Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0448-17
Intern Med 57: 2197-2201, 2018
http://internmed.jp

【 CASE REPORT 】

Budd-Chiari Syndrome and Esophageal Achalasia: Unrecognized Intrahepatic Cholangiocarcinoma Invading Multiple Organs

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Abstract:
Intrahepatic cholangiocarcinoma (ICC) is the second-most common primary liver cancer, although its occurrence is relatively rare. Budd-Chiari syndrome (BCS) is characterized by outflow obstruction from the liver, with hepatocellular carcinoma being the most common cause of malignant BCS. In this case report, we describe the occurrence of an unrecognized ICC that induced BCS and esophageal achalasia.

Key words: Esophageal invasion, ICC, pseudoachalasia

(Intern Med 57: 2197-2201, 2018)
(DOI: 10.2169/internalmedicine.0448-17)

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a tumor of high malignant potential that is often asymptomatic in the early stages (1). As such, ICC is typically associated with a poor prognosis. An increasing incidence of ICC has been reported worldwide (1, 2). Thus, a clinical algorithm for the diagnosis and management of ICC needs to be developed in order to improve the outcomes of patients with ICC (3-6).

Budd-Chiari syndrome (BCS) is defined as the obstruction of the venous outflow of the liver due to various causes, including hepatomegaly, ascites, development of collateral veins, and lower limb edema (7). The prevalence of BCS is 1.4 per million in Western countries and 2.4 per million in Japan (8, 9). In practice, BCS is usually caused by multiple concurrent factors, including coagulopathy, hepatic neoplasm, or vascular malformation (6, 7). The natural course of BCS is improved by an accurate diagnosis and suitable treatment strategy (10), although BCS is induced by a malignant tumor in 1.3-4.5% of cases (8, 11).

In contrast, esophageal achalasia is characterized by a grossly contorted and dilated esophagus due to the absence of lower esophageal sphincter relaxation (12). Primary esophageal achalasia results from a decrease in the number of neurons in the myenteric plexuses, while secondary esophageal achalasia results from extra-esophageal diseases, such as gastric cancer, ICC, breast cancer, or other diseases (13-16).

In this case report, we describe the occurrence of an unrecognized ICC that induced BCS and esophageal achalasia.

Case Report

A 68-year-old woman presented to our department for the assessment of lower limb edema and was admitted for a further examination and diagnosis. The salient features on a physical examination included a linear scar in the right hypochondrium from a previous cholecystectomy, performed 42 years earlier, and pitting edema of the lower limbs. Laboratory testing revealed elevated D-dimer levels, suggesting a diagnosis of deep venous thrombosis in the lower limbs. However, there was no evidence of hematological disease, and computed tomography (CT) revealed intact veins of the lower limbs but constriction of the inferior vena cava (IVC) and deformity of the liver (Fig. 1A). In the absence of any evidence of a tumor on the images, a diagnosis of probable BCS due to thrombosis of the IVC was made. In-

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Received: November 1, 2017; Accepted: January 9, 2018; Advance Publication by J-STAGE: March 9, 2018
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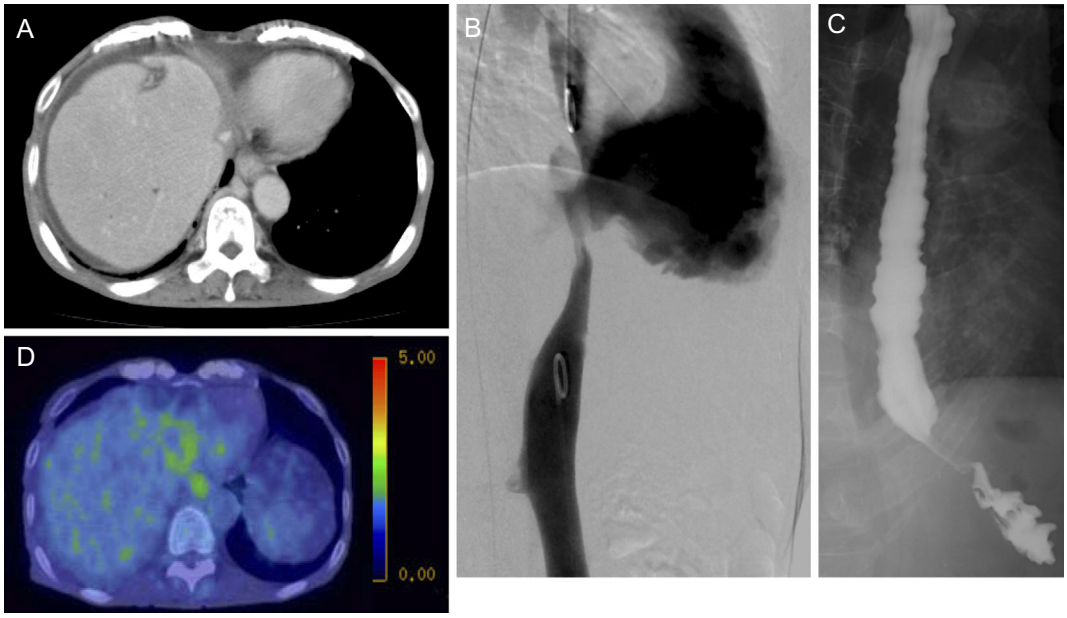

