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【 CASE REPORT 】

Disseminated Carcinomatosis of Bone Marrow as the Initial Presentation of Intrahepatic Cholangiocarcinoma without Jaundice: An Autopsy Case Report

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Abstract:
Disseminated carcinomatosis of the bone marrow (DCBM) is often accompanied by disseminated intravascular coagulation (DIC) and has a poor prognosis. DCBM develops most frequently in gastric cancer and is rarely associated with intrahepatic cholangiocarcinoma. A 41-year-old man was incidentally found to have DIC on his regular visit for ulcerative colitis and was diagnosed with DCBM with intrahepatic cholangiocarcinoma. He received intensive care, including chemotherapy, but died suddenly from hyperkalemia, possibly due to tumor lysis syndrome (TLS). The autopsy showed the periductal infiltrating type of intrahepatic cholangiocarcinoma and tumor necrosis, possibly due to chemotherapy, indicating the effectiveness of chemotherapy for DCBM with intrahepatic cholangiocarcinoma.

Key words: intrahepatic cholangiocarcinoma, disseminated carcinomatosis of the bone marrrow, disseminated intravascular coagulation

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Introduction

Disseminated carcinomatosis of the bone marrow (DCBM) is caused by diffuse infiltration of the bone marrow by malignant tumors and is often associated with disseminated intravascular coagulation (DIC). It is characterized by three main symptoms (anemia, lower back pain, and bleeding tendency) and elevated serum alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels (1). The prognosis of patients with DCBM is generally poor (2). DCBM develops most frequently in gastric cancer among solid tumors (3). However, DCBM from intrahepatic cholangiocarcinoma is extremely rare, and our search of the literature revealed no reports of DCBM arising from cholangiocarcinoma. Cases of the periductal infiltrative type intrahepatic cholangiocarcinoma without jaundice have also not been reported.

We herein report an autopsy case of a 41-year-old man who had DCBM associated with the periductal infiltrative type of intrahepatic cholangiocarcinoma without jaundice.

Case Report

A 41-year-old man patient visited our hospital with a 2-month history of diarrhea and 3-week history of bloody stool. He had a history of autoimmune hepatitis that had developed 15 years ago and had been treated with 25 mg/day prednisolone orally. He had been in complete remission for his autoimmune hepatitis. Based on the clinical findings, including total colonoscopy, we diagnosed the patient with ulcerative colitis, and he was initially treated with 5-aminosalicylic acid orally. Subsequently, he was prescribed oral amoxicillin, tetracycline and metronidazole (ATM therapy). His clinical condition improved by these medications.

However, his laboratory data incidentally showed elevated ALP (1,925 U/L) and γ-glutamyl transpeptidase (γGT) (336 U/L) levels. At a regular hospital visit one month later, he

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had abdominal fullness and low back pain. Laboratory data showed further elevated ALP (3,112 U/L) and γGT (426 U/L) levels but no jaundice (total bilirubin: 1.1 mg/dL). The aspartate aminotransferase (AST) level was elevated at 83 IU/L, LDH was 1,529 U/L, and alanine aminotransferase (ALT) was 30 IU/L, and he showed anemia (hemoglobin 8.7 g/dL) and thrombocytopenia (47,000/μL). The coagulation test showed a PT-INR of 1.09, fibrinogen level of 78.0 mg/dL, fibrin/fibrinogen degradation products (FDP) level of 191.3 μg/dL, and D-dimer level of 57.3 μg/mL. These laboratory findings suggested that he had DIC. In addition, his serum levels of carcinoembryonic antigen (CEA) (319 ng/mL) and carbohydrate antigen 19-9 (CA19-9) (751,600 U/mL) were highly elevated. He was admitted for a further work-up and therapy for DIC.

Abdominal ultrasonography showed dilatation of the left hepatic duct, and bile duct wall thickening was observed near the hepatic hilum, indicating primary sclerosing cholangitis or bile duct carcinoma (Fig. 1). In addition, there was a medium amount of abdominal ascites and right-sided pleural effusion. Abdominal computed tomography (CT) revealed disruption of the left hepatic duct and dilation of the peripheral bile duct from that point. In the stenosis, soft tissue shadow appeared to extend along the bile duct and the Grisson capsule (Fig. 2A-C). There were multiple abdominal lymph node metastases including the hilum and para-aortic region. In addition, multiple micronodules were found along the peritoneum in the pelvic cavity, indicating peritoneal dissemination. Furthermore, he had multiple osteolytic bone metastases, such as to the ilium and vertebrae, that were thought to be the cause of low back pain.

