Intrahepatic Sarcomatoid Cholangiocarcinoma: Clinical Analysis of Seven Cases during a 15-year Period

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Background: Intrahepatic cholangiocarcinoma with sarcomatous changes is seldom reported and its clinicopathological characteristics are largely unknown.

Methods: Of 466 patients treated in our institution for intrahepatic cholangiocarcinoma from 1991-2005, seven who exhibited sarcomatous features were included in this study.

Results: Most of the tumors were diagnosed in the advanced stage and abdominal pain was the most common presenting symptom. In three cases, the tumors were associated with hepatolithiasis. The tumors frequently appeared as mixed-echoic masses on ultrasonography. They were hypo-attenuated masses on plain computed tomography scans and most appeared with ring-like enhancement after contrast medium injection. Histologically, two of the three resected tumors exhibited complete sarcomatoid change. Four of the liver biopsies also showed only sarcomatous features. Immunohistochemically, tumor cells in the region with sarcomatous features stained positive for both cytokeratin and vimentin antibodies. Follow-up was available in six patients: five died of disease one week to two months after diagnosis; one who remained disease-free 4 years after diagnosis had early stage disease and complete surgical resection.

Conclusions: Intrahepatic sarcomatoid cholangiocarcinoma is a rare but aggressive malignancy. The diagnosis needs to be confirmed by immunohistochemical study. Early detection and complete surgical resection offer the only chance for long term survival in patients with this cholangiocarcinoma variant.

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Key words: intrahepatic cholangiocarcinoma, sarcomatous change, clinicopathology

Epithelial tumors with sarcomatoid features are occasionally observed in various organs, including the liver.[1] Most sarcomatoid carcinomas in the liver are regarded as sarcomatous differentiation from hepatocellular carcinomas (HCC), and their clinical characteristics and pathologic significance have been satisfactorily elucidated.[1-3] Intrahepatic cholangiocarcinomas with sarcomatous changes are very rare, and, to the best of our knowledge, only nineteen cases have been reported in the English-language medical literature.[3-12] Clinical as well as imaging and pathologic information on this tumor are still limited. This study therefore analyzed seven such cases to clarify the clinicopathologic characteristics

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of this rare tumor.

METHODS

From 1991 to 2005, 446 patients were treated for pathology-proven primary intrahepatic cholangiocarcinoma at Chang Gung Memorial Hospital, Taipei, Taiwan. Among them, seven cases with sarcomatous features were enrolled in this study. All seven cases were diagnosed as sarcomatoid cholangiocarcinoma by both pathologic and immunohistochemical study. Three (cases 5-7) of the seven patients underwent surgical resection while the other four (cases 1-4) underwent only percutaneous needle biopsy because of inoperable disease. This report summarizes and discusses the clinical, imaging and pathological features of this rare disease.

RESULTS

Clinical and laboratory findings (Table 1)

The ages of the patients ranged from 50 to 77 years (mean, 63.4 years). The male-to-female ratio was 4:3. Liver cirrhosis was observed in one case (case 3), and concomitant hepatolithiasis was observed in three (cases 3, 6 and 7). The initial presentation was abdominal pain in five (71.4%) cases, weight loss in four (57.1%), palpable abdominal mass in two (28.6%), back pain in one (14.3%) and dyspnea in one (14.3%).

Three cases (cases 2, 6 and 7) had a solitary liver tumor while the others had intrahepatic metastatic daughter nodules. The main tumors were observed in the left lobe in four cases (cases 1, 3, 5 and 7) and the right lobe in another three cases. Tumor size varied from 2.5-14 cm in the greatest dimension.

Serum alanine aminotransferase levels were 8-47 (median 34, normal < 36) U/L. Serum alkaline phosphatase levels were elevated in six (85.7%) patients (cases 3, 6, 4, 7, 2 and 5, in order of high to low), with a range of 68 to 174 (median 130, normal < 94) U/L. Serum total bilirubin levels in all patients were within the normal range. Serum hepatitis B surface antigen was positive in two (28.6%) patients, and hepatitis C antibody was negative in all cases. Serum α-fetoprotein was within the normal range in all six patients tested. An elevated serum carcinoem-

Table 1. Clinical Features of Patients with Cholangiocarcinoma with Sarcomatous Change

Case	Age/ Sex	Initial symptoms	Number, Size, Location of the tumors	Metastatic sites	Treatment	Outcome
1	77/F	Abdominal pain, palpable mass, BWL	Main + daughter nodules Main 14 cm, left lobe	Intrahepatic, retroperitoneum	None	Died 2 months PD
2	62/M	Abdominal pain, BWL	Solitary, 3 cm, right lobe	Celiac and SMA lymph nodes	unknown	Lost to follow-up
3	59/M	Abdominal pain, palpable mass, BWL	Main + daughter nodules Main 11 cm, left lobe	Intrahepatic, Lung, T-L spine	None	Died 1 month PD
4	63/M	Dyspnea, BWL	Main + daughter nodules Main 14 cm, right lobe	Intrahepatic, Lung, Mediastinum	None	Died 1 week PD
5	64/M	Back pain	Main + daughter nodules Main 11 cm, left lobe	Intrahepatic, T-L spine	Left lobectomy; R/T for spinal metastasis	Died 2 months PO
6	50/F	Abdominal pain	Solitary, 4.5 cm, right lobe	No	Segmentectomy (margin involved)	Died 2 months PO
7	69/F	Abdominal pain, fever	Solitary, 2.5 cm, left lobe	No	Segmentectomy (margin free)	Alive 4 years PO

Abbreviations: F: female; M: male; BWL: body weight loss; SMA: superior mesenteric artery; T-L: thoracolumbar; R/T: radiotherapy; PD: post diagnosis; PO: postoperative.

bryonic antigen level was detected in two of the six patients tested (9 and 10 ng/mL in cases 3 and 5, respectively, normal < 5). Elevated serum carbohydrate antigen 19-9 levels were detected in two of the four patients tested (4920 and 51 U/mL in cases 3 and 6, respectively, normal < 3 7).

Imaging features, treatment and outcome (Table 1)

Abdominal ultrasonography performed in six cases revealed mixed-echoic hepatic masses in five cases (cases 1-4, 6; Fig. 1) and no tumor in one case (case 7). Six patients (cases 1-6) underwent computed tomography (CT) scans, three (cases 2-3, 5) of them with dynamic study. The tumors appeared as hypo-attenuated masses on plain radiographs, and had peripheral ring enhancement after contrast medium injection (Fig. 2A) except for two, the main tumor in case 1 without contrast enhancement (Fig. 2B) and the main tumor in case 3 with progressive enhancement to the central region.

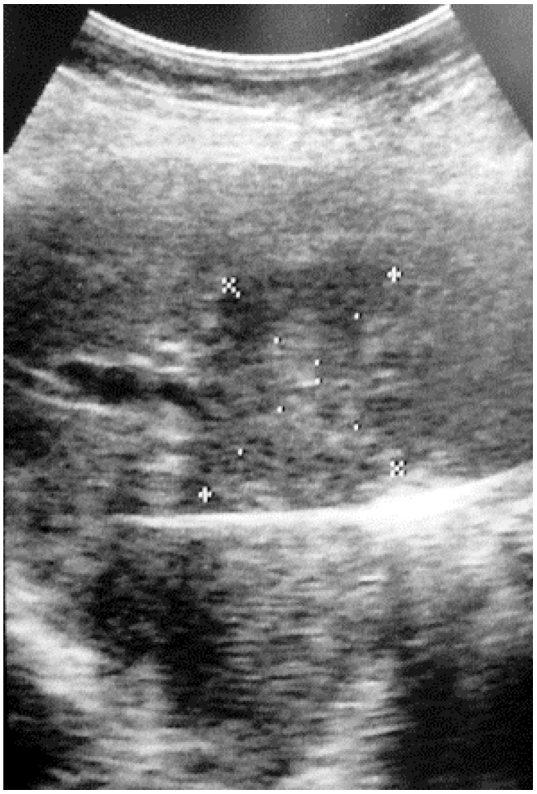

Fig. 1 Abdominal ultrasonography in case 6 showing a mixed-echoic tumor in the right hepatic lobe.

Follow-up was available in six cases. Three patients (cases 1, 3-4) with inoperable disease were treated symptomatically and died of disease between one week and two months after diagnosis. Case 5 underwent a left extended lobectomy for the primary tumor and radiotherapy for spinal metastasis. The patient died of disease 2 months after the operation. Case 6 underwent a right segmentectomy with a positive resection margin but died 2 months later from dissemination of the tumor. The liver tumor in case 7

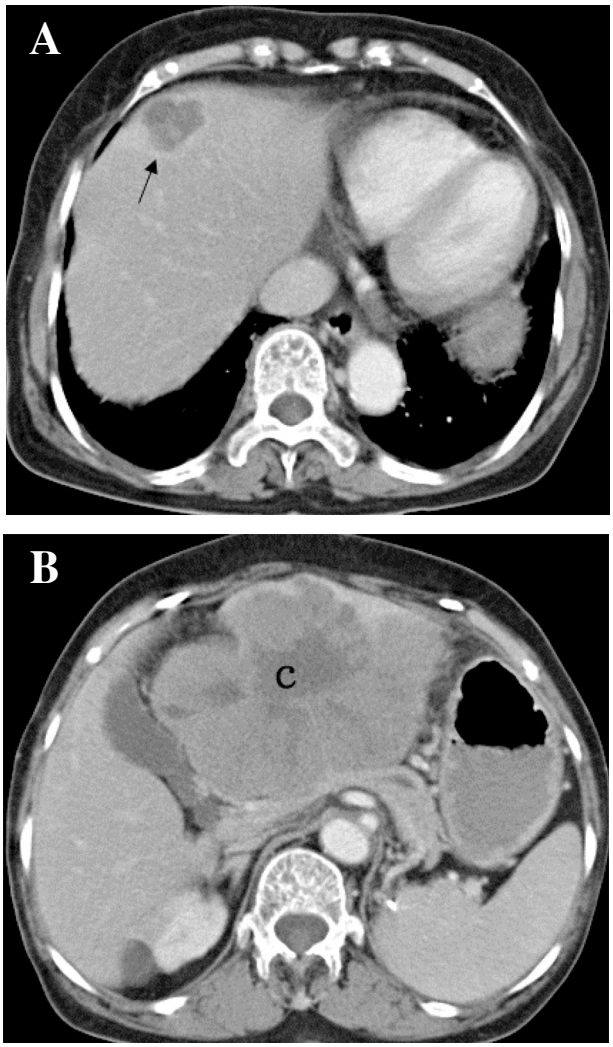

Fig. 2. Enhanced computed tomography scans of case 1 showing an intrahepatic metastatic tumor (Fig. 2A) exhibits peripheral ring enhancement in the right hepatic lobe (arrow), whereas the main tumor with central necrosis (C) without contrast enhancement in the left hepatic lobe (Fig. 2B).

was found incidentally during surgery for left intrahepatic bile duct stones and was resected completely. At the 4-year follow-up, the patient exhibited no tumor recurrence.

Pathologic features and immunohistochemical study (Table 2)

Findings from the H&E-stained specimens did not show any glandular formation in any of the four biopsied patients (cases 1-4) or the two surgical patients (cases 5-6). The tumor in case 7 was predominantly sarcomatous with areas of well-to-moderately differentiated adenocarcinoma (Fig. 3). All tumors with sarcomatoid features were composed of spindle cells arranged in sheets or bundles and intermixed with varying numbers of pleomorphic giant cells in all cases. Immunohistochemicaly, the sarcomatous component of all tumors reacted positively to both cytokeratin and vimentin antibodies but did not react to hepatocyte paraffin-1, C-KIT, smooth muscle actin or S-100 protein. Biopsy of the metastatic lung

