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## Case Report

# Gastric metastases from invasive lobular carcinoma of the breast: Case report <sup>☆</sup>

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## ABSTRACT

Invasive lobular carcinoma is the second most common type of invasive carcinoma of the breast. Although rare, invasive lobular carcinoma can lead to gastric metastases, which may appear several years after the initial diagnosis. The diagnosis is difficult, either because of its rarity or because of overlapping symptoms and imaging findings with primary gastric carcinoma. Immunohistochemistry is the key to diagnosis. We report a case of a 40-year-old woman with a previous history of invasive lobular carcinoma of the breast 2 years before, who presented recurrent and nonspecific gastrointestinal symptoms. Imaging findings revealed linitis plastica and the biopsy showed the presence of signet ring cell neoplasia. After gastrectomy, immunohistochemistry demonstrated diffuse expression of GATA-3 and the presence of estrogen receptors in some neoplastic cells with CK20<sup>+</sup>, leading to the final diagnosis of gastric metastases from invasive lobular carcinoma of the breast.

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## Introduction

The 2 most common histologic types of invasive breast cancer are invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). ILC corresponds to less than 10% of all malignant breast tumors [1,2] and has a higher rate of bilaterality and multifocality than does IDC. It is the most difficult tumor to diagnose on mammography, with architectural distortion being the most frequent alteration. These lesions uncommonly present themselves with microcalcifications. For

this reason, at the time of diagnosis, 60% of all patients will have lymph node or distant organ metastases [2]. IDC usually metastasize to local and distant lymph nodes, liver, lungs, brain, and bone [3,4]. In contrast, ILC shows a distinct systemic metastatic pattern and has a higher incidence of metastases to the gastrointestinal tract, gynecological organs, meninges, pleura, peritoneum, and skin [1–6].

Breast cancer is one of the most common malignancies that metastasizes to the gastrointestinal tract, along with melanoma and lung carcinoma [1]. However, gastric metastases of lobular breast cancer are uncommon, with a

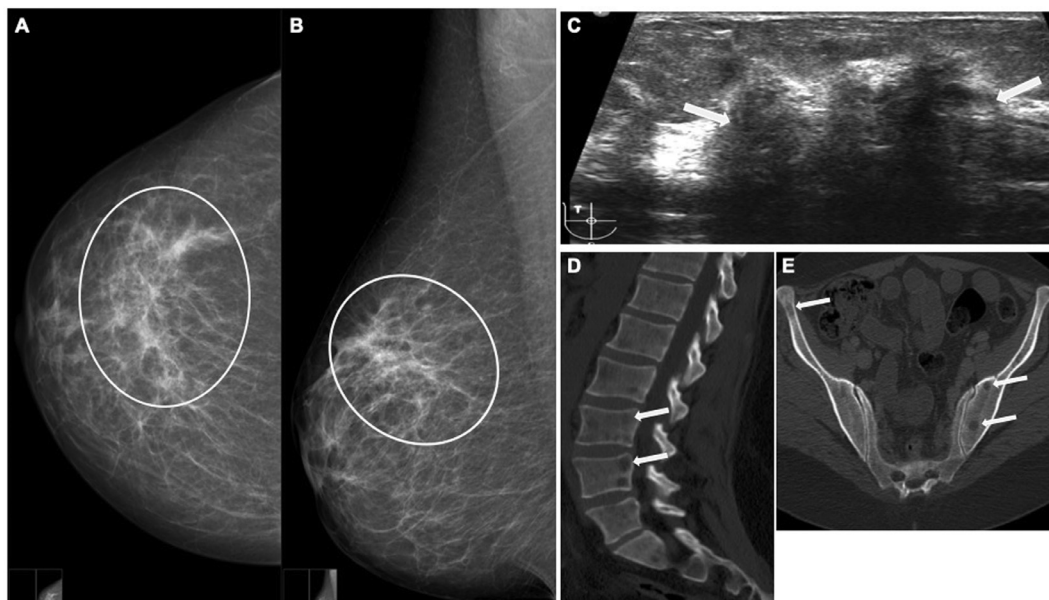
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**Fig. 1** – On mammography, craniocaudal (A) and mediolateral oblique (B) views show a focal asymmetry in the upper right breast (circle) with an extension of approximately 9.5 cm. On ultrasound (C), this alteration corresponds to a hypoechoic and ill-defined lesion with posterior acoustic shadowing (arrows). Computed tomography images (D-E) show diffuse lytic bone lesions consistent with metastases in the axial skeleton (arrows).

