between ILC and diffuse-type gastric adenocarcinoma. When signet-ring cells are seen on a gastric biopsy, primary diffuse-type gastric adenocarcinoma is generally the more likely diagnosis. However, ILC can also present with a signet-ring cell morphology. The presence of signet-ring cells has been reported in approximately 10%–20% of cases of ILC.^[3] This morphological similarity complicates histopathological differentiation.^[12] In metastatic ILC, signet-ring cells tend to infiltrate the submucosa and muscularis propria while often sparing the mucosa, which may lead to false-negative results on superficial mucosal biopsies.^[6] Therefore, deep and extensive biopsies are crucial for an accurate diagnosis, especially when the endoscopic appearance is atypical.^[9] Comparing histopathological findings from gastric biopsies with prior breast cancer specimens can also help determine the primary tumor origin. In the present case, the initial endoscopic findings revealed skipped mucosal lesions and ulcers, and histopathology demonstrated mucosal infiltration of poorly differentiated adenocarcinoma with signet-ring cell features, making it challenging to distinguish between a primary and metastatic malignancy.

IHC analysis is crucial for clarifying the tumor's origin. CK7 and CK20 are often used in the initial diagnostic workup. CK7 is typically expressed in breast, lung, ovarian (non-mucinous), and upper GI tract adenocarcinomas, but not in most colorectal cancers. CK20 is usually positive in colorectal, gastric, pancreatic, and some urothelial carcinomas, but negative in breast and lung cancers.^[13] The typical IHC profile for breast carcinomas is CK7+/CK20–, whereas gastric adenocarcinomas often show CK7+/CK20+ or CK7+/CK20– patterns, and only rarely CK7–/CK20+.^[14] CDX2, a nuclear transcription factor critical for intestinal epithelial differentiation, is highly expressed in colorectal and intestinal-type gastric cancers but absent in breast carcinomas.^[15] As such, the combination of CK7, CK20, and CDX2 provides a valuable initial strategy for distinguishing between tumors of breast or GI origin.

Metastatic ILC typically expresses ER, PR, GATA3, and gross cystic disease fluid protein-15 (GCDFP-15), along with loss of E-cadherin.^[12] In contrast, primary gastric cancers typically lack these breast-specific markers. GATA3 and ER are

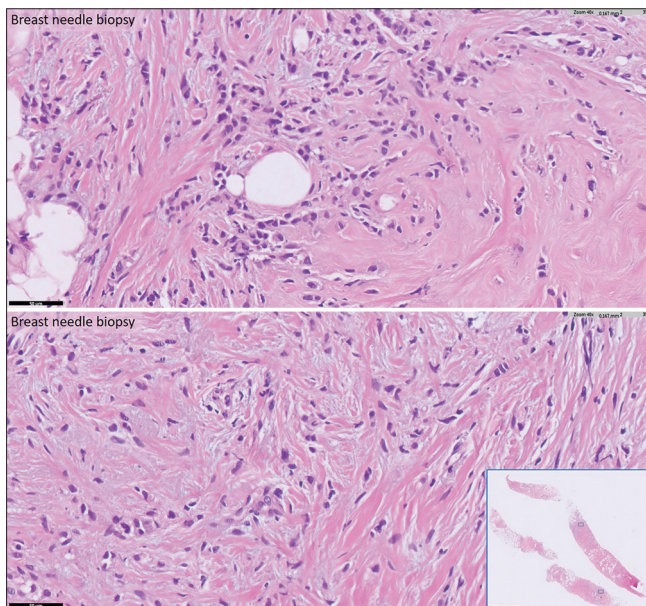


Figure 3: Core needle biopsy of a breast lump showing invasive lobular carcinoma, but no evident signet-ring cells (H and E, $\times 40$)

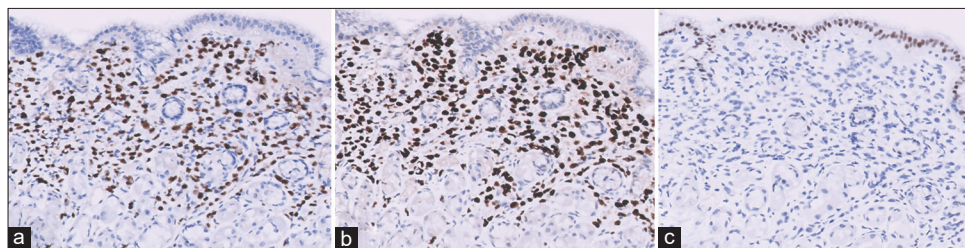


Figure 4: A retrospective review of the endoscopic biopsy with additional immunohistochemical staining was (a) positive for estrogen receptor ($\times 20$), (b) positive for GATA3 ($\times 20$), (c) negative for HNF4a ($\times 20$), indicating breast origin

