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Clinical Aspect of Peripheral Cholangiocarcinoma: A Study of 7 Hepatectomy Cases

Takatoshi Shimoyama, M. D.,[1] Teruhisa Shimizu, M. D.,[2] Hiroyuki Kusano, M. D,[2] Kiyoomi Nishikawa, M. D.,[1] Kohji Azuma, M. D.,[1] Kiyoto Shinkai, M. D.,[1] Ken Hayashida, M. D.,[1] Harumi Kida, M. D.,[1] Ryusuke Terada, M. D.,[2] Nobufumi Sasaki, M. D.,[2] Tetsuya Uchikawa, M. D.,[2] Atsushi Nanashima, M. D.,[2] Ryuichiro Yoshida, M. D.,[2] Tohru Nakagoe, M. D.,[2] Toshio Miura, M. D[2] and Masao Tomita, M. D.[2]

1) Department of Surgery, National Ureshino Hospital, Saga, Japan
2) The First Department of Surgery, Nagasaki University School of Medicine, Nagasaki, Japan

To clarify the features and problems presented by a peripheral cholangiocarcinoma (CCC), seven patients with hepatectomy from the First Department of Surgery, Nagasaki University School of Medicine (6 patients), and from Department of Surgery, National Ureshino Hospital (one patient) were reviewed. Men predominate with ratio of 5:2, and an average age was 65.4 years. Tumor location was left lateral segment in 4 patients, right lobe, middle lobe and posterior segment in one, respectively. Three patients were associated with hepatolithiasis. Underlying liver disease was found in 4 patients (57%); cirrhosis in 3 patients, and chronic hepatitis in one. Initial symptoms were abdominal pain, fever and palpable abdominal mass. In imaging modalities available, the detection rates of tumor were 100% in CT and 67% in US and angiography, respectively. Combination of MRI and CT clearly showed tumor characteristics. The serum CEA was slightly elevated in 5 patients (83%), but serum CA19-9 rose strikingly in 3 patients. Most tumors showed an infiltrating growth along intrahepatic bile duct, with a portal vein thrombus and/or satellite tumors frequently. In 3 patients, early recurrence with intrahepatic metastasis occured within the first 6 months. The patient of poorly differentiated adenocarcinoma containing a squamous or signet ring cell carinoma showed an extremely poor prognosis. This study suggests that early detection of small CCC and an extended resection are the most important factors for the survival of patient.

Key Words: Peripheral cholangiocarcinoma, Tumor marker, Imaging diagnosis, Liver resection.

Introduction

Cholangiocarcinoma which arises from the hepatic bile duct is uncommon among primary liver tumors, although hepatocellular carcinoma (HCC) is not a rare disease in Japan.[1] According to the survey conducted by the Liver Cancer Study Group of Japan, the histology of 4,765 cases of primary liver cancer was analyzed as hepatocellular carcinoma in 91.4%, cholangiocellular carcinoma in 5.4%, mixed carcinoma in 1.0%, hepatoblastoma in 0.5% and the others in 1.8%.[2] On the other hand, cholangiocarcinoma have been classified into two types: the peripheral type originating from the intrahepatic bile duct and the hilar type originating from the major hepatic ducts at or near the junction of the right and left hepatic duct.[3-5] In 1990, the 25th Meeting of Liver Cancer Study Group of Japan provided a main theme of intrahepatic cholangiocarcinoma, in which the clinical and pathological features were discussed by many authors.[6] In this Meeting, it was found that the numbers of peripheral CCC in most centers were between 2 and 18 cases, with lower resectability because of advanced stage at operation, a cause of poor prognosis. The purpose of this article is to review our experience of 7 patients with peripheral CCC with particular reference to clinical features and pathological factors which might affect the patient's survival.

Address: Department of Surgery, National Ureshino Hospital, 2436 Ureshinocho, Fujitsugun, Saga, 843-03 JAPAN, Takatoshi Shimoyama, M. D.

Patients and Materials

A total of 7 patients with peripheral CCC who underwent hepatectomy at our hospitals were retrospectively reviewed. There were 6 patients from the First Department of Surgery, Nagasaki University School of Medicine since 1975, and one patient from the Department of Surgery, National Ureshino Hospital in 1993. In accordance with the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan, the main tumor of CCC locating within the liver was difined as peripheral CCC.[2] All patients were histologically confirmed as cholangiocellular carcinoma on the resected specimens. Patients with mixed tumors with both elements of HCC and CCC were excluded. Clinical and pathological findings were evaluated on the basis of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer or on Cancer

of Biliary Tract in Japan.[2,3]

Results

Clinical features

There were 5 men and 2 women ranging from 56 to 79 years of age, with an average of 65.4 years. Primary sites of the tumor were the lateral segment in 4 patients, and the right lobe, the middle lobe and the posterior segment in one, respectively. Peripheral CCC associated with hepatolithiasis was found in 3 patients (Table 1). Initial symptoms and physical findings were usually nonspecific. Five patients presented with abdominal pain and/or fever, two patients had a palpable mass, and one patient was detected the tumor during follow-up examination for underlying liver disease (Case 3). One patient was diagnosed during operation for gastric ulcer (Case 1). No patient had jaundice or gallstone disease.

Imaging Modalities

The detection for tumor by ultrasonography (US), computed tomography (CT) and angiography are shown in Table 1. For peripheral CCC, CT had the highest detection rate (100%) compared with angiography and US (67%, respectively). In 2 patients associated with hepatolithiasis, it was difficult to detect the tumor by US. The MRI examination was performed for the recent case (Case 7). The tumor was shown as an irregular central hypointensity on T1-weighted imaging and as a hyperintensity with an irregular central area of hypointensity on T2-weighted imaging (Fig. 1). One patient (Case 2) was histologically comfirmed cholangiocarcinoma by US-guided needle biopsy.

Tumor markers

The values of serum AFP, CEA, CA19-9 and HBsAg of patients are tabulated in Table 2. In 5 out of 6 patients (83%), the serum CEA value was maderately elevated. Three patients showed a remarkable rise of serum CA19-9 more than 1,000U/ml. Only one patient (Case 2) had abnormal serum AFP levels with 1,365ng/ml. None had positive serum HBsAg.

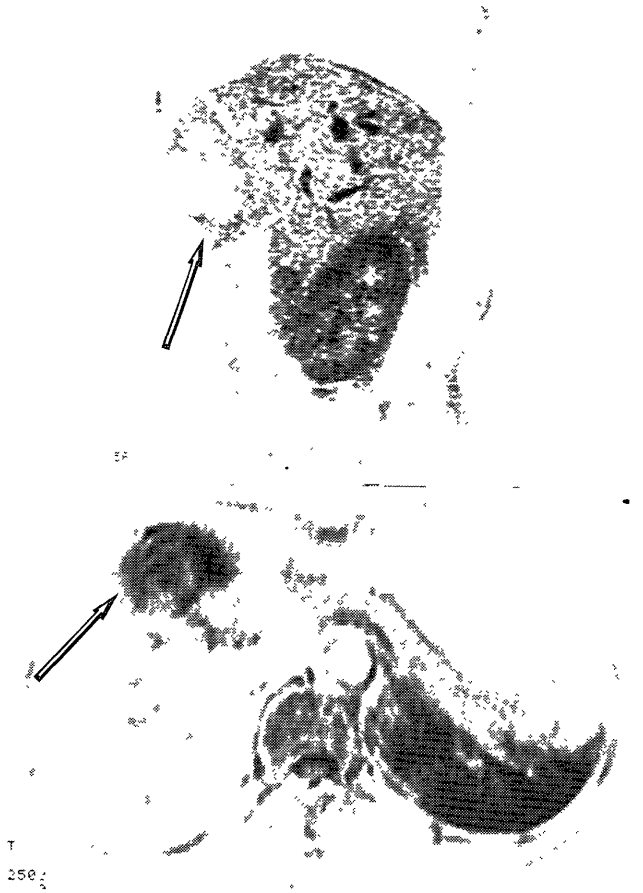

Fig. 1. Sagital T1-weighted MR imaging of peripheral CCC in Case 7 showing 7.0 × 4.2cm low-intensity area in middle lobe (above). Also mass on transverse T2-weighted MR imaging was high-intensity, with an irregular central area of hypointensity (below).

Table 1. Clinical Features of Cholangiocarcinoma

No.	1	2	3	4	5	6	7
Age, Sex	56•M	61•M	61•M	60•F	67•F	79•M	69•M
Tumor Location	L	P	L	L	PA	L	M
Stone	−	−	−	+	+	+	−
US	ND	+	+	NR	+	NR	+
CT-scan	ND	+	+	+	+	+	+
Angiography	+	+	+	ND	+	NR	NR
Resection	HR2 (L, M)	HR1 (P)	HR1 (L)	HR1 (L)	HR1 (P)	HR1 (L) CBD	HR1 (M)
Survival	6M died	3M died	9M died	3Y11M died	3M died	7M died	7M alive

ND: not done, NR: not remarkable, +: positive findings

Table 2. Laboratory Findings on Admission

No.	1	2	3	4	5	6	7
Age, Sex	56•M	61•M	61•M	60•F	67•F	79•M	69•M
AFP ng/ml	4.0	1,365	5.0	3.8	1.0	5.7	1.3
CEA ng/ml	ND	6.6	2.9	1.9	4.1	5.1	4.7
CA19-9 U/ml	ND	35	31	ND	3,363	1,204	2,600
HB_s-Ag	ND	–	–	–	–	–	–
HB_s-Ab	ND	–	–	+	–	+	–

ND: not done

Pathologic Features

Pathologic findings of the tumors removed at operation are summarized in Table 3. Four out of 7 patients (57%) had underlying liver diseases; chronic hepatitis in one (14%); and cirrhosis in 3 (43%). But, none had severe cirrhosis. The remaining 3 patients showed the normal liver. The maximum diameter of tumors ranged from 2.0cm to 13.0cm. Following classification of the macroscopic distribution of the primary liver cancer, there were 5 patients of "massive", one patient of "nodular" and the other one of "multinodular", of which 6 patients demonstrated infiltrating growth along intrahepatic bile duct (Fig. 2 and 3). Only one patient had the thinly encapsulated tumor which showed expanding growth. The histology of tumor was well differentiated adenocarcinoma in 4 patients, moderately differentiated adenocarcinoma in one, and poorly differentiated adenocarcinoma in 2. However, in a part of the region of poorly differentiated adenocarcinoma, a component of signet ring cell or adenosquamous cell carcinoma was observed. Microscopically, the presence of tumor thrombus in small portal branches (Vp_1) was observed in 5 patients (71%).

Table 3. Pathological Findings of Tumor

No.	1	2	3	4	5	6	7
Age, Sex	56•M	61•M	61•M	60•F	67•F	79•M	69•M
Tumor size (cm)	5 × 6	10 × 10	2.2 × 2	4.5 × 3	13 × 8	7 × 3.5	7 × 4.2
Growth form	massive	multiple nodular	single nodular	massive	massive	massive	massive
s	S_1	S_2	S_1	S_2	S_1	S_1	S_1
vp	1	1	0	1	1	1	0
IM	IM_1	IM_2	IM_1	IM_0	IM_1	IM_0	IM_1
P	P_0	P_1	P_0	P_0	P_0	P_0	P_0
Cell differentiation	well pap	poorly sig	moderate	well	poorly as	well	well
Stage	III	III	II	III	III	III	III
Noncancerous tissue	LC	LC	LC	NC	NC	CH	NC

NC: noncirrhotic liver, CH: chronic hepatitis, LC: liver cirrhosis, pap: papillary, sig: signet ring cell, as: adenosquamous.

Fig. 2. Cut surface of peripheral CCC in Case 3 showing 2.2 × 2cm grey-white tumor which infiltrates along the intrahepatic bile duct (arrow).

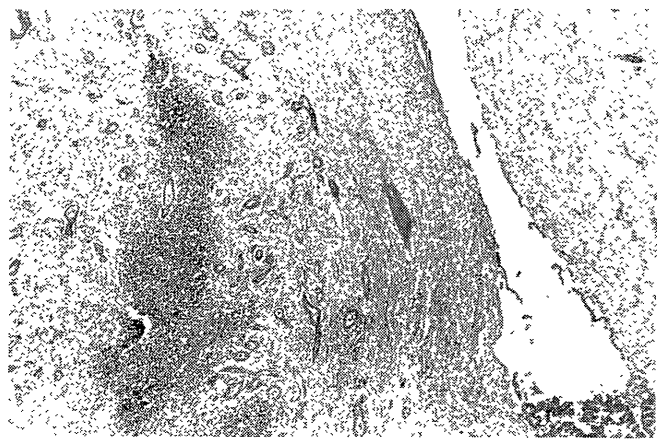

Fig. 3. Histological findings in Case 6 showing periductal invasion of CCC (H. E. X 36).

Operation and Survival

All main tumors of 7 patients were surgically removed (Table 1). In one patient (Case 7) who underwent middle hepatic lobectomy, a satellite tumor infiltrating the middle hepatic vein was left in place. This satellite nodule was repeatedly treated by transhepatic Ethanol injection therapy (PEIT) after surgery. He is still alive 7 months after operation. The operations were considered radical in 6 patients judged by intraoperative findings and US or CT. Two of these patients died of cancer-unrelated diseases; hepatic failure in Case 1 and suicide in Case 3. There were 3 recurrences after surgical treatment (Case 2, 4 and 6), i. e., an incidence of 42.9%. Among them, 2 patients with poorly differentiated adenocarcinoma had early recurrence of resected margin and/or intrahepatic matastasis at the first one month, who died 3 and 7 postoperative months, respectively (Case 2 and 6). In Case 2, the tumor of posterior segment showed dense adhesion to parietal peritoneum with milliary dissemination surrounding it (P_1), that was considered to be disseminated by preoperative needle biopsy. In patient (Case 4) with well differentiated adenocarcinoma, intrahepatic metastasis was observed at 6 months postoperatively. She was alive with cancer for 3.5 years. The patient with right lobectomy subsequently developed hepatic failure because of cirrhosis, following uneventful course despite medication (Case 1).

