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Case report

Spindle Cell-Type Undifferentiated Carcinoma of the Common Bile Duct of the Hepatic Hilus

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Running title: Spindle cell carcinoma of the common bile duct

Abstract

Spindle cell-type undifferentiated carcinoma arising from the extrahepatic bile duct is extremely rare. We report herein a case of this type of carcinoma in the common bile duct of the hepatic hilus. A 59-year-old man was admitted to our hospital complaining of jaundice. Laboratory data revealed elevation of serum CA 19-9. Cholangiography revealed complete obliteration of the left hepatic bile duct and stenosis of the bile duct from the superior to the right hepatic bile duct. Computed tomography showed the tumor, measuring 15×12 mm, in the hepatic hilus, obliteration of the right to main trunk of the portal vein and a lymph node in the hepato-duodenum ligament swelling. Arteriography revealed a kink of the right hepatic artery, so encasement of the right hepatic artery was suspected. We preoperatively diagnosed hilus bile duct carcinoma and scheduled right trisection hepatectomy. Intraoperative frozen sections taken from the tumor and tissues around hepatic arteries showed spindle cells and inflammatory cells, so inflammatory pseudotumor was diagnosed intraoperatively. Because the right hepatic bile duct was occluded, right lobe hepatectomy was performed. However, permanent section revealed both spindle cells and poorly differentiated tubular adenocarcinoma cells positive for CAM5.2, AE1/AE3 and vimentin. Based on these findings, the tumor was finally diagnosed as spindle cell-type undifferentiated carcinoma. The patient died of pulmonary infarction 11 days after the operation.

Introduction

Most of malignant neoplasm arising in the extrahepatic bile duct is tubular adenocarcinoma. Conversely, undifferentiated carcinoma is a rare malignant neoplasm in the biliary tract.^{1,2} Especially, spindle cell type of undifferentiated carcinoma arising from the extrahepatic bile duct is not known widely, because there are only a few case reports in English literatures.³⁻⁸ Moreover, spindle cells of undifferentiated carcinoma are sometime difficult to be distinguished from fibroblast cells on only routine hematoxylin-eosin stained specimens. Therefore, there is possibility that spindle cell type of undifferentiated carcinoma is misdiagnosed as inflammatory change, even after biopsy examinations. We report herein a case of this type of carcinoma in the common bile duct of the hepatic hilus that was misdiagnosed as an inflammatory pseudotumor by findings of the intraoperative frozen section.

Case report

A 59-year-old Japanese man was admitted to a local hospital complaining of abdominal fullness and jaundice. He had a history of gastric ulcer (no malignancy) at 48-years-old and fracture of the pelvis at 49-years-old, but had no past history of liver or biliary disease. Several days later, he was referred and admitted to our hospital after serum bilirubin levels increased. Laboratory data on admission were as follow: red blood cells $409 \times 10^4 / \mu\ell$, white blood cells $6,300 / \mu\ell$, platelets $36.6 \times 10^4 / \mu\ell$, serum total protein 6.6 g/dl, serum total bilirubin 20.1 mg/dl (normal, 0.2-1.2), serum direct bilirubin 13.4 mg/dl (normal, <0.3), serum aspartate aminotransferase (AST) 28 IU/l (normal, 5-40), alanine aminotransferase (ALT) 62 IU/l (normal, 4-45), lactate dehydrogenase (LDH) 295 IU/l (normal, 119-229), serum gamma-glutamyl transpeptidase (γ -GTP) 546 IU/l (normal, 5-30), serum alkaline phosphatase (ALP) 1017 IU/l (normal, 103-335), serum amylase 64 IU/l (normal, 40-160), serum carcinoembryonic antigen (CEA) 2.5 ng/ml (normal, 1-6.5), serum carbohydrate antigen (CA) 19-9 54.2 U/ml (normal, <37). After hospitalization, a percutaneous transhepatic biliary drainage (PTBD) tube was immediately inserted into both sides of the intrahepatic bile ducts. Cholangiography using both PTBD tubes revealed complete obliteration of the left hepatic bile duct and stenosis of the bile duct from the superior to the right hepatic bile duct (**Fig. 1**). Computed tomography (CT) showed the low density tumor with unclear edge, measuring 15×12 mm in the hepatic hilus, a lymph node in the

