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Metastatic Invasive Lobular Carcinoma of Bilateral Breasts Presenting with an Abdominal Mass

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ABSTRACT

Background: Breast cancer remains the most frequent malignancy in women, with the two most common histological subtypes of breast cancer being the invasive ductal carcinomas (IDC) and invasive lobular carcinomas (ILC). The most common sites of breast cancer metastases are the liver, lung, pleura, brain and bone. Gastrointestinal, peritoneal, gynaecological and renal metastases are less common, often masquerading as primary malignancies and causing diagnostic confusion, mostly occurring in ILC as compared to IDC.

Case Presentation: We report a case of a young woman presenting with an enlarging abdominal mass which was suspicious of a primary abdominal malignancy. Endoscopy and gastric biopsy revealed poorly differentiated carcinoma. On the top-most slices of her abdominal CT, bilateral enhancing breast lesions were detected, suspicious of metastases. Ultrasound and biopsy done for the breast lesions showed bilateral ILCs. Further staining of the gastric biopsy specimen confirmed the final diagnosis of gastric metastases from bilateral breast ILCs rather than a primary gastric tumour with breast metastases.

Conclusion: This case highlights how breast cancer metastases to the GI tract may mimic primary GI cancers as well as the importance of breast examination, family history, radiological and pathological examination in detecting the breast origin of advanced carcinomas. Awareness of the different patterns of metastatic spread of ILC and IDC is also important due to the infiltrating nature and non-specific imaging findings of these tumours, requiring a high index of suspicion from the surgeons, oncologists, radiologists and pathologists.

INTRODUCTION

Female breast cancer remains the most frequent malignancy comprising 11.7% of all new cancers diagnosed in 2020 globally, followed by cancers of the lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%).[1] The two most common histological subtypes of breast cancer are invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) with different metastatic patterns.[2,3] Breast cancers metastases may occur in the early presymptomatic stage, along the course of the disease or remain dormant for years before becoming clinically evident.[4–8] The most common sites of breast

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cancer metastases are the liver, lung, pleura, brain and bone. Gastrointestinal, peritoneal, gynaecological and renal metastases are less common, often masquerading as primary malignancies and causing diagnostic confusion, mostly occurring in ILC as compared to IDC.[4–10] We present a case of a young woman with an enlarging abdominal mass in which the final diagnosis turned out to be gastrointestinal metastasis from ILC of bilateral breasts.

CASE PRESENTATION

A 35-year-old lady presented to our district hospital with generalized abdominal pain for two months, worsening two weeks prior to admission. The pain was predominantly at the epigastric region associated with colicky pain and occasional dyspepsia as well as gradually increasing abdominal distention. She also had early satiety, intermittent vomiting with fluid content, loss of appetite, lethargy and significant loss of weight. She had a history of a left breast lumpectomy for a fibroadenoma 2 years ago and her paternal aunt was diagnosed with breast carcinoma at the age of 40. Otherwise, she had menarche at the age of 12 and did not have a history of oral contraceptive use.

Clinically, she was cachexic and had a distended abdomen with a large palpable epigastric mass extending to the right iliac fossa. She was pancytopenic on admission with a hemoglobin level of 4.8 g/dL, white cell count of $2.93x10^3$/uL and platelet count of $99x10^3$/uL. Peripheral blood film showed pancytopenia with leucoerythoblastic picture in which underlying bone marrow infiltration by malignancy needed to be excluded. Serum cancer antigen (CA) 125 was elevated (254.4U/ml). The rest of the tumor markers, namely carcinoembryonic antigen (CEA), alphafetoprotein (AFP) and CA19-9 were within normal limits. Total bilirubin was at the upper limits of normal but she was not jaundiced.

Initial ultrasound of her abdomen revealed a large upper abdominal predominantly cystic mass with solid component and multiple septations within. She also had moderate ascites. Due to the size of the mass, we were unable to ascertain the origin of the mass. A contrasted abdominal computed tomography (CT) scan was performed, revealing a large well-defined predominantly cystic mass with hyperdense solid component within and rim enhancement occupying the entire lesser sac, causing mass effect and compression onto the body of stomach and pylorus with no clear fat plane in between (Figure 1A).