Discussion

It has been generally agreed that the tumor-associated symptoms in the patient with peripheral CCC were uncommon even in advanced stage, a cause of poor prognosis.[6-8] In the present series, unusual presentations, such as a palpable abdominal mass, intractable pain, fever and periodic follow-up examination for their underlying liver disease led to tumor detection.

Serum CEA and CA19-9 measurements have been frequently the useful screening test of CCC to differentiate from HCC. In Japan series, the positive rate of CEA for cholangiocarcinoma was 42.7%.[9] However, there was none of our patient whose serum CEA measurement was the first diagnostic clue for CCC, although serum CEA values in 83% of the patients were moderately elevated. Therefore, the utility of serum CEA measurement for CCC has some limitation. An extremely high elevation of serum CA19-9 level higher than 1,000U/ml was found in our 3 patients in agreement with other reports with high frequency ranging from 70% to 80%.[6] This suggested that serum CA19-9 measurement might be useful as a screening test for peripheral CCC. The elevation of serum AFP level were occasionally observed. In our series, only one patient showed a remarkable rise of serum AFP higher than 1,000ng/ml. Japan series described similar cases in 6.4% among 205 cholangiocarcinoma.[3] Thus, initial and laboratory abnormalities are generally minimal with this tumor, so that the role of imaging procedures for diagnosis of the tumor is important.

According to Japan series, the detection rates for cholangiocarcinoma by US, CT and angiography were described as 92%, 94% and 83%, respectively.[12] However, US or CT findings of peripheral CCC have previously been described as somewhat nonspecific. This tumor usually manifests as a low-attenuation homogeneous mass with irregular margin.[10] Recently, the useful information of MR imaging on peripheral cholangiocarcinoma have been published in several articles.[10-12] Tani et al, in a prospective study comparing CT and MR imaging on the patients with this tumor, indicated that MR (long TR/TE SE) imaging was the most effective initial screening method in demonstrating the presence and determining resectability.[12]

Cholangiocarcinoma associated with hepatolithiasis was uncommon, ranging from 1.5 to 9.4% among hepatolithiasis.[13] This tumor usually occurs in the left intrahepatic duct. However, the diagnosis is very difficult. In one of our patients, the tumor was overlooked because images of US and CT were insufficient to demonstrate the mass due to the coexistence of stones. The possibility of existence of peripheral CCC should still be kept in mind even if the preoperative examination of hepatolithiasis is negative for associated carcinoma. On the other hand, underlying liver disease was present in 4 of our patients, a figure much lower than for HCC and in agreement with Japan series with incidence of 9.9% fibrosis and 14% cirrhosis.[2]

Most peripheral CCC, regardless of their cause, develop in the small bile ducts and grow in a nodular, massive, or diffuse pattern with early infiltration into the hepatic parenchyma. Although the process of this morphogenesis differs from that of HCC, several important pathologic features of this tumor affecting the prognosis have been pointed out. These include the growth pattern infiltrating along intrahepatic duct, the direct invasion to portal vein branches, the infiltration into surrounding nerves, lymphatic metastasis clustered along hepatic arteries and/or celiac arteries, and the presence of satellite tumors.[6, 14, 15] In this series, we confirmed histologically these factors by the analysis of the resected specimens.

For hepatic resection of peripheral CCC, the important factors are these pathological features. However, the prognosis is still extremely poor despite curative resection.[6] Three patients (43%) of our series subsequently developed recurrences at resected margin and/or intrahepatic metastasis within 6 months after operation. Especially, early recurrence was observed in 2 patients with poorly differentiated adenocarcinoma containing a component of signet ring cell carcinoma or adenosquamous cell carcinoma. Nakajima, et al. reported a poor prognosis of the patient with cholangiocarcinoma containing a component of squamous or adenosquamous cell carcinoma.[16] It seems that the

poorly differentiated adenocarcinoma with these components may lead to rapid dissemination of the disease resulting in death within a short period of time as has been noted for some other human tumors.

Attitudes to operation on the liver tumor have changed in recent years, and results have improved with better facilities for intensive care and introduction of new technology. However, the curative resection rate for peripheral CCC have been reported to be lower than that for HCC by many centers. According to Japan series, 86 out of 234 cases (36.8%) with resection for CCC were curative, whereas the curative resection rate for HCC was 55.1% (2,189 out of 4,152 cases).[2] This was attributed to advanced stage of the lesion due to delayed diagnosis, and the technical difficult for sufficient resection at tumor margin because of the infiltration of cancer cells along intrahepatic bile duct. In conclusion, early detection of small peripheral CCC and an adequate hepatic resection including extensive lobectomy for noncirrhotic liver are most important for the excellent prognosis of the patients.

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