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Case Report

Repeat Hepatectomy for Intrahepatic Recurrence of Cholangiolocellular Carcinoma

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Abstract

A 68-year-old man underwent a partial resection of the liver and lymph node dissection for a tumor, 3.0 cm in diameter, in S4 of the liver under the diagnosis of cholangiocellular carcinoma (CCC). The histological diagnosis was cholangiolocellular carcinoma (CoCC) and lymphatic permeation and venous invasion were recognized. Seven months after surgery, CT demonstrated two recurrent nodules in S7 and S8 of the liver, then a partial resection of the liver was performed. The gross and pathological findings were the same as the previously resected tumor. Four months after the second operation, CT demonstrated dilated intrahepatic bile ducts and lymph node swelling of the hepatic hilum. The patient died of disease thirteen months after the first operation. On the basis of the clinical and pathological features of this case, we consider that CoCC clinically resembles CCC and prognosis may be unfavorable, although it has characteristic pathological findings. It is still controversial whether CoCC should be accepted as a separate entity. The significance of repeat hepatectomy for recurrence and adjuvant chemotherapy should be clarified to improve the prognosis of CoCC.

Key words : Cholangiolocellular carcinoma・Recurrence・Hepatectomy・Chemotherapy

Introduction

CoCC of the liver is a rare type of primary liver cancer that was first proposed by Steiner and Higginson in 1959[1]. They suggested that CoCC tended to occur later in life, and that it was relatively more common in women, based on materials studied in Africa[1)2)]. Shiota et al.[3] reported that the frequency of CoCC was 0.56% of the 708 consecutively resected cases of primary liver cancer. However, to our knowledge, only a few reports of this disease have been published[1)~6)], and the clinical features of CoCC have not yet been clearly defined.

We herein report a patient with CoCC who underwent repeat hepatic resection for intrahepatic recurrence and discuss the histopathological and clinical features of CoCC.

Case report

A 68-year-old man was admitted to our hospital after the ultrasonographic detection of a mass in his liver. He did not have any symptoms. The patient's history included a cholecystectomy for cholecystolithiasis 40 years ago and an interferon therapy for chronic hepatitis C 11 years ago. Laboratory data on admission were as follows ; total bilirubin 0.8 mg/dl, serum albumin

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4.4 g/dl, aspartate aminotransferase 23 IU/l, alanine aminotransferase 20 IU/l, γ-glutamyl transpeptidase 21 IU/l, total cholesterol 150 mg/dl, prothrombin time 99.2%, white blood cell 4, 200/mm^3, hemoglobin 12.9 g/dl, platelet 17.3x10^4 /mm^3. Indocianine green retension at 15 minutes was 6.8%. Tumor markers including α-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9 were normal. Hepatitic C virus antibody was positive and hepatitis B surface antigen was negative. Abdominal ultrasonography revealed a hypoechoic mass, 3cm in diameter, in the medial segment (S4) of the liver. Computed tomography (CT) demonstrated a low-density mass with peripheral enhancement (Fig. 1). Magnetic resonance imaging (MRI) revealed a high intensity mass on T2-weighted images (Fig. 2). Abdominal angiography demonstrated a weak staining in the periphery of the tumor. Gastroduodenal and colon endoscopy showed no abnormalities.

He underwent a partial resection of medial segment of the liver and lymph node dissection under the diagnosis of CCC. The gross findings revealed a white fibrous nodular mass of 3.0 x 3.0 cm, with no capsule formation and an irregularly shaped margin (Fig. 3). An intraoperative ultrasonography demonstrated no residual tumors. There were no regional lymph nodes swelling. Microscopically, the tumor was composed of small cuboidal cells possessing oval nuclei and resembling cholangiole (Fig. 4). These formed small

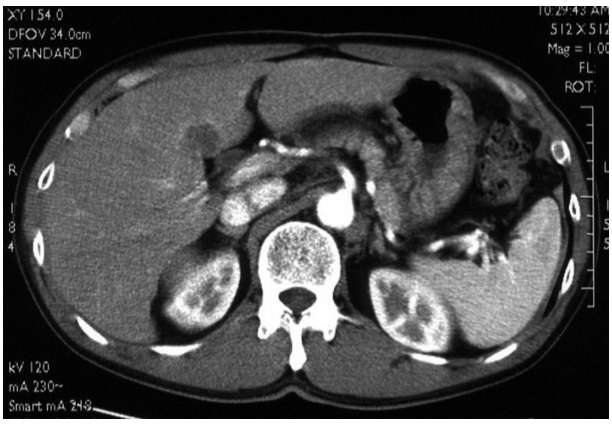

Fig. 1 CT demonstrated a low-density mass with peripheral enhancement in a hepatic arterial phase.