Hepato-duodenum ligament swelling, and a thickened wall of the hepatic hilus bile duct (**Fig. 2a**). Arteriography revealed a kink of the right hepatic artery, so encasement of the right hepatic artery was suspected. Portal veinographic CT revealed obliteration of the right portal vein to the main portal trunk (**Fig. 2b**). Although biopsy under cholangioscopy was not examined for preventing from deterioration or recurrence of cholangitis, carcinoma arising from the bile duct of the hepatic hilus was preoperatively diagnosed from the above findings. However, surgery was postponed due to continuous cholangitis and predicted lack of residual hepatic volume after hepatectomy. As a result of obliteration of the right portal vein, however, volume of the left hepatic lobe increased so that tolerance rate for reduced hepatic volume as estimated by CT and KICG test increased about 4 months after admission, and cholangitis had recovered by this stage. Therefore, right trisection hepatectomy were scheduled and excision laparotomy was performed.

Intraoperative findings showed a nodule in the common bile duct of the hepatic hilus. This nodule adhered to both hepatic arteries too strongly to be ablated completely. The reconstruction of the left hepatic artery by using microsurgical technique was impossible, because of small diameter and anatomically deep site of the left hepatic artery. If the tumor was malignant, the operation should have been called off at this point, because curative resection was impossible. However, intraoperative frozen sections of tissues taken from around the hepatic arteries and main tumor showed spindle cells like fibroblast cell and inflammatory cells (**Fig. 3a**), and no findings suspicious of adenocarcinoma. Given these findings, the intraoperative diagnosis was inflammatory pseudotumor. However, extrahepatic bile duct resection alone could not be performed, because the right bile duct of the hepatic hilus was completely obliterated and its lumen was lost sight of. Finally, the right hepatectomy was performed.

The resected specimen showed a nodule, 4×2cm in diameter, at the bile duct of the hepatic hilus. Tumor embolism was present in the right portal vein. Histopathological examination revealed a nodule comprising spindle cells and poorly differentiated tubular adenocarcinoma (**Fig. 3b**). No giant cells were apparent. Immunohistochemical study revealed that tumor cells were positive for AE1/AE3 (**Fig. 3c**), CAM5.2 and vimentin, but negative for CD23, CD34, LCA and factor-VIII-associated antigen. According to the above findings, the tumor was diagnosed as spindle cell-type undifferentiated carcinoma.

The patient died suddenly 11 days after operation. Autopsy revealed that the cause of death was pulmonary infarction.

Discussion

The most common histological type of carcinoma occurring in the extrahepatic bile duct is adenocarcinoma. According to Albores-Saavedra and Henson, in the Armed Forces Institute of Pathology (AFIP) series on tumor pathology of the gallbladder and extrahepatic bile duct, the proportion of adenocarcinomas is about 88.6%¹. Conversely, undifferentiated carcinoma comprises only 0.38%. The World Health Organization (WHO) histological classification of tumors of the gallbladder and extrahepatic bile duct defines 4 histological variants of undifferentiated carcinoma: spindle and giant cell-type; undifferentiated carcinoma with osteoclast-like giant cells; small cell-type; and nodular- or lobular-type². Spindle cell-type undifferentiated carcinoma arising in the extrahepatic bile duct is extremely rare. To the best of our knowledge, only 6 cases of this type of carcinoma arising from the extrahepatic bile duct have been reported in the English literature (**Table 1**)³⁻⁸.