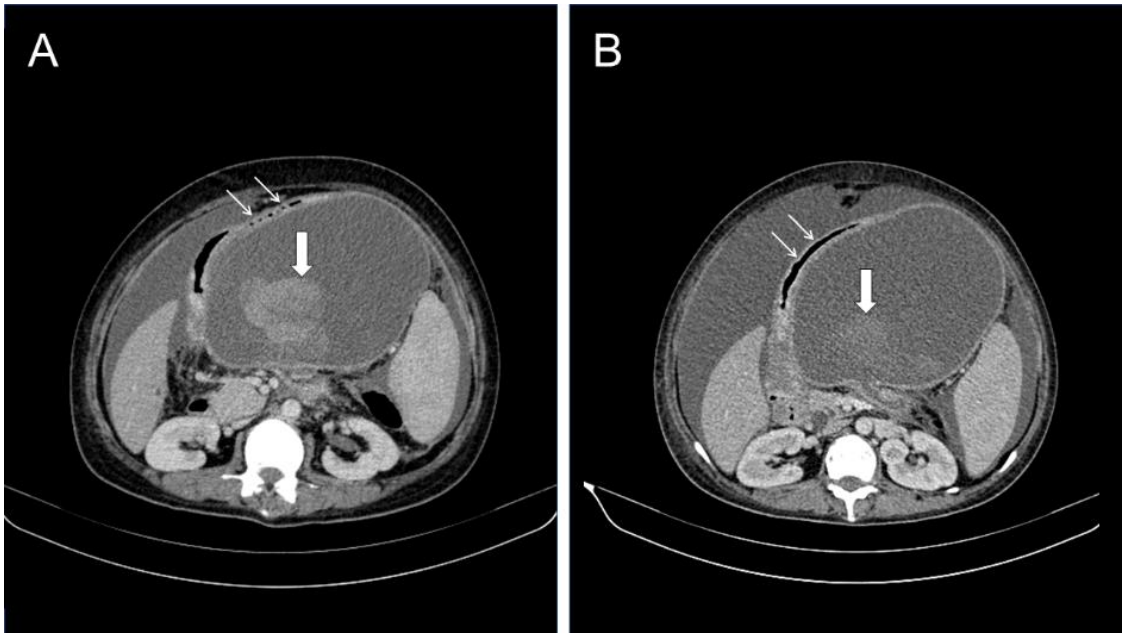

Figure 1. A: Abdominal CT showed a large predominantly cystic mass in the lesser sac compressing the stomach anteriorly (thin white arrows). Hyperdense soft tissue component seen within (large white arrow). **B:** Abdominal CT done 2 weeks later showed similar mass compressing the stomach with reducing hyperdense soft tissue component (large white arrow), suggestive of hemorrhagic component.

The intra- and extrahepatic ducts as well as proximal pancreatic duct were dilated with no evidence of radiodense intraductal calculus, periampullary mass or external compression (Figure 2A). She also had hepatosplenomegaly with a segment VI hypodense liver lesion, gross ascites and multiple lytic-sclerotic bony lesions suggestive of metastasis (Figure 2B). Incidentally, at the upper-most slices of her abdominal CT scan images, multiple enhancing nodules were seen in the visualized bilateral breasts with the largest measuring up to 2.0cm (Figure 3A). At this point, our differential

diagnosis was of a pancreatic or gastrointestinal malignancy.

Diagnostic and therapeutic abdominal paracentesis was done in which CA125 in the fluid was elevated (484.70U/ml), but no malignant cells were detected. In view of persistently low hemoglobin levels despite multiple transfusions, a multiphase contrasted pancreatic CT scan was performed two weeks later to exclude a pancreatic tumor as well as to identify any source of bleeding. No active bleed was seen and there was reduction in the hyperdense solid components within the mass, suggestive of resolving hemorrhagic component (Figure 1B). There was no evidence of any pancreatic mass as the cause of biliary obstruction. The rest of the findings were unchanged.

