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CASE REPORT

A resected case of gallbladder metastasis with symptoms of acute cholecystitis in multiple metastatic ductal carcinoma of the breast

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Abstract
Gallbladder metastasis from breast cancer, especially from ductal carcinoma, is rare. Herein, we report a rare case of gallbladder metastasis from ductal carcinoma of the breast that was diagnosed after laparoscopic cholecystectomy (LC) for acute cholecystitis. A 78-year-old woman presented with right upper abdominal tenderness and positive Murphy's sign during chemotherapy for advanced multiple metastases of the breast cancer. Abdominal ultrasonography and computed tomography showed a slightly thickened gallbladder wall and two calculi. After a diagnosis of acute calculous cholecystitis was established, LC was performed. Pathological examination revealed poorly differentiated adenocarcinoma infiltrating the submucosal and subserosal layer over the entire gallbladder, and a lymph node metastasis in the gallbladder neck. Immunohistochemical examination revealed that the tumor cells tested positive for estrogen receptor and negative for progesterone receptor, which was consistent with primary breast cancer. The patient was uneventfully discharged without abdominal pain 7 days later. Although she subsequently underwent several chemotherapies, she died 16 months later. In conclusion, gallbladder metastasis should be considered in patients with multiple metastatic breast cancer who present with signs or symptoms of cholecystitis. Moreover, LC should be considered to relieve the symptoms of cholecystitis for improved prognosis, even in a patient with multiple metastases.

Keywords Breast cancer · Ductal carcinoma · Gallbladder metastasis · Laparoscopic cholecystectomy

Background

Breast cancer is known to metastasize to the bones, lungs, and liver; however, it rarely metastasizes to the gallbladder. Gallbladder metastasis from breast cancer has been reported to occur in 4–7% of breast cancer autopsy cases [1]. Compared to ductal carcinomas, lobular carcinomas often show a preference to metastasize to the gastrointestinal tract [2]. To our knowledge, very few cases of gallbladder metastasis from breast cancer, especially ductal carcinoma, have been reported. Herein, we report a rare case of gallbladder metastasis in advanced multiple metastases from invasive ductal carcinoma of the breast that was diagnosed after laparoscopic cholecystectomy (LC) for acute cholecystitis.

Case report

A 78-year-old woman was admitted to our hospital with right upper abdominal pain that had persisted for a few days. Her medical history included right mastectomy for right breast cancer 45 years ago, and neoadjuvant chemotherapy and left mastectomy with axillary dissection for left invasive ductal carcinoma of the left breast (pT2/N3c/M0/Stage IIIc) 6 years ago. The patient had undergone adjuvant chemotherapy followed by endocrine therapy after the operation. In addition, she had undergone tumorectomy for local recurrence in the left large pectoral muscle 4 years ago, and she had continued another endocrine therapy. She underwent endocrine therapies or chemotherapies with bone modifying agents for multiple metastases, including bones, para-aortic lymph nodes, lungs, and liver, within the last

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3 years. Tumor markers were measured and positron emission tomography–computed tomography (PET-CT) was performed appropriately to evaluate the effect of drug therapies and to predict the patient's prognosis. The clinical course with tumor markers is summarized in Fig. 1 and the follow-up PET-CT images are shown in Fig. 2.

Physical examination demonstrated abdominal tenderness in the right upper quadrant and positive Murphy's sign. Laboratory investigations revealed a normal white blood cell count (7410/μL; segmented neutrophils, 86.2%), an elevated C-reactive protein level (3.24 mg/dL), an elevated aspartate aminotransferase level (37 IU/L), and hyperbilirubinemia (total bilirubin level, 2.27 mg/dL; direct bilirubin level, 0.26 mg/dL). The levels of carcinoembryonic antigen and carbohydrate antigen 15-3 were elevated to 45.5 ng/mL and 60.3 U/mL, respectively. Abdominal ultrasonography showed gallbladder enlargement, a slightly thickened wall over the entire gallbladder, and two calculi in the body, which were likely to be associated with cystic duct obstruction (Fig. 3a). There were debris in the gallbladder (Fig. 3b). Abdominal computed tomography also showed similar findings, with slight inflammation of the fat tissue around the gallbladder (Fig. 3c, d). Although it was unclear whether the calculi positioned in the body of the gallbladder were related to acute cholecystitis, a diagnosis of acute cholecystitis owing to the presence of the calculi was made. Although this case presented an advanced stage of breast cancer, the patient was thought to have a better prognosis by undergoing chemotherapy. Therefore, LC was selected to relieve the symptoms of acute cholecystitis rather than conservative therapies. Intraoperative examination showed that the gallbladder was markedly tense, and the thickened wall was discolored to a purplish red color (Fig. 4). On gross examination, the gallbladder wall was markedly thickened with edema and bleeding (Fig. 5a). Two cholesterol gallstones and hematoma were found in the gallbladder. Pathological examination revealed a poorly differentiated adenocarcinoma infiltrating the submucosal and subserosal layer