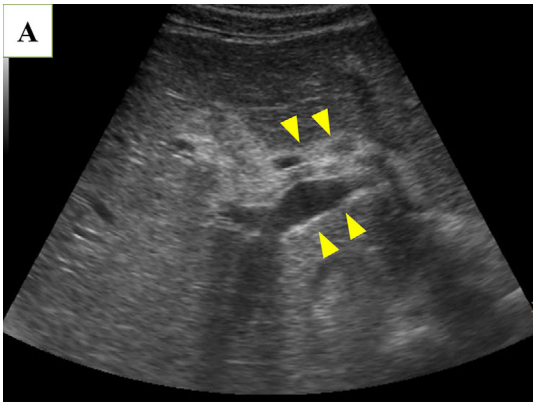

Figure 1. Abdominal ultrasonography. Abdominal ultrasonography showed dilatation of the left hepatic duct, and bile duct wall thickening was observed near the hepatic hilum (arrow heads).

The day after admission, he was transferred to a higher-level medical institution to receive intensive care for DIC. Magnetic resonance imaging (MRI) after the transfer demonstrated the presence of disruption of the left hepatic duct and dilation of the peripheral bile duct, as shown on CT. MRI also showed a soft tissue shadow with a low signal intensity on T1-weighted images extending along the Grisson capsule on the left branch of the portal vein, showing a lower signal intensity than the surrounding normal liver after contrast enhancement (Fig. 3A-D). The cytologic evaluation of the ascites revealed a class V status under the Papanicolaou classification, indicating poorly differentiated adenocarcinoma. A bone marrow biopsy was performed, showing poorly differentiated adenocarcinoma. Esophagogastroduodenoscopy and total colonoscopy did not show any signs of malignancy. Based on these findings, he was considered likely to have intrahepatic cholangiocarcinoma with diffuse bone metastases and peritoneal dissemination. In addition, he was considered to have DIC from DCBM based on bone metastases diffusely invading the bone marrow with DIC, elevated serum ALP and LDH levels, and low back pain.

He was treated with human soluble thrombomodulin for a week after the transfer (day 1 to 7 of transfer). After this administration, the laboratory findings showed improvement in DIC, such as an increase in fibrinogen and a decrease in D-dimer, but the platelet count remained at about 50,000/μL. He started to receive biweekly gemcitabine chemotherapy for bile duct carcinoma with DCBM on day 13 of transfer using platelet transfusion for bone marrow suppression, with progressive disease revealed on CT on day 49 of transfer after 3 doses of gemcitabine. The laboratory findings showed an increasing trend in ALP and γGT levels, but the bilirubin level was in the normal range, and he did not have jaundice. He was re-transferred to our hospital, as his clinical findings had not improved despite treatment for about two months.

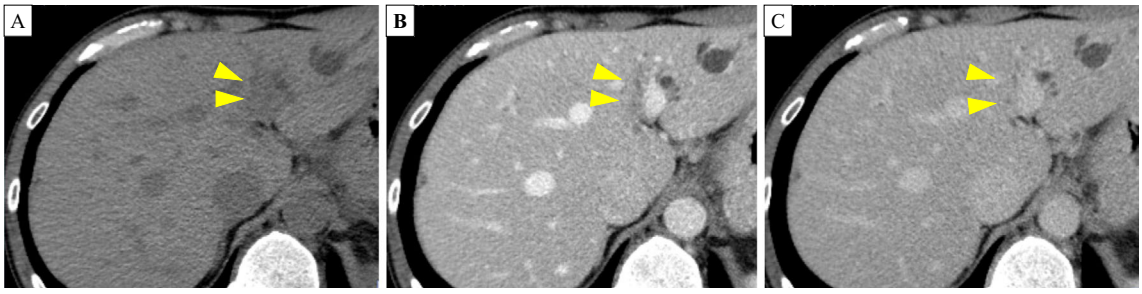

Figure 2. Abdominal computed tomography (CT). A: unenhanced phase, B: arterial phase, C: venous phase. A soft-tissue shadow appeared to extend along the bile duct and the Grisson capsule (arrowheads).