reported incidence varying between 2.8% and 27% [2]. Gastric metastases can be diagnosed after a long period of time from primary tumor diagnosis (on average 7 years) [3–5]. The attributable symptoms are indistinguishable from the symptoms of a primary gastric cancer: Indigestion, dyspepsia, anorexia, pyrosis, nausea, epigastric pain, early satiety, vomiting, bleeding, and weight loss [1–3,7]. In addition, the correct diagnosis may be difficult because metastatic disease involving the stomach is hard to differentiate from a primary gastric cancer on clinical, imaging, and pathological examinations [1,4,8].

Radiological findings are nonspecific and the most frequent change is asymmetrical or diffuse thickening of the gastric wall. Endoscopic examination may also be very similar to primary gastric carcinomas and the most common pattern is a linitis plastica with diffuse infiltration of the submucosa and muscularis propria in 73%–83% of cases [1,4,9]. On pathologic examination of the gastric biopsies, the presence of signet ring-shaped cells may be interpreted as primary gastric cancer. Ultimately, the definitive diagnosis is based on immunohistochemical analysis and supported by previous clinical history [3].

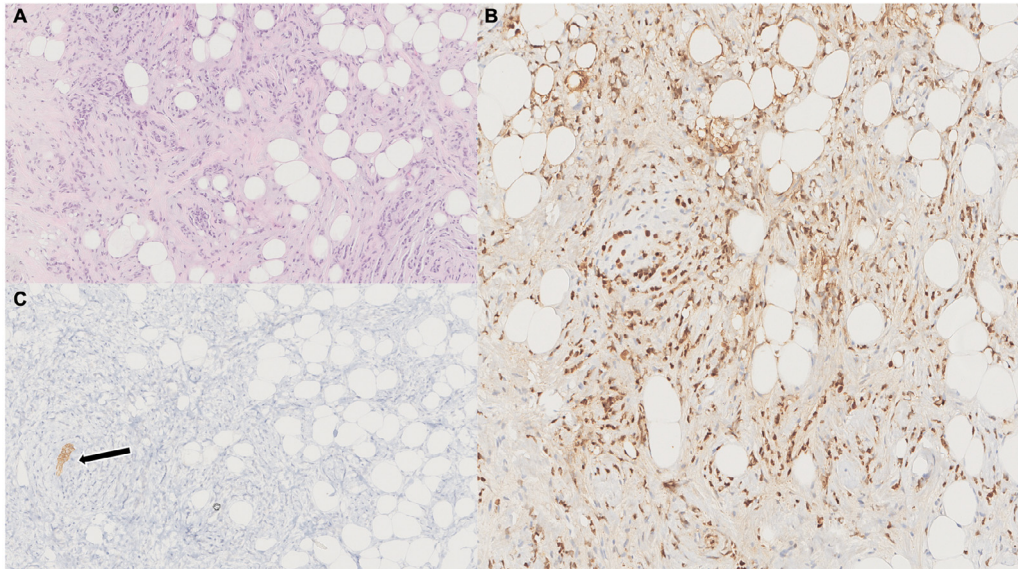
## Case report

A 40-year-old woman came to the emergency service with complaints of recurrent low back pain. A computed tomography scan was performed, showing diffuse lytic bone lesions in the axial skeleton suspicious of metastases. After a physical examination, a hard lump was palpated in the upper right