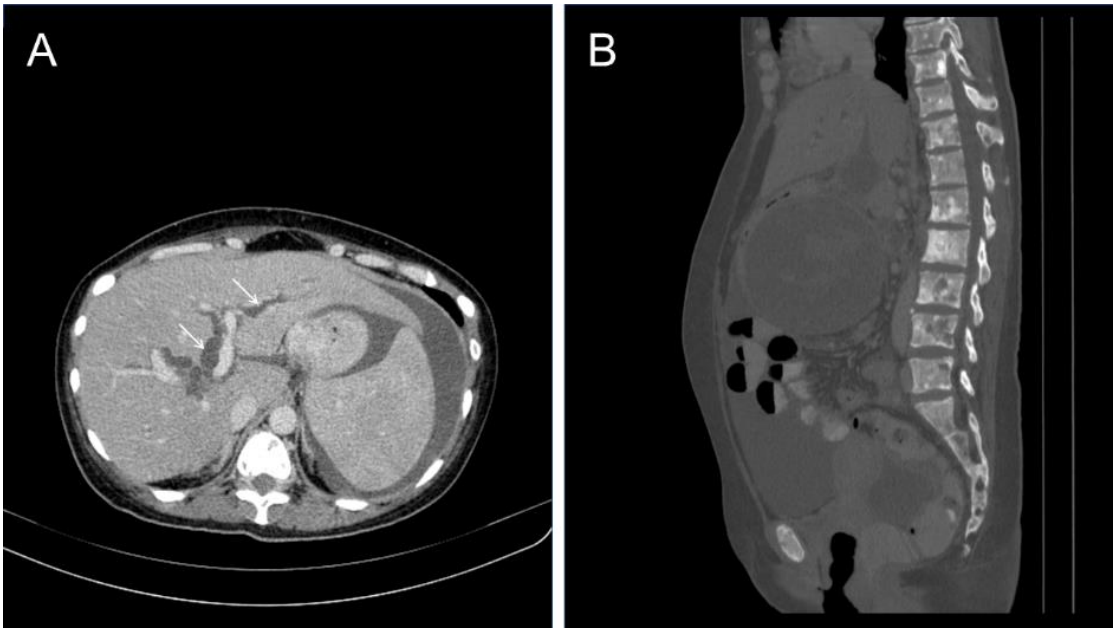

Figure 2. Abdominal CT showing **A**: dilated intrahepatic ducts (white arrows) and **B**: diffuse lytic-sclerotic vertebral lesions suggestive of bone metastases.

Due to suspected upper gastrointestinal bleed, an upper gastrointestinal endoscopy (OGDS) was done for this patient, which found the stomach to be small and poorly distended despite inflation, with possible external compression and multiple bleeding ulcers seen within. The ulcers were biopsied and histopathology showed multiple fragments of gastric tissue focally infiltrated by singly distributed malignant cells, which were hyperchromatic with mild nuclear pleomorphism. These cells were positive for pancytokeratin and negative for LCA, CD 20, CD 79a, CD3, CK7, CK20 and CDX 2. Features were therefore consistent with a poorly differentiated carcinoma (Figure 4B and 4D).

Retrospectively, her breasts were examined and multiple lumps were palpable bilaterally, corresponding to the lesions seen on CT. Ultrasound showed multiple lobulated heterogeneously hypoechoic lesions in both breasts (Figure 3B).

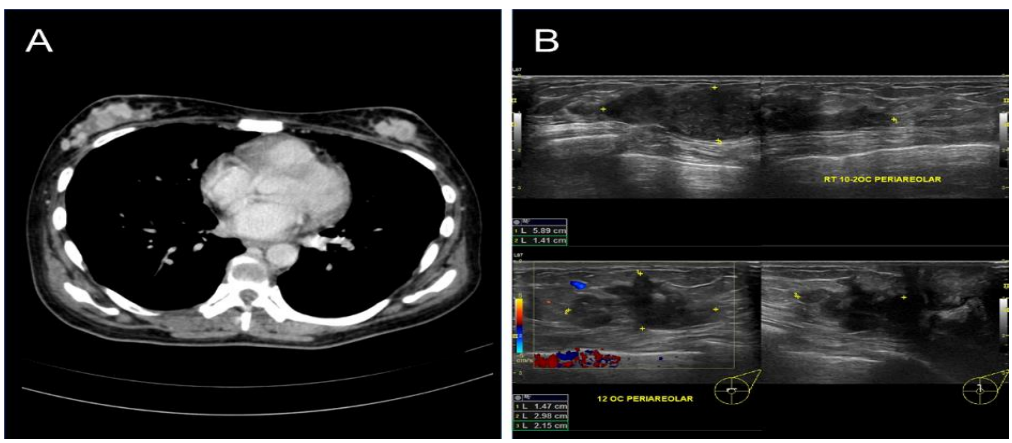

Figure 3. A: Bilateral enhancing breast lesions seen on the upper most slices of the abdominal CT. **B:** Ultrasound of both breasts showed bilateral suspicious hypoechoic masses with irregular, angular and spiculated margins.

In view of suspected primary abdominal tumor, these lesions were initially thought to represent breast metastases. They were biopsied and subsequently confirmed to be bilateral invasive lobular carcinomas (Figure 4A), which was strongly estrogen receptor (ER) positive (>95%), progesterone receptor (PR) positive (20%) and equivocal for human epidermal factor 2 (HER2). Immunohistochemistry (IHC) showed that the tumor cells were diffusely positive for pancytokeratin with patchy CK7 positivity. They were negative for CK20, p63, CDX2 and E-cadherin. Further IHC staining was then performed on the initial gastric biopsy specimen revealing it to be strongly ER positive (90%), PR and E-cadherin negative, suggestive of metastatic ILC (Figure 4C). Therefore, the final diagnosis for this patient was of bilateral breast ILCs with stomach and bony metastases.