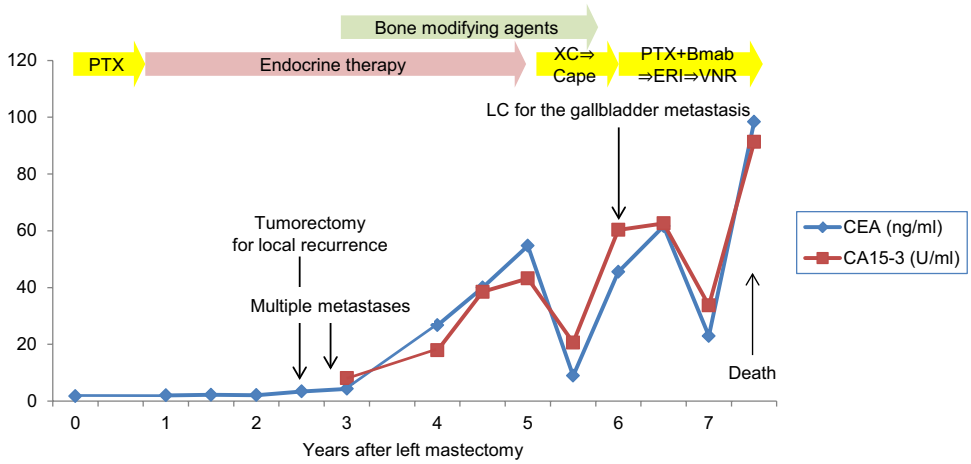

Fig. 1 Clinical course of the serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA15-3) levels. *PTX* paclitaxel, *XC* capecitabine + cyclophosphamide, *Cape* capecitabine, *Bmab* bevacizumab, *ERI* eribulin, *VNR* vinorelbine, LC laparoscopic cholecystectomy

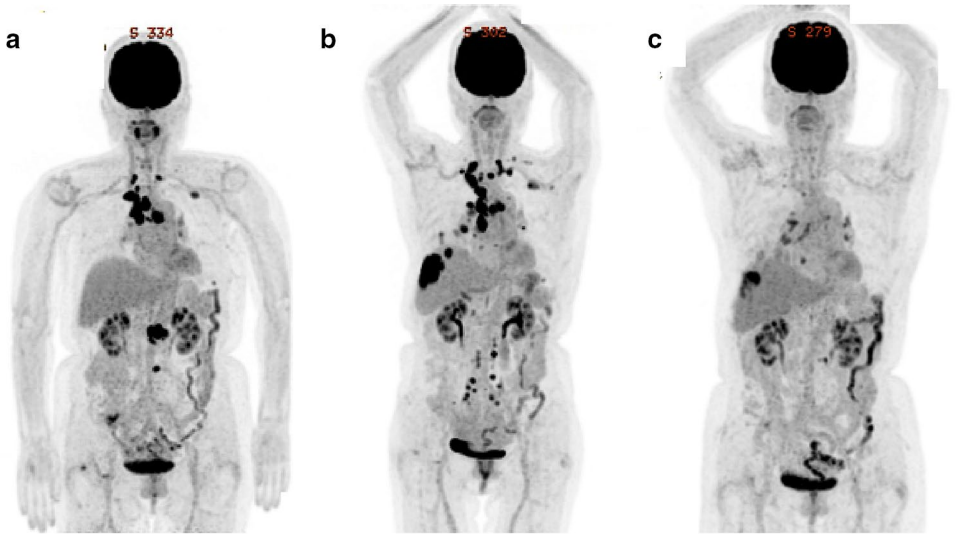

Fig. 2 Clinical course of the positron emission tomography (PET) after left mastectomy. **a** PET image showed multiple metastases, including bones and mediastinal and para-aortic lymph nodes, 3 years later. **b** PET image showed liver and lung metastases 4 years later. **c** The PET image showed that all metastases had regressed by chemotherapy 5 years and 10 months later