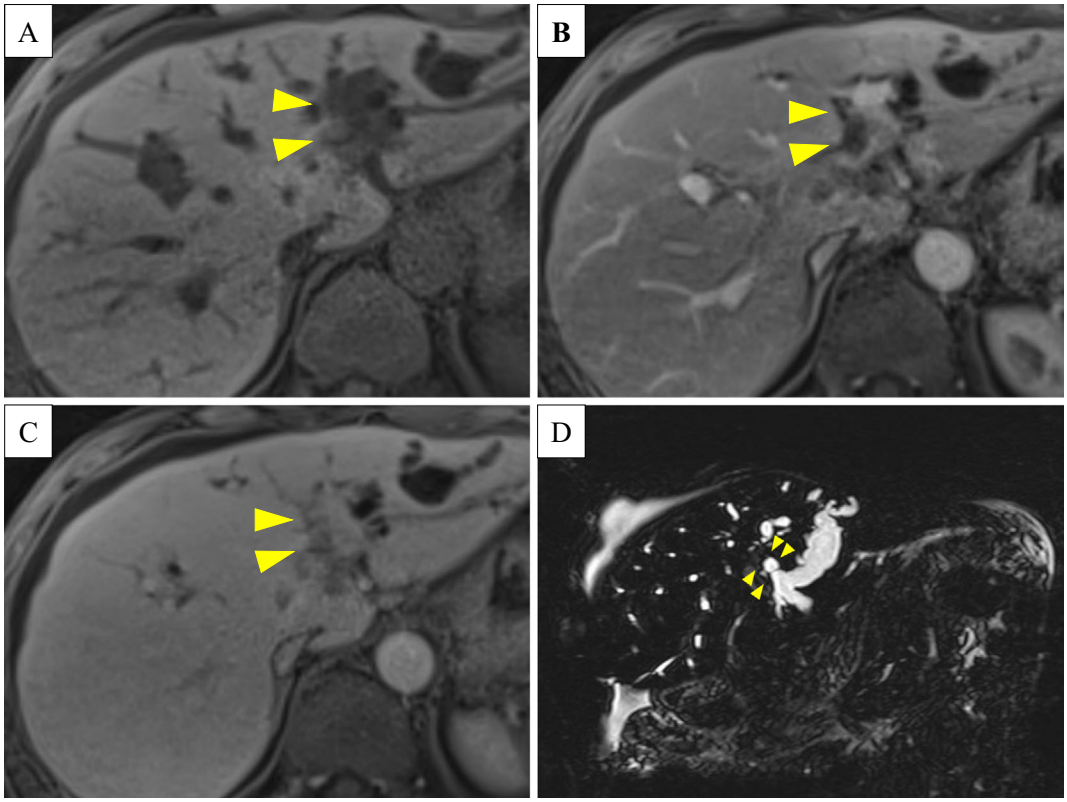

Figure 3. **Magnetic resonance imaging (MRI). A: T1-weighted image, B: arterial phase, C: late-phase, D: magnetic resonance cholangiopancreatgraphy (MRCP). MRI showed the soft-tissue shadow with a low signal intensity on T1-weighted images extending along the Grisson capsule on the left branch of the portal vein. It had a lower signal intensity than the surrounding normal liver after contrast enhancement (arrowheads). MRCP showed the disruption of the left hepatic duct and the dilation of the peripheral bile duct (arrowheads).**