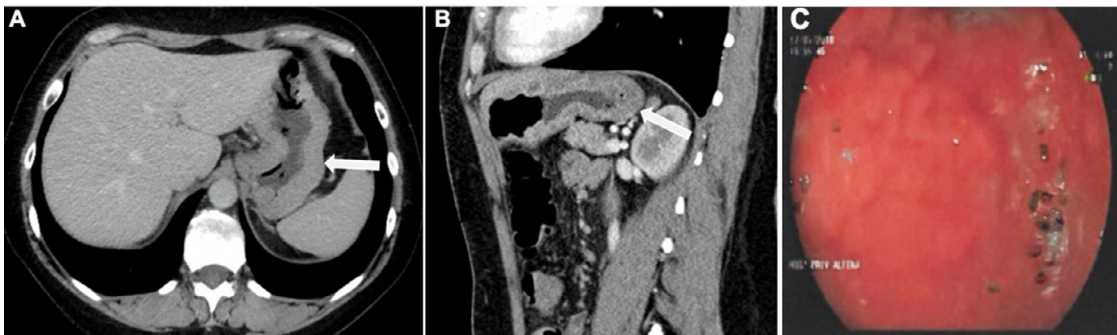
breast, associated with skin retraction. On the mammography, a focal asymmetry was observed in the upper right breast, with an extension of approximately 9.5 cm. On the breast ultrasound, this alteration corresponded to a suspicious hypoechoic and ill-defined lesion, with posterior acoustic shadowing (Fig. 1). Ipsilateral axillary adenopathy was also present. Ultrasound-guided biopsy was performed and grade 2 invasive lobular carcinoma was diagnosed. Estrogen receptors (ER) were positive (100%), progesterone receptors (PR) were positive (10%) and Her-2 receptors were negative, with no E-cadherin expression (Fig. 2). The final diagnosis was stage IV luminal B right breast carcinoma. After a discussion in a multidisciplinary meeting, the patient started neoadjuvant chemotherapy with desunomab® and paclitaxel®.

After finishing 9 cycles of chemotherapy, magnetic resonance imaging was performed, showing a residual small lesion in the upper outer quadrant of the right breast. Conservative surgery followed by radiation therapy to the right breast and the ipsilateral axillary was performed. Due to the presence of bone metastases, the patient was also treated with fulvestrant® and palbociclib®, achieving clinical and imaging stability.

After 2 years of follow-up, the patient showed with complaints of recurrent nausea, epigastric discomfort, early satiety, and weight loss. An abdominal computed tomography depicted diffuse thickening of the gastric wall with a small lumen, in a leather bottle-like appearance. No other significant abdominal findings were visualized, such as abdominal adenopathy, liver metastases, peritoneal implants, or ascites. Upper gastrointestinal endoscopy revealed marked rigidity for the gastric wall with a narrow lumen and a heterogeneous mucosa with thickened folds, which was suspicious of dif-



**Fig. 2** – Histology from the breast biopsy shows discohesive neoplastic cells invading the stroma, individually dispersed or arranged in single-file linear cords (Hematoxylin and eosin (H&E) staining, 100 $\times$ ) (A); immunohistochemical analysis reveals diffuse positivity for estrogen receptors (Immunohistochemistry (IHC) for ER, 100 $\times$ ) (B), and absence of E-Cadherin expression (IHC for E-Cadherin, 100 $\times$ ) (C). Note the retained expression of E-cadherin in a non-neoplastic duct (arrow).