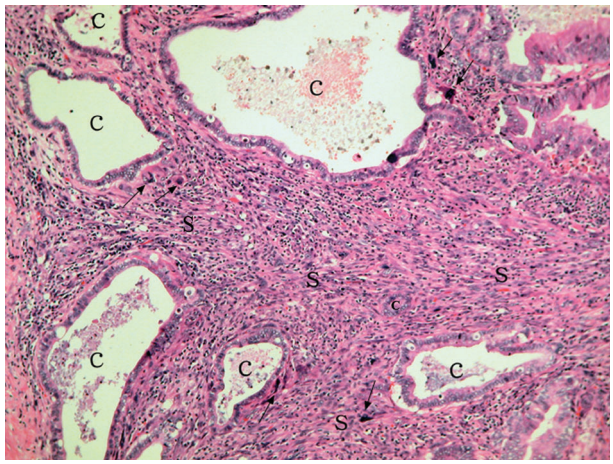

Fig. 3 Microscopic findings of the resected specimen in case 7 showing both carcinomatous (C) and sarcomatous (S) components. The carcinoma areas are composed of well- to moderately-differentiated adenocarcinoma cells, and the sarcomatous areas are composed of spindle cells arranged in sheets or bundles and interspersed with pleomorphic giant cells (arrows) and numerous inflammatory cells (H&E, x 100).

Table 2. Pathological Features and Immunohistochemical Study

Case	Specimen	Histologic type		Area of sarcomatous component	Immunohistochemical results of sarcomatous component	
		Carcinomatous component	Sarcomatous component		Positive for	Negative for
1	biopsy	—	Spindle, pleomorphic	All of the specimen	CK7, AE1/AE3, vimentin	HepPar-1, desmin, c-KIT, S-100
2	biopsy	—	Spindle, pleomorphic	All of the specimen	CK7, AE1/AE3, vimentin	HepPar-1, c-KIT
3	biopsy	—	Spindle, pleomorphic	All of the specimen	CK7, AE1/AE3, vimentin	HepPar-1, c-KIT, S-100, CD34, Actin
4	biopsy	—	Spindle, pleomorphic	All of the specimen	CK7, AE1/AE3, vimentin	C-KIT, CD34, Actin
5	resection	—	Spindle, pleomorphic	All of the specimen	CK7, AE1/AE3, vimentin	HepPar-1, S-100, Actin
6	resection	—	Spindle, pleomorphic	All of the specimen	CK19, AE1/AE3, vimentin, CA19-9	— CEA, EMA, Actin
7	resection	Well to moderately differentiated	Spindle, pleomorphic	Predominant	CK7, vimentin	

Abbreviations: CK: cytokeratin; AE1/AE3: pancytokeratin AE1/AE3; CA 19-9: carbohydrate antigen 19-9; HepPar-1: hepatocyte paraffin-1; CEA: carcinoembryonic antigen; EMA: epithelial membrane antigen; CD: cluster of differentiation.

nodules in case 4 and all resected daughter nodules in case 5 also indicated only sarcomatous elements.

DISCUSSION

Intrahepatic cholangiocarcinoma with sarcomatoid changes is reported in only 4.5% of surgical and autopsied cases.[5] In this study, the frequency of sarcomatoid cholangiocarcinoma was 1.6% in all biopsied and surgical cases. This figure is relatively low because some cases might not be detected via biopsy alone, and most liver tumor deaths are not autopsied.

The mean patient age was 63.4 years, and the most common presenting symptom was abdominal pain, which is consistent with previous reports.[4,5] Liver biochemistry tests were normal or slightly elevated and not disease specific. In previous reports, abdominal ultrasonography and CT scan studies were mentioned in only 3 and 6 cases, respectively. Ultrasonography in this study indicated the tumors were mixed-echoic lesions, which differed from the hypoechoic lesions in previous reports.[4,6,7] Plain film CT scans showed the tumors to be hypo-attenuated masses, and contrast medium injection indicated peripheral region enhancement in most tumors, in agreement with the literature.[4,6-9,12] These features resemble those of ordinary cholangiocarcinoma, and they are difficult to differentiate by imaging.