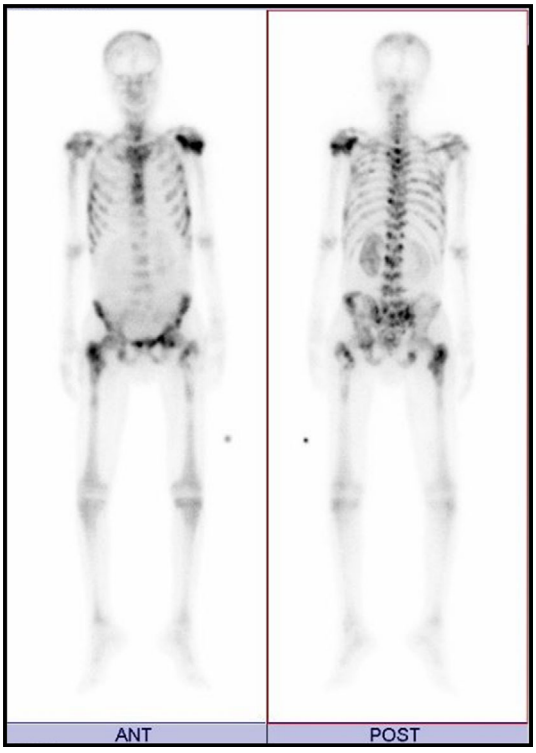

Figure 4. **Bone scintigraphy. Bone scintigraphy revealed a diffuse abnormal uptake of isotope.**

Further chemotherapy carried an increased risk of adverse events, such as myelosuppression, but second-line chemotherapy (S-1) was started on the day of re-transfer, as the patient desired aggressive treatment. After 14 days of chemotherapy with S-1, laboratory findings showed improvement in his DIC, such as an increased platelet count to about 80,000/μL, although his ALP and γGT levels remained high. However, no jaundice appeared at this time. Bone scintigraphy on day 14 of re-transfer revealed a diffuse abnormal uptake of isotope, indicating multiple bone metastases (Fig. 4). The microsatellite instability analysis performed using ascitic fluid cell block showed a low level of microsatellite instability (MSI-Low).

He had no fever, and his vital signs were stable, but his dietary intake gradually decreased during the chemotherapy-free period from day 15 of re-transfer. Laboratory findings showed a trend toward elevated serum potassium and creatinine levels (Fig. 5). Serum uric acid, phosphorus and calcium levels were not regularly measured. He suddenly developed cardiopulmonary arrest in the restroom on the morning of day 19 of re-transfer and died despite cardiopulmonary resuscitation (CPR) being performed.

The laboratory findings during CPR showed hyperuricemia (serum uric acid 12.1 mg/dL), hyperkalemia (serum potassium 11.2 mmol/L) and progression of renal dysfunction

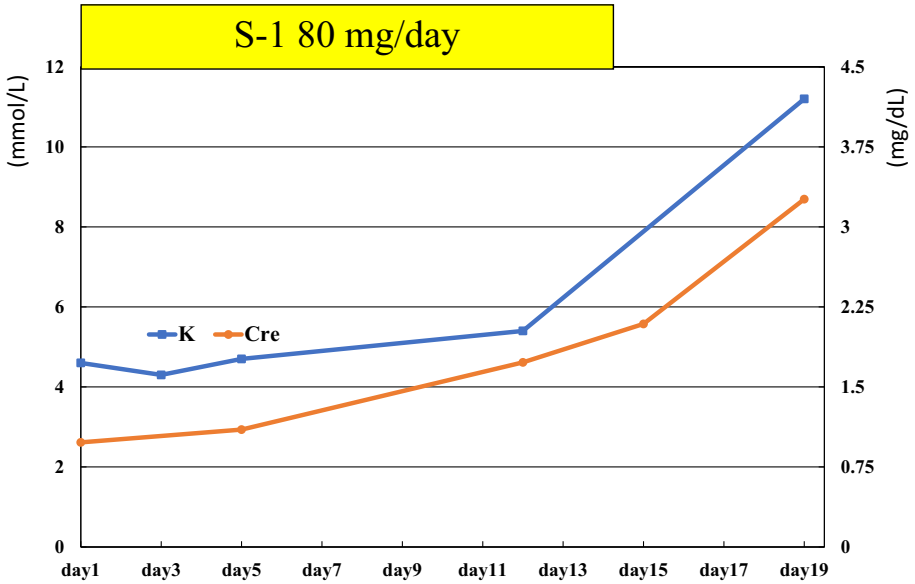

Figure 5. **Day 1 is the re-transfer date, and day 19 is the death date. The changes in potassium and creatinine levels during the hospital course from re-transfer to the patient's death are shown.**

(serum creatinine 3.26 mg/dL). The cause of the episode was considered to be hyperkalemia possibly due to spontaneous or chemotherapy-induced tumor lysis syndrome (TLS).