Figure 1. **Radiographic studies of the present case. A: Abdominal computed tomography with contrast enhancement revealed an unenhanced lesion near the hepatic vein on horizontal section images. B: Inferior venography showing narrowing of the hepatic segment of the inferior vena cava. C: An esophagogram showing a narrowed segment at the esophagogastric junction. D: Positron emission tomography combined with computed tomography showing an abnormal accumulation around the inferior vena cava and esophagus.**

ferior vena cavography was performed for a further diagnosis of the BCS, revealing tapered narrowing of the IVC (Fig. 1B). After dilatation of the IVC by interventional radiology at day 42 post-admission, anticoagulation therapy using warfarin was initiated. The patient was discharged on day 60 of hospitalization with an improving edema status of her lower limbs, although a collateral vein developed on her abdomen during this time.

Although the patient did not complain of further BCS-associated symptoms, the levels of tumor markers, including CEA, CA19-9, and SPan-1, gradually increased. Further examinations of the gastrointestinal tract, lung, and pancreas were performed to rule out malignancy, with no evidence of neoplasms on CT, magnetic resonance imaging, esophagogastroduodenoscopy (EGD), or colonoscopy. On day 234 after the initial assessment, the patient reported symptoms of food impaction and vomiting and was re-admitted for treatment of dehydration. A re-examination of the upper gastrointestinal tract using EGD revealed obstruction at the esophagogastric junction (EGJ) due to extra-esophageal compression. An esophagogram was performed for the further evaluation of the esophageal obstruction, revealing a narrowed segment at the EGJ (Fig. 1C). Due to the progressive worsening of dysphagia due to the extra-esophageal compression and evidence of spreading of the intraperitoneal structure around esophagus on CT, the presence of a neoplasm was suspected. A review of the CT images obtained at the time of the BCS diagnosis helped identify the intraperitoneal structure. Positron emission tomography combined with CT (PET-CT) was performed, revealing an abnormal accumulation around the IVC and esophagus (Fig. 1D). A CT-guided biopsy was performed, and the specimen obtained from the abnormal accumulation identified on PET-CT revealed desmoplastic changes and a ductular structure on Hematoxylin and Eosin (HE) staining (Fig. 2A). A well-differentiated adenocarcinoma with positivity for cytokeratin (CK) 7 and CK 19 and negativity for CK 20 was identified on immunohistochemistry (Fig. 2B-D). We confirmed a diagnosis of ICC in the atrophic liver, with the BCS and dysphagia having been induced by the ICC.

For treatment, the narrowed segment of the EGJ was dilated using an expandable metallic stent with EGD. Although the patient was able to eat, the serum transaminase levels progressively increased. Due to the patient's health status, aggressive treatment for ICC was contraindicated, and the patient died on day 309 after the initial diagnosis of BCS. An autopsy was performed, revealing that the ICC had spread from the liver parenchyma, with desmoplastic changes that extended to the pericardium, myocardia, esophageal adventitia, IVC, diaphragm, and right lung (Fig. 2E and F). There was no evidence of liver lobectomy, and hepaticolithiasis was identified (Fig. 2F).

