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Sarcomatous carcinoma in biliary system

A retrospective study

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Abstract

Sarcomatous carcinoma in biliary system, including sarcomatous intrahepatic cholangiocarcinoma (SIC) and sarcomatous choledochal carcinoma (SCC), is extremely rare and malignant.

This retrospective study included 5 patients with SIC and 4 patients with SCC. Their basic characteristics, preoperative lab tests, preoperative imaging features, perioperative status, and follow-up information have been collected and analyzed.

Lesions at different locations induced various preoperative symptoms. The history of choledocholithiasis or hepatolithiasis was remarkable in patients with SIC. Cancer antigen 19-9 appeared to be a key factor for both SIC and SCC. However, preoperative lab tests or imaging features could not distinguish SIC from intrahepatic cholangiocarcinoma, or SCC from choledochal carcinoma. Surgical treatments for all 9 patients were successful. Efficacy of adjuvant chemotherapy was not ideal. The prognosis of sarcomatous biliary carcinoma was enormously poor.

Sarcomatous carcinoma in biliary system is extremely rare and malignant. Chronic inflammation could be critical in the currently unknown occurrence mechanism. Further research is urgently needed to improve the prognosis.

Abbreviations: CBD = common bile duct, CT = computed tomography, ICC = intrahepatic cholangiocarcinoma, MRI = magnetic resonance imaging, SCC = sarcomatous choledochal carcinoma, SIC = sarcomatous intrahepatic cholangiocarcinoma.

Keywords: pathologic diagnosis, prognosis, sarcomatous choledochal carcinoma, sarcomatous intrahepatic cholangiocarcinoma, surgical treatment

1. Introduction

Sarcomatous intrahepatic cholangiocarcinoma (SIC) is a rare variant of intrahepatic cholangiocarcinoma (ICC). Histopathologically, it is defined as a cholangiocarcinoma with spindle cell areas resembling spindle cell sarcoma or fibrosarcoma or with features of malignant fibrous histiocytoma in the World Health Organization classification of tumors.[1] To our knowledge, only 36 nonrepeated cases of SIC have been reported.[2–16]

Sarcomatous carcinoma arising in the common bile duct (CBD) (sarcomatous choledochal carcinoma, SCC) is extremely rare and has been reported only in 2 cases.[16,17] Primary treatment for SIC and SCC is curative surgery. Potential benefits of curative surgery include: a definite pathologic diagnosis, a longer survival in some populations, and the possibility of an intensive adjuvant chemotherapy to improve prognosis after surgery.[2,3,16] Studies have showed a more aggressive behavior of SIC than ordinary ICC. The prognoses for patients with SIC with or without surgery were worse than those for ICC. The median survival time of SIC with surgery was 11 months, similar to that of ICC without surgery.[17] On the contrary, the prognosis of SCC is more promising. Two cases have reported uneventful 1-year and 3-year postoperative survival, respectively.[16,17] Here we describe 5 cases of SIC and 4 cases of SCC. Due to the rarity of the disease and the similarity in histopathologic features, we summarize their clinical and radiologic manifestations, diagnosis and differential diagnoses, treatments, and prognoses together, to give more knowledge about this kind of rare disease.

2. Materials and methods

This is a retrospective descriptive study without any experiment conducted on human or the use of human tissue samples, nor any experimental protocol. All methods were carried out in accordance with relevant guidelines and regulations, and all the informed consents were received. We searched our hospital's pathologic database for tumors in the hepatobiliary-pancreatic system from January 2007 to July 2018 using the search terms "sarcomatous" or "sarcomatoid." Our search identified 21 consecutive patients who had sarcomatous carcinoma based on pathology. Twelve patients were excluded because the tumor was either originated from or was a metastasis of hepatocellular, gallbladder, renal, or adrenal carcinoma. The final cohort included 9 patients with carcinoma in the intrahepatic bile ducts or in the CBD. Before surgical treatments, all patients had undergone computed tomography (CT), magnetic resonance imaging (MRI) or magnetic resonanced cholangio-pancreatography, and ultrasonography examinations. They had also taken blood routine, liver and renal function, coagulation, and serum carcinoembryonic antigen tests. All patients had primary curative operations performed.

