CASE REPORT

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Gallbladder metastasis secondary to gastric cancer as a first site of recurrence presented with acute cholecystitis: Case report and literature review

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Metastasis to the gallbladder from other malignancies is extremely rare and is related with a very poor prognosis. Malignant melanoma has been reported to be the most common origin of gallbladder metastasis. Although only eight cases of gallbladder metastasis originating from gastric cancer have been documented in the literature based on small series, of these cases, only one case with signet ring cell carcinoma histology has been reported previously. We report the case of a 58-year-old male with early-stage signet ring cell carcinoma of the stomach who presented with acute cholecystitis previously treated with curative gastrectomy. After laparoscopic cholecystectomy, the diagnosis of gallbladder metastasis with signet ring cell histology secondary to gastric cancer was made. To our knowledge, this is only the second case of signet ring cell carcinoma of the stomach metastasized to the gallbladder as a first site of recurrence. We suggest that for patients with gastric cancer who complain of the findings of acute cholecystitis or cholecystolithiasis, gallbladder metastasis from gastric cancer should be considered in the differential diagnosis.

Key words: Gallbladder, gastric cancer, metastasis, signet ring cell carcinoma

Akut kolesistitle prezente olan mide kanserine bağlı ilk nüks bölgesi olarak safra kesesi metastazı: Vaka sunumu ve literatürün gözden geçirilmesi

Malignitelere bağlı safra kesesine metastaz oldukça nadir olup, kötü prognozla ilişkilidir. Malign melanom safra kesesi metastazı'nın ek sık köken aldığı kanser olarak bildirilmiştir. Mide kanserine bağlı safra kesesi metastazı küçük bir seriye dayanarak yalnızca 8 olgu olarak dokümente edilmiş olmasına rağmen, bu vakalardan yalnızca bir tanesi taşlı yüzük hücreli karsinom histolojisi ile bildirilmiştir. Bu yazıda 58 yaşında küratif gastrektomi uygulanmış ve akut kolesistitle prezente olan erken evre taşlı yüzük hücreli mide kanserli vaka sunuldu. Laparoskopik kolesistektomi sonrasında mide kanserine bağlı taşlı yüzük hücreli safra kesesi metastazı tanısı konuldu. Bilgimize göre, bu olgu ilk nüks bölgesi olarak taşlı yüzük hücreli mide kanserine bağlı ikinci safra kesesi metastazı olgusudur. Akut kolesistit ya da kolanjit bulgularıyla başvuran mide kanserli hastalarda safra kesesi metastazı ayırıcı tanıda akılda tutulmalıdır.

Anahtar kelimeler: Safra kesesi, mide kanseri, metastaz, taşlı yüzük hücreli karsinom

INTRODUCTION

Metastasis to the gallbladder is an unusual presentation of a tumor as a first site of recurrence in clinical oncology practice (1). Gallbladder metastasis (GBM) secondary to malignant melanoma and renal cell carcinoma has previously been reported in single case reports and autopsy series (2,3). On the other hand, only eight cases of GBM as a first site of recurrence with origin from gastric cancer have been documented in the literature based on small series of GBMs (4). However, of these cases,

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only one case with signet ring cell carcinoma (SRCC) histology has been reported previously (4). We describe here the second case of SRCC of the stomach metastasized to the gallbladder as the first manifestation of recurrence, and we review the related literature.

CASE REPORT

A 58-year-old male was admitted to our hospital in January 2009 with a four-month history of epigastric discomfort after meals and nausea. His medical history was not significant and he was not taking any medications. His family history was noncontributory. The physical examination was normal except for epigastric and left upper quadrant tenderness. Initial laboratory results were as follows: white blood cell (WBC) 7500/mm^3, platelets 224000/mm^3, hematocrit 36.2%, mean corpuscular volume (MCV) 80.4 fL, iron (Fe) 51 µ/dL, total iron binding capacity 251 µ/dl, ferritin 65.3 ng/ml, CA 19-9 18.9 U/mL (0-37), and CEA 1.46 ng/ml (0-3.4). Other laboratory values were within normal limits. Esophagogastroscopy revealed an ulcerative mass in the gastric antrum on the lesser curvature measuring 4.5x5 cm. Histopathological examination of endoscopic biopsies showed a moderate differentiated intestinal-type gastric SRCC. Chest and abdominopelvic computed tomography (CT) scans were negative for distant metastasis. Thereafter, subtotal gastrectomy with D_2 regional lymph node dissection was performed. Postoperative pathology examination confirmed the presence of a moderate-differentiated signet cell gastric carcinoma measuring 5.5 cm in diameter, infiltrating the submucosa of the stomach, while none of the 34 resected lymph nodes contained metastasis. The patients was staged as IB (pT2N0M0) SRC gastric carcinoma according to the American Joint Committee on Cancer (AJCC) TNM staging system. Management by surveillance was then started.

