

CASE REPORT

# Infiltrating Lobular Breast Cancer Presenting as Isolated Gastric Metastasis: a Case Report

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Received: 15 May 2016 / Accepted: 12 September 2017 / Published online: 23 September 2017  
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## Introduction

The common sites of breast cancer metastasis include the lungs, liver, bones, soft tissue, brain, and adrenal glands. Metastasis of breast cancer to the gastrointestinal tract (MBGI) is considered rare in clinical practice [1]; however, the occurrence in autopsy series varies from 4 to 35% [2, 3]. Most series report a greater propensity for lobular carcinoma to metastasize to the GI tract [4]. In addition, the majority of MBGI is positive for hormonal receptors (80%) [5].

Since isolated metastasis to stomach from a primary breast cancer is uncommon and peculiar, the main problem is to recognize them in patients affected by breast cancer as the treatment plan for these two malignancies are different [6]. Several factors can complicate the diagnosis and delay the treatment. These include a potentially long disease free interval between primary breast cancer and occurrence of gastric metastasis, totally asymptomatic or non-specific symptoms at synchronous presentation, which often mimic the symptoms of other GI disorders. Moreover, ideal treatment protocols are not established as the reports on this subject in the literature are fragmentary, poor, and mostly limited to case reports.

In this article, we present a rare case of infiltrating lobular carcinoma of the breast with isolated metastasis to the stomach. Our goal in this case report is to increase the awareness of

surgeons and clinicians to rule out the possibility of mammary origin metastasis in case of gastric cancer presenting in females even in patients without a previous or concurrent history of breast carcinoma.

## Case Summary

Patient is a 68-year-old female with no comorbidities who had complaints of weight loss (10–12 kg) and dysphagia for 3 months. She was evaluated outside for the same. UGI endoscopy revealed non-distensible stomach with thickened antrum and body. Multiple biopsies taken from suspicious areas showed signet-ring cell (mucinous) adenocarcinoma. CECT (contrast-enhanced computerized tomography) of the abdomen revealed thickened non-distensible stomach with enlarged perigastric and left axillary nodes. PET scan showed low-grade metabolic activity (max SUV 4.5) in thickened body and antrum of the stomach with non-avid sub-centimeter perigastric nodes (Fig. 1). The left axillary nodes did not show uptake (Fig. 2). She was diagnosed as a case of metastatic signet-ring cell adenocarcinoma of the stomach. The patient had a small lump in the left breast since last 2 years which had gradually increased in size since last 3 months. This was not elicited in history and was missed in the clinical examination. So, no mammography or biopsy was performed. The presumed diagnosis of metastatic gastric cancer was based on biopsy from the stomach and axillary adenopathy on CT scan. She was subjected to 3 cycles of chemotherapy (docetaxel, oxaliplatin, and oral capecitabine).

Patient came to our OPD after completing 3 cycles of chemotherapy. History of left breast lump was noted and corroborated by clinical examination. Patient also gave history of progressive gastric outlet obstruction. Post-chemotherapy PET scan showed complete metabolic regression and decrease

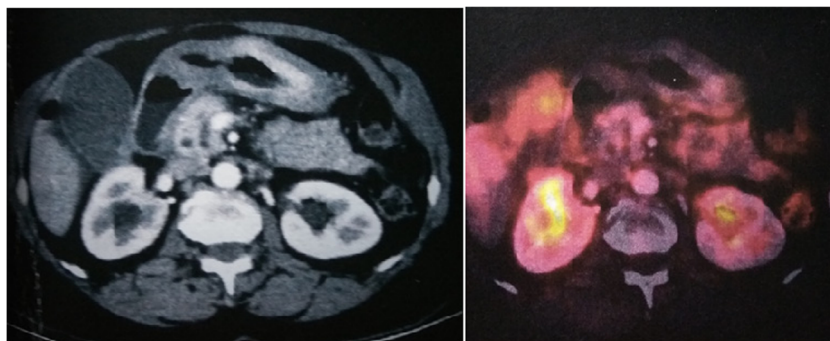
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**Fig. 1** Combined CT and PET scan images showing thickened antrum with low-grade metabolic activity



in size of primary gastric thickening and perigastric nodes with no active disease or lesion elsewhere. PET scan did not show breast lump. Mammography revealed approximately  $4 \times 4$ -cm lesion in the left breast which appeared malignant. The slides or blocks of previous stomach biopsy could not be reviewed as the patient could not provide them.