The pathogenesis of sarcomatoid cholangiocarcinoma has not yet been clarified. Anticancer chemotherapy and transcatheter arterial embolization have been found to lead to sarcomatous transformation in patients with HCC,[2,3] but none of the cases in this study underwent this treatment before diagnosis. The reported prevalence of hepatolithiasis in patients with cholangiocarcinoma was 65.4% in Taiwan.[13] Three of the seven cases had associated hepatolithiasis which may further demonstrate this high prevalence. The pathogenetic relationship between hepatolithiasis and cholangiocarcinoma has been confirmed but why sarcomatous changes should occur in these cases is still unknown. However, repeated hepatolithiasis and infections were believed to play a role in accelerating tumorigenesis in a reported case of intrahepatic cholangiocarcinoma with sarcomatoid and giant cell tumor-like features.[9]

Although H&E-stained specimens were available in six cases (cases 1-6) they showed only sarcomatous components. These tumors were judged to have epithelial differentiation according to the results of immunohistochemical study. Sarcomatous components in all seven cases showed immunoreaction to both vimentin and cytokeratin. The former in the epithelium-derived neoplasm may reflect a sarcomatous transformation process, and the latter suggests that transformed sarcomatous carcinoma cells still retain some phenotype of carcinoma cells.[5,6,14] Patients with all tumor cells showing sarcomatous features are very rare. A literature review revealed only two case reports of HCC and two of cholangiocarcinoma.[3,7] At least two of the present cases (cases 5-6) exhibited entire sarcomatous change from intrahepatic cholangiocarcinoma.

The prognosis for intrahepatic sarcomatoid cholangiocarcinoma was reportedly worse than that of ordinary cholangiocarcinoma.[4] The majority of the cases in this study had poor outcomes. The poor prognosis can be ascribed to the tendency of symptoms to occur at a later stage of the disease, at which time curative resection is often impossible when a tumor is found, as in cases 1-5. Another factor is the aggressive intrahepatic spreading and frequent metastasis of sarcomatous cells,[5] as in case 5 and possibly case 4. Case 6 died of recurrent and metastasized disease shortly after her operation, revealing the aggressive behavior of the tumor. Conversely, in patient 7, a tumor was found in the early stage and resected radically, and the patient outcome was substantially better.

In conclusion, cholangiocarcinoma with sarcomatoid features is a rare but aggressive malignancy. Diagnosis is only possible by pathology and immunohistochemical study since clinicomorphological findings are not disease specific. Early detection and complete resection of the tumor offer the only chance for long term survival.

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肝內肉瘤狀膽管癌

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背 景： 肝內肉瘤狀膽管癌是一罕見的腫瘤，在以英文報告的文獻中目前只有 19 例病例報告，因此對於它的臨床及病理特徵所知有限。本研究的目的在於闡明肝內肉瘤狀膽管癌的臨床表現及病理特徵。

方 法： 我們回溯性地收集 1991 年至 2005 年間在本院區診斷爲肝內膽管癌並經病理學證實的病例共計 446 例。其中七個病理組織有肉瘤狀變化的病例被納入本研究。七位患者中有三位接受手術切除肝內病灶，另外四位患者因疾病晚期只接受肝生檢。

結 果： 大部分的患者都在疾病的晚期才被診斷，而腹痛是最常見的臨床症狀。有三位患者同時有肝內膽管結石的情形。腹部超音波檢查顯示病灶常表現爲混合性回音的腫瘤；電腦斷層顯現爲低密度病灶，並且大部分的腫瘤於注射顯影劑後出現戒指環狀的顯影增強。三位接受手術切除的其中兩位患者，以及四位接受肝生檢的患者，其標本在病理組織學上都顯示爲完全的肉瘤樣變化；而所有的腫瘤標本中出現肉瘤樣變化的區域，在免疫組織化學染色的檢查都同時有 cytokeratin 及 vimentin 抗體陽性的反應。在六位有資料可查的患者中，五位於診斷後的一星期至兩個月內死亡；另外一位有早期疾病的患者，經手術完全切除腫瘤後的四年仍存活著，且無腫瘤復發的情形。

結 論： 肝內肉瘤狀膽管癌是一罕見且高度惡性的腫瘤。臨床表現及影像學檢查並無特徵性，故診斷需靠組織病理學以及免疫組織化學染色的檢查來證實。早期發現及手術完全切除才能提供患者長期存活的機會。

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關鍵詞： 肝內膽管癌，肉瘤狀變化，臨床病理學

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