

Metastatic breast carcinoma initially presenting as acute cholecystitis: a case report and review of the literature

A. Manouras, M.D., Ph.D.; E.E. Lagoudianakis, M.D.; M. Genetzakis, M.D.;
N. Pararas, M.D.; A. Papadima, M.D.; P.B. Kekis, M.D., Ph.D.

First Department of Propaedeutic Surgery, Hippocrateion Hospital, Athens Medical School, Athens (Greece)

Summary

Introduction: The gallbladder is an infrequent site of metastatic malignant disease. Although malignant melanoma, renal cell and cervical carcinoma have been documented, breast carcinoma has rarely been reported to metastasize in the gallbladder. **Case Report:** We describe such a case that manifested as acute cholecystitis and was incidentally recognized after cholecystectomy, in an otherwise disease-free 46-year-old female who had undergone mastectomy for breast cancer two years before. The patient was subjected to adjuvant chemotherapy, but unfortunately died just a year after diagnosis because of generalized peritoneal seeding of the tumor. **Discussion:** Metastatic gallbladder involvement is rare, especially in cases of primary breast carcinoma, usually leading to symptoms of abdominal pain, mimicking acute or chronic cholecystitis. Thus, abdominal pain in a patient with a previous history of breast carcinoma should raise suspicion of gallbladder metastasis.

Key words: Metastatic breast cancer; Acute cholecystitis; Ductal breast carcinoma; Gallbladder metastasis.

Introduction

Breast cancer mostly metastasizes to the liver, bones and lungs. Less frequently, metastatic sites of breast carcinoma include the central nervous system, the skin, endocrine organs (ovary, adrenal, pituitary), the pericardium and the peritoneum [1]. Generally, no site is immune to the spread of the tumor, either at the time of presentation or later in the course of the disease.

The occurrence of metastases to the gallbladder is rare and has only been reported in the literature exceptionally. Malignant melanoma is the tumor that is most likely to metastasize to the gallbladder [2]. In a series of 7,910 cholecystectomy specimens, 36 cases of metastatic carcinoma were found, all deriving from biliary or gastrointestinal primaries [3]. Metastatic breast cancer to the gallbladder is even less frequent with only four cases having been reported [1, 4, 5].

We report a case of metastatic breast cancer that was discovered incidentally in the specimen of a laparoscopic cholecystectomy in a patient undergoing surgery for acute cholecystitis.

Case Report

A 46-year-old female was admitted to our department complaining of right upper quadrant colic pain. She had experienced similar episodes twice during the preceding six months. According to her medical history, the patient had undergone a right modified radical mastectomy because of an infiltrating ductal breast carcinoma, measuring 2.5 x 3 cm two years before. Pathology had revealed two axillary nodes to be infiltrated. The work-up (chest X-ray, abdominal CT scan) that had been conducted showed no signs of metastatic breast disease.

On admission, the patient was suffering from tenderness on palpation of the right upper quadrant. Examination revealed no signs of metastatic breast disease. Abdominal ultrasound imaging showed thickening of the wall of the gallbladder, indicating cholecystitis, multiple cholelithiasis of the cyst and no common bile duct dilatation. Based on the imaging control and the clinical and laboratory examination, the diagnosis of acute cholecystitis was established. Laparoscopic cholecystectomy was decided and successfully conducted within the first 48 hours after the onset of the symptoms. The gallbladder was found to be hydropic, while no evidence of other intraabdominal pathology was viewed during laparoscopy. Multiple small gallstones were found in the specimen. The patient had an uneventful postoperative course.

Histological examination confirmed the diagnosis of cholecystitis, showing features of chronic cholecystitis with fibrosis of the gallbladder wall and a chronic inflammatory infiltrate, but also revealed glandular poorly differentiated metastasis of a breast carcinoma invading the muscularis and serosa. Hematoxylin and eosin stain showed moderately differentiated adenocarcinoma (Figures 1 and 2). Characteristically scattered signet-ring cells were viewed in the infiltrated mucosa of the gallbladder. The cells of the tumor were immunohistochemically proven to be positive for lactalbumin (Figure 3) as well as, cytokeratin 7-positive and cytokeratin 20-negative. Estrogen and progesterone receptors were negative. Not even a clue of a primary carcinoma or mucosal dysplasia was found, in spite of sectioning the entire gallbladder. Searching for a primary in the biliary tree, stomach and ovaries yielded no evidence. Histological sections of the mammary specimen, from the previous mastectomy, were obtained anew and re-evaluated. It was proven that both carcinomas examined were of the same histologic nature.

The patient was subjected to additional laboratory tests as well as imaging tests afterwards. Carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), and thyroid transcription factor 1 (TTF1) were negative. Blood tumor markers showed CA125, CA19-9, alpha-fetoprotein (AFP), and CEA to be normal, and only CA 15-3 was increased (1784 IU/ml). Mammography of the other breast was normal. Computed tomography (CT) of the brain, chest, abdomen, and pelvis was performed without any pathological findings. Bone Tc-99 scintigraphy was normal.