Discussion

BCS is a rare disease, and patients present with several symptoms associated with venous obstruction and portal hypertension (7). Although BCS caused by tumor invasion of the IVC has previously been reported, that induced by ICC

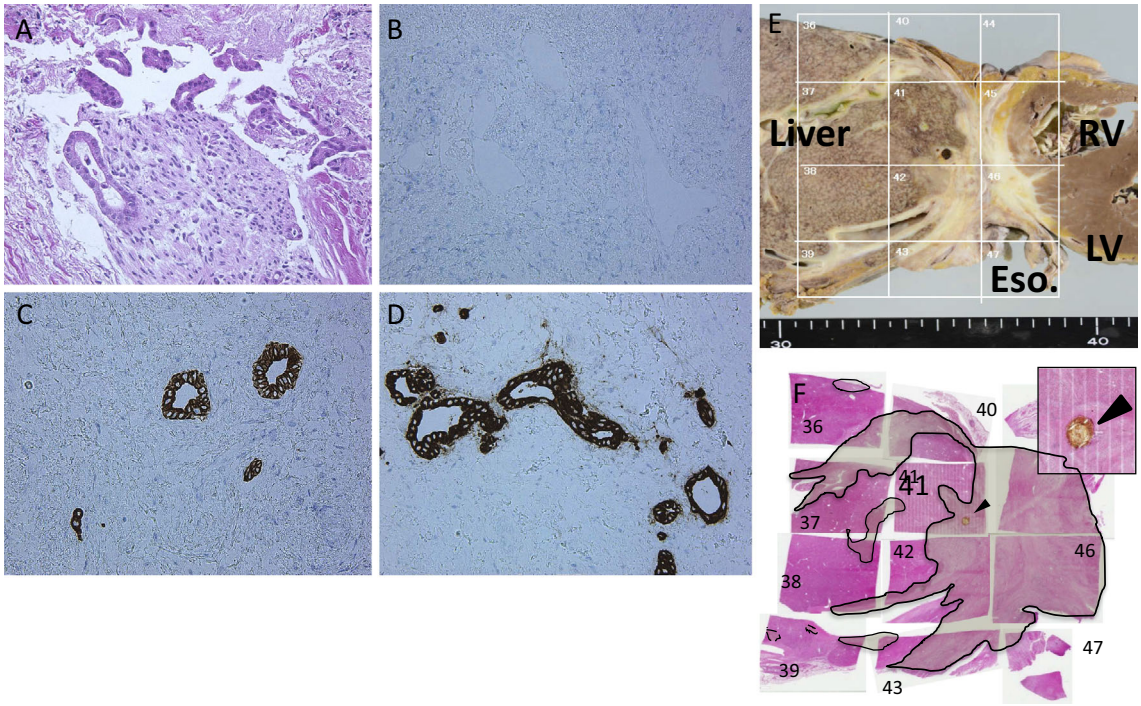

Figure 2. **Immunohistochemistry of the biopsy specimen, and macroscopic and microscopic findings from the autopsy. A, B, C and D: Microscopic findings of the biopsy specimen obtained from the left stromal area of the liver revealed desmoplastic changes and a ductular structure using Hematoxylin and Eosin staining, with negative staining for CK20 (A) but positive staining for CK19 (B) and CK7 (C) (original magnification×200). E: Macroscopic findings of the autopsy showing stromal change around the liver, esophagus (Eso.), right ventricle (RV), and left ventricle (LV). F: Microscopic findings of the autopsy showing tumor cells diffusely infiltrating the stromal tissue. Hepatolithiasis was found in specimen #41 (black arrow).**

Table. **Reported Cases of Budd-Chiari Syndrome (BCS) Due to Intrahepatic Cholangiocarcinoma (ICC).**

Reference	Age/Sex	Location	Involvement in BCS
18	ND	ND	ND
19	67/M	S6/7	Tumor thrombosis in the IVC
20	44/M	Left lobe	Tumor thrombosis in the IVC
21	70/M	ND	Tumor thrombosis in the IVC
Present case	68/F	Atrophic lobe	Direct invasion to the IVC

BCS: Budd-Chiari syndrome, F: female, ICC: intrahepatic cholangiocarcinoma, IVC: inferior vena cava, M: male, ND: not described, S: segment

is rarely reported. Previous reports of BCS due to ICC are summarized in the Table (17-21). After reviewing these previous reports and the present case, ours is the only BCS case in which ICC developed from the atrophic lobe. Furthermore, ICC has never been reported as the cause of esophageal achalasia. Moreover, to our knowledge, direct ICC invasion of the diaphragm, right lower lung lobe, myocardium, and esophageal adventitia, inducing BCS, has also not been previously reported.

