ABSTRACT

Breast cancer is the most common cancer affecting women worldwide and has a rising incidence. Important prognostic factors include size, grade and hormone receptor status of the primary tumours, regional node involvement and distant metastases. Lobular breast carcinoma accounts for 10% of invasive breast cancers and is the second most common type following ductal breast carcinoma. Lobular breast cancer is often diagnosed at a later stage owing to challenging detection on screening mammograms and/or ultrasounds. Gallbladder involvement of distant breast metastases is very rare and is typically found in patients with terminally advanced disease. We present a rare case of solitary gallbladder metastasis from lobular breast carcinoma in a 76-year-old Caucasian female with no known history of breast cancer. Clinical presentation and imaging investigations were consistent with cholecystitis, prompting cholecystectomy. Histopathological examination confirmed chronic cholecystitis and metastatic lobular breast carcinoma. Subsequent investigations revealed invasive lobular breast carcinoma of the left breast but no nodal or systemic involvement. Gallbladder involvement in metastatic breast carcinoma is mostly reported incidentally in patients who undergo cholecystectomy for biliary colic or cholecystitis. Our case demonstrates an incidental solitary gallbladder metastasis leading to the diagnosis of invasive lobular breast carcinoma. It highlights the challenges of diagnosing lobular breast cancer on conventional imaging.

KEYWORDS

metastatic lobular breast cancer, cholecystitis, gallbladder involvement in metastatic breast cancer, invasive lobular breast carcinoma

Introduction

An estimated 1 in 55 Australian women is diagnosed with breast cancer daily in 2021 [1, 2]. It is the most common cancer affecting this population group. Despite improvement in breast cancer mortality and survival from rigorous national screening programs and improved treatment modalities, breast cancer has a rising incidence. It remains the second most common cause of cancer-related deaths in Australian females [3]. Most breast cancers are ductal type, accounting for 80% of diagnosed invasive breast cancer [4]. The second most common is lobular breast cancer (10% of all invasive breast cancer), with a tendency for multifocal, multicentric and/or bilateral breast involvement at diagnosis [5, 6].

The prognosis and treatment of breast cancer patients depend on the size, grade and hormone receptor status of the primary disease, regional node involvement and the presence of metastases [3]. Early diagnosis achieved through screening mammograms and ultrasound has improved patient outcomes. The hallmark feature of invasive breast cancer on mammograms is the appearance of a high-density spiculated mass [7]. However, it is well documented that diagnosing lobular breast cancer on mammograms can be challenging. This is because lobular breast cancer grows diffusely and does not stimulate a significant desmoplastic reaction, resulting in a high-density spiculated mass. As such, lobular breast cancer tends to be detected later than ductal breast cancer [8].

Further, breast cancer commonly metastasizes to regional lymph nodes, lungs, bones, brain, and liver [9]. In contrast, invasive lobular breast cancer has an unusual tendency for uncommon sites such as the gastrointestinal tract, gynecologic organs
and peritoneum [6]. However, the involvement of gallbladder in distant breast cancer metastases is very rarely reported in the current literature and is mostly found in patients with multiple organ involvement and terminally advanced disease [10]. It is usually incidentally found on histopathological examination following biliary colic or cholecystitis surgery. There is typically very little evidence for carcinomatous involvement in pre-operative investigations.

Here, we describe the first case of solitary gallbladder involvement of metastatic lobular breast carcinoma presenting as cholecystitis in a previously undiagnosed patient. In addition, we discuss the challenges of diagnosing lobular breast carcinoma on imaging.

Case report
We describe a 76-year-old Caucasian female who presented with a 24-hour history of post-prandial epigastric pain radiating to the back. She had nausea but no vomiting and fever. She had no known cholelithiasis or previous history of biliary colic. Her past medical history includes obesity (BMI 41), hypothyroidism, osteoporosis, type 2 diabetes, granulomatous colitis, excretory dyspepsia related to heart failure (ejection fraction of 45%) and morbid obesity. She had known stable right lung nodules for 10 years and a recent finding of stable right pleural thickening over 6 months. Her regular medications were thyroxine and pantoprazole.