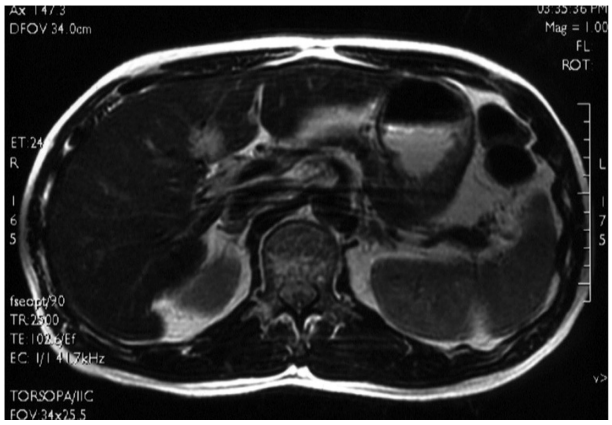

Fig. 2 MRI revealed a high intensity mass on T2-weighted images.

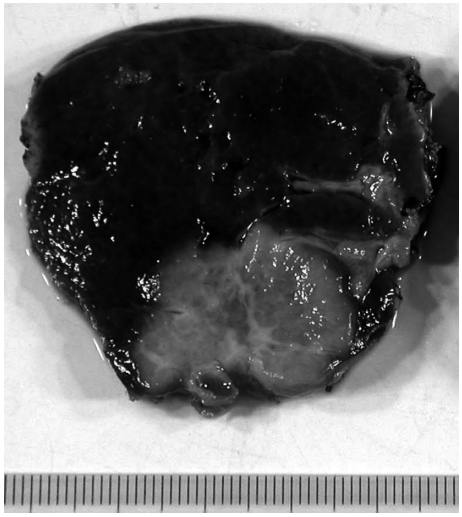

Fig. 3 The gross findings revealed a white nodular mass with no capsule formation.

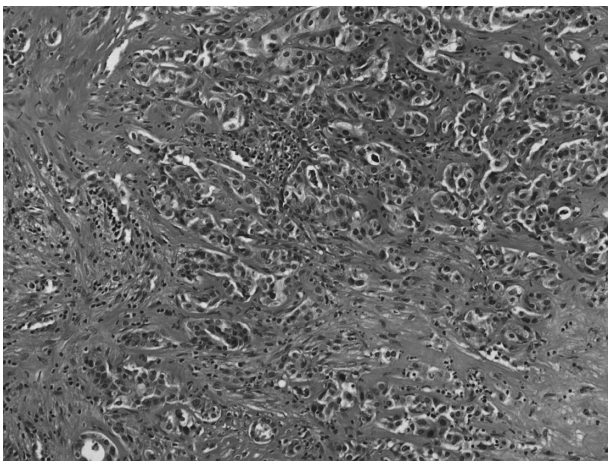

Fig. 4 Micoscopically, the tumor was composed of small cuboidal cells possessing oval nuclei and resembling cholangiole. The tumor proliferated in an anastomosing pattern of Hering's canal-like small glands with an abundant fibrous stroma.

tubular structures with fibrous stroma. Lymphatic permeation and venous invasion were recognized. The tumor did not include HCC or CCC elements. The surgical margin was free of the tumor cells. No metastasis was found in the resected lymph nodes. The non-cancerous liver parenchyma showed chronic hepatitis with mild fibrosis. Postoperative course was unremarkable and the patient was discharged from our hospital on postoperative day 12. The patients did not receive postoperative adjuvant chemotherapy.

Seven months after surgery, CT demonstrated two recurrent nodules in S7 and S8 of the liver. A partial resection of the liver was performed for each intrahepatic recurrence, respectively. The gross specimen showed two irregularly shaped white nodular tumors in S7 and S8, 2.0 cm and 1.5 cm in size, respectively. The histopathological findings were the same as those in the previously resected tumor. No lymph node metastasis was observed, however, miliary metastatic nodule on the surface of the hepatoduodenal ligament was recognized. The patient was discharged on postoperative day 10.

Although the patient underwent chemotherapy with oral tegafur and uracil (UFT) 450 mg/day, CT demonstrated dilated intrahepatic bile ducts and lymph node swelling of the hepatic hilum about four months after the second operation. He admitted for stenting for the treatment of obstructive jaundice. Eventually he died of disease thirteen months after the first operation.