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Tissue samples for light microscopic study were obtained from primary lesions during surgery. Sections were stained with hematoxylin and eosin. For immunohistochemical studies, many antibodies were used, including cytokeratin, desmin, mucin, vimentin, α-fetoprotein, carcinoembryonic antigen, smooth muscle actin, and s-100 protein. Patients were followed up with postoperatively regarding their metastasis or recurrence, adjuvant therapy, quality of life, and serum test results.

3. Results

3.1. Basic characteristics of patients

The basic characteristics of the 9 patients are summarized in Table 1. Overall, 5 patients were diagnosed with SIC, and 4 patients were diagnosed with SCC. The average age of these 9 patients was 62.22 years, ranging from 54 to 68 years. Among them, 3 were males and 6 were females. The disease courses were rather variable, from 2 weeks to 8 years. While it seemed that the patients with SCC had shorter disease courses, possibly because of the early discovery of jaundice due to the special locations of SCC lesions. Abdominal pain, weak, anorexia, and weight loss were other main symptoms, wherein lies not much differences from that of ICC and choledochal carcinoma. There was nothing notable in the personal history or in the findings during physical examinations. However, the history of choledocholithiasis or hepatolithiasis was critical for patients with SIC, which reflected an abnormal situation of the hepatobiliary system (Table 1).

The results of preoperative lab tests were not distinctive from that of ICC and choledochal carcinoma. Increased levels of total bilirubin, direct bilirubin, and some other indexes in the patients with SCC were most likely due to the obstruction of CBD. Cancer antigen 19-9, as known to all, was an important predictor of malignancy in pancreaticobiliary system. Some other tumor markers, including cancer antigen 242, carcinoembryonic antigen, and α-fetoprotein, mostly remained within the normal range, with no special prompted significance (Table 1).

As for the preoperative adjuvant imaging examinations, the diameter (or size) of some tumors was hard to measure. In such situations, the description of the mass might be "atrophy of the left hepatic lobe" (patient 5), or "multiple uneven segment stenosis of CBD" (patient 6). Additionally, the dilation of CBD was inevitable in the patients with SCC, while the dilation of intrahepatic bile duct was uncertain (Table 1). Some typical images from those patients of SIC and SCC were arranged in Figures 1 and 2.

