

# Inflammatory metastatic breast cancer with gallbladder metastasis: an incidental finding

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**B**reast cancer is the most frequently diagnosed cancer in women, with an estimated 231,840 new cases representing 14.0% of all new cancer cases in the United States in 2015.<sup>1</sup> Early screening and modern techniques of imaging and diagnosis have led to a significant improvement in detecting early-stage breast cancers and to a decrease in the incidence of metastatic breast cancer (MBC).<sup>2</sup> About 20%-30% of patients who are initially diagnosed with an early-stage, nonmetastatic breast cancer will subsequently develop a distant metastatic disease. Between 6%-10% of the new breast cancer cases present initially as stage IV, referred to as *de novo* MBC. The most common sites of breast cancer metastases are lymph nodes, chest wall, skeleton, lung, skin, and the central nervous system (CNS).<sup>3</sup> Lobular carcinoma, in particular, may metastasize to the gastrointestinal tract, peritoneum, and retroperitoneum.<sup>4</sup> Gallbladder metastasis from breast cancer is very rare, and only 15-20 cases have been reported in the literature.<sup>5-7</sup> Most of those cases have been associated particularly with a lobular histology. We report an additional rare case of MBC to the gallbladder, but with a ductal histology.

## Case presentation

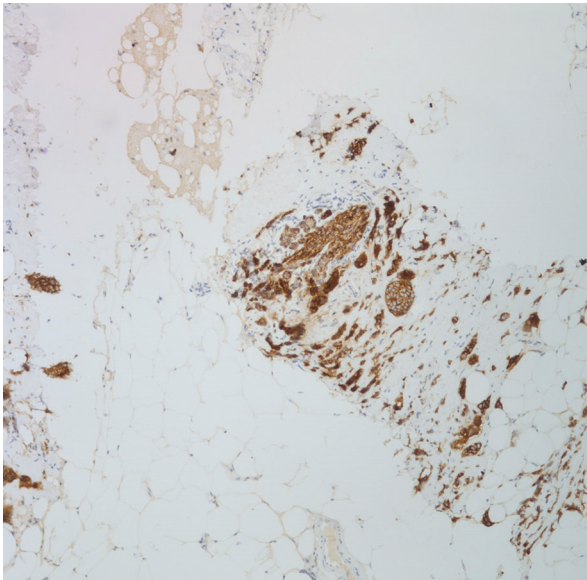
A 65-year-old postmenopausal black woman presented with left breast swelling and mass. She had been up to date with annual screening mammograms. She noted redness of the left breast only 2 weeks before her scheduled bilateral annual screening mammogram. A bilateral mammogram noted a left breast lesion. A diagnostic bilateral mammogram confirmed a large left breast mass. The redness and swelling had increased significantly in a few weeks with develop-

ment of warmth and tender breast. She had a surgical evaluation, and her physical exam was remarkable for a *peau d'orange* sign, nipple retraction, a 6 x 3-cm firm mass, and a palpable left axillary adenopathy. Her clinical examination was consistent with an inflammatory breast cancer (IBC).

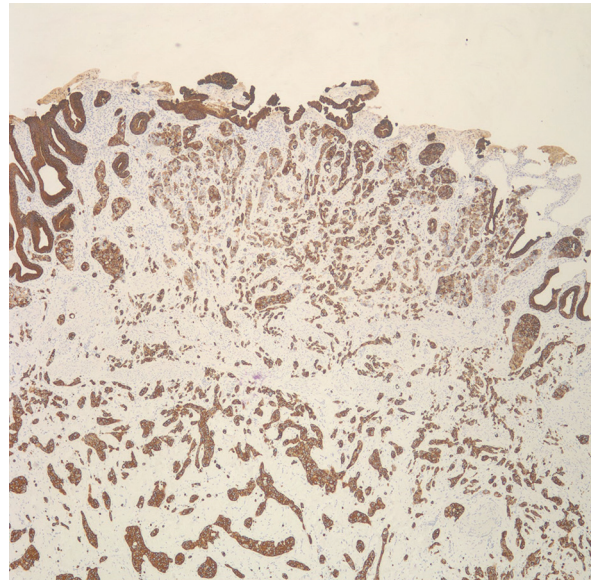
The patient underwent an image-guided left breast biopsy, which revealed an invasive mammary carcinoma: estrogen receptor (ER) positive (96%), progesterone receptor (PgR) positive (12%), and HER2-negative (+1). An epithelial cadherin (e-cadherin) stain was positive, consistent with ductal histology. She underwent a staging workup for a chest computed-tomography (CT) scan, followed by a positron-emission tomography (PET)-CT scan. The chest CT scan showed a widespread metastatic disease with a large left breast mass and right axillary, retropectoral, right hilar, and mediastinal adenopathy; a moderate bilateral pleural effusion; multiple pulmonary masses; a suspicious right hepatic lobe lesion; and several osteolytic lesions in the thoracic vertebrae. Cholelithiasis was also noted without signs of cholecystitis. The PET-CT scan showed increased activity throughout the left breast; left axillary, left supraclavicular, and mediastinal lymph nodes; in the bilateral pulmonary nodules; numerous hypermetabolic skeletal lesions; and a calcified gallstone. She did not have any biliary colic.

She underwent thoracentesis twice and cytology of the pleural fluid confirmed a malignant effusion. A drainage catheter was inserted into her chest. The woman has a medical history significant only for hypertension and arthritis. She had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1.

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**FIGURE 1** A needle core biopsy of the left breast lesion with both in situ and invasive mammary carcinoma that is e-cadherin positive, consistent with ductal differentiation.



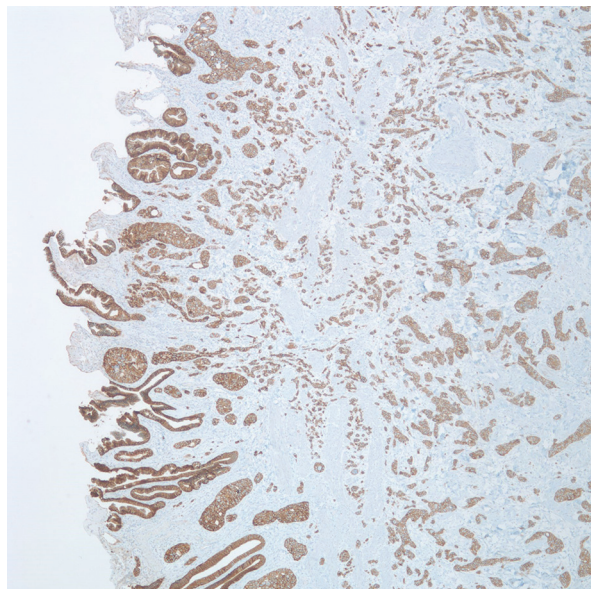
**FIGURE 2** An additional section of immune-stained gallbladder wall nodule containing e-cadherin positive glands, similar to the original breast biopsy consistent with ductal differentiation.

Because of her aggressive presentation and rapidly progressive visceral disease, we elected to initiate palliative cytotoxic therapy rather than endocrine therapy, and we started her on weekly paclitaxel. After 2 months of therapy, she underwent a restaging PET-CT scan for response evaluation. The results showed an unchanged left breast activity, very slight interval decrease in size and metabolic activity of left axillary, left supraclavicular, subcarinal adenopathy, and the skeletal metastasis; unchanged or minimally decreased pulmonary nodules; and again, a calcified gallstone. Two days later, she presented to the emergency department with a right upper quadrant abdominal pain associated with nausea and vomiting consistent with biliary colic. A kidney, ureter and bladder X-ray showed gallstones. The patient underwent a laparoscopic cholecystectomy, and the gallbladder seemed to have chronic inflammation. Pathology revealed a 6 x 2.2-cm gallbladder by gross examination, containing a large black multifaceted gallstone measuring 2 cm at maximum diameter. A 7 x 6-mm nodule with a pale yellow-white solid cut surface was noted in the gallbladder wall. H&E stained sections of the nodule revealed malignant glands morphologically consistent with a mammary carcinoma. Immunostains showed the tumor cells were strongly ER- and PgR-positive, which is consistent with metastatic carcinoma of a mammary origin. An e-cadherin staining was performed on the metastatic carcinoma and was strongly positive, which is consistent with a ductal origin.

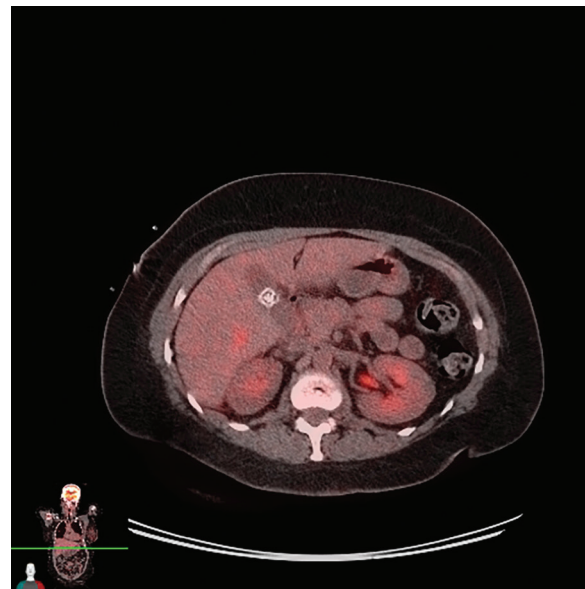
## Discussion

Most breast cancer cases are diagnosed at an early, at a nonmetastatic stage, and are curable by surgery. Recurrence rates have declined with the development of the multidisciplinary team approach and the incorporation of adjuvant and neoadjuvant therapy that includes chemotherapy, endocrine therapy, anti-HER2 targeted therapy, and radiation therapy. Nevertheless, a small percentage of patients will recur with distant metastatic disease, and an even smaller percentage will present with de novo MBC. Generally speaking, MBC is not curable; however, with the advancements in systemic therapies, cytotoxic therapy, endocrine therapy, and anti-HER2 agents, a significant improvement in survival has been achieved.<sup>8-10</sup>

Breast cancer is a heterogeneous disease, comprising multiple entities associated with distinctive biological and histological features, and clinical presentations. IBC is an aggressive form of breast cancer characterized by a rapid progression, high angiogenesis, and significant potential for metastasis.<sup>11,12</sup> The diagnosis of IBC is made based on characteristic clinical findings. Dermal lymphatic involvement supports the diagnosis of IBC but it is not necessary for making the diagnosis. Patients with IBC typically present with pain and a tender, firm, and large breast. The skin over the breast is reddened, warm, and thickened, with a peau d'orange sign.<sup>13</sup> Although IBC is relatively rare, accounting for 1%-5% of invasive breast cancers cases, it accounts for a greater proportion of cases presenting as advanced disease.



**FIGURE 3** A microscopic section of gallbladder wall nodule with positively staining glands for estrogen receptor, indicating a metastasis of mammary carcinoma origin.



**FIGURE 4** Restaging PET-CT scan showing a calcified gallstone without any abnormal hypermetabolic activity in the liver.

Several molecular features have been identified in IBC and possibly linked to its aggressive behavior. p53 gene mutations and nuclear overexpression were noted more in IBC and were associated with higher risk of death.<sup>14,15</sup> Molecular studies of human IBC samples have provided an evidence of increased angiogenesis and lymphangiogenesis in IBC. A significant increased microvessel density was observed in IBC specimens compared to non-inflammatory breast cancer (NIBC).<sup>16</sup> IBC overexpress vascular endothelial growth factor C (VEGF-C), which is associated with increased lymph node metastasis, and VEGF-D, which promotes tumor angiogenesis and lymphangiogenesis. Most IBCs are hormone receptor negative.<sup>17</sup> In one report, 83% of IBC cases were hormone receptor negative, compared with NIBCs, which are mostly hormone receptor positive. HER2 is overexpressed more in IBC than in NIBC.<sup>18</sup> All of the aforementioned unfavorable characteristics of IBC attribute to its aggressiveness and worse outcomes.

The current case represents a distinctive presentation of a rather unusual ER-PgR-positive, HER2-negative IBC with metastasis to a rare site, the gallbladder. Most of the rare reported cases of MBC with gallbladder metastasis were associated with lobular histology.<sup>5-7</sup> The case is exceptional for being associated with a ductal histology as suggested by the positive e-cadherin staining on the primary and metastatic specimens. Perhaps, this confirms the aggressive nature of IBC irrespective of the histology and tumor markers.

In conclusion, our case substantiates the propensity of breast cancer to metastasize to many different sites, and sometimes to rare sites such as the gallbladder. Inflammatory breast cancer is a naturally aggressive neoplasm with great metastasis potential and poor outcomes irrespective to the tumor marker profile or the histology, ductal or lobular. A gallbladder neoplasm in a patient with metastatic breast cancer is a possible metastasis and should not be presumed as a second primary unless confirmed by histology and immunostaining.

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