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# Concomitant endometrial and gallbladder metastasis in advanced multiple metastatic invasive lobular carcinoma of the breast: A rare case report

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## ABSTRACT

**INTRODUCTION:** At time of presentation, fewer than 10% of patients have metastatic breast cancer. The most common sites of metastasis in order of frequency are bone, lung, pleura, soft tissue, and liver. Breast cancer metastasis to the uterus or gallbladder is rare and has infrequently been reported in the English literature.

**PRESENTATION OF CASE:** A 47 year old female with a recent history of thrombocytopenia presented with abnormal vaginal bleeding. Pelvic ultrasound revealed multiple uterine fibroids and endometrial curettings revealed cells consistent with lobular carcinoma of the breast. Breast examination revealed edema and induration of the lower half of the right breast. Biopsy of the right breast revealed invasive lobular carcinoma. Bone marrow aspiration obtained at a previous outpatient visit revealed extensive involvement by metastatic breast carcinoma. Shortly after discharge, the patient presented with acute cholecystitis and underwent cholecystectomy. Microscopic examination of the gallbladder revealed metastatic infiltrating lobular carcinoma. The final diagnosis was invasive lobular carcinoma of the right breast with metastasis to the bone marrow, endometrium, gallbladder, regional lymph nodes, and peritoneum.

**DISCUSSION:** The growth pattern of invasive lobular carcinoma of the breast is unique and poses a challenge in diagnosing the cancer at an early stage. Unlike other types of breast cancer, it tends to metastasize more to the peritoneum, ovary, and gastrointestinal tract. Metastasis to the endometrium or gallbladder is rare.

**CONCLUSION:** Metastatic spread should be considered in the differential diagnosis of patients with invasive lobular breast carcinoma presenting with abnormal vaginal bleeding or acute cholecystitis.

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## 1. Introduction

Fewer than 10% of patients have metastatic breast cancer at time of presentation [1]. The most frequent site of breast cancer metastasis is bone, followed by lung, pleura, soft tissue, and liver. Metastasis to the gallbladder has been reported to occur in about 4–7% of breast carcinoma cases [2]. The endometrium accounts for 4.7% of metastatic sites to the female genital tract from extragenital tumors [3]. Invasive lobular carcinoma comprises 10% of all types of invasive breast cancers, and is the second most common type of invasive carcinoma of the breast after invasive ductal carcinoma. Invasive lobular carcinoma has a wide array of initial presentations ranging from inconspicuous disease to masses that involve the

entire breast. It has the propensity to be multifocal, multi-centric, and involve bilateral breasts [4]. Invasive lobular carcinoma is more likely to metastasize to the peritoneum, ovary, and gastrointestinal system [5]. Sixty percent of patients with invasive lobular carcinoma will already have metastatic disease at time of diagnosis [6]. Patients with metastatic invasive lobular carcinoma may have a delay in the diagnosis and management of their disease as they may present with nonspecific symptoms. Here, we report a rare case of invasive lobular carcinoma with metastases to the bone marrow, endometrium, gallbladder, regional lymph nodes, and peritoneum.

## 2. Case presentation

A 47-year-old African American female with a BMI of 40 presented to the emergency department with a 10 day history of abnormal vaginal bleeding. She had a history of thrombocytopenia 26 days earlier attributed to NSAID use and history of a