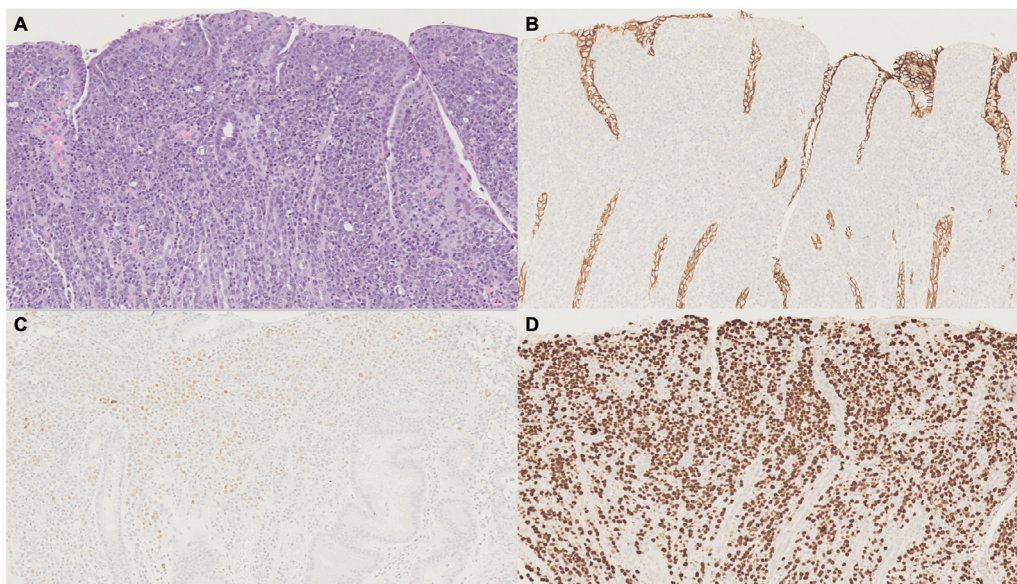


**Fig. 3** – Axial (A) and sagittal (B) contrast-enhanced computed tomography images show diffuse thickening of the gastric wall (arrow), with a narrow lumen, typical of linitis plastica. Endoscopy shows marked rigidity of the gastric wall, with mucosal integrity but slight gastric fold swelling (C). These characteristics are suspicious for infiltrative invasion of the submucosa.

fuse malignant infiltration of the submucosa (linitis plastica, Fig. 3). Gastric biopsies were compatible with adenocarcinoma with signet ring cells, which was interpreted as probable primary gastric neoplasia. Consequently, the patient underwent a total gastrectomy. The pathological evaluation of the surgical specimen revealed involvement of the entire stomach by a malignant neoplasm, invading the entire wall thickness, and formed by poorly cohesive cells with focal signet ring features. The subsequent immunohistochemical study revealed diffuse expression of GATA-3 and estrogen receptors (about 10% of the cells), in the absence of CK20, and E-cadherin expression (Fig. 4). Thus, immunohistochemical analysis was compatible with gastric metastases of previously diagnosed lobular breast carcinoma.

## Discussion

Invasive lobular carcinoma of the breast usually presents with a distinct metastatic pattern in comparison to other invasive breast carcinomas. This may be explained by the fact that around 90% of ILCs have E-cadherin loss, a molecule responsible for cell-cell adhesion [1,4,7–9]. Consequently, the ILC is formed by noncohesive small cells, with preferential growth at sites of metastases. Frequently, gastric metastases spread to the submucosal layer in a diffuse infiltrative pattern without major involvement of the mucosa, which may accordingly lead to normal endoscopic examinations in up to 50% of cases and misleading false-negative biopsies [1,4,7].



**Fig. 4 – Histology of the surgical specimen shows diffuse involvement of the gastric wall by neoplasia, consisting of poorly cohesive cells (H&E staining, 100 ×) (A); immunohistochemical analysis reveals absence of E-cadherin expression (IHC for E-cadherin, 100 ×) (B), weak immunoreactivity for estrogen receptors in about 10% of the neoplastic cells (IHC for ER, 100 ×) (C); diffuse expression of GATA-3, compatible with gastric metastases from a previously diagnosed lobular breast carcinoma (IHC for GATA-3, 100 ×) (D). Note that the residual E-cadherin positivity in the preserved gastric glands (B).**

The histological features of metastatic ILC to the stomach consist of infiltration of the gastric tissue by noncohesive small tumor cells with an occasional intracytoplasmic lumen arranged on linear cords between the normal gastric glands [5,7,10]. Therefore, as in the breast, metastatic ILC tends to infiltrate the affected organs in a diffuse process instead of forming a tumor nodule [11]. On imaging studies, the infiltration of the stomach wall can give an appearance of linitis plastica (water-bottle stomach), created by circumferential thickening and stiffness of the gastric wall, with narrowed lumen [11]. Peritoneal and retroperitoneal spread typically appears as tiny nodules that tend to become confluent and may cause “omental caking.” In the genitourinary system, the most frequent findings are bilateral cystic and solid ovarian masses (Krukenberg syndrome) [11].

The differentiation between primary gastric carcinoma and metastases of breast carcinoma is challenging, especially when gastric biopsies contain signet ring-shaped cells on pathologic examination [1,5]. Tumor cells with these features are characteristic of a subtype of primary gastric malignancy: Signet ring cell type gastric carcinoma [5]. However, tumor cells of ILC also have this morphology, making diagnosis a difficult task [1,2,6]. Therefore, the only way to reach the diagnosis is through immunohistochemical study. The immunohistochemical study is essential for the diagnosis of metastases in rare locations. For example, Singh T et al reported an extremely rare case of duodenal metastasization from endometrial carcinoma, which was confirmed through immunohistochemistry [12].

ILCs usually are ER and PR positive, without overexpression or amplification of the human epidermal growth factor receptor 2 (HER-2/neu) and E-cadherin [1,7]. ER and PR can be used

as markers; however, they are not always suitable diagnostic markers to confirm tumor has originated. These receptors may be positive in patients with primary gastric carcinoma (ER in 32% and PR in 12% of the cases) [3], and if the primary lesion is negative for ER and PR, these markers are not useful in the diagnosis of breast cancer metastases in the stomach [8]. In addition, it is well known that ER and PR may change in expression at metastatic sites over the course of disease progression, usually resulting in loss or decrease in expression, with discrepancy between primary breast cancer and metastases in 15%-40% of the cases [9].

Other markers have emerged to distinguish between gastric metastases from breast cancer and primary gastric malignancy. While metastatic breast carcinoma is usually positive for cytokeratin 7 (CK7, 90%), gross cystic disease fluid protein 15 (GCDFP-15), and negative for cytokeratin 20 (CK20) [1–3,6,9], primary gastric carcinoma is negative for CK7 and GCDFP-15 and positive for CK20 [6–8]. Recently, GATA-3 has emerged as a marker of urothelial and breast carcinoma. It has 100% positivity in lobular breast carcinoma and 96% positivity in ductal carcinoma of the breast [3]. In primary gastric carcinoma it is positive in only 5% (in well-differentiated adenocarcinomas, with no reported cases in carcinomas with poorly cohesive cells, such as signet ring carcinomas) [13].

Our patient had a strong diffuse nuclear expression of GATA-3, which together with a previous medical history of ILC of the breast, CK20-, slight ER positivity, and absence of E-cadherin was consistent with the diagnosis of gastric metastases from invasive lobular carcinoma of the breast. In this case, there was a change of the expression of ER in the gastric metastases, as the expression was diffuse in the neoplas-

tic cells in the breast and only discreet in the metastatic cells (not exceeding 10%).

Unfortunately, the definitive diagnosis in this case was only performed after total gastrectomy, due to the fact that the immunohistochemical study was not performed on the previous gastric biopsy and was interpreted as primary gastric carcinoma. Despite the similar clinical, endoscopic, and histological characteristics, the differentiation between primary and metastatic gastric carcinoma is pivotal, because the treatment and prognosis are dissimilar [2,6,9]. The treatment recommendation for gastric metastases of breast cancer is predictably systemic treatment with chemotherapy and hormone therapy [1,2,7]. Surgical intervention should be reserved for palliation or certain cases of solitary resectable gastrointestinal tract metastases [5–6]. On the other hand, in the case of primary gastric cancer, surgical resection is the primary treatment in the absence of distant metastases [9]. Additionally, some authors state the importance of regular endoscopy in patients with a history of invasive lobular breast cancer. The hypothesis of gastric metastases should always be considered in these patients and an immunohistochemical study carried out for the definitive diagnosis [1].

In conclusion, although gastric metastases from ILCs are rare, this clinical hypothesis should always be considered in patients with gastrointestinal symptoms (such as nausea, epigastric pain, early satiety, vomiting, and weight loss) and endoscopic changes (for example, gastric wall rigidity and heterogeneous mucosa with thickened folds). The final diagnosis may be challenging due to endoscopic limitations (endoscopy can be normal along with falsely negative biopsies) and pathological interpretation (overlapping features with primary gastric carcinoma). In general, immunohistochemical study offers the key to the definitive diagnosis.

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### Patient consent statement

Unfortunately, the patient in this clinical case died last year, so it was not possible to obtain informed consent.

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