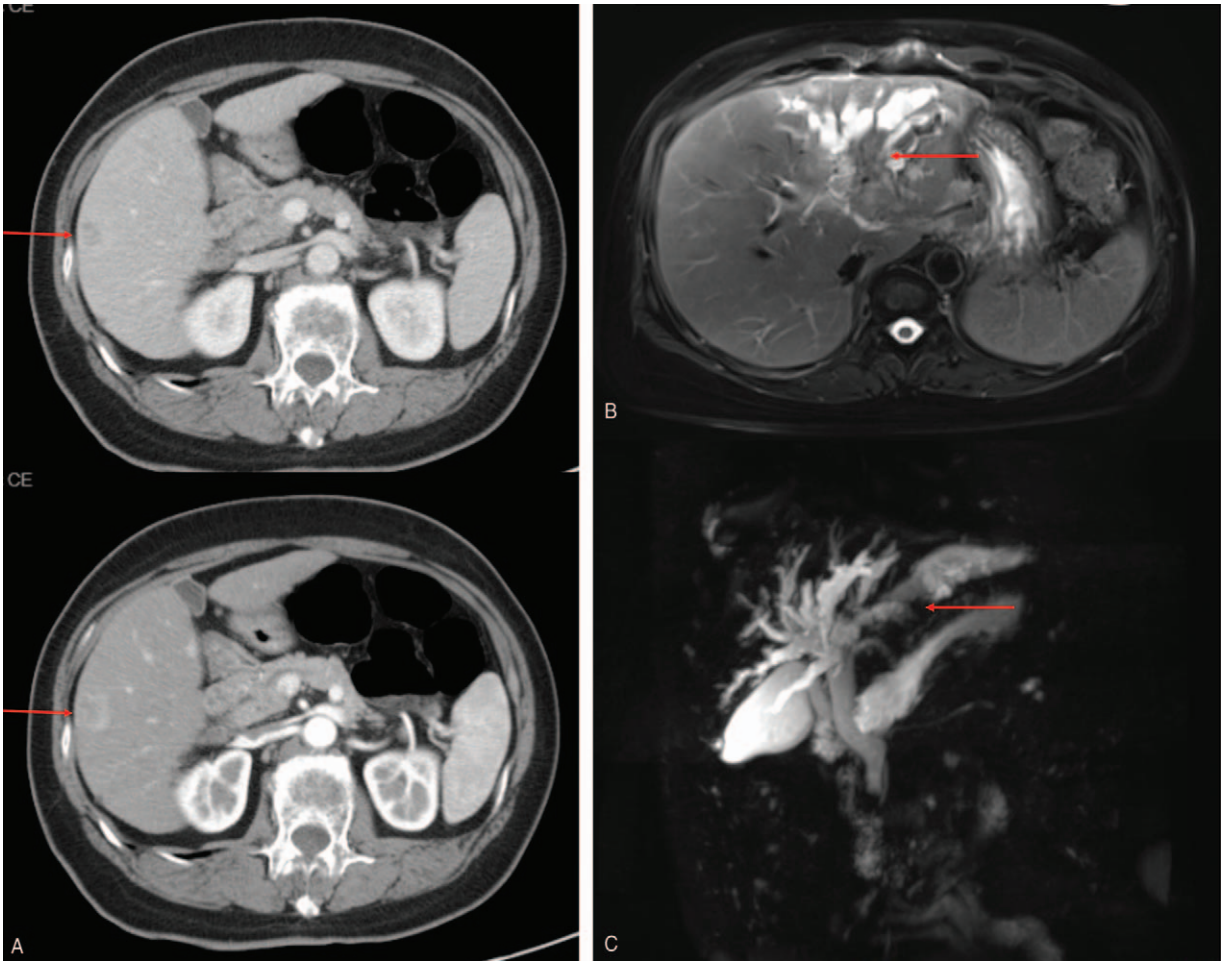

Figure 1. The preoperative images of patients with sarcomatous intrahepatic cholangiocarcinoma (SIC) with typical changes. (A) The computed tomography images of a patient with SIC showed a hypodense hepatic lesion with peripheral enhancement (arrow). (B) The magnetic resonance imaging image of a patient with SIC showed a low-intensity hepatic lesion on T2 weighted image (arrow). (C) The magnetic resonanced cholangio-pancreatography image of a patient with SIC showed a low-intensity lesion in hepatic duct, with dilation of corresponding bile ducts (arrow).