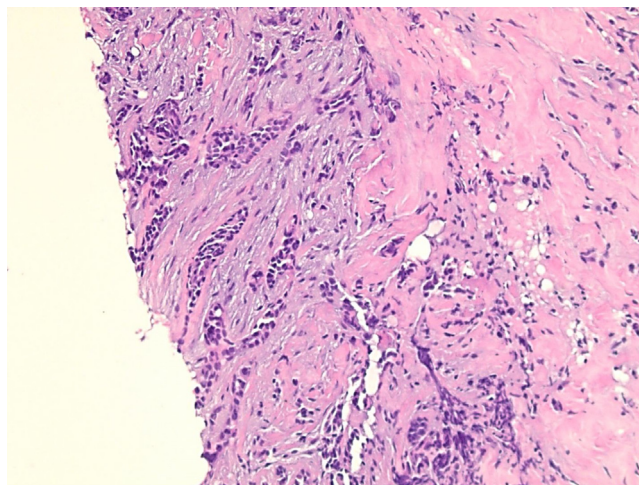
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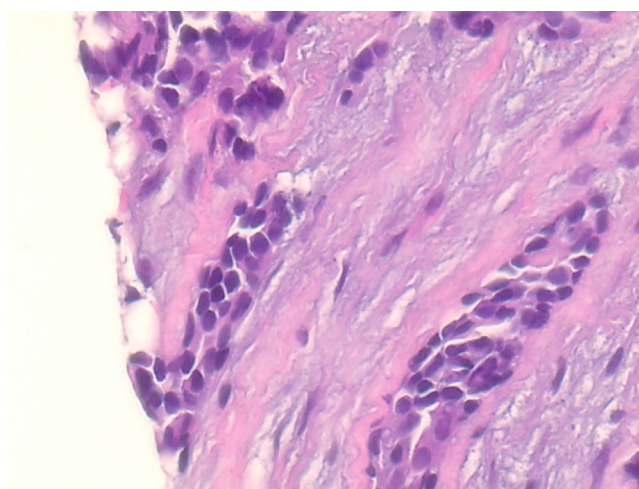
similar episode one year earlier attributed to uterine fibroids that were planned for surgical treatment, but the patient was lost to follow-up. Past medical history consisted of systemic lupus erythematosus, rheumatoid arthritis, thalassemia, fibromyalgia, migraine headaches, and back pain. Reproductive history consisted of menarche at age 13, one full-term pregnancy at age 42 and one abortion. Family history was doubtful for cervical or breast cancer. Medication history included 2 weeks of ibuprofen use for back pain prior to presentation. Social history was positive for occasional use of alcohol and marijuana. The patient had a bone marrow aspirate and biopsy performed after a prior evaluation for thrombocytopenia, the results of which were pending at time of presentation. A mammogram performed one year earlier was negative.

On examination, vital signs revealed tachycardia (102 beats/min) and were otherwise normal. Physical examination revealed pale conjunctiva, skin pallor, suprapubic tenderness, and tenderness surrounding the vagina with moderate dark red vaginal bleeding. With the past history of bleeding uterine fibroids, this was provisionally suspected to be the cause of re-bleeding and breast examination was missed being done at this point. Laboratory values revealed low hemoglobin (7.2 g/dL), low platelet count (20,000/mm<sup>3</sup>), and an elevated white blood cell count (13,800/mm<sup>3</sup>) with a left shift including metamyelocytes and bandemia. Chemistry panel revealed an elevated total calcium (11.6 mg/dL) and was otherwise normal. Urinalysis revealed white blood cells (15–25/HPF) and red blood cells (15–25/HPF) as well as few bacteria. Pelvic ultrasound revealed multiple uterine fibroids, with the largest measuring 3.7 cm, and an irregular endometrium measuring 13 mm in thickness. The patient was admitted for symptomatic anemia, red blood cell and platelet transfusions, and obstetrical and gynecological consultation.