Revised manuscript accepted for publication July 9, 2007

The patient was set on a scheme of adjuvant chemotherapy consisting of doxorubicin, cyclophosphamide and 5-FU. Our patient did not receive any hormonal therapy due to her unfavorable hormonal receptor status. A year later she died because of generalized peritoneal seeding of the tumor.

Discussion

Gallbladder cancer is an incidental finding in 1-2% of all open cholecystectomies, while in laparoscopic cholecystectomies it is less than 1%. In case of acute cholecystitis an incidence up to even 8.8% has been reported, also including metastatic gallbladder carcinoma [6]. The gallbladder wall rarely comprises a metastatic site in the course of malignant disease, with a reporting incidence of only 5.8% in a large series of autopsies [7, 8]. Primary tumors can metastasize to the gallbladder either by direct extension, such as hepatocellular and pancreatic carcinoma, or by hematogenous spread. The tumor most likely to metastasize via the latter way is malignant melanoma. Breast carcinoma metastasizes to the gallbladder extremely rarely, with scattered cases being reported worldwide and mostly diagnosed incidentally from the specimen after cholecystectomy [1, 4, 9]. In autopsy series, however, breast carcinoma metastasizing to the gallbladder arises in 4-7% of cases [4, 5, 10]. In contrast, breast carcinoma, except for lymphatic spread, frequently metastasizes to the bones, lungs and gastrointestinal system, especially to the liver and extrahepatic biliary system [1, 4, 6].

Metastatic breast carcinoma first detected in the gallbladder appears to be even more infrequent, with only four cases documented in the literature [1, 4, 5]. Autopsy findings have shown that secondary hematogenous metastases from primary organs to the gallbladder initially generate small flat nodules below the mucosal layer, which then grow as a pedunculated tumor, rarely reaching greater than several millimeters in size. This explains why most gallbladder metastases do not cause any symptoms, and are rarely detected during the person's lifetime [10]. The most frequent symptomatic presentation is acute cholecystitis [11]. Obstructive jaundice, hemobilia, even bile peritonitis due to perforation are rarely described [5, 12-17].

Among the reported cases of gallbladder metastasis manifesting as the first finding of breast cancer recurrence, the first was discovered three years after mastectomy [1] whereas the others were detected after a routine cholecystectomy [9, 18]. The case reported here is unusual due to the long time that had elapsed since mastectomy, as well as being an incidental finding due to coexisting cholecystitis.

The differential diagnosis between primary carcinoma of the gallbladder and metastatic breast carcinoma to the gallbladder is of great significance [14]. Thus, immunohistochemical evaluation is necessary. The most reliable markers are gross cystic disease fluid protein-15 (GCDFP-15), cytokeratin 7, cytokeratin 20, and estrogen and progesterone receptors. Metastatic breast carcinomas are usually positive for GCDFP-15, positive for cytokeratin 7, and negative for cytokeratin 20, and they are often positive for estrogen receptor and/or progesterone recep-

tor [19]. Likewise, the distinction between metastatic breast carcinoma to the gallbladder and diffuse carcinoma of the liver is also essential, because patients suffering from the latter present with a poorer prognosis [14]. Detecting the primary tumor site is based on pathology as well as specific immunohistochemical stains, such as casein and lactalbumin [20]. Moreover, metastases often do not form glands or tubular structures, but do infiltrate as small nests and strands of tumor cells, which are usually of the signet-ring type. In addition, the "signet-ring" morphology of lobular carcinoma may mimic other primary tumors, e.g., gastric carcinoma. Referring to the reported case, the tumor cells were proven to be immunohistochemically positive for lactalbumin. Moreover, primary breast carcinoma and metastasis to the gallbladder were similar in pathology. This evidence is in favor of the diagnosis of metastatic breast carcinoma to the gallbladder [21].

For ten years following initial treatment, distant metastases are the most common cause of death in breast cancer patients. Sixty percent of cases developing distant metastases, being present at the time of diagnosis, will be manifested within 24 months of treatment of the primary cancer [22]. Metastases may become evident as late as ten to 20 years after the initial treatment [23]. Adjuvant therapy does not seem to prolong survival significantly, to date. In case of metastatic breast cancer to the gallbladder and according to the literature, resection of the gallbladder leads to a median survival of 2.5 years, while in coexistence with a metastasis to the liver decreases to 15 months [16, 24]. Survival generally ranges from a few months to three years [14]. In the presented case, the histological features of the metastatic carcinoma combined with those of the primary breast cancer were both suggestive of ductal carcinoma. Prognosis of invasive ductal carcinoma has proven to have worse short- and long-term survival than invasive lobular carcinoma [25].

In general, the treatment of metastatic breast carcinoma is usually aggressive, combining surgery, chemotherapy and hormonotherapy [17]. Multiple-chemotherapy includes two or more cytostatic agents, such as doxorubicin and 5-FU, achieving much better disease-free intervals and overall survival than monotherapy. In our patient, the applied scheme of chemotherapy consisted of three cytostatic agents, while no hormonotherapy was provided as no receptors were detected, neither at the primary nor the metastatic tumor. Prognosis of metastatic breast cancer to solid organs is regarded as dismal. Although resection should be considered as palliative treatment in a patient with gallbladder metastasis from breast carcinoma, it is recommended in a case which exhibits symptoms.

In conclusion, metastatic gallbladder involvement is rare, especially in a case of primary breast carcinoma. It usually manifests with abdominal pain, mimicking acute or chronic cholecystitis. Its prognosis is poor [26]. Thus, right hypochondrial pain in a patient with a history of breast carcinoma should raise the suspicion of metastatic gallbladder disease which should be treated aggressively as it portends a poor prognosis.

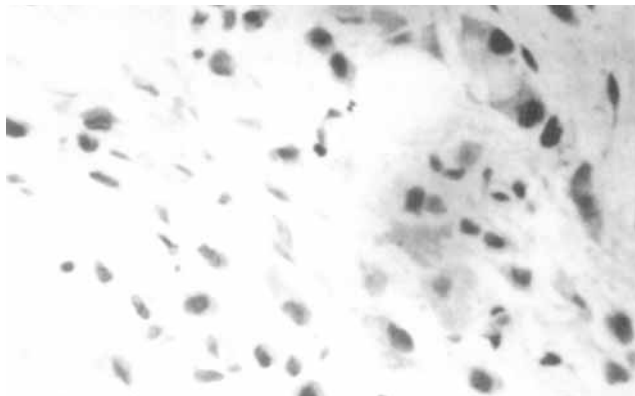


Fig. 1

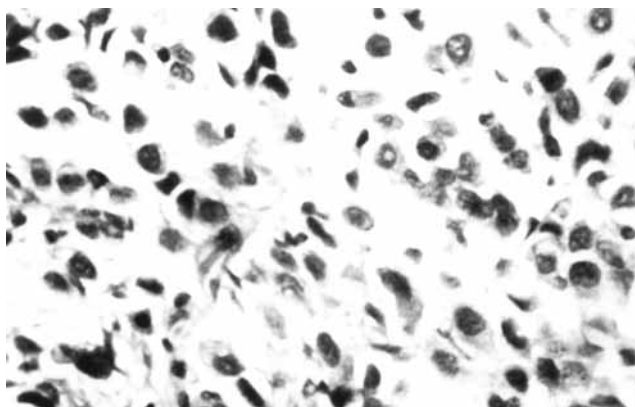


Fig. 3

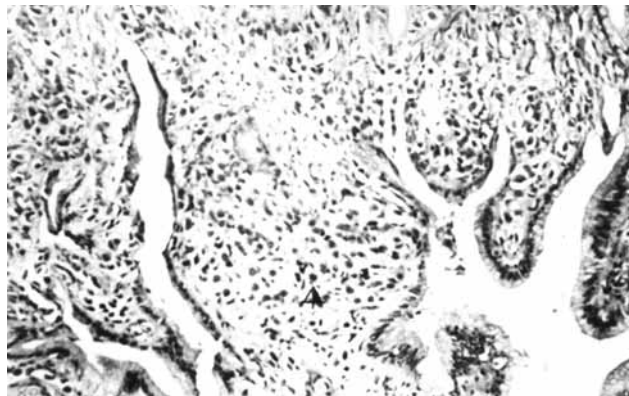


Fig. 2

Figure 1. — Tumor cells infiltrating the mucosa of the gallbladder (H&E x 100).

Figure 2. — Infiltration of the gallbladder mucosa by tumor cells with histological characteristics consistent with those of ductal breast carcinoma (H&E x 400).

Figure 3. — Immunohistochemically positive stain of the tumor cells for lactalbumin (x 400).