While the patient remained in remission during a follow-up of 18 months, he was referred to our clinic in July 2010 with abdominal pain, shaking chills, anorexia, nausea, and vomiting, which had started three days before. On the physical examination, his temperature was 38.4°C. He was not jaundiced, and epigastric and right upper quadrant tenderness were noted. The results of laboratory tests were as follows: alanine aminotransferase (ALT) 107 U/L, aspartate aminotransferase (AST) 91 U/L, alkaline phosphatase (ALP) 588 IU/L, lactate dehydrogenase (LDH) 379 IU/L, γ-glutamyl transpeptidase 256 U/L, amylase 30 U/L, total bilirubin 1.31 mg/dl, direct bilirubin 0.97 mg/dl, total protein 6.89 g/dl, albumin 4.03 g/dl, erythrocyte sedimentation rate (ESR) 81 mm/h, C-reactive protein (CRP) 90.3 mg/L, WBC 15500/mm^3, platelets 264000/mm^3, and hematocrit 33.2%. The patient was first treated with intravenous (i.v.) fluids and ceftriaxone 1 g/day i.v. for presumed cholangitis. Thereafter, his fever improved. Blood culture and urine cultures were negative. A diagnostic work-up for possible acute cholangitis or cholecystitis was initiated. Abdominal ultrasonography (US) and magnetic resonance imaging (MRI) revealed asymmetrical wall thickening of the gallbladder without visible stone and fixed filling defects in the gallbladder. Then, fluorodeoxyglucose (FDG) positron emission tomography/CT (PET/CT) revealed intense heterogeneous uptake foci in the gallbladder, which was primarily compatible with inflammation (maximum standardized uptake value [SUVmax]: 2.4) (Figure 1). In light of these findings, laparoscopic cholecystectomy was carried out. Histopathological examination of the gallbladder specimen showed SRCC. Immunohistochemical analysis indicated: cytokeratin (CK) 7 (+), CK 20 focal (+) and polyclonal CEA (+) (Figure 2A-D). After the gallbladder specimen was determined to be comparable histomorphologically with gastric cancer, the diagnosis of GBM originating from stomach cancer was made. He received six courses of combination chemotherapy with docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 on day 1, followed by fluorouracil 750 mg/m^2/ (continuous intravenous infusion) for 5 days (DCF) every three weeks. No side effects were observed associated with DCF chemotherapy. He had no specific symptom and remained in remission during a follow-up of 11 months.

DISCUSSION

Gallbladder metastasis (GBM) is an extremely rare entity in clinical oncology practice and indicates a very poor prognosis (5). Malignant melanoma has been reported previously to be the most common site of GBM (1,6,7). In an autopsy series performed by Dasgupta et al. (8), 15% of patients with malignant melanoma had GBM. Despite being clinically rare, GBM secondary to malignant melanoma accounts for 30-60% of all metastatic lesions involving this site (9). In addition, GBM related with the other malignancies including renal cell

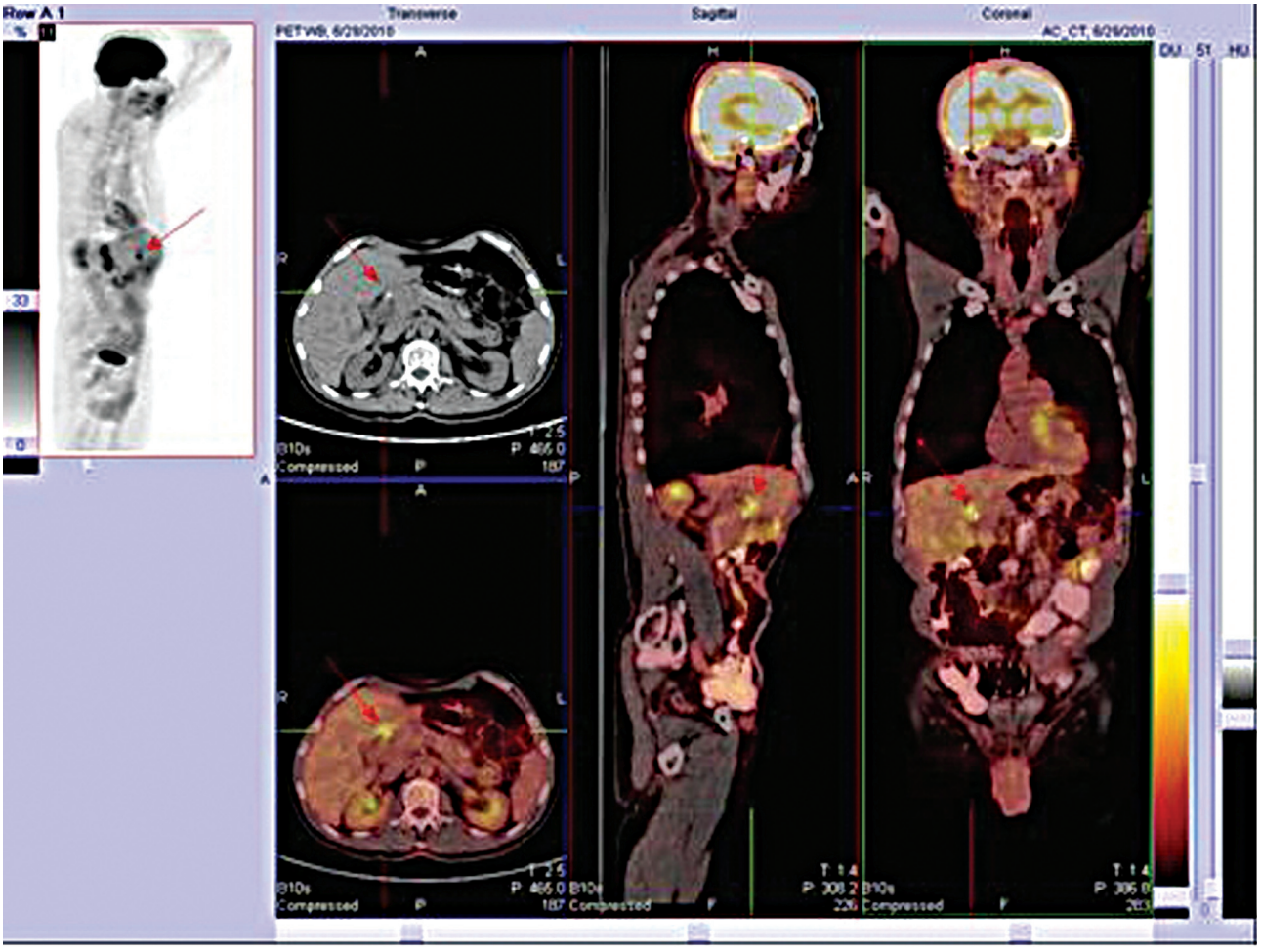

Figure 1. FDG PET/CT shows intense heterogeneous uptake foci in the gallbladder, which was primarily compatible with inflammation (SUVmax: 2.4).

carcinoma (2), breast cancer (10,11) and hepatocellular carcinoma (12) has been documented in the literature in the form of single case reports.

Metastasis to the gallbladder originating from stomach cancer had not been reported until the study of Yoon et al. (4). The authors analyzed 417 cases with gallbladder malignancies. Of these, 20 patients were GBM, accounting for 4.8% of the gallbladder malignancies. They showed that only eight cases of GBM had arisen from gastric cancer. On the other hand, seven patients had adenocarcinoma histology, while there was only one case with SRC gastric carcinoma (4). Interestingly, the stomach was found to be the most common site of GBM in their analysis, in contrast to the literature (1,6,7). Their study included a small sample and only Korean patients, which may have influenced their results.

The patients with isolated GBM from the other malignancies generally present with obstructive jaundice if the tumor is located in the common bile duct or with upper abdominal pain mimicking symptomatic cholecystolithiasis (3,11,12), but asymptomatic cases were also reported (4,12). Our patient presented with right upper abdominal pain and fever without obstructive jaundice; therefore, our patient was compatible with the literature. We investigated the patient for acute cholangitis or cholecystitis, but did not find typical findings of cholecystolithiasis on US or MRI. However, intense heterogeneous uptake foci in the gallbladder, which was primarily compatible with inflammation, were detected in the PET/CT. Because of a possible cholecystitis diagnosis, laparoscopic cholecystectomy was performed after his fever had improved. After gallbladder specimen findings were determined comparable histomorphologically with

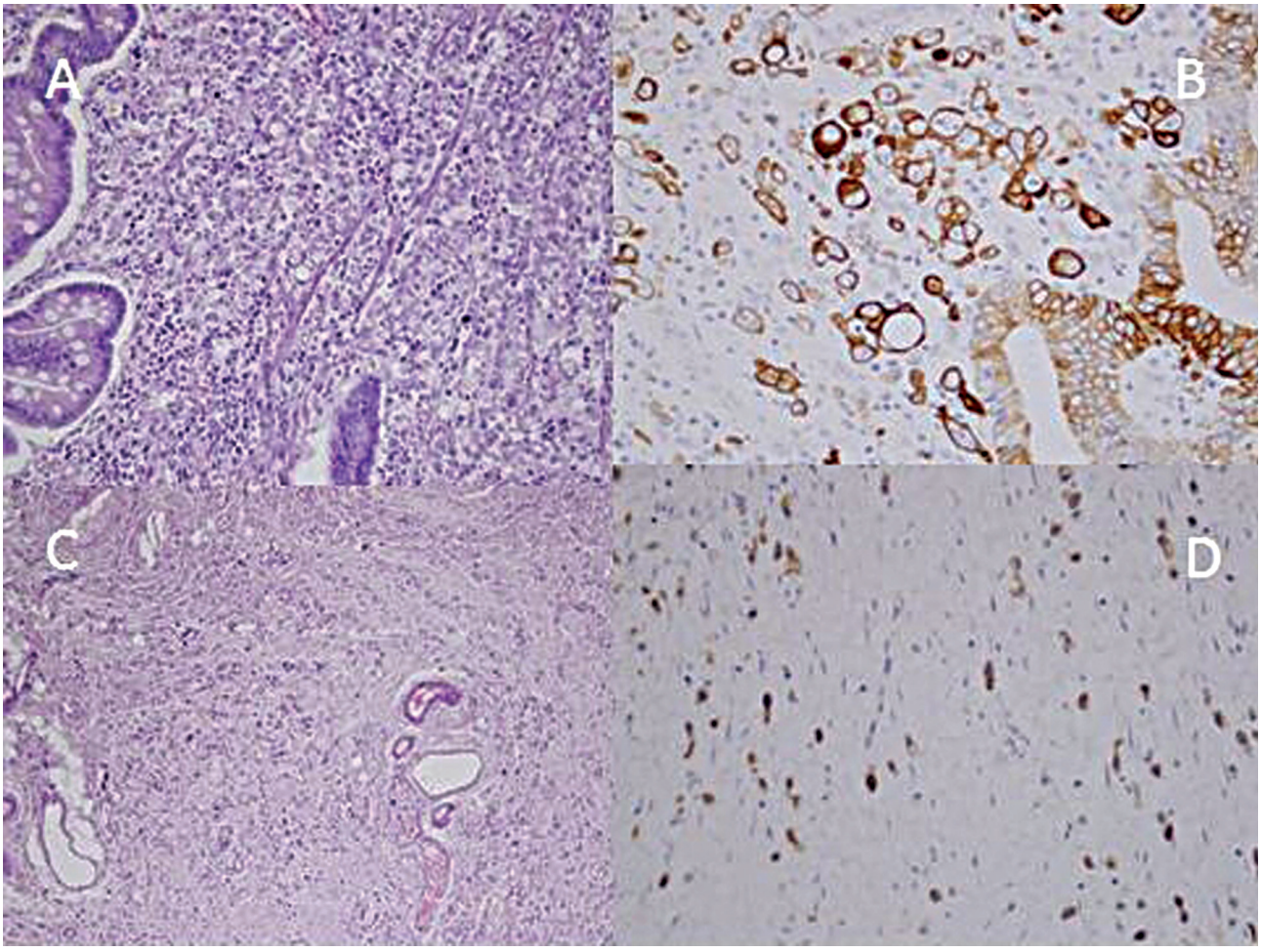

Figure 2A-D: (A) Signet ring cell infiltration at the submucosa of the stomach (hematoxylin & eosin, x200). **(B)** Neoplastic cells immunostained with cytokeratin (CK) 7 (x400) in the stomach. **(C)** Histopathological appearance of gallbladder infiltration by signet ring cells (hematoxylin & eosin, x100). **(D)** Tumor cells show an immunoreactivity to CK 7 in the gallbladder wall (x400).

gastric cancer, the diagnosis of GBM secondary to stomach cancer was made.

The prognosis of GBM arising from malignant melanoma is very poor (5). In the small series of Yoon et al. (4), they reported that the median survival after the diagnosis of GBM was 8.7 months. In addition, R_0 resection and the presentation of GBM with acute cholecystitis were found to be independent prognostic factors for survival in their analysis (4). Our patient was compatible with their results because he presented with acute cholecystitis, and R_0 resection was carried out. There are limited data on the treatment options for GBMs. After surgery plus combination chemotherapy, our patient had no specific symptom and had remained in remission during a follow-up of 11 months.

This report constitutes only the second case in the literature of SRC gastric carcinoma metastasized to the gallbladder. In patients with gastric cancer who present with the findings mimicking acute cholecystitis, GBM of gastric cancer should be considered in the differential diagnosis of upper abdominal pain as acute cholecystitis or cholecystolithiasis. In this situation, our case highlights the importance of excluding cholecystolithiasis in patients with GBMs.

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