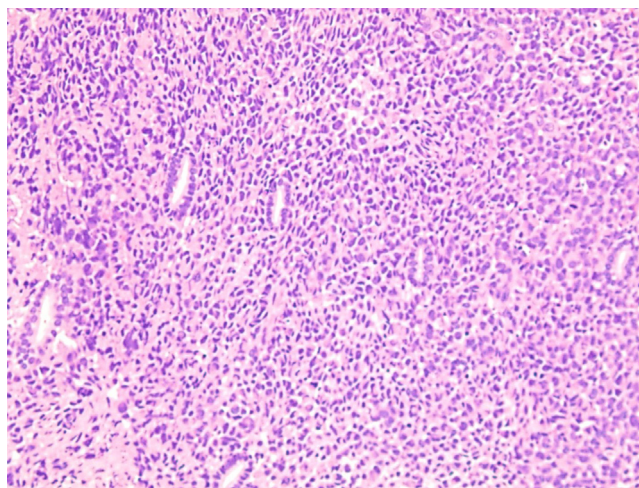
Breast examination was performed and revealed edema and induration of the lower half of the right breast and was unremarkable in the left breast. Shortly after admission, the results of her bone marrow biopsy were retrieved and revealed a hypercellular bone marrow with marked diffuse fibrosis and extensive involvement by metastatic carcinoma of the breast. Mammography was performed and revealed no concerning findings in the left breast and multi-centric lesions in the right breast with non-muscle like abnormal enhancements in the upper and lower right quadrants suspicious for malignancy (BI-RADS 4A). Bilateral axillary lymph nodes were detected in the infra-pectoral and retro-pectoral regions. CT of the chest was performed and revealed skin thickening of the right breast, bilateral axillary lymphadenopathy with the largest measuring 1.8 cm × 1.3 cm, diffuse heterogeneous sclerotic changes involving the sternum, thoracic vertebrae, multiple ribs, bilateral scapula, and mild free fluid in the upper abdomen. CT of the abdomen and pelvis was performed and revealed prominent retroperitoneal lymph nodes and diffuse lytic lesions with heterogeneous bone marrow in the lumbar spine. MRI of lumbar spine revealed metastatic disease of lumbar spine, sacrum, and iliac bones. Bone scan was performed and revealed no evidence of bone metastasis. Biopsy of the right breast revealed a Grade 2 invasive lobular carcinoma in multiple cores, with a maximum single core linear length of 1.8 cm (Figs. 1 and 2). Endocrine receptor assays revealed the tumor to be ER positive (50%) and PR positive (70%). The malignancy was further found to be HER2/neu negative. Additionally, the patient underwent dilatation and curettage of the uterus with microscopic examination of endometrial curettings that revealed cells consistent with lobular carcinoma of the breast that were positive for AE1/3 and GATA-3 (Figs. 3–6). Her final diagnosis prior to discharge described a right breast invasive lobular carcinoma with metastasis to the bone marrow and endometrium (stage 4). She was discharged to follow-up with the oncology service and consideration of chemotherapy and hormonal management.



**Fig. 1.** Initial biopsy showing an infiltrating lobular carcinoma of the breast (100× magnification, H&E stain).



**Fig. 2.** Infiltrating lobular carcinoma of the breast (400× magnification, H&E stain).



**Fig. 3.** Endometrial biopsy (D&C) showing stromal tumor (40× magnification, H&E stain).

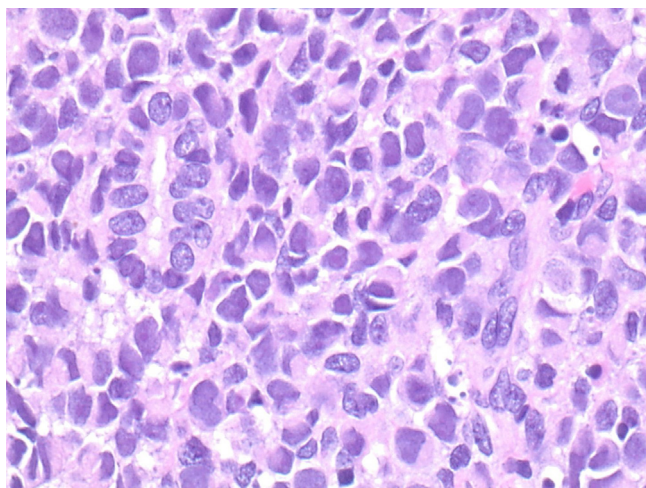


Fig. 4. Endometrial biopsy showing stromal tumor (400× magnification, H&E stain).

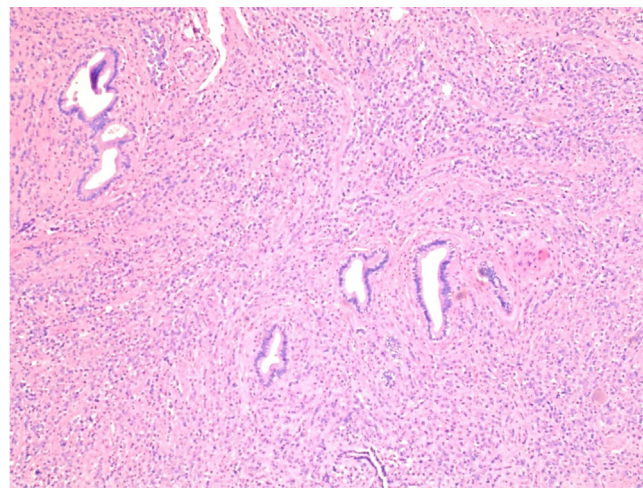


Fig. 7. Few remnants of the gall bladder showing normal gall bladder gland with stroma infiltrate (100× magnification, H&E stain).

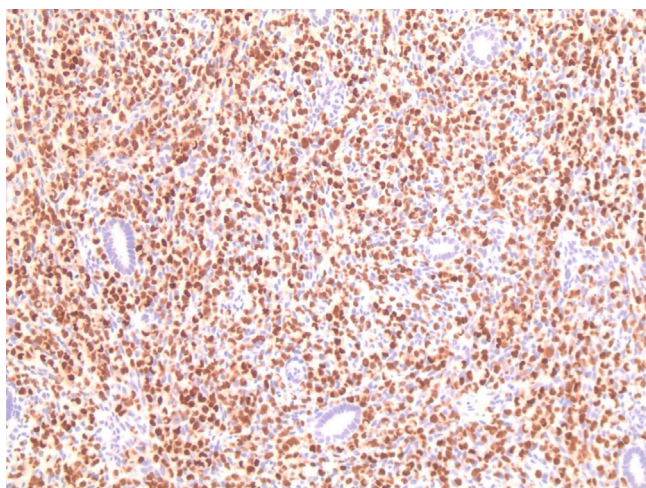


Fig. 5. Immunohistochemical stain for keratin (AE1/AE3) showing stromal infiltrate is epithelial in nature.

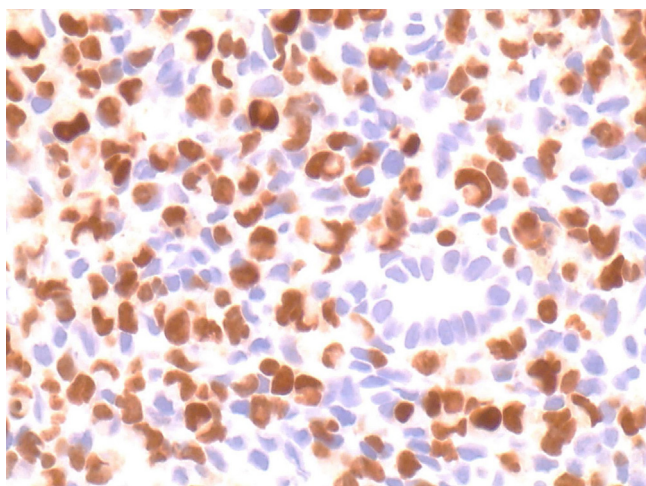
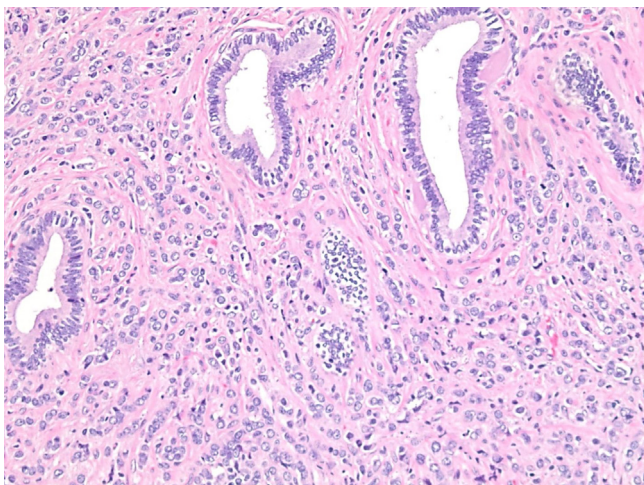


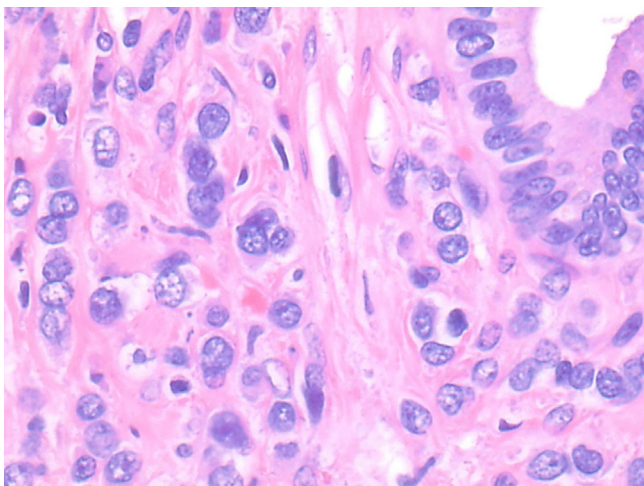
Fig. 6. Immunohistochemical stain for keratin (AE1/AE3) showing stromal infiltrate is epithelial in nature (400× magnification).