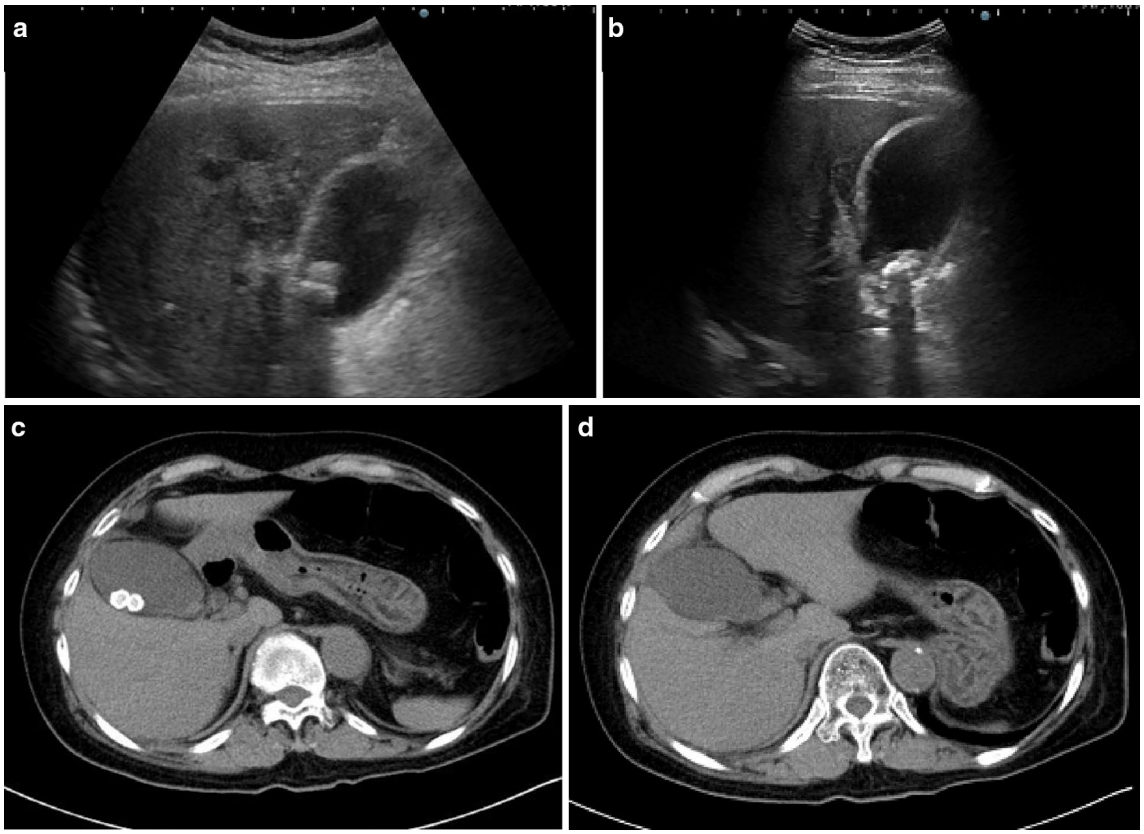

Fig. 3 Preoperative images showing acute cholecystitis with gallstones. **a, b** Abdominal ultrasonography and **c, d** computed tomography images showing a slight thickened gallbladder wall and two calculi

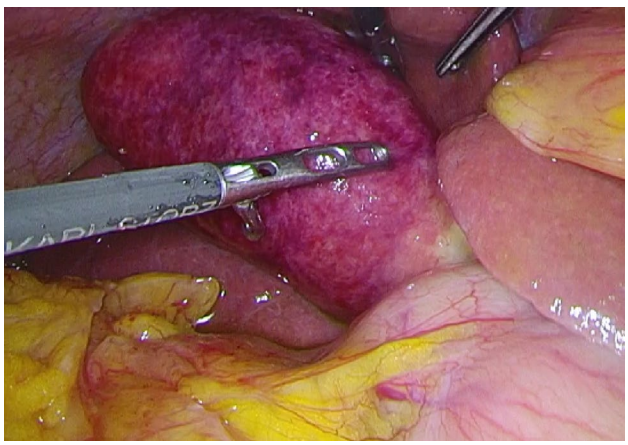

Fig. 4 Intraoperative findings during laparoscopic cholecystectomy. The gallbladder is markedly tense and the thickened wall is discolored to purplish red color

over the entire gallbladder (Fig. 5b, c). It also revealed tumor involvement of the mucosa layer of the gallbladder and tumor extension to the cystic duct. A lymph node metastasis was found around the gallbladder neck. Poor infiltration of inflammatory cells in the gallbladder wall and bleeding associated with invasion of the tumor were observed. On immunohistochemical examination, the tumor cells were positive for estrogen receptor, negative for progesterone receptor, and negative for human epidermal growth factor receptor 2, with less than 20% Ki-67 labeling index (Fig. 5e). These results were consistent with primary left breast cancer (Fig. 5d, f).

The patient reported immediate resolution of abdominal pain and was uneventfully discharged 7 days later. Although she subsequently underwent several chemotherapies, she died 16 months later.

Discussion

The gallbladder is an uncommon site for metastatic malignant disease. In one large autopsy series, metastases to the gallbladder were found in only 5.8% of patients with cancer and in 6.6% of patients with breast cancer [3]. Although metastases of malignant melanoma, renal cell carcinoma, and cervical carcinoma to the gallbladder have been reported, breast cancer has rarely been reported to metastasize in the gallbladder [2]. To our knowledge, there are

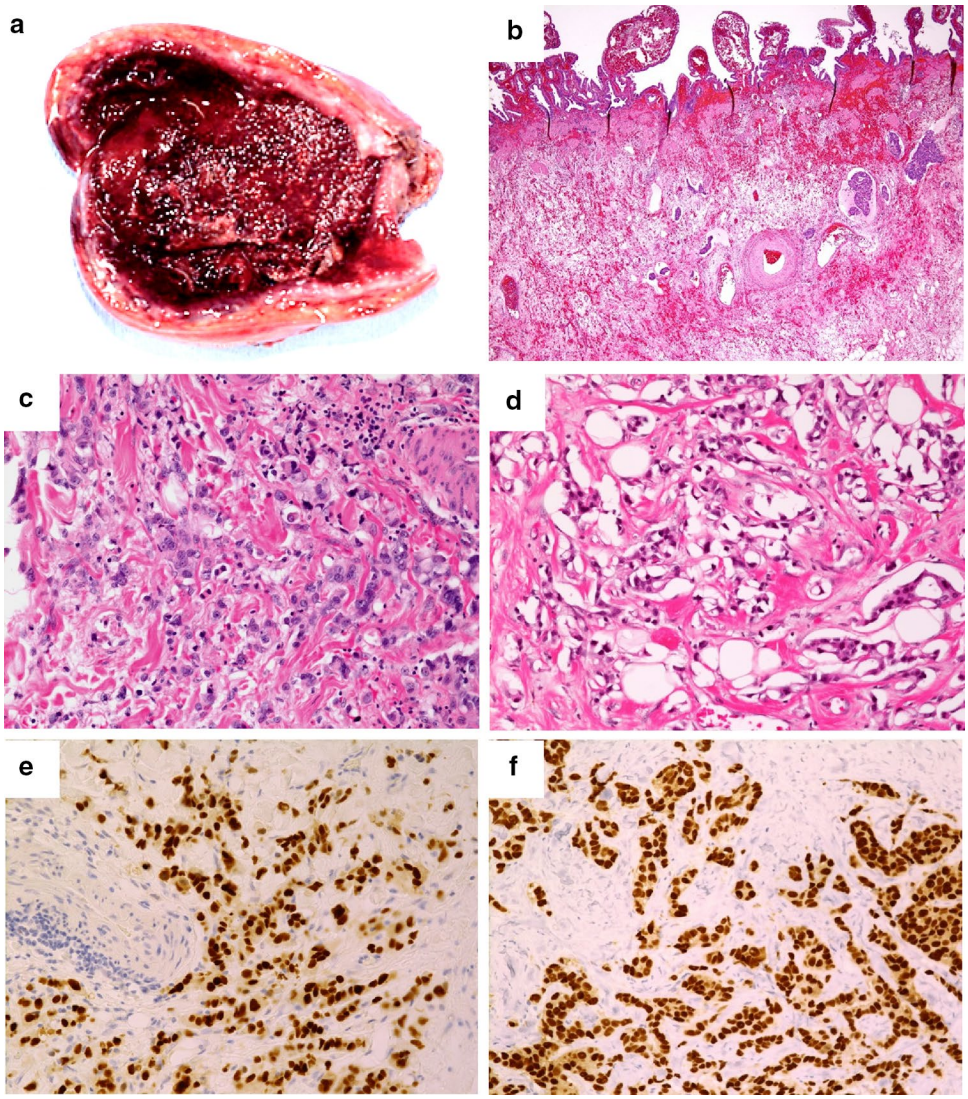

Fig. 5 Histopathological findings of the resected specimen. **a** Macroscopically, the gallbladder wall appears markedly thickened with edema and bleeding. **b, c** Pathological examination reveals a poorly differentiated adenocarcinoma infiltrating the submucosal and subserosal layer over the entire gallbladder (Hematoxylin and eosin [H&E] staining, original magnification; **b** H&E, ×20; **c** H&E, ×200). **d** The primary breast cancer was an invasive ductal carcinoma (Hematoxylin & eosin, ×200). **e** Immunohistochemical examination reveals that the tumor cells of the gallbladder are positive for estrogen receptor (immunohistochemical staining, ×200). **f** Immunohistochemical examination revealed that the tumor cells of the primary breast cancer were positive for estrogen receptor (immunohistochemical staining, ×200)

a few reports of gallbladder metastasis from ductal carcinoma [4–8]. Di Vita et al. reported that synchronous gallbladder metastases were observed in 40% of the patients, while metachronous metastases were observed in 60% of the patients. The reported time interval between the treatment of the primary breast cancer and the detection of gallbladder metastasis varies from 2 to 15 years [9]. In the present case, the gallbladder metastasis was detected 6 years after surgery for the left breast cancer, although the patient had multiple metastases.

Patients with metastatic breast cancer involving the gallbladder or biliary tract, have been reported to typically present with abdominal pain mimicking acute or chronic cholecystitis, and obstructive jaundice [9–11]. In patients with gallbladder stones, as in our case, a provisional diagnosis of acute calculous cholecystitis is often established before surgery. Cholecystectomy and histopathological examination of the gallbladder are necessary for accurate diagnosis of gallbladder metastasis. From the pathological findings, the symptoms of cholecystitis were considered to be attributed to obstruction of the cystic duct by bleeding of the gallbladder wall associated with invasion of the tumor. Preoperative images did not indicate tumor invasion in the neck of the gallbladder. It was difficult to make an accurate diagnosis preoperatively. In addition, the differential diagnosis between gallbladder metastasis and primary gallbladder cancer is very important to manage the disease. Immunohistochemical examination, including estrogen receptor and progesterone receptor testing, is necessary when gallbladder metastasis is strongly suspected.

In principle, abdominal metastases of breast cancer are no longer considered as an indication of operation. We should consider conservative therapies, including percutaneous transhepatic gallbladder aspiration and drainage, and other stenting procedures, in this advanced situation with multiple metastases. However, patients with gallbladder

metastasis of breast cancer have been reported to survive for 12–34 months when treated surgically [9]. In addition, the prognosis for breast cancer has improved owing to the advances in chemotherapy and endocrine therapy over the years. Therefore, cholecystectomy should be considered as palliative treatment in a patient with gallbladder metastasis from breast cancer, and it is recommended in symptomatic patients [6, 9]. In this case, the patient was thought to have a better prognosis by undergoing chemotherapy because her activities of daily living were relatively normal. Therefore, LC was selected to relieve the symptoms of acute cholecystitis completely. Moreover, Brinkman et al. recommend that the initial approach should be diagnostic laparoscopy, and that LC can be performed if the intraoperative findings necessitate removal of the gallbladder and if the operating surgeon is experienced enough [12]. In addition, we recommend LC rather than open cholecystectomy to decide the next course of treatment as soon as possible, especially in patients at advanced stages of breast cancer.

Conclusions

Gallbladder metastasis is rare in patients with breast cancer, especially in those with ductal carcinoma of the breast. This diagnosis should be considered for patients with multiple metastatic breast cancer who present with signs and symptoms of cholecystitis. Moreover, LC should be performed to relieve the symptoms of cholecystitis for better prognosis in patients with multiple metastases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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