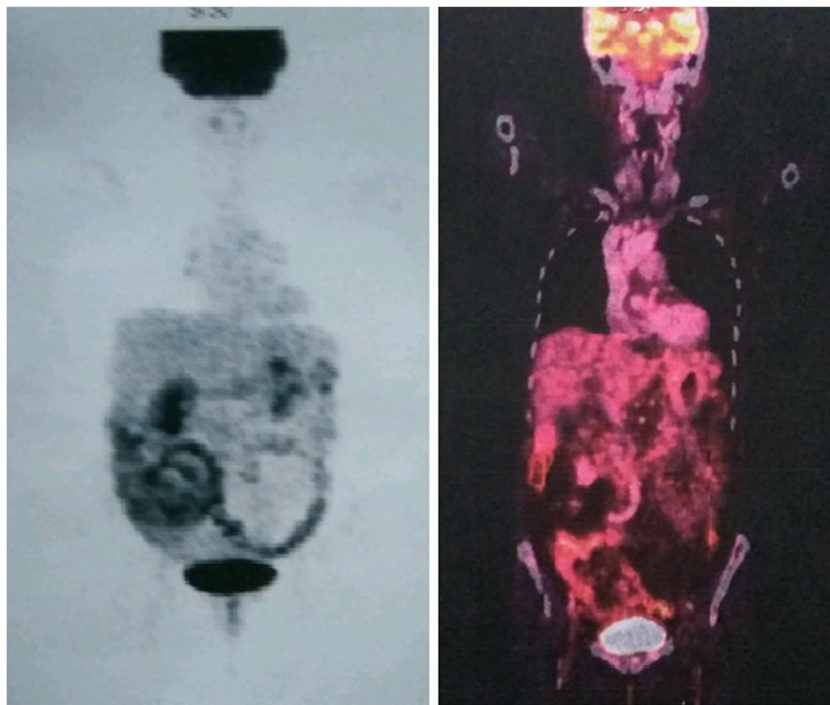
Patient was advised a core biopsy of the breast lesion to rule out synchronous second primary from a metastasis of gastric cancer. She was also counseled about the need for surgical intervention for gastric outlet obstruction. However, patient refused breast biopsy and requested for excision of the breast lump in the same sitting when the outlet obstruction was to be addressed.

Wide excision of the breast lesion was performed, and frozen section analysis was done which showed infiltrating lobular carcinoma with negative margins. Keeping this in mind, the clinical scenario was reassessed and presumptive diagnosis of synchronous gastric + breast cancer was made. As this

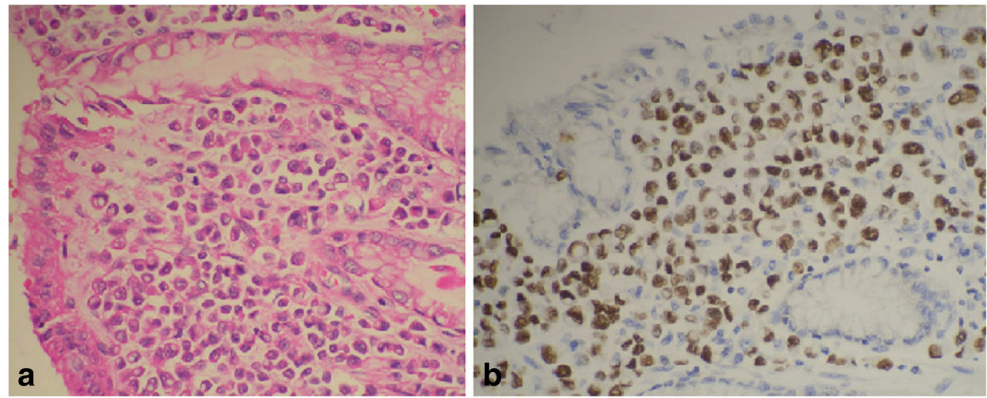
made the gastric cancer only a locally advanced disease, we performed a distal gastrectomy with D2 lymphadenectomy. Left axillary clearance was also done.