Nineteen days after discharge, the patient presented again to the emergency department with complaints of repeated vomiting of clear liquid, abdominal pain, and diarrhea for one week. On examination the patient was anicteric and in moderate distress. Vital signs revealed tachycardia (130 beats/min) and were otherwise normal. Physical examination of the abdomen revealed right upper quadrant tenderness and mild right lower quadrant tenderness without rebound and was otherwise unremarkable. Laboratory studies revealed an elevated white blood cell count (11,700/mm<sup>3</sup>), low hemoglobin (7.5 g/dL), low platelet count (12,000/mm<sup>3</sup>), elevated ALT (172 IU/L), elevated AST (168 IU/L), mildly elevated direct bilirubin (0.4 mg/dL), and elevated alkaline phosphatase (224 IU/L). Plain abdominal X-rays were performed and were unremarkable. Abdominal ultrasound revealed a contracted gallbladder with a large gallstone impacted within the gallbladder, a thickened wall and pericholecystic fluid consistent with acute cholecystitis. There was a positive sonographic Murphy's sign. The gallbladder wall thickness was 2.7 mm and there was no dilatation of the extrahepatic bile ducts. She was admitted for red blood cell and platelet transfusions, intravenous antibiotics, endoscopic retrograde cholangiopancreatography (ERCP), and cholecystectomy for acute cholecystitis.

Post-admission, the patient continued to complain of moderate abdominal pain and vomiting that were managed medically, and received multiple transfusions of packed red blood cells and platelets until deemed fit for surgery. ERCP was not performed due to patient refusal. On post-admission day 4, she underwent a laparoscopic cholecystectomy. Immediately preoperatively, the white blood count was 14,200/mm<sup>3</sup>, hemoglobin was 9.0 g/dL, and platelets were 91,000/mm<sup>3</sup>. Intra-operatively, there was moderate hemorrhagic peritoneal fluid upon entry into the peritoneal cavity. The gallbladder was found to be fibrotic and contracted with florid adenopathy at the base including Calot's node. Postoperatively, the patient required transfusion of packed red cells for a low hemoglobin (6.8 d/dL) but her course was otherwise uneventful. Histopathological examination of the gallbladder revealed a grossly hard, hemorrhagic, greenish pink gallbladder measuring 4.5 cm x 3.5 cm x 2.5 cm, with a wall thickness ranging from 0.2 cm to 0.6 cm. The lumen contained a single 2.5 cm calculus. Calot's node was white and firm measuring 0.6 cm in diameter. Microscopic examination of the gallbladder revealed metastatic infiltrating lobular carcinoma (Figs. 7–9). The final diagnosis was invasive lobular carcinoma of the right breast with metastasis to the bone marrow, endometrium, gallbladder, regional lymph nodes, and peritoneum.



**Fig. 8.** Section of the gall bladder wall showing metastatic infiltrating lobular carcinoma (100× magnification, H&E stain).



**Fig. 9.** Section of the gall bladder wall showing metastatic infiltrating lobular carcinoma (400× magnification, H&E stain).

The patient was discharged on postoperative day 3 for follow-up with her oncologist. About one month later, hormonal and chemotherapy were discontinued due to debility and weakness secondary to advanced disease and the patient died shortly thereafter.

### 3. Discussion

Infiltrating lobular carcinoma is typically diagnosed at a median age of 64 [5]. It is most commonly found to be localized to the upper outer quadrant of the breast [7]. Tumors of invasive lobular carcinoma tend to be multifocal and multi-centric. The growth pattern of invasive lobular carcinoma is unique in that it is diffuse and does not disrupt the normal architecture of the breast. Therefore, many women often fail to present with a mass that is palpable on physical examination or detectable on mammography, posing a challenge in diagnosing invasive lobular carcinoma at an early stage. Some, however, may present with thickening and induration of the breast tissue on physical examination, which is a sign of early stage disease [8]. Compared to ultrasound and mammography, the most accurate diagnostic imaging modality at determining the extent of lobular carcinoma appears to be MRI [9].