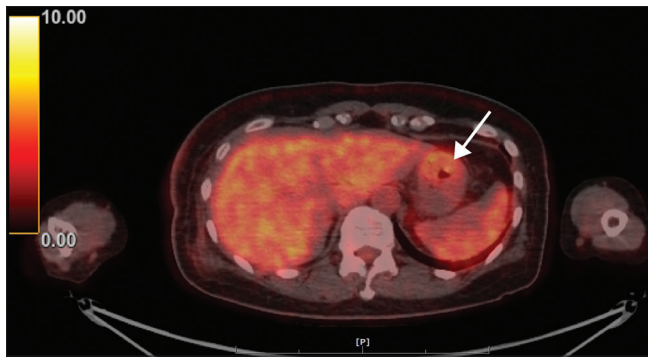


Figure 5: Whole-body positron emission tomography showed diffuse gastric wall thickening with a small lumen, and diffuse fluorodeoxyglucose uptake in the stomach (arrow)

highly sensitive and specific for breast origin (GATA3: 100% sensitivity, 98% specificity; ER: 82% sensitivity, 100% specificity).^[12] GCDFP-15 is often expressed in hormone receptor-positive and apocrine-type breast cancers, and further supports a breast origin when positive (sensitivity 55%–76%, specificity 95%–100%).^[16] While GCDFP-15 positivity is correlated with lower tumor grade, potentially indicating a favorable prognosis, its sensitivity alone is inadequate, necessitating its use as part of a broader marker panel.^[17] Clinically, a GCDFP-15-positive tumor – especially when combined with other markers such as ER, PR, and GATA3 – strongly supports a breast origin for metastatic adenocarcinoma.^[18]

The loss of E-cadherin, resulting from CDH1 gene deletions or epigenetic silencing, is a hallmark of ILC and disrupts cell-cell adhesion, enabling the characteristic noncohesive growth pattern of ILC and often mimicking primary gastric cancers when metastasizing to the GI tract.^[19,20] However, approximately 65% of diffuse-type gastric carcinomas also exhibit reduced or absent E-cadherin expression, limiting its diagnostic specificity. Therefore, E-cadherin should always be interpreted in the context of other IHC markers and the patient's clinical history.

HNF4 α is widely used as an IHC marker to identify tumors of hepatocellular and GI origin. In the GI tract, HNF4 α is also expressed in normal and neoplastic gastric and colonic epithelial cells, and its detection can help distinguish primary GI tumors from metastases of other origins.^[21]

In the present case, the diagnostic pitfall was at the time of the initial gastric biopsy, where poorly differentiated adenocarcinoma with signet-ring cell morphology was interpreted as primary gastric cancer, and a core needle biopsy of the breast lump did not disclose obvious signet-ring cells under routine pathology practice. To prevent such a delay in the diagnosis, several critical steps should be emphasized. First, making an accurate diagnosis requires comprehensive clinical history-taking, focused physical examination, and systematic evaluation for concurrent malignancies. Pathology should never be interpreted

separately from the full clinical context, particularly when a new breast mass is identified.

Second, although signet-ring cells in a gastric biopsy most commonly suggest primary gastric carcinoma, alternative diagnoses, and especially metastatic disease, must be considered from the outset. Therefore, the initial workup should include a parallel, broad IHC panel (e.g., GATA3, ER, CDX2, claudin-18) rather than a sequential or limited “rule-in” approach focused solely on GI markers. A parallel panel ensures equal evaluation of gastric and extra-gastric primary tumors and minimizes diagnostic anchoring.

Third, when both a gastric signet-ring lesion and breast cancer, particularly ILC, are present, clinicians must recognize that metastatic ILC is more common than synchronous double primary tumors. This epidemiologic pattern mandates reexamination of the original gastric biopsy and, if necessary, closer review of the breast core needle biopsy, where rare signet-ring cells may be extremely focal and easily missed. Early reassessment can facilitate the correct identification of metastatic ILC and prevent delays in staging and management.

This case illustrates how metastatic ILC can closely resemble primary gastric adenocarcinoma, particularly when signet-ring cells are present, and highlights the importance of careful clinicopathologic correlation and targeted IHC assessments.

Limitations

As a single-patient case report, this study is inherently limited in its ability to establish efficacy due to the lack of statistical power, generalizability, and the possibility of selection bias. The findings should be interpreted with caution and considered hypothesis-generating rather than conclusive.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author contributions

Chun-Yu Liu contributed to the conception and design of the study. Ting-Wei Chang, Chun-Yu Liu, Chih-Yi Hsu, and Yen-Po Wang contributed to data acquisition and analysis and/or interpretation of data. Ting-Wei Chang and Chun-Yu Liu drafted the manuscript. Ting-Wei Chang, Chun-Yu Liu, Chih-Yi Hsu, and Yen-Po Wang critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript to be published.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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