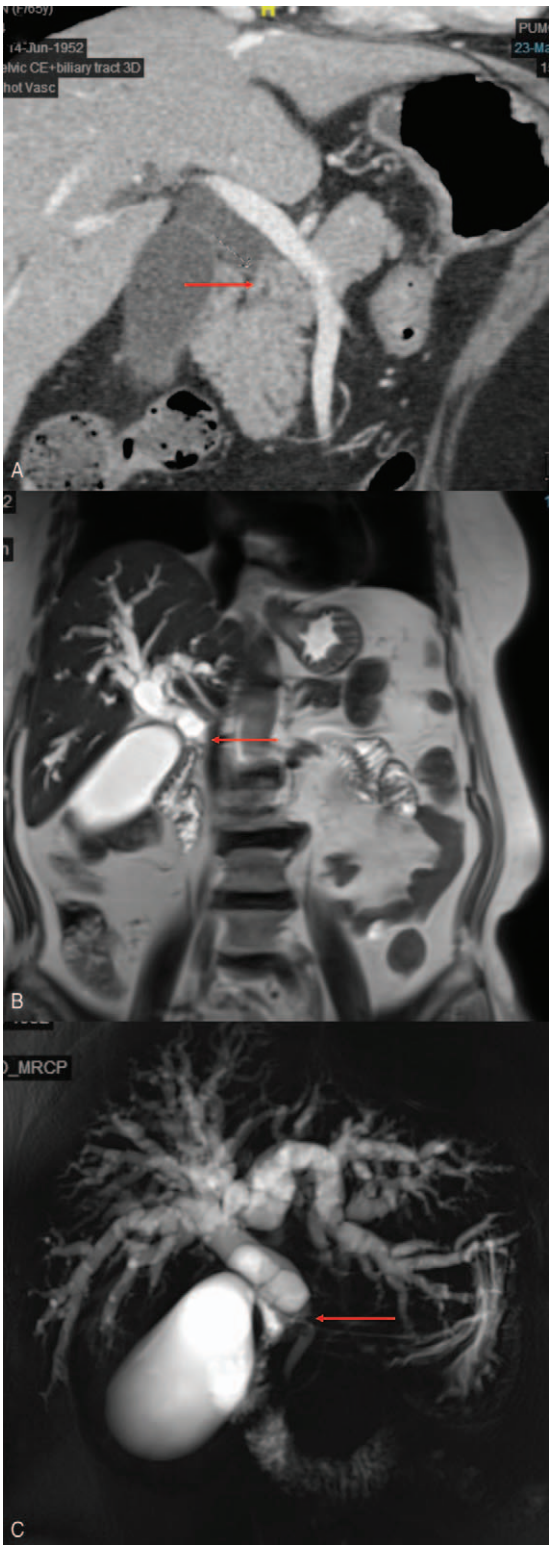

Figure 2. The preoperative images of patients with sarcomatous choledochal carcinoma (SCC) with typical changes. (A) The computed tomography image of a patient with SCC showed a hypodense lesion in common bile duct (CBD) (arrow). (B) The magnetic resonance imaging image of a patient with SCC showed multiple uneven segmental stenosis and dilation of CBD on T1 weighted image (arrow). (C) The magnetic resonanced cholangio-pancreatography image of a patient with SCC showed multiple high-intensity signals in CBD (arrow).

3.2. Perioperative status and follow-up

For radical surgical treatments, partial resection of liver, including half hepatectomy, lobectomy, and segmentectomy, combined with lymphadenectomy, was performed for SIC, and pancreaticoduodenectomy, or tumorectomy and choledochojejunostomy was performed for SCC according to different locations. The operation time, blood loss, and the blood transfusion varied due to different surgical methods. R0 resected margins were achieved in all patients. No operative or hospital deaths, nor any postoperative complications (Clavien–Dindo grade ≥ 3[18]) occurred (Table 2).

The pathologic diagnosis of metastasis of lymph nodes, and the higher level of Ki-67 index of the tumor were key features for indicating the possible shorter survival of patients with cancer. In our study, 4 patients with SIC and all 4 patients with SCC were free from lymph nodes metastasis. The level of Ki-67 index differed greatly from one patient to another, ranged from 10% to 85%. However, it appeared that there was no obvious relationship between lymph nodes metastasis or higher levels of Ki-67 index, and shorter postoperative survival duration of patients in our study. To date, 3 patients with SIC and another 3 patients with SCC were known to have died within a year after surgery, while 1 patient with SIC and another patient with SCC would live longer than 1 year. As a result, the prognoses of SIC and SCC were worse than that of ICC and choledochal carcinoma (Table 2).