On examination, she was alert, afebrile, hemodynamically stable with a heart rate of 65 beats per minute. Her abdominal exam revealed tenderness in the epigastrium and right upper quadrant. Laboratory investigations demonstrated an elevated white cell count of 15x10^9/L and a normal liver function test. A computed tomography (CT) scan was first performed and revealed a thickened gallbladder wall with trace pericholecystic fluid, raising the suspicion of acute cholecystitis (Figure 1). In addition, there was an incidental finding of hepatosplenomegaly with hepatic steatosis, but the bowel and regional nodes appeared unremarkable. An ultrasound of the upper abdomen revealed a thickened gallbladder wall with trace pericholecystic fluid, raising the suspicion of acute cholecystitis (Figure 1). In addition, there was an incidental finding of hepatosplenomegaly with hepatic steatosis, but the bowel and regional nodes appeared unremarkable. An ultrasound of the upper abdomen was done to clarify her diagnosis further. This demonstrated a thickened gallbladder wall of 8mm and a 20mm non-mobile gallstone at the neck of the gallbladder with a normal common bile duct calibre of 6mm (Figure 2). The provisional diagnosis raised inflammatory markers from her laboratory tests and cholecystitis imaging findings based on her clinical presentation.

The patient was initially commenced on intravenous ceftriaxone and metronidazole for her cholecystitis, and she remained hemodynamically stable and well throughout her admission, but her symptoms did not improve pre-operatively. Therefore, she was offered emergency laparoscopic cholecystectomy within 48 hours of admission. Intraoperatively, the gallbladder was thick-walled, inflamed and oedematous with omental adhesions around the gallbladder, consistent with cholecystitis without suggesting malignant involvement. Within the limits of the intra-operative examination, there was no evidence of gross nodular disease of the peritoneum. Her abdominal symptoms improved significantly postoperatively, however she developed hospital-acquired pneumonia and decompensated heart failure. Nevertheless, she made a full recovery 2 weeks later.

Histopathological examination of the gallbladder demonstrated severe chronic cholecystitis, and an infiltrate of malignant epithelioid cells forming cords and discohesive clusters within the gallbladder wall. Some cells have mucinous cytoplasm, and a few cells resemble signet ring cells. There was background intestinal metaplasia of the gallbladder mucosa, but no biliary dysplasia was seen. The malignant cells stained positively for cytokeratin markers AE1/AE3, CK8/18, CK7, and GATA3 and were E-cadherin negative. This immunohistochemical staining pattern was consistent with metastatic lobular carcinoma of the breast (estrogen positive, progesterone positive and HER-2 negative).

A focused breast history taking revealed no previous history or risk factors for breast cancer, and the patient had normal breast cancer screening results just 3 years prior to her presentation. She had no family history of breast or ovarian cancer. Examination of her breast revealed no suspicious findings of breast malignancy.

A subsequent mammogram demonstrated an area of dense parenchyma without focal distortion in the upper inner quadrant in the left breast. Correspondingly, an increased density and shadowing was noted on ultrasound between 8 and 12 o’clock. However, a discrete mass was not identifiable or measurable (Figure 3). Random biopsies of this dense area in the left breast upper inner quadrant confirmed invasive lobular breast carcinoma. Post-biopsy magnetic resonance imaging (MRI) demonstrated the area of subtle distortion to be 4.1 x 2 x 3.8cm. However, this area failed to show differential enhancement in the post-contrast phases (Figure 4). Imaging did not reveal any evidence of regional nodal involvement. No other organ involvement was demonstrated on staging CT of the brain, chest, abdomen, pelvis, and bone scan.

She was discussed in the breast multidisciplinary team meeting and was started on Letrozole and Palbociclib. Surgical management of the primary breast malignancy will be reserved if the patient develops systemic therapy complications or for local control.

Discussion
Here we present the first case of solitary gallbladder metastasis presenting as cholecystitis secondary to lobular breast carcinoma in a patient with no known history of breast cancer. Gallbladder involvement in metastatic carcinoma of any type is rare (an estimated 5.8% of cancer patients in an autopsy series), most commonly malignant melanoma [11, 12]. Gallbladder metastasis from breast cancer is even rarer, with only a handful of case reports available in the literature to date. Almost all cases of breast cancer metastasis found in the gallbladder occur in
Figure 2: Ultrasound images of the gallbladder (GB) demonstrating thickened gallbladder wall to 8mm (arrow, left) and a 20mm immobile cholelithiasis at the gallbladder neck (arrowhead, right). No hyperemia of the gallbladder wall or pericholecystic fluid was demonstrated on the ultrasound.