Spindle and giant cell-type carcinoma resembles sarcoma and consists of variable proportions of spindle, giant and polygonal cells², and is sometimes accompanied by glandular components^{4,5,8}. In addition, 2 cases showing squamoid features have been reported^{5,8}. In our case, poorly differentiated tubular adenocarcinoma components mixed with spindle cells were clearly apparent on permanent sections, but not on intraoperative frozen sections. Giant cells were not identified, even on permanent sections. Albores-Saavedra et al. recently reported 4 cases of tumors comprising only giant cell components of the extrahepatic bile duct, and suggested that giant cell tumors of the extrahepatic biliary tree represent benign true histiocytic neoplasms that should be distinguished from spindle and giant cell carcinomas⁹.

Immunohistochemical study may help to distinguish this type of tumor from sarcoma. Cytokeratins^{3,4,5,7,8} including CAM5.2 and AE1/AE3⁶ are usually positive for this type of carcinoma. In our case, both components of spindle cells and poorly differentiated tubular adenocarcinoma were positive for cytokeratin, CAM5.2 and AE1/AE3. No reports of immunohistochemical studies have revealed positive results for desmin and S-100 protein. Vimentin staining is usually positive, particularly in spindle cell components^{4,5,7,8}. In our case, both adenocarcinoma and spindle cells were positive for

vimentin.

Prognosis for this type carcinoma is not clear, as too few cases have been accumulated. However, the prognosis of patients with spindle cell-type undifferentiated carcinoma of the pancreas, gallbladder and intrahepatic bile ducts has been reported to be poor.¹⁰⁻¹³ Moreover, local recurrence only 7 months postoperatively has been reported, so this type of carcinoma of the bile duct suggests poor prognosis.⁵

In the present case, preoperative imaging showed findings indicative of hilus bile duct carcinoma, namely serum level of CA19-9 elevating, a lymph node swelling, obstruction of the portal vein, and encasement of the right hepatic artery.¹⁴ However, on intraoperative frozen section, spindle cells comprising the tumor were thought to represent fibroblastic proliferation and the tumor was suspected to be inflammatory pseudotumor, so right hepatectomy was performed. Recently, even intraoperative frozen sections are learned to be performed immunohistochemical examination, for example evaluation of metastasis of sentinel lymph nodes of breast carcinoma.^{15,16} To diagnose accurately, the possibility of spindle cell carcinoma must be considered whenever we preoperatively suspect bile duct carcinoma by some findings and face spindle cell proliferating lesions and pre- or intra-operative tissue should be performed immunohistochemical examination used by cytokeratins.

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Figure legends

Figure 1: PTBD tube-enhanced image. The left hepatic duct is completely obstructed and stenosis of the bile duct is present from the right hepatic duct to the superior common bile duct.

Figure 2a: Enhanced CT. Tumor is present at the hepatic hilus.

Figure 2b: CT of the portal vein phase reveals obstruction of the right branch to main trunk portal vein.

Figure 3a: Frozen section taken from the main tumor reveals spindle cells in suspected fibroblastic proliferation and inflammatory cells (HE; original magnification $\times 400$).

Figure 3b: Permanent section taken from the main tumor reveals spindle cells and poorly differentiated adenocarcinoma cells (HE; original magnification $\times 400$).

Figure 3c: Both spindle cells and poorly differentiated adenocarcinoma are positive for cytokeratins (AE1/AE3 stain; original magnification $\times 400$).

Table1: Literatures about undifferentiated carcinoma, spindle and giant cell type of the extrahepatic bile duct in English.

author	year	location	size	surgical procedure	prognosis
Nonomura A	1994	within choledochal cyst	4.0×2.4cm	PD with cyst resection	no recurrence at 15 months
Yuan CY	1995	hepatic hilus	3.5×2.0×1.5cm	extended left hepatic lobectomy	dead of liver dysfunction 10 days later
Mokuno Y	2000	common hepatic bile duct	9.2×3.3×1.2cm	PPPD	local recurrence 7months and dead 10 months
Nagai E	2002	distal common bile duct	1.0×1.0cm	PD	no recurrence at 15 months
Dowaki S	2003	lower extrahepatic bile duc	1.2×0.6cm	PD	no recurrence at 5 years and 10 months
Ghi-suk Yoon	2004	low common bile duct	4×3×3cm	PD	no description
present case	2006	hepatic hilius	4×2cm	right trisection hepatectomy	dead of pulmonary infarction 11days later

surgical procedure: PD; pancretioduodenectomy. PPPD; pylous presrving pancreaticoduodenectomy