An autopsy was subsequently performed. The portal vein area of the hepatic hilum, mainly the left hepatic duct, was dilated and yellowish-white in color. The peripheral intrahepatic bile duct had dilated in a beaded shape, although it did not show clear mass formation (Fig. 6A). Microscopically, atypical cells grew along the surface of the left intrahepatic bile duct but did not occupy the bile duct and had progressed by replacing the hepatocytes at the periphery (Fig. 6B). In addition, there was infiltration of adenocarcinoma spreading the Grisson capsule from the bile duct (Fig. 6C). These findings suggested a diagnosis of intrahepatic cholangiocarcinoma, whose macroscopic classification was considered to correspond to the periductal infiltrating type. Histopathological findings revealed moderately differentiated tubular adenocarcinoma. Multiple bone and bone marrow metastases were observed mainly in the spine and ilium (Fig. 6D). Adenocarcinoma had developed peritoneal dissemination, and metastatic lesions were also observed in the bilateral pulmonary lobes, kidneys, and adrenal glands. About 50% of tumors that had invaded the liver showed necrosis, probably indicating the effect of chemotherapy. Fibrin thrombi indicating DIC were also found in the glomeruli on both sides and in the sinusoids of the liver as well as lungs.

Discussion

DCBM, defined by Hayashi et al. in 1979, is a clinical condition with a poor prognosis often accompanied by DIC due to diffuse bone metastases from solid tumors.

DCBM is derived most often from gastric cancer but sometimes from colorectal cancer, lung cancer, breast cancer and prostate cancer (4). Therefore, when searching for the primary focus in a case of DCBM, esophagogastroduodenoscopy and total colonoscopy should be performed, as in our case.

However, the present case was one of DCBM associated with intrahepatic cholangiocarcinoma with no primary focus in the gastrointestinal tract, and our search of the literature showed no reports of DCBM arising from cholangiocarcinoma.

Bone is a common site of metastasis from several tumors, including those from the breast, prostate, lung, and kidneys. Bone metastases from cholangiocarcinoma are not uncommon, being found in 22 (8.3%) of the 264 cases with extrahepatic metastases in a previous report (5). There is a dissociation between the frequency of bone metastases and DCBM in cholangiocarcinoma. The reason for the rarity of DCBM in cholangiocarcinoma has not yet been elucidated. DCBM from intrahepatic cholangiocarcinoma may be more likely to occur in the periductal infiltrating type, as in our case, than in others because the primary and metastatic lesions of DCBM are characterized by poor nodularity (1). If so, the rarity of DCBM may be related to the infrequency of the periductal infiltrating type, reported to account for 4.4% of intrahepatic cholangiocarcinoma cases (5).

DCBM is a clinical condition with a poor prognosis, and the condition at the first visit of our case was also very severe. In addition, Dowsiriroj et al. reported that cases of cholangiocarcinoma with metastasis to the spine even without DCMM have a poor prognosis (6). Furthermore, it has been reported that younger patients have a poored prognosis for gastric cancer with DCBM than older patients (1, 7). The present patient died at 41 years old, less than 4 months after the initial visit. This may be because he had multiple conditions with a poor prognosis, referring to past reports.