4. Discussion

Sarcomatous carcinoma in the intrahepatic bile ducts or in the CBD is an extremely rare histologic variant of cholangiocarcinoma. According to previous literatures, SIC is distinguishable from ICC with sarcomatoid transformation and carcinosarcoma judged by the following criteria: coexistence of not only adenocarcinoma (ICC) but also sarcomatous components in the tumor morphologically, and histopathologically, the expression of both epithelial (e.g., cytokeratin) and mesenchymal (e.g., vimentin) features on sarcomatous component is characteristic.[2,3] On macroscopic examination, ICC with sarcomatoid transformation and carcinosarcoma are composed of both carcinomatous and sarcomatous components. However, in ICC with sarcomatoid transformation, only molecular features of epithelium were expressed in the sarcomatous lesion, and in carcinosarcoma, only molecular features of mesenchyme were expressed in the sarcomatous lesion. We distinguished SCC from ordinary choledochal carcinoma using the same criteria.

As for preoperative diagnosis, it is almost impossible to differentiate SIC from ICC, hepatocellular carcinoma, or sarcomatous hepatocellular carcinoma.[19] Shimada et al reported that serum alkaline phosphatase level in SIC patients was significantly lower than that in ordinary ICC patients, while Watanabe et al found that was even higher.[9,19] Thus, the level of alkaline phosphatase, as well as other liver function indexes including alanine transaminase and glutamyl transpeptidase, may be good indicators for further studies about the differential diagnoses of SIC and ICC.

Meanwhile, it is hard to distinguish SIC and SCC from ICC and ordinary choledochal carcinoma through preoperative radiologic images. Hypoechoic tumor in ultrasound, low-density mass with enhancement in the periphery by contrast medium in CT, hypointensity in T1-weighted MRI, and hyperintensity on

Table 1

Demographic and clinical characteristics of 9 patients.

Disease	Sarcomatous intrahepatic cholangiocarcinoma					Sarcomatous choledochal carcinoma			
Patients' number	1	2	3	4	5[22]	6	7	8	9
Age, yr	54	64	60	63	63	61	66	61	68
Gender	Female	Female	Male	Female	Male	Female	Male	Female	Female
Disease course, mo	96	1	3	1	1	30	0.5	0.5	2
Symptoms									
Abdominal pain	Y	N	N	N	Y	Y	N	N	N
Jaundice	N	N	N	N	N	Y	Y	Y	Y
Abdominal distension	Y	N	N	N	N	N	N	N	N
Nausea/vomiting	N	N	N	N	N	N	N	N	N
Weak	N	Y	Y	N	N	Y	N	N	Y
Anorexia	N	Y	N	N	N	Y	Y	N	Y
Rediating pain	N	N	N	N	N	Y	N	N	N
Diarrhea	N	N	N	N	N	Y	N	Y	N
Fever	N	N	Y	N	N	N	N	N	N
Weight loss	N	Y	Y	N	N	Y	Y	N	Y
Medical history									
Choledocholithiasis	Y	Y	Y	N	UN	N	N	N	N
Hepatolithiasis	Y	N	UN	N	Y	N	N	N	N
Cholecystolithiasis	N	N	N	N	Y	N	N	N	N
Personal history									
Smoking	N	N	Y	N	Y	N	N	N	N
Drinking	N	N	Y	N	N	N	N	N	N
Physical examinations									
Body mass index	25.32	22.66	21.30	23.42	24.34	23.07	16.73	29.30	19.03
Abdominal pressing pain	Y	N	N	N	Y	Y	Y	N	N
Preoperative lab tests									
Alanine transaminase, U/L	28	27	19	13	19	58↑	35	280↑	119↑
Total bilirubin, μmol/L	6.4	9.4	12.8	9.3	8.4	243.8↑	32.1↑	257.4↑	28.8↑
Direct bilirubin, μmol/L	3.1	4.4	7.4↑	3.0	2.7	166.2↑	25.4↑	206↑	22.7↑
Glutamyl transpeptidase, U/L	179↑	75↑	169↑	21	125↑	307↑	222↑	1556↑	603↑
Aspartate transaminase, U/L	22	35	21	17	25	76↑	25	187↑	101↑
Alkaline phosphatase, U/L	256↑	215↑	134↑	57	110	220↑	360↑	545↑	101
Prothrombin time, s	13.2↑	12.8↑	14.3↑	13.2↑	11.7	13.3↑	11.7	12.0	13.4↑
Prothrombin time, %	81.2	74.2	71.5↓	78.2	109.2	80.6	92.4	88	74.7
Activated partial thromboplastin time, s	29.9	31.2	27.0	31.4	22.5	22.3↓	34.4↑	25.6	28.9
Cancer antigen 19–9, U/L	7833↑	7.8	14.2	28.1	100.5↑	59.2↑	12.4	57.1↑	181.5↑
Cancer antigen 242, U/L	4.0	0.1	1.7	0.3	2.8	1.0	0.8	3.3	3.9
Carcinoembryonic antigen, ng/mL	22.6↑	0.5	2.18	3.2	2.17	3.69	2.4	2.35	4.92
α-fetoprotein, ng/mL	20.0	1.9	4.9	1.5	2.2	13.6	3.0	3.0	2.6
Preoperative adjuvant examinations									
Diameter, cm	3.8	6.3	7.9	3.1	–	–	3.0	1.8	1.3
Dilation of CBD	N	N	N	N	N	Y	Y	Y	Y
Dilation of IBD	–	–	–	–	Y	N	Y	–	–