The post-operative period remained uneventful. The final histopathology report of resected breast specimen revealed  $1.3 \times 1.1 \times 1.0$ -cm residual viable invasive lobular carcinoma (ILC), grade II, with positive margins. Twenty-one out of 21 (21/21) axillary nodes showed metastatic carcinoma with perinodal extension. The gastrectomy specimen revealed diffuse carcinoma infiltrating all coats of the gastric wall. The tumor resembled invasive lobular carcinoma of the breast and expressed estrogen receptors (ER) but negative for progesterone receptor (PR) as did the breast cancer (Fig. 3). Both breast and stomach cancer were human epidermal growth factor receptor 2 (HER 2) (Cerb B2) negative. Fifteen out of 26 perigastric nodes (15/26) showed metastatic disease with perinodal extension. The omentum also showed metastatic tumor deposits. Since the two tumors showed similar

**Fig. 2** PET images showing uptake in the perigastric nodes but not in the left breast and axillary nodes



**Fig. 3** Stomach mucosa and submucosa. The submucosa is infiltrated with cancer cells (a), which show ER positivity on IHC staining (b) lack of HER 2 receptor expression



immunophenotype and receptor expression, it was concluded that it was ILC of the breast with metastasis to the stomach and omentum.

Since the breast lump excision had positive margins and there was no disease anywhere in the body after surgery, she was offered a completion mastectomy to achieve R 0 status. But patient did not wish to undergo another surgery. So she was given 6 cycles of FEC-based chemotherapy followed by local breast radiotherapy and hormonal therapy (aromatase inhibitor).

She was followed up every three monthly with detailed history and clinical examination. A PET scan was done at the end of 1 year which did not show any recurrent disease. The patient is at present living her normal life.

## Discussion

The real incidence of gastrointestinal metastases in breast cancer patients is probably underestimated. However, during the last 30 years, more than 1000 cases of gastrointestinal metastases from breast cancer have been reported. Reviewing the literature, breast cancer is reported to be the second commonest primary tumor responsible for gastrointestinal metastases after malignant melanoma [7]. The upper GI tract specially the stomach has been more commonly reported to be involved with breast cancer metastasis than the colon and the lower GI tract [8]. Based on clinical and autopsy findings, the reported incidence of gastric metastasis was 0.2–1.7% [9].

In 1968, Ash et al. [10] published the largest case series of breast cancer metastasis that reported metastasis to the GI system including the stomach. In 1993, Borst and Ingold [11] in a landmark study reported metastasis of breast cancer to the GI tract (MBGI) in only 17 of 2604 cases (less than 1%) over an 18-year period with infiltrating lobular carcinoma being the most common histological type. McLemore et al. [12] reported that only 41 (0.34%) of 12,001 patients with metastatic breast cancer had pathologically confirmed MBGI, with a mean interval of 7 years since the diagnosis of the primary

cancer. It was also shown in the study that metastasis to the stomach accounted for approximately 28% of the gastrointestinal metastasis. Ambroggi et al. [13] after reviewing the literature found 125 out of 206 patients had metastases to the stomach (60%), with 57 patients presenting with linitis plastica.

## Clinical, Endoscopic and Radiological Evaluation

The clinical presentation of gastric metastases from breast cancer mimics a primary gastric tumor. In the present case also though patient had breast lump, she sought medical attention for her GI symptoms.

The endoscopic and radiological findings are non-specific and may be hard to distinguish from primary gastric cancer. The most common pattern found on endoscopy is linitis plastica with diffuse infiltration of the submucosa and muscularis propria, while the pattern of discrete nodules or external compression is less common [14]. Radiological findings on CT scan include encasement of the whole stomach as seen in linitis plastica. Similar findings were seen in the present case. Because the lesion is often limited to the submucosal and seromuscular layers of the stomach, the endoscopic evaluation may be normal in 50% of cases or may show only discrete mucosal abnormalities.

## Pathology and Pathogenesis

ILC exhibits a distinct pathologic behavior compared to the ductal variant of breast cancer. ILC is most likely to occur in older, postmenopausal females, tends to be multicentric and bilateral with large, well-differentiated, ER-positive tumors and less vessel invasion [15]. Compared to infiltrating ductal carcinoma (IDC), ILC has higher propensity for metastatic spread to the stomach, intestine, and peritoneum wherein the gastric involvement is diffuse infiltration [12, 14, 16].



The reason for spread to the GI tract more frequent in lobular histology is unknown, but some authors think that it could be related to a particular tropism of lobular cells [12]. Loss of E-cadherin expression on lobular cells is implicated in this tropism. Studies looking at E-cadherin expression found that ILCs, in contrast to IDCs, stained negative for E-cadherins [17, 18]. Therefore, ILCs form irregularly bordered tumors with diffuse infiltration, are more invasive and dedifferentiated, contrary to IDCs, which form cohesive tumor groups.