Figure 3: Mammographic images. Left breast craniocaudal (A) and left breast mediolateral (B) views show the area of dense parenchyma without focal distortion (circles). Random biopsies taken from circled areas confirmed invasive lobular breast carcinoma. For comparison, right breast craniocaudal (C) and right breast mediolateral (D) views were included.

Figure 4: Magnetic resonance imaging (MRI) of the breast showing an area of distortion in the left breast in a T1 axial contrast image (left, arrow) and T1 sagittal contrast image (right, arrow).

patients with a previous history of treated breast cancer or a synchronous diagnosis [13, 14]. Patients frequently present with right upper quadrant pain of variable duration, with accompanying symptoms and signs suggestive of either biliary colic or acute cholecystitis prompting cholecystectomy. Invasive lobular breast carcinoma is most commonly responsible for metastatic involvement of the gallbladder, with invasive ductal breast carcinoma being the second most common [14]. This is consistent with our case.

To the authors' review, only one published case report had reported gallbladder metastasis leading to the diagnosis of metastatic lobular breast cancer in a patient with no previous breast cancer [15]. Salita et al. 2021 describe a case of elective cholecystectomy for biliary colic leading to an incidental diagnosis of metastatic ductal and lobular breast cancer, which was subsequently found to have bilateral breast cancer with nodal and diffuse osseous metastases. Interestingly, only lobular carcinoma was seen invading the gallbladder. Gallbladder metastasis of breast cancer usually appears as protruding mural nodules on ultrasound and gross anatomical examination [10]. Our case demonstrated no specific features on imaging or gross anatomical examination to suggest any carcinomatous involvement. As such, it remains challenging to diagnose gallbladder involvement of metastatic lobular breast cancer pre-operatively. A review by Missori et al. 2020 shows that gallbladder involvement in distant breast cancer metastases is usually diagnosed incidentally during histopathological examination following surgery performed for symptomatic biliary colic or cholecystitis. Similar to published literature, our case demonstrates an incidental finding of invasive lobular cancer metastasizing to the gallbladder [15, 16]. However, our patient represents the first case in literature to demonstrate a solitary gallbladder metastasis and no other organ involvement.

This case also highlights the difficulty of identifying lobular carcinoma of the breast on clinical examination or conventional imaging. Lobular breast cancer grows in infiltrative patterns without altering underlying anatomic structures or eliciting desmoplastic reactions [17]. As a result, mammographic detection has a much lower sensitivity compared to ductal breast cancer. Our case also showed the challenges in diagnosing lobular breast cancer on conventional imaging. Mammographic images did not reveal a focal area of distortion. Rather, only a diffuse area of dense parenchyma was detected in the left inner upper quadrant. Prompted by her incidental gallbladder metastasis, random biopsies of this area were performed and diagnosis her breast cancer. This subsequently led to an MRI of her breast, as MRI has a higher sensitivity (overall 93%) for detecting lobular breast cancer [7]. The increased sensitivity of MRI is due to higher spatial resolution as well as malignant cells with neovascularisation cause a rapid uptake and washout of the gadolinium contrast. This differential contrast enhancement increases the detection of malignant cells compared to surrounding benign breast parenchyma. Consistent with the infiltrative pattern of the cancerous growth, a diffuse area of distortion was found on her MRI. However, the area failed to show differential contrast enhancement. Overall, this case emphasizes the challenges in diagnosing and assessing lobular breast cancers. Despite staging investigations revealing no evidence of another metastatic disease, small volume metastatic disease is suspected and therefore, systemic treatment was favoured.

Conclusion

Gallbladder metastasis from breast cancer typically presents with biliary colic or cholecystitis. In most cases, gallbladder...
metastasis is detected late, and patients often have advanced disease with multiple organ involvement. Diagnosis is challenging pre-operatively and is only confirmed on histopathological examination. Here we demonstrate a rare case of incidental solitary gallbladder metastasis leading to the diagnosis of lobular breast carcinoma. This case also highlights the difficulty in identifying lobular breast cancer primary on conventional imaging.

**Abbreviation**

CT Computed tomography  
MRI Magnetic resonance imaging

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**Conflict of interest**

There are no conflicts of interest to declare by any of the authors of this study.

**References**