In order of frequency, breast cancer most commonly metastasizes to bone, lung, pleura, soft tissue, and liver [4]. Lobular carcinoma of the breast, the second most common type of invasive breast carcinoma tends to metastasize more to the peritoneum, ovary, and gastrointestinal tract [4,5]. Breast cancer metastasis to the endometrium or gallbladder is rare [2,10]. To our knowledge, this is the first reported case of invasive lobular carcinoma of the breast with concomitant metastasis to the endometrium and gallbladder.

The female genital tract is not a frequent site of metastasis especially from primary extragenital neoplasms. According to an analysis by Mazur et al. of 325 cases of metastatic carcinoma of the female genital tract, the most common sites of metastasis are the ovary and vagina, regardless of the site of the primary tumor. Out of 149 cases in which the primary tumors were extragenital, 52 primary sites were from the breast of which only 2 metastasized to the endometrium [10]. Another analysis of uterine metastases from primary extragenital neoplasms revealed that the myometrium is more common than the endometrium as the site of metastasis. Abnormal vaginal bleeding may be a sign of neoplastic uterine involvement although this is also infrequent [11]. This may include abnormal duration of periods, bleeding between periods, and postmenopausal bleeding [9].

The gallbladder is also not a common site of metastasis from the breast. In an autopsy analysis of 1000 cases with malignant neoplasms of epithelial origin, only 5.8% of cases had metastasis to the gallbladder [12]. Another autopsy series report revealed that only 4–7% of patients with breast carcinoma had metastatic disease in the gallbladder [2]. The most common presenting condition appears to be cholecystitis, although cholelithiasis, jaundice, and biliary dyskinesia have also been reported as presentations. Breast carcinoma metastasis to the gallbladder is often diagnosed on histopathological examination following cholecystectomy [13–23]. After performing a search of the PubMed database, a review of 12 articles on breast carcinoma metastasis to the gallbladder revealed that the time between breast cancer diagnosis and presentation of gallbladder metastasis ranges from 1 month to 10 years [13–24].

### 4. Conclusion

Invasive lobular breast carcinoma may metastasize to multiple sites including synchronous endometrial and gallbladder metastasis. Invasive lobular carcinoma has a unique pattern of metastasis compared to most other types of breast cancer. Its unusual growth pattern presents diagnostic challenges as many affected patients do not present with a palpable breast mass or a mass that is detected by mammography. Early metastasis may occur to the bone marrow prior to diagnosis and thrombocytopenia in females should trigger suspicion and thorough investigation to rule out possible underlying metastatic breast carcinoma. A high index of suspicion should be maintained for unusual patterns of metastases. Metastatic spread should be considered in the differential diagnosis of patients with invasive lobular breast carcinoma presenting with abnormal vaginal bleeding or acute cholecystitis.

### Consent

The patient was deceased before writing this article. Exhaustive attempts have been made to contact the family and have been unsuccessful. A letter signed by the Trauma Services Department director taking responsibility to publish this article is included with this submission with description of attempts made to contact the family. The article has been sufficiently anonymized not to cause harm to the patient or their family.

**Conflicts of interest**

None.