CBD = common bile duct, cm = centimeter, IBD = intrahepatic bile duct, mo = month, – = no reports, N = No, UN = the patient did not know the situation but the adjuvant examinations reported, Y = Yes, yr = year.

T2-weighted MRI were reported as dominant features of SIC. However, these features were also very common in ICC.[19] Consequently, the gold standards of the diagnoses of SIC and SCC remain postoperative histopathologic examinations.[20]

Interestingly, many SIC cases occurred in patients in Asia. Whether this is related to the history of hepatolithiasis or choledocholithiasis caused by clonorchis sinensis is worth discussing. There was a report indicating that the prevalence of hepatolithiasis in the patients with ICC was up to 65.4%, which obviously confirmed the development from hepatolithiasis and chronic inflammation to carcinoma.[21] But the relationship between hepatolithiasis, choledocholithiasis, and the sarcomatoid changes of ICC, and finally SIC, remains a mystery. More clinical and genetic research is required.

As for the treatments of SIC and SCC, there is still no specific consensus due to their rarity. Besides, it is also almost impossible to make a differential diagnosis during the operations.[19] Fortunately, this kind of confusing situation would neither affect the decision of surgical treatments, nor the resection area. Additionally, Kaibori et al found that the prognosis for SIC treated with hepatectomy was better than that without hepatectomy.[20] Combined with our data, partial hepatectomy with regional lymphadenectomy is recommended for patients with any suspicion of SIC. By the same logic, pancreaticoduodenectomy with sufficient lymphadenectomy for SCC at lower part of CBD, and tumorectomy with choledochojejunostomy and lymphadenectomy for SCC at higher part of CBD were recommended surgical methods.

According to our study, lymphatic metastasis might not be the major approach of the progression of SIC and SCC. Hematogenous metastasis, or even direct seeding, was more likely to explain the poor prognoses of the diseases. Adjuvant chemotherapy was a

Table 2

Perioperative status and long-term follow-up.

