Signet-ring Cell Carcinoma of the Gallbladder Complicated by Pulmonary Tumor Thrombotic Microangiopathy

Yoshinori Ohno¹, Teru Kumagi^{1,2}, Taira Kuroda¹, Mitsuhiro Koizumi¹, Nobuaki Azemoto¹, Hirofumi Yamanishi¹, Mayu Oda³, Masashi Hirooka¹, Masanori Abe¹, Yoshio Ikeda¹, Bunzo Matsuura¹, Morikazu Onji¹, Yoshiko Soga⁴, Yousuke Mizuno⁴, Atsuro Sugita⁴ and Yoichi Hiasa¹

Abstract

Biliary drainage was performed in a 71-year-old man with obstructive jaundice of unknown origin; however, he died due to acute pulmonary failure. At autopsy, proliferation of adenocarcinoma cells was observed in the gallbladder mucosa transitioning from isolated signet-ring cell carcinoma (SRCC) to the subserosa and bile ducts without growth toward the gallbladder lumen. Furthermore, fibrocellular intimal proliferation, tumor emboli and organized thrombi were observed in the small pulmonary arteries. The final diagnosis was gallbladder carcinoma complicated by SRCC associated pulmonary tumor thrombotic microangiopathy (PTTM). PTTM may present as rapidly progressive dyspnea, and a high level of clinical suspicion is required to make the differential diagnosis.

Key words: signet-ring cell carcinoma, gallbladder, pulmonary tumor thrombotic microangiopathy

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Introduction

Gallbladder carcinoma (GBC) is known to be an aggressive neoplasm, thus providing early detection and radical surgery is mandatory in order to achieve a better prognosis (1). However, approximately 50% of patients with GBC present with the disease at advanced stage, with locoregional spread and lymph node metastasis (2). Adenocarcinoma is the most appreciated histological type of GBC, while signet-ring cell carcinoma (SRCC) is extremely rare (2). In general, the aggressive behavior of SRCC is evidenced by its infiltration of the surrounding stroma, broad dissemination and a high tendency to produce peritoneal metastases in the gastrointestinal tract (3). In addition, in patients with pulmonary tumor thrombotic microangiopathy (PTTM), histological examinations reveal medial and intimal hypertrophy, intimal fibrosis and fibrinoid necrosis of the internal elastic

lamina of small arteries and arterioles (4, 5). Pulmonary hypertension and cor pulmonale induced by tumor emboli causing PTTM are rare and extremely difficult to diagnose prior to death (6). We herein present a case of SRCC of the gallbladder complicated by PTTM.

Case Report

A 71-year-old Japanese man was admitted to our hospital due to right upper abdominal pain and jaundice in May 2011. He had a history of total gastrectomy for gastric malignant lymphoma in 1986. On admission, he was jaundiced, and a mass was palpable in the right upper abdomen with tenderness. Laboratory tests showed abnormalities in the levels of hepatobiliary enzymes and bilirubin: AST=380 U/L, ALT=252 U/L, ALP=2,591 U/L, GGT=1,087 U/L and total bilirubin=8.6 mg/dL. The levels of tumor markers were also elevated: carcinoembryonic antigen=529 ng/mL and carbo-

¹Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Japan, ²Department of Community Medicine, Ehime University Graduate School of Medicine, Japan, ³Residency Program, Ehime University Hospital, Japan and ⁴Pathology Division, Ehime University Hospital, Japan

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Correspondence to Dr. Teru Kumagi, terukuma@m.ehime-u.ac.jp

Figure 1. (a, b) Abdominal contrast-enhanced computed tomography (CE-CT): (a) early phase; (b) late phase. CE-CT showed slight enhancement of soft tissue surrounding the bile duct and areas adjacent to the celiac artery. (c) Abdominal MRI with T2-weighted imaging revealed a lesion of high signal intensity along the intrahepatic bile duct with a focus in the hepatic portal region. (d) MRCP demonstrated a slightly dilated intrahepatic bile duct and diffuse narrowing of the extrahepatic bile duct.

hydrate antigen 19-9=82 U/mL.

Imaging studies

Abdominal ultrasonography revealed biliary sludge and swelling of the gallbladder, although no wall thickness or polypoid lesions were observed. Abdominal contrast-enhanced computed tomography (CT) showed slight enhancement of soft tissue surrounding the bile duct and areas adjacent to the celiac artery (Fig. 1a, b), with lymphadenopathy in the abdominal cavity. Chest CT did not show any significant findings. Abdominal MRI with T2-weighted imaging showed a lesion of high signal intensity along the intrahepatic bile duct with a focus in the hepatic portal region (Fig. 1c). Magnetic resonance cholangiopancreatography (MRCP) also demonstrated a slightly dilated intrahepatic bile duct and diffuse narrowing of the extrahepatic bile duct (Fig. 1d).

Clinical course

A diagnosis of bile duct carcinoma was suspected based on the above-mentioned findings, although the features observed on the imaging studies were atypical. The dilatation of the intrahepatic bile duct was relatively mild compared to the degree of extrahepatic bile duct stenosis. Therefore, hematological disorders, including malignant lymphoma, were included in the differential diagnosis. Percutaneous transhe-

patic gallbladder drainage was initially performed to reduce the patient's symptoms, which revealed mucus in the gallbladder. Percutaneous transhepatic biliary drainage was also performed, as the intrahepatic bile duct exhibited sufficient dilatation for needle insertion; however, both procedures failed to improve the patient's jaundice, and instead his condition progressed. Bile cytology of specimens obtained using both procedures were negative. Dyspnea and a decrease in the blood oxygen level were observed, and the patient's condition further deteriorated the day before his death. He died on the 16th hospital day due to rapid progression of the disease. An autopsy was performed after obtaining consent from his family.

Autopsy

At autopsy, the macroscopic findings were significant for Glisson's capsule expansion in the hepatic portal tract, and the patient's gallbladder was fully packed with mucus, although the mucosal surface of the gallbladder was smooth. There was congestion in both lungs; however, no thrombi were detected in the hilum of the pulmonary artery. Microscopically, infiltration of SRCC was observed surrounding the intrahepatic and extrahepatic bile ducts, although the tumor itself had not infiltrated the bile duct mucosa (Fig. 2a, b). In addition, infiltration of signet ring cells was noted in the lymphatic vessels. The proliferation of well-

Figure 2. Histopathological findings. (a) Proliferation of SRCC around the bile duct (B), [Hematoxylin and Eosin (H&E) staining, ×40]. (b) SRCC (H&E staining, ×200). (c, d) The gallbladder. (c) Proliferation of well-differentiated adenocarcinoma (H&E staining, ×20), (d) destroying the muscle layer (arrow) and infiltration of SRCC into the subserosa (H&E staining, ×200) (arrowheads).

Figure 3. Histopathological findings of PTM in the pulmonary arteries of the periphery of both lungs (left panels, Hematoxylin and Eosin staining; right panels, Elastica-Masson staining). (a, b) Fibrocellular intimal proliferation: (a) 300 μm in diameter; (b) 500 μm in diameter. (c) Tumor emboli. (d) Organized thrombi.

differentiated adenocarcinoma was observed in the gallbladder mucosa, infiltrating into the subserosa without growth toward the gallbladder lumen (Fig. 2c). Additionally, transi-

tion from well-differentiated adenocarcinoma to SRCC was detected in the areas of infiltration (Fig. 2d). Lymph node metastasis, as well as direct invasion to the pancreas and

duodenum, was also seen. Furthermore, fibrocellular intimal proliferation with the presence of tumor emboli and organized thrombi was observed in the periphery of the small pulmonary arteries with a diameter of 300-500 μm (Fig. 3). The final diagnosis was SRCC of the gallbladder extending to the extra- and intrahepatic bile ducts and directly invading adjacent organs complicated by PTTM.

Discussion

We encountered a case of SRCC of the gallbladder complicated by PTTM that was diagnosed at autopsy. Adenocarcinoma is the most common histological type of gallbladder carcinoma, while SRCC is extremely rare. Nevertheless, conventional adenocarcinoma may occasionally be seen admixed with SRCC (7). SRCC can arise in virtually any organ, although most lesions originate from the stomach, breast or colon (8, 9). SRCC frequently metastasizes to peritoneal surfaces, as well as the regional lymph nodes, ovaries and lungs (9). In Japan, the incidence of SRCC has been reported to be approximately 1% of cases of primary gallbladder carcinoma diagnosed at autopsy (10). Minami et al. summarized 21 cases of SRCC of the gallbladder in Japan (11). Their results showed a slightly higher prevalence among women, with higher rates of cases admixed with other types of organized mucinous carcinoma, well-differentiated adenocarcinoma and/or squamous cell carcinoma. In addition, many cases involving elevated lesions in the gallbladder lumen were observed. Many of the patients were diagnosed with SRCC of the gallbladder after undergoing cholecystectomy. The average survival rate was as short as 19 months.

Making the diagnosis was very difficult in the present case for two reasons. First, poor findings of gallbladder carcinoma were observed in the various imaging studies due to an unusual pattern of expansion; i.e., the tumor not growing into the gallbladder lumen, but rather infiltrating the subserosa. Second, the tumor exhibited poor expansion into the intrahepatic bile duct compared to the degree of common bile duct stenosis, and infiltration of SRCC was observed surrounding the intrahepatic and extrahepatic bile ducts.

In the present case, there was also marked intimal fibroplasia and medial hypertrophy involving small pulmonary arterioles consistent with a diagnosis of PTTM, which is characterized by the presence of multiple microthrombi and intimal myofibroblast proliferation (5). Patients with PTTM often present with rapidly progressive dyspnea and acute pulmonary hypertension (12). PTTM has been reported to be observed in 0.9-3.3% of cadavers with extrathoracic malignancies. Gastric adenocarcinoma is the malignancy most frequently associated with PTTM (5). Only two cases of PTTM arising from metastatic gallbladder carcinoma have been reported, one of which involved SRCC of the gallbladder (6, 13). Uruga et al. reported that, among 2,215 consecutive autopsy cases of carcinoma, 30 patients (1.4%) were diagnosed with definitive PTTM (14). The median sur-

vival time following the initiation of oxygen supplementation was nine days. There are some reports of the antemortem diagnosis of PTTM using pulmonary wedge aspiration cytology, lung biopsies, positron emission tomography or lung perfusion scans (12, 15-18). However, PTTM is generally difficult to diagnose prior to death and is primarily detected based on pathologic findings, as observed in the present case.

In summary, we herein reported a case of SRCC of the gallbladder associated with PTTM. It is important to recognize the origin of the primary tumor in order to optimize treatment. The proliferation of signet-ring cells in patients with gallbladder adenocarcinoma worsens the prognosis. A high level of clinical suspicion is required to make an antemortem diagnosis of PTTM.

The authors state that they have no Conflict of Interest (COI).

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