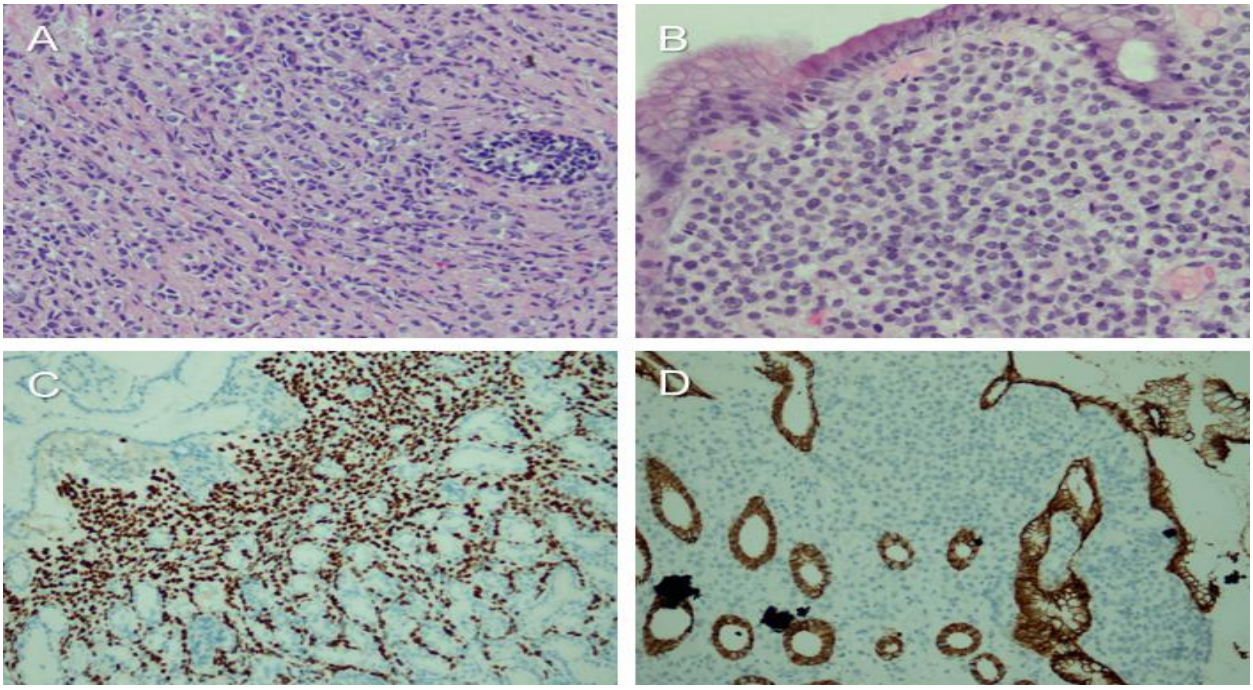

Figure 4. Pathology and immunohistochemical staining of invasive lobular carcinoma **A:** Breast specimen (H&E) showing diffuse malignant cells arranged in singly distributed cells (magnification 20x) **B:** Gastric specimen (H&E) showing malignant cells that are single lying and dispersedly distributed within the lamina propria (magnification 40x). **C:** Gastric specimen showing strong ER positivity, suggestive of breast origin **D:** Negative E-cadherin staining of ILC cells in the gastric specimen.

She was referred to the oncology team and was started on chemotherapy and hormonal therapy. However, she was unable to tolerate further chemotherapy after 2 cycles due to severe bone marrow suppression and opted for palliative care.

DISCUSSION

Breast cancers remain the most common malignancy in women and are the fifth leading cause of cancer mortality globally.[1] The two most common histological subtypes of breast cancer include the invasive ductal carcinomas (IDC), also known as invasive carcinomas of no special type and the ILC. ILC, originally described by Foote and Stewart in 1946, is less common than IDC, comprising 10-15% of invasive breast cancers, usually with an infiltrative growth pattern, and are often multifocal and bilateral.[11,12] The metastatic patterns of IDC and ILC are different, with ILC having higher occurrence of bone, gastrointestinal, ovarian, peritoneal and retroperitoneal metastases as compared to IDC which tends to metastasize to the liver, lung, pleura and brain.[9,10,12] The cause of the different patterns of metastases is still not well-understood, but some postulate that it may be due to the unique biology of the tumor cells, the loss of E-cadherin or the microenvironment of the gastrointestinal tract, ovary or peritoneum, favoring ILC cells over IDC cells.[10,12] Breast cancers can also be divided into molecular subtypes, based on the differences in gene expression and receptor subtypes, broadly categorized into luminal A/B (ER and PR-positive), HER2-positive and triple-negative breast cancers, each having different patterns of metastases.[2,3] ER- and PR-positive subtypes, as seen in our patient, tend to have the lowest incidence of metastases which develop late with the highest propensity for bone metastases among all subtypes.[2]

Sonography is more sensitive (rate ranging from 84-98%) than mammography in detecting ILC, most

commonly appearing as a hypoechoic mass with or without posterior acoustic shadowing.[11,13] They may also be seen as an area of posterior acoustic shadowing without a visibly distinct mass, may be infiltrative, multifocal, multicentric or even have no findings in ultrasound.[13] In our patient, the breast lesions were bilateral, multifocal, heterogeneously hypoechoic with irregular, angular and spiculated margins, warranting biopsy (Figure 3B). On mammography, ILC can often be subtle, and may present as a spiculated or ill-defined mass, density or architectural distortion, with improved detection on digital breast tomosynthesis, contrast-enhanced mammography and MRI.[11,14] Pre-operative MRI is especially useful as it is more sensitive and accurate in determining the multicentricity and extent of the disease as compared to other imaging modalities to aid surgical planning.[11,15]

Gastrointestinal (GI) metastases from breast cancer are rare and may masquerade as primary tumours with non-specific symptoms such as epigastric pain, dyspepsia, bloating, diarrhea, nausea and vomiting, loss of appetite and weight loss, bowel obstruction, anemia and bleeding.[4–8,16] Due to their infiltrative pattern, imaging findings are also non-specific, adding to the difficulty in differentiating GI metastases from primary GI malignancy or inflammatory bowel disease. Establishing the correct diagnosis is vital as treatment for primary GI malignancy usually involves surgical resection while breast cancer GI metastases are usually treated with systemic chemotherapy and/or hormonal therapy.[4,6,16] They also have different prognosis, with the latter faring better compared to patients with stage IV gastric cancer.[17]

Primary GI tumours are often seen as exophytic or focal masses, while GI metastases from the breasts, especially from ILC, should be considered when there is circumferential, nodular and diffuse infiltration seen, especially in the stomach.[7,8,16] While any region of the GI tract may be involved, the most common site is the stomach, with presentation mimicking linitis plastica.[8,14,16] Xu *et al.* demonstrated that gastric metastases from breast cancer are more commonly seen from ILCs (65.4%) compared to IDCs (24.4%)[7] while Hong *et al.* concluded that luminal-type breast cancer and ILCs more commonly metastasize to the stomach as compared to the other types of breast cancer.[17] Histological confirmation is required to establish the diagnosis, with immunohistochemistry staining being crucial in differentiation primary and secondary GI malignancies as was seen with our case.[6,18]

Our patient's presentation of an enlarging abdominal mass led to the initial suspicion of a primary abdominal malignancy. On CT, no obvious gastric mass or wall thickening was seen due to marked compression by the lesser sac mass, which could represent hemorrhagic components from the bleeding gastric ulcers. OGDS findings were suspicious of linitis plastica, in which gastric biopsy initially revealed poorly differentiated carcinoma. Tumor markers, however, were not convincing of a primary gastrointestinal malignancy as the serum and ascitic fluid samples demonstrated normal CEA levels. One the other hand, her serum and ascitic fluid CA125 levels were elevated, which can be seen in breast cancer patients and is related to late tumour stage and poorer outcomes.[19] Further IHC staining of the gastric biopsy specimens, which revealed strong ER positivity, helped to confirm that the gastric lesions were indeed metastases from the underlying ILCs rather than a primary gastric tumor with breast metastases (Figure 4C).

Due to the previous history of biopsy proven fibroadenoma of the breast, more attention was placed on her primary complaint of abdominal symptoms, causing diagnostic confusion and delay. The patient initially denied having any family history of malignancy, but on further questioning after the detection of her breast lesions, she revealed a family history of breast carcinoma (paternal aunt), which raised the possibility of familiar breast carcinoma. To prevent diagnostic delay, proper attention to family history and a thorough clinical examination, especially of the breasts, should always be performed in advanced cancers of unknown cause. If a high index of suspicion for a breast primary tumor was raised, the appropriate IHC staining could have been performed in the first instance. Genetic counselling is also important in her case, in view of her young age at presentation and positive family history of breast carcinoma. Although the breast lesions in her case should have been first detected clinically, it is important to always review the visualized breasts in abdominal CTs to detect non-palpable breast lesions.

Pancreatic metastases from breast cancer are uncommon, usually presenting as a discrete mass, appearing similar to primary pancreatic tumors. Nevertheless, due to the infiltrative pattern of ILCs in the rest of the body, ILC metastases in the pancreas may also be subtle on imaging and not well seen on cross sectional imaging or endoscopic ultrasound (EUS).[14] In our case, as there was no obvious cause for biliary obstruction seen on CT, occult infiltrative metastatic involvement of the pancreatic head had to be considered.

CONCLUSION

This case highlights how breast cancer metastases to the GI tract may mimic primary GI cancers, especially when the breast cancer is occult or

metastatic at time of diagnosis. It also emphasizes the importance of breast examination and attention to family history in detecting the breast origin of advanced carcinomas. Nevertheless, the visualized breasts in abdominal CTs should always be reviewed for lesions which may be clinically occult. Immunohistochemistry staining is very useful in differentiating between primary and secondary GI malignancies as was seen with our case. Last but not least, awareness of the different patterns of metastatic spread of ILC and IDC is important as both the ILCs and their metastatic lesions are not always easily diagnosed due to the infiltrating nature and non-specific imaging findings of these tumors, requiring a high index of suspicion by the surgeons, oncologists, radiologists and pathologists.

ETHICAL CONSIDERATIONS

Written informed consent was obtained from the patient to publish this case report and its accompanying images.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest related to the publication of this manuscript.

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