ICC in the present case was diagnosed using immunohistochemistry. Ductal formation of carcinoma cells was found in the liver, with negative staining for CK20 but positive staining for CK19 and CK7 (22). Furthermore, diffuse desmoplastic changes around the cancer cells were found. Taken together, these findings supported the diagnosis of ICC (22). Previous review articles have identified several risk factors for cholangiocarcinoma (1, 3, 6), with definite risk factors for ICC including primary sclerosing cholangitis, liver fluke infection, hepatolithiasis, biliary malformation, and thorotrast. Although the patient in our case report had previously undergone abdominal surgery for cholecystectomy 40 years prior to the current health events, the details from that surgery were unknown. The autopsy findings revealed the presence of bile stones in the intrahepatic bile duct, and the middle hepatic arteries were identified in the peripheral region of the liver adjacent to the ICC. These

findings suggest that hepatolithiasis may have induced liver atrophy, with the ICC developing in the atrophic liver.

Secondary esophageal achalasia is generally believed to result from incomplete relaxation of the lower esophageal sphincter due to extra-esophageal disease, such as gastric cancer invasion or metastasis from other tumors (13-16). Achalasia in the present case was induced by direct invasion of the esophageal adventitia by the ICC, which was confirmed by an autopsy. A previous study reported that, in contrast to primary achalasia, secondary achalasia presents as a long, narrow segment of the EGJ, a short duration of dysphagia, and a small esophageal diameter (23). In the present case, we did identify a long, narrow segment of the EGJ. Although secondary esophageal achalasia due to ICC invasion has never been reported, it was the only logical cause of achalasia in this case. Another study compared the clinical symptoms and patient characteristics between primary and secondary achalasia (24). In that study, patients with secondary achalasia due to malignancy tended to be older at the time of the diagnosis, have a shorter duration of symptoms, and have a greater loss of body weight than those with primary achalasia (24). Because these symptoms and their characteristics may overlap to some degree among primary and secondary achalasia (25), endoscopic or imaging examinations need to be performed for a definitive diagnosis.

The main diagnostic difficulty in this case was the lack of recognition of the ICC on the initial CT examination; although deformity of the liver was visible, the tumor was not. During the diagnostic process, PET-CT provided critical information, revealing a 'hotspot' in the left liver, which prompted us to perform a CT-guided liver biopsy and make an accurate ICC diagnosis. Therefore, PET-CT should be considered a useful tool for assessing potential neoplasms that are not identifiable on plain CT. Our case certainly indicates the necessity of ruling out neoplasms as a cause of BCS in patients without hematological disease. Although 84% of patients with BCS have at least 1 risk factor associated with coagulopathy, the present case had no hematological disease. Furthermore, it has been reported that 10% of BCS cases and 70% of secondary esophageal achalasia cases are caused by malignancy. Based on this etiology, PET-CT seems a useful modality for the detection of malignant tumors if achalasia due to malignant tumor cannot be ruled out.

Our findings of an ICC developing in an atrophic liver and invading the surrounding organs, inducing BCS and secondary esophageal achalasia, and the increasing prevalence of ICC worldwide support the need to establish new tools for the accurate diagnosis of ICC and develop targeted treatments (5, 26).

Written informed consent was obtained from the patient's deputy for publication of this case report and any accompanying images.