Discussion

It has been controversial whether CoCC should be accepted as a separate entity, because the histopathological pattern shows multiple forms and the clinical features have not yet been clarified. Clinical features of 10 cases of CoCC including previously reported 9 cases and our case were summarized in Table 1. Six cases were HCVAb positive and one case was HbsAg positive. AFP was elevated in at least two cases. A few reports described that CoCC had the clinical features resembling HCC but the morphologic features resembling CCC. Yamamoto et al.[4] mentioned that the entity of CoCC should be distinguished from CCC, and instead be recognized as an intermediate type somewhere between HCC and CCC on the basis of the characteristic clinical and histopathological features. Shiota et al.[6] clinicopathologically studied 6 resected cases of CoCC. They described that 4 cases were clinically diagnosed as HCC and 2 cases as CCC, while four of the 6 tumors (83%) histologically consisted of only CoCC and other 2 tumors contained CCC-like area and HCC-like area in a part of the nodules, respectively. It is suggested that CoCC cells might be derived from Hering's canal or stem cells that may possess the multipotentiality to differentiate towards both hepatocytes and cholangiole and have the intermediate features between hepatocytes and bile duct epithelium. Maeno et al.[7] demonstrated

Table 1 Clinical Features of Cholangiolocellular Carcinomas.

	Age (years)	Sex	HCVAb	HBsAg	AFP (ng/ml)	CEA (ng/ml)	Tumor Size (cm)
Case 1[*1]	58	F	+	−	−	1.6	9.0
Case 2[*2]	56	M	+	−	−	−	2.8
Case 3[*2]	66	M	−	−	−	−	7.0
Case 4[*3]	63	F	+	−	30.3	ND	
Case 5[*3]	72	F	−	+	1463.0	3.7	
Case 6[*3]	69	M	−	−	ND	2.0	1.6-7.5
Case 7[*3]	69	F	+	−	−	−	(3.7 ± 2.2)[*4]
Case 8[*3]	62	M	+	−	10	ND	
Case 9[*3]	62	M	−	−	ND	−	
Our case	68	M	+	−	2.0	1.7	3.0

*1, Ref. 3 ; *2, Ref. 5 ; *3, Ref. 4 ; *4, mean ± SD ; ND, not done.

immunohistochemical study of CoCC, and concluded that CoCC may originate from interlobular ducts. On the other hand, Fukukura et al.[5] reported two cases of surgically proved CoCC of the liver and concluded that helical CT and MRI features of these CoCCs were thought to be similar to those of CCC. In this case, CT and MRI features of CoCC were thought to be similar to those of CCC, and the tumor histologically consisted only of CoCC and did not contain HCC or CCC-like area.

The recurrence pattern and prognosis of surgically resected CoCC have not been clarified. Hepatic recurrence after hepatectomy in CCC occurs at an advanced stage of the condition[4)8)~11)]. Yamamoto et al.[4] described that they have not experienced a resectable hepatic recurrence in over 50 surgically treated cases of CCC. It is thus considered that the tumor invasion pattern is directly related to tumor recurrence. HCC mainly invades the portal vein, while CCC invades the lymphatic and perineural spaces in the portal tract. In this case, lymphatic permeation and venous invasion as well as perineural invasion of the tumor cells were prominent, although portal venous invasion was not recognized. It suggests that biologic behavior of the tumor was similar to that of CCC rather than HCC.

We herein reported the patient with resectable intrahepatic recurrence of CoCC. CoCC clinically resembles CCC and the prognosis may be poor like as CCC, although it has characteristic pathological findings. A wider understanding of the histopathological and clinical features of CoCC may therefore encourage recognition of this condition as a separate entity. Further studies are necessary to clarify the significance of repeat hepatectomy for recurrence of CoCC and adjuvant chemotherapy.

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（和文抄録）

肝内胆管癌の肝内再発巣に対して再切除を行った1例

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68才，男性．肝S4の径3 cmの胆管細胞癌の診断で肝部分切除およびリンパ節廓清術を施行した．病理組織診断は細胆管細胞癌でリンパ管侵襲と静脈侵襲を伴っていた．7ヶ月後のCTで肝S7とS8に2個の再発腫瘍を認めたため，再肝切除術を行った．肉眼および病理所見は前回の腫瘍と同様であった．2回目の手術から4ヶ月後のCTで肝内胆管の拡張と肝門部のリンパ節腫大を認め，初回手術から13ヶ月後に癌死した．

本症例の臨床病理学的特徴からは，細胆管細胞癌は特異的な病理学的特徴を有するものの，臨床的には胆管細胞癌と類似し予後不良であると考えられる．細胆管細胞癌の予後の向上のために，再発に対する再肝切除や補助化学療法の意義を明らかにすべきである．