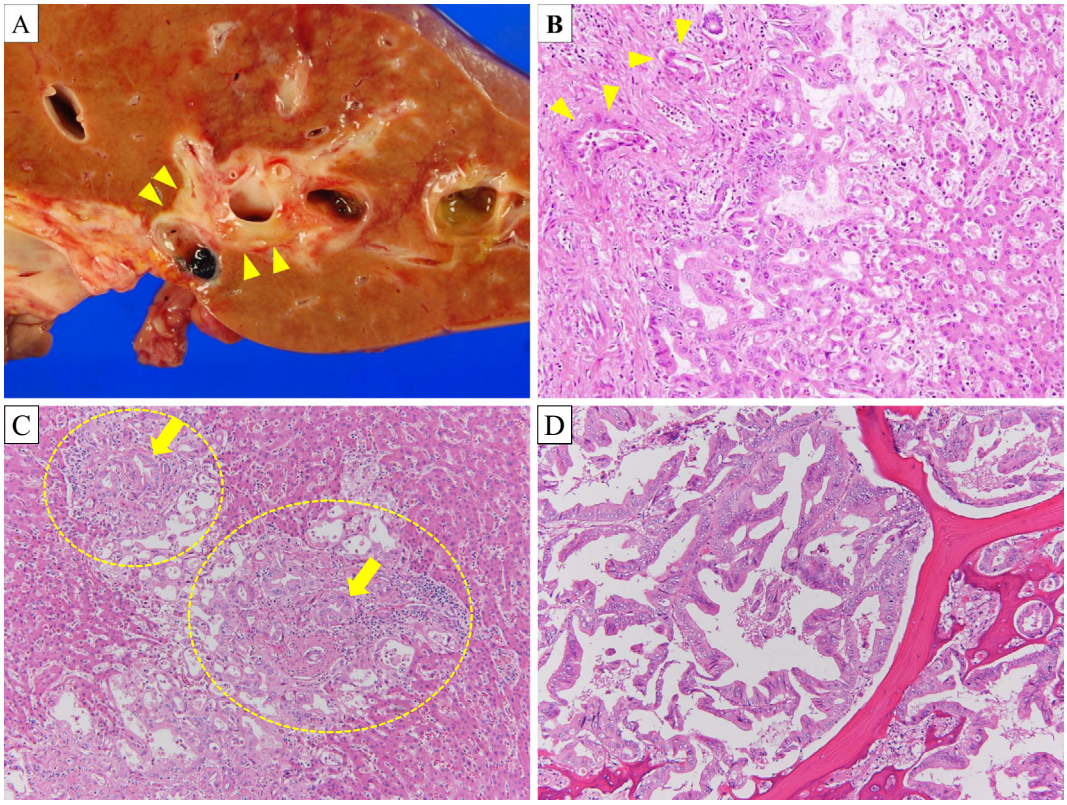

Figure 6. **A: The autopsy findings. The portal vein area of the hepatic hilum, mainly the left hepatic duct, was dilated and yellowish-white in color (arrowheads). B: Specimen of the liver from the autopsy. Hematoxylin and Eosin (H&E) staining of the liver specimen showed the progressive replacement of hepatocytes at the periphery with atypical cells (arrowheads). C: Region including the Grisson capsule. The specimen showed the infiltration of adenocarcinoma spreading to the Grisson capsule from the bile duct. Arrows indicate the bile ducts, and dotted circles surround the Grison region. D: Bone marrow specimen from the autopsy. H&E staining of the bone marrow specimen showed adenocarcinoma cells.**

Patients with DCBM are often associated with DIC, and the clinical condition is generally severe. Many previous reports have described patients already showing disseminated carcinomatosis of the bone marrow at their first visit (8, 9). Thus, chemotherapy for patients with DCBM is challenging because of the presence of cytopenia or a poor performance status. However, Kim et al. reported that chemotherapy resulted in a better prognosis than no treatment in patients with DCBM with gastric cancer (10). In addition, there have been some reports of DCBM successfully treated with chemotherapy (3, 11). In the present case as well, chemotherapy may have been effective, considering the platelet elevation after the start of treatment with S-1 and the tumor necrosis observed at the autopsy. However, as can be seen from the sudden death of our patient due to hyperkalemia, it is necessary to fully explain that the administration of chemotherapy can cause fatal complications.

The cause of the episode in this patient was considered to be hyperkalemia, possibly due to spontaneous or chemotherapy-induced TLS. While rare, several cases of TLS with cholangiocarcinoma have been reported, although the precise frequency is unknown (12, 13). Previous reports have suggested that risk factors for TLS with solid tumors include elevated levels of serum uric acid, potassium, creatinine and phosphorus (12-14). Our case was categorized as having an intermediate risk of TLS based on the renal dysfunction, but the uric acid and phosphorus levels were not regularly measured (15). TLS is rare in patients with solid tumors, so proper management for TLS was not performed in our case. However, it is essential to keep in mind that solid tumors can also lead to TLS.

Conclusions

In conclusion, we described the first case of DCBM from intrahepatic cholangiocarcinoma, which is extremely rare. It may be more common in periductal infiltration type than in other types and is not always accompanied by jaundice. In addition, chemotherapy may be effective for DCBM associated with intrahepatic cholangiocarcinoma.

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

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