Occasionally, lobular breast carcinoma may produce a signet-ring morphology which can be confused with a primary gastric adenocarcinoma. The large number of signet-ring cells combined with a gastric mucosal spreading pattern can mean that metastatic disease to the stomach is almost indistinguishable from primary gastric linitis plastica. This was the reason why the primary treating team diagnosed this case as gastric cancer. However, breast signet-ring cell carcinoma may show some morphological differences from gastric and colonic signet-ring cell carcinoma. But identifying such a morphological variation requires expertise.

### Immunohistochemistry

Doing ER/PR and HER status alone cannot differentiate a stomach primary from a MBGI because ER and PR positivity with weak to moderate staining intensity has been reported in 32 and 12%, respectively, in patients with gastric cancer [22]. CEA, CK7, CK20, and GCDFP-15 are the other molecular markers which can be used to resolve the dilemma. CK20 proves to be particularly positive in gastric, colorectal, pancreatic, and in transitional cell carcinomas, while it is not observed in any carcinomas of the breast [19]. CK7 in contrast is extensively expressed in 90% of breast carcinomas and its expression was also observed in 50–64% of primary gastric adenocarcinoma [20]. Cytoplasmic positivity for GCDFP-15, absence of E-cadherin, and ER $\alpha$  positivity indicate a breast primary [21, 22].

### CDH 1 Testing

In patients with potentially synchronous neoplasms, it is also reasonable to pursue possible genetic explanations. *CDH1* is a tumor suppressor gene that encodes E-cadherin. Germline mutations in this gene have been implicated in hereditary diffuse gastric cancer (HDGC) syndrome, a clinical syndrome associated with more than 80% lifetime risk of gastric cancers, more than 60% of which have signet-ring cells [23] and a 60% lifetime risk of developing lobular breast carcinoma by age 80 [24].

### Treatment Approach

Breast cancer metastasis to the stomach represents systemic disease and systemic therapy, such as chemotherapy and/or hormonal therapy, rather than surgical resection seems to be an ideal option [25]. But in the present case, the metastatic disease was limited to stomach and omentum only which can be considered oligometastatic disease. It is now widely recognized that oligometastatic breast cancer (OMBC) behaves differently than multimetastatic disease. There is no clear definition for OMBC, but a limited number of metastases which can be resected completely can be safely considered oligometastatic.

Data on accurate management of OMBC is sparse and retrospective so is the role of metastatectomy in OMBC. The largest data on role of metastatectomy in OMBC is on pulmonary metastatectomy, which showed that number of metastases and completeness of resections are important prognostic factors for long-term outcomes [26]. However, metastatectomy in OMBC for therapeutic benefit is not considered standard of care but should be considered on case to case basis. It also helps in ruling out other diagnosis [27]. In the present case, the aggressive line of treatment was initially due to the presumptive diagnosis of two synchronous primaries and later due to the fact that it turned out to be oligometastatic disease, and surgical intervention had removed all the macroscopic disease except for positive margins on the breast lump.

In 2001, Zelek et al. [28] reported a median survival of 21 months for patients who received chemotherapy, whereas it was less than 12 months for those who underwent upfront gastrectomy for metastasis from breast cancer. McLemore et al. [12] reported that surgical intervention in select patients with metastasis only to the gastrointestinal tract who underwent palliative surgical resection tended to have a more prolonged median survival (44 vs. 9 months). In Rodriguez et al. report of 12 breast cancer patients with gastric metastasis, four patients underwent surgery. All four had gastrectomy along with D2 lymphadenectomy. These patients showed better survival compared to others getting non-surgical therapy alone (38 vs. 14 months) [29].

This data indicates that there is a role for gastrectomy in metastatic setting when the disease is limited. Though there is no significant high level evidence for this, improvement in survival has been reported in several case reports [30–33].

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. If there is evidence of metastatic disease elsewhere, the complications of breast cancer metastasis to the stomach can be managed non-surgically by end luminal stenting for gastric outlet obstruction; bleeding may be controlled by endoscopic or endovascular therapy.

## Conclusion

Gastric metastasis from ILC is rare but can give rise to diagnostic dilemma. Endoscopic biopsy and standard IHC panel are unlikely to confirm or rule out second primary. Clinical awareness and additional IHC testing are necessary to come to correct diagnosis. In limited disease burden, surgery plays a vital role and in association with adjuvant therapy can achieve good outcomes.

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