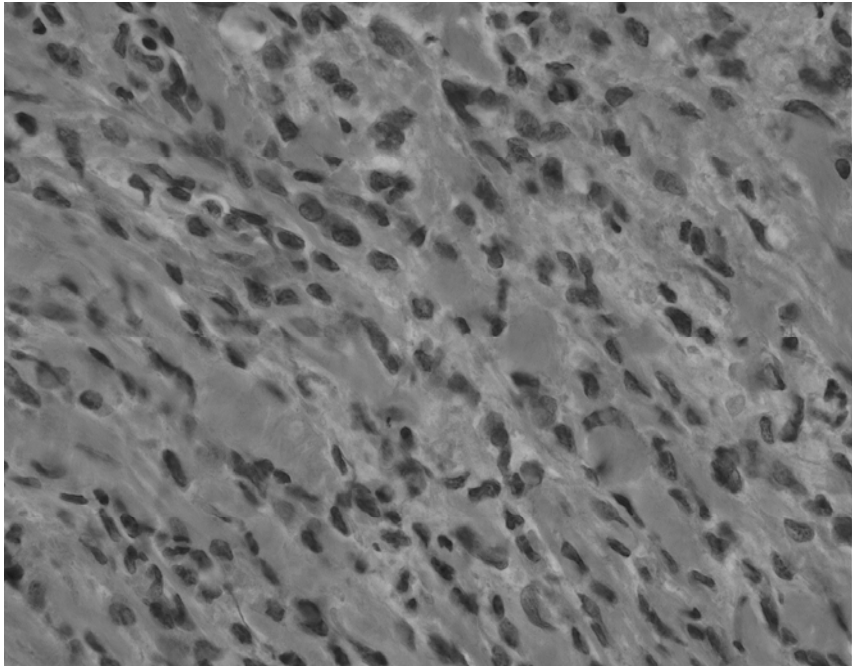


Fig3a

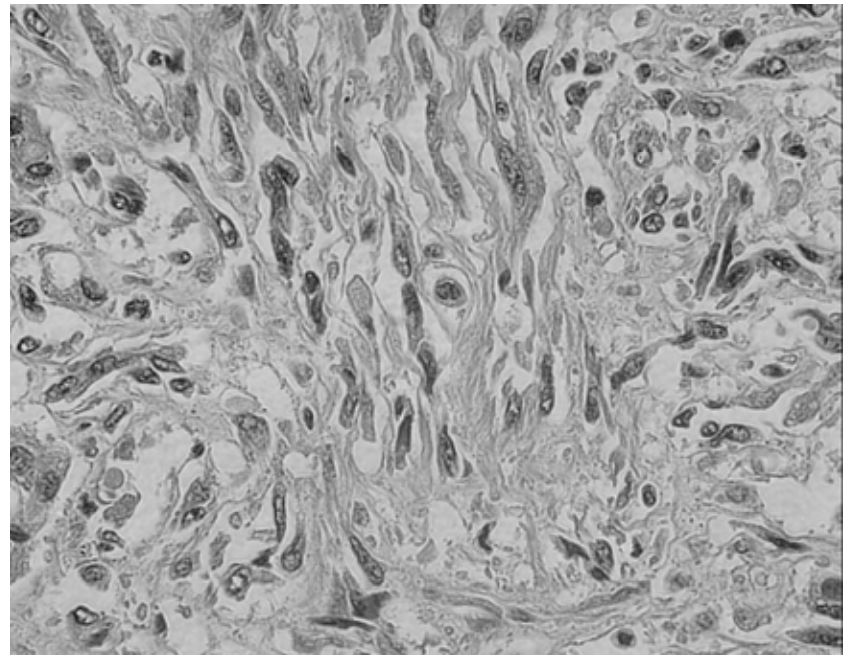
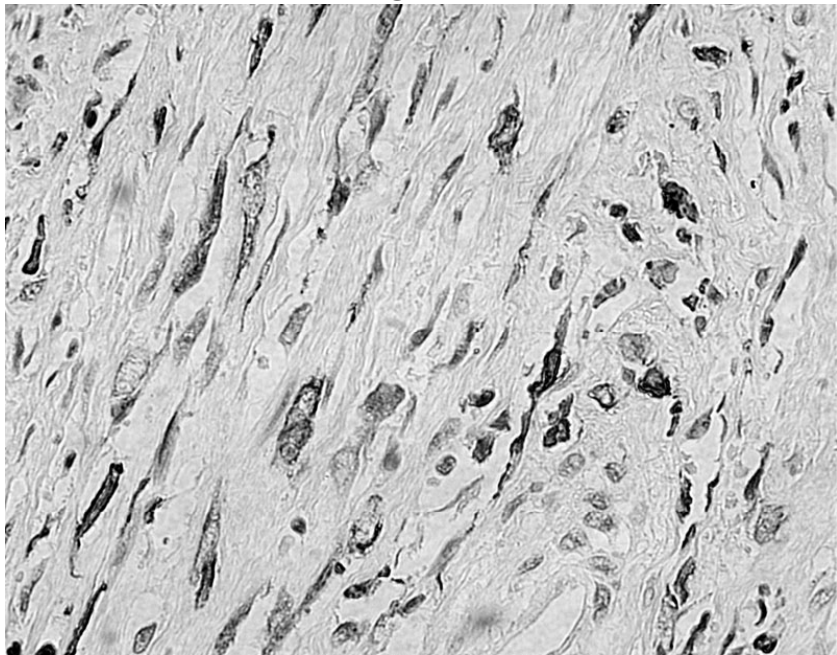