**References**

- [1] D.F. Roses, *Breast Cancer*, 2nd ed., Elsevier, Pennsylvania, 2005, p.812.
- [2] Y.T. Lee, Breast carcinoma: pattern of metastases at autopsy, *J. Surg. Oncol.* 23 (3) (1983) 175–180.
- [3] H.L. Abrams, R. Spiro, N. Goldstein, Metastases in carcinoma; analysis of 1000 autopsied cases, *Cancer* 3 (1) (1950) 74–85.
- [4] K.K. Hunt, J.R. Robertson, K.I. Bland, et al., The breast, in: F. Bruncardi, D.K. Andersen, T.R. Billiar (Eds.), *Schwartz's Principles of Surgery*, 10th ed., McGraw-Hill, New York, 2014.
- [5] G. Arpino, V.J. Bardou, G.M. Clark, R.M. Elledge, Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome, *Breast Cancer Res.* 6 (2004) R149–R156.
- [6] J.R. Harris, M. Morrow, L. Norton, Malignant tumours of the breast, in: S. Hellman, S.A. Rosenberg (Eds.), *Cancer: Principles & Practice of Oncology*, 5th ed., Lippincott-Raven, Pennsylvania, 1997, pp. 1457–1616.
- [7] D.J. Winchester, H.R. Chang, T.A. Graves, H.R. Menck, K.I. Bland, D.P. Winchester, A comparative analysis of lobular and ductal carcinoma of the breast: presentation, treatment, and outcomes, *J. Am. Coll. Surg.* 186 (4) (1998) 416–422.
- [8] K.J. Dedes, D. Fink, Clinical presentation and surgical management of invasive lobular carcinoma of the breast, *Breast Dis.* 30 (2008–2009) 31–37.
- [9] M.V. Nijenhuis, E.L. Rutgers, Who should not undergo breast conservation? *Breast* 22 (Suppl. 2) (2013) S110–S114.
- [10] M.T. Mazur, S. Hsueh, D.J. Gersell, Metastases to the female genital tract: analysis of 325 cases, *Cancer* 53 (9) (1984) 1978–1984.
- [11] N.B. Kumar, W.R. Hart, Metastases to the uterine corpus from extragenital cancers: a clinicopathologic study of 63 cases, *Cancer* 50 (10) (1982) 2163–2169.
- [12] H.L. Abrams, R. Spiro, N. Goldstein, Metastases in carcinoma; analysis of 1000 autopsied cases, *Cancer* 3 (1) (1950) 74–85.
- [13] F. Fleres, M. Rossitto, A. Foti, A. Macrì, E. Cucinotta, Metastasis of the gallbladder from the breast cancer, *Ann. Ital. Chir.* (2014) 85.
- [14] B. Abdelilah, O. Mohamed, R. Yamoul, I. Elkhayat, B. Al, A. ouzidi, S. Alkandry, et al., Acute cholecystitis as a rare presentation of metastatic breast carcinoma of the gallbladder: a case report and review of the literature, *Pan Afr. Med. J.* 17 (2014) 216.
- [15] B. Essola, P. Malvaux, J. Landenne, S. Kargar, C. Dopchie, F. Waignein, et al., Gallbladder metastasis from breast carcinoma: a new case report, *Rev. Med. Brux.* 33 (3) (2012) 171–175.
- [16] M. Di Vita, A. Zanghì, S. Lanzafame, A. Cavallaro, G. Piccolo, M. Berretta, et al., Gallbladder metastasis of breast cancer: from clinical-pathological patterns to diagnostic and therapeutic strategy, *Clin. Ter.* 162 (5) (2011) 451–456.
- [17] A. Markelov, H. Taheri, K. Vunnamadala, G. Ibrahim, Biliary dyskinesia as a rare presentation of metastatic breast carcinoma of the gallbladder: a case report, *Case Rep. Pathol.* 2011 (2011) 806570.
- [18] A. Manouras, E.E. Lagoudianakis, M. Genetzakis, N. Pararas, A. Papadima, P.B. Kekis, Metastatic breast carcinoma initially presenting as acute cholecystitis: a case report and review of the literature, *Eur. J. Gynaecol. Oncol.* 29 (2) (2008) 179–181.
- [19] F. Zagouri, T.N. Sergentanis, D. Koulocheri, A. Nonni, A. Bousiotou, P. Domeyer, et al., Bilateral synchronous breast carcinomas followed by a metastasis to the gallbladder: a case report, *World J. Surg. Oncol.* 5 (2007) 101.
- [20] M. Sand, F.G. Bechara, J. Kopp, N. Krins, D. Behringer, B. Mann, Gallbladder metastasis from renal cell carcinoma mimicking acute cholecystitis, *Eur. J. Med. Res.* 14 (2) (2009) 90–92.
- [21] D.C. Doval, K. Bhatia, K. Pavithran, J.B. Sharma, A.K. Vaid, D. Hazarika, Breast carcinoma with metastasis to the gallbladder: an unusual case report with a short review of literature, *Hepatobiliary Pancreat. Dis. Int.* 5 (2) (2006) 305–307.
- [22] I. Pappo, E. Feigin, B. Uziely, G. Amir, Biliary and pancreatic metastases of breast carcinoma: is surgical palliation indicated, *J. Surg. Oncol.* 46 (3) (1991) 211–214.
- [23] B.L. Beaver, D.A. Denning, J.P. Minton, Metastatic breast carcinoma of the gallbladder, *J. Surg. Oncol.* 31 (4) (1986) 240–242.
- [24] N. Riaz, R. Ahmed, S. Afzal, N. Masood, Breast carcinoma with asymptomatic metastasis to the gallbladder, *Singapore Med. J.* 53 (7) (2012) 136–138.

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