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

References

1. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol **8**: 512-522, 2011.
2. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. Hepatology **54**: 173-184, 2011.
3. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol **60**: 1268-1289, 2014.
4. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology **145**: 1215-1229, 2013.
5. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2017 (Epub ahead of print).
6. Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol **13**: 261-280, 2016.
7. MacNicholas R, Olliff S, Elias E, Tripathi D. An update on the diagnosis and management of Budd-Chiari syndrome. Expert Rev Gastroenterol Hepatol **6**: 731-744, 2012.
8. Okuda H, Yamagata H, Obata H, et al. Epidemiological and clinical features of Budd-Chiari syndrome in Japan. J Hepatol **22**: 1-9, 1995.
9. Rajani R, Melin T, Bjornsson E, et al. Budd-Chiari syndrome in Sweden: epidemiology, clinical characteristics and survival - an 18-year experience. Liver Int **29**: 253-259, 2009.
10. Seijo S, Plessier A, Hoekstra J, et al. Good long-term outcome of Budd-Chiari syndrome with a step-wise management. Hepatology **57**: 1962-1968, 2013.
11. Mahmoud AE, Mendoza A, Meshikhes AN, et al. Clinical spectrum, investigations and treatment of Budd-Chiari syndrome. QJM **89**: 37-43, 1996.
12. Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. Lancet **383**: 83-93, 2014.
13. Campo SM, Lorenzetti R, de Matthaeis M, et al. Palliation with oesophageal metal stent of pseudoachalasia from gastric carcinoma at the cardia: a case report. Diagn Ther Endosc **2009**: 791627, 2009.
14. Pastor DM, Eggers AD, Drabick JJ, Loughran TP, Bayerl MG, Shope TR. Retroperitoneal diffuse large B-cell lymphoma presenting as pseudoachalasia. J Clin Oncol **28**: e184-e187, 2010.
15. Paulsen JM, Aragon GC, Ali MA, Brody FJ, Borum ML. Pseudoachalasia secondary to metastatic breast carcinoma. Dig Dis Sciences **55**: 1179-1181, 2010.
16. Sousa RG, Figueiredo PC, Pinto-Marques P, et al. An unusual cause of pseudoachalasia: the Alport syndrome-diffuse leiomyomatosis association. Eur J Gastroenterol Hepatol **25**: 1352-1357, 2013.
17. Bandyopadhyay SK, Sarkar N, Ghosh S, Dasgupta S. Cholangiocarcinoma presenting with recurrent venous thrombosis. J Assoc Physicians India **51**: 824-825, 2003.
18. De BK, De KK, Sen S, et al. Etiology based prevalence of Budd-Chiari syndrome in eastern India. J Assoc Physicians India **48**: 800-803, 2000.
19. Katoh M, Shigematsu H. Primary liver carcinoma complicating membranous obstruction of the inferior vena cava. Pathol Int **49**: 253-257, 1999.
20. Kwon OS, Jun DW, Kim SH, et al. Distant skeletal muscle metastasis from intrahepatic cholangiocarcinoma presenting as Budd-Chiari syndrome. World J Gastroenterol **13**: 3141-3143, 2007.
21. Law JK, Davis J, Buckley A, Salh B. Intrahepatic cholangiocarci-

noma presenting as the Budd-Chiari syndrome: a case report and literature review. Can J Gastroenterol **19**: 723-728, 2005.

22. Shimonishi T, Miyazaki K, Nakanuma Y. Cytokeratin profile relates to histological subtypes and intrahepatic location of intrahepatic cholangiocarcinoma and primary sites of metastatic adenocarcinoma of liver. Histopathology **37**: 55-63, 2000.

23. Woodfield CA, Levine MS, Rubesin SE, Langlotz CP, Laufer I. Diagnosis of primary versus secondary achalasia: reassessment of clinical and radiographic criteria. AJR Am J Roentgenol **175**: 727-731, 2000.

24. Ponds FA, van Raath MI, Mohamed SMM, Smout A, Bredenoord AJ. Diagnostic features of malignancy-associated pseudoachalasia. Aliment Pharmacol Ther **45**: 1449-1458, 2017.

25. Tracey JP, Traube M. Difficulties in the diagnosis of pseudoachalasia. Am J Gastroenterol **89**: 2014-2018, 1994.

26. Mertens JC, Rizvi S, Gores GJ. Targeting cholangiocarcinoma. Biochim Biophys Acta 2017.