Fig3b



←Fig3c



Fig1(left)

Fig2s(below)



Fig2a

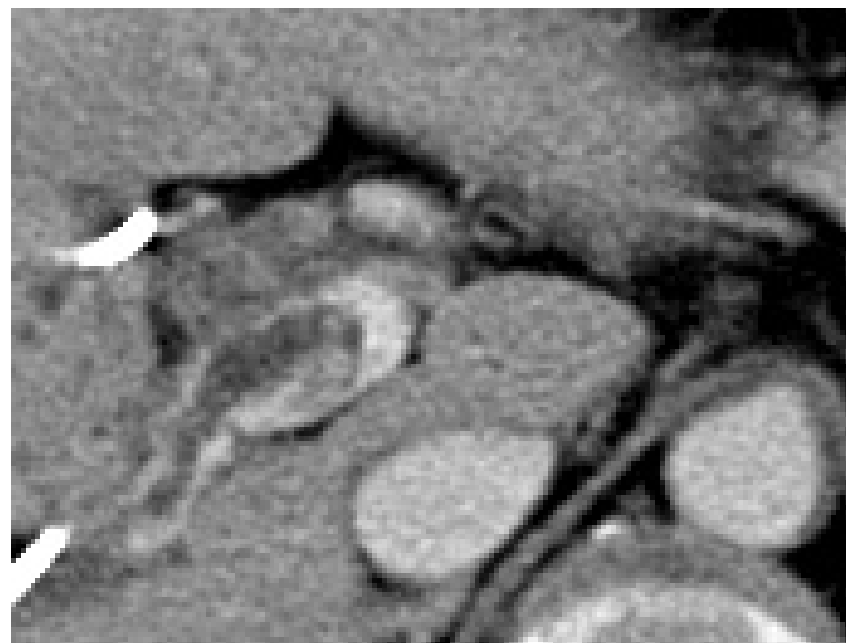


Fig2b