References

- [1] Beaver B.L., Denning D.A., Minton J.P.: "Metastatic breast carcinoma of the gallbladder". *J. Surg. Oncol.*, 1986, 31, 240.
- [2] Langley R.G.B., Bailey E.M., Sober A.J.: "Acute cholecystitis from metastatic melanoma to the gallbladder in a patient with a low-risk melanoma". *Br. J. Dermatol.*, 1997, 136, 279.
- [3] Chan K.W.: "Review of 253 cases of significant pathology to 7,910 cholecystectomies in Hong Kong". *Pathology*, 1988, 20, 20.
- [4] Crawford D.L., Yeh I.T., Moore J.T.: "Metastatic breast carcinoma presenting as cholecystitis". *Am. Surg.*, 1996, 62, 745.
- [5] Shah R.J., Koehler A., Long J.D.: "Bile peritonitis secondary to breast cancer metastatic to the gallbladder". *Am. J. Gastroenterol.*, 2000, 95, 1379.
- [6] Lam C.M., Yuen A.W., Wai A.C., Leung R.M., Lee A.Y., Ng K.K., Fan S.T.: "Gallbladder cancer presenting with acute cholecystitis". *Surg. Endosc.*, 2005, 19, 697.
- [7] Abrams H.L., Spiro R., Goldstein N.: "Metastases in carcinoma, analysis of 1000 autopsied cases". *Cancer*, 1950, 3, 74.
- [8] Lee Y.N.: "Breast carcinoma: Pattern of metastasis at autopsy". *J. Surg. Oncol.*, 1987, 5, 969.
- [9] Rubin A., Tate J.J.: "Breast carcinoma metastatic to the gallbladder". *J. Clin. Pathol.*, 1987, 46, 1223.
- [10] Yeu-Tsu M.L.N.: "Breast carcinoma: pattern of metastasis at autopsy". *J. Surg. Oncol.*, 1983, 23, 175.
- [11] Bush E., Geradts J., O'Connor T.: "An unusual cause of cholecystitis?". *Am. J. Clin. Oncol.*, 2005, 28, 529.
- [12] Pappo I., Feigin E., Uziely B., Amir G.: "Biliary and pancreatic metastases of breast carcinoma: Is surgical palliation indicated?". *J. Surg. Oncol.*, 1991, 46, 211.
- [13] Lokich J.J., Kane R.A., Harrison D.A., McDermott W.V.: "Biliary tract obstruction secondary to cancer: Management guidelines and selected literature review". *J. Clin. Oncol.*, 1987, 5, 969.
- [14] Popp J.W., Schapiro R.H., Warshaw A.L.: "Extrahepatic biliary obstruction caused by metastatic breast carcinoma". *Ann. Intern. Med.*, 1979, 91, 568.
- [15] Rabin M.S., Richter I.A.: "Metastatic breast carcinoma presenting as obstructive jaundice. A report of three cases". *S. Afr. Med. J.*, 1979, 55, 388.
- [16] Franco D., Martin B., Smadja C.: "Biliary metastases of breast carcinoma: the case of resection". *Cancer*, 1987, 60, 96.
- [17] Kopelson G., Chu A.M., Doucette J.A., Gunderson L.L.: "Extrahepatic biliary tract metastases from breast cancer". *Int. J. Radiat. Oncol. Biol. Phys.*, 1980, 6, 497.
- [18] Howel A., Harris M.: "Infiltrating lobular carcinoma of the breast". *Br. J. Med.*, 1985, 291, 1371.
- [19] Kaufman O., Deidesheimer T., Muehlenberg M.: "Immunohistochemical differentiation of metastatic breast carcinomas from metastatic adenocarcinomas of other common primary sites". *Histopathology*, 1996, 29, 233.
- [20] Lee A.K., DeLellis R.A., Rosen P.P.: "Alphalactalbumin as an immuno-histochemical marker for metastatic breast carcinomas". *Am. J. Surg. Pathol.*, 1984, 8, 93.
- [21] Boari B., Pansini G., Pedriali M., Cavazzini L., Manfredini R.: "Acute cholecystitis as a presentation of metastatic breast carcinoma of the gallbladder: a case report". *JAGS*, 2005, 53, 2041.
- [22] Jemal A., Murray T., Samuels A.: "Cancer statistics". *Cancer J. Clin.*, 2003, 53, 5.
- [23] Murguia E., Quiroga D., Canteros G., San Martino C., Barreiro M., Herrera J.: "Gallbladder metastases from ductal papillary carcinoma of the breast". *J. Hepatobiliary Pancreat. Surg.*, 2006, 13, 591.
- [24] Engel J.J., Trujillo Y., Spelberg M.: "Metastatic carcinoma of the breast: A cause of obstructive jaundice". *Gastroent.*, 1980, 78, 132.
- [25] Toikkanen S., Pylkkanen L., Joensuu H.: "Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma". *Br. J. Cancer*, 1997, 76, 1234.
- [26] Doval C.D., Bhatia K., Pavithran K., Sharma J.B., Vaid A.K., Hazarika D.: "Breast carcinoma with metastasis to the gallbladder: an unusual case report with a short review of the literature". *Hepatobiliary Pancreat Dis. Int.*, 2006, 5, 305.

Address reprint requests to:
A. MANOURAS, M.D., Ph.D.
Department of Propaedeutic Surgery
Athens University Medical School
Hippocrateion Hospital
Q. Sophia, 114 - 11527 Athens (Greece)
e-mail: amanouras@hippocratio.gr