Disease	Sarcomatous intrahepatic cholangiocarcinoma					Sarcomatous choledochal carcinoma			
Patients' number	1	2	3	4	5[22]	6	7	8	9
Intraoperative data									
Operation	Left hepatectomy	Hepatic segmentectomy	Hepatic segmentectomy	Hepatic segmentectomy	Hepatic lobectomy	PD	Tumorectomy + choledochojejunostomy	PD	PD
Lymph nodes dissection	Y	Y	Y	Y	Y	Y	Y	Y	Y
R0 resection	Y	Y	Y	Y	Y	Y	Y	Y	Y
Operation time, h	5.0	2.5	3.0	2.5	3.5	5.0	4.0	5.5	5.0
Blood loss, mL	800	100	300	100	350	400	400	400	200
Blood transfusion	Y	N	Y	N	N	N	Y	Y	N
Postoperative data									
Mortality	N	N	N	N	N	N	N	N	N
Overall complications (Clavien–Dindo)	1	1	1	1	1	1	1	1	1
Postoperative hemorrhage	N	N	N	N	N	N	N	N	N
Intraperitoneal infection	N	N	N	N	N	N	N	N	N
Thromboembolism	N	N	N	N	N	N	N	N	N
Pancreatic fistula (≥ISGPF grade B)	N	N	N	N	N	N	N	N	N
Biliary fistula	N	N	N	N	N	N	N	N	N
Delayed gastric emptying (≥ISGPS grade B)	N	N	N	N	N	N	N	N	N
Others	N	N	N	N	N	N	N	N	N
Length of the hospital stay after surgery, d	18	9	8	8	6	37	13	36	20
Pathology									
Diameter, cm	2	5.0	9.0	1.5	8	1.2	1.2	1	1.5
Lymph nodes metastasis	Y	N	N	N	N	N	N	N	N
Ki-67 index, %	40	15	20	80	50	15	10	15	85
Follow-up									
Follow-up duration	6	5	6	12	7	12	7	8	6
Adjuvant chemotherapy	Y	Y	Y	Y	Y	Y	Y	Y	Y
Situation	Dead	Dead	Dead	Alive	Alive	Alive	Dead	Dead	Dead

cm = centimeter, d = day, h = hour, mL = milliliter, ISGPF = International Study Group of Pancreatic Fistula, ISGPS = International Study Group on Pancreatic Surgery, N = no, NA = not applicable, PD = pancreaticoduodenectomy, Y = yes.

routine treatment for all patients in our study, while the chemotherapy plans differed greatly from 1 patient to another, since there lacked standard treatment consensus for SIC and SCC. Some reports suggested Gemcitabin, but there was no any assessment of efficacy, due to the rarity of the diseases, and the short survival time. Thus, more studies or analyses are needed.

Although there was no clear explanation of the causes and developments of SIC and SCC, some researchers assumed that these kinds of biphasic tumors may arise from totipotent stem cells, which are able to develop into both epithelial and mesenchymal cells. Others hypothesized that the neoplastic cells of conventional ICCs were capable of transforming into multipotent immature cells, which, in turn, redeveloped into sarcomatous components. Whatever the disease causes are, chronic inflammation plays an important role in the developmental process.

The primary limitation to this study is the small sample size and thus lack of statistical analysis. In conclusion, sarcomatous biliary carcinoma, including SIC and SCC, is very rare and malignant, which is diagnosed by postoperative histopathologic examinations. The prognoses of SIC and SCC were worse than that of ICC[22] and choledochal carcinoma. The pathologic diagnosis of metastasis of lymph nodes, and level of Ki-67 index of the tumor were possible indicators for postoperative survival. Besides, differences of gene expression and protein function in different patients could certainly result in different follow-up situation. The sample size in our study was too small to get a universal conclusion about the prognosis of the disease. Therefore, further studies or analyses are urgently needed to address the current unmet need and questions. For instance, further studies ought to analyze any factors or markers that are correlated with long-term survival or better prognosis, or potential originating mechanisms of this rare disease that could be helpful in early diagnosis or targeted therapy.

Author contributions

NZ, YL, and MZ are co-first authors in this article, while NZ helped in surgical treatments and data collection; YL was in charge of clinical data collection, analysis, and language editing; and MZ was in charge of clinical data collection. All these 3 authors contributed equally. XC was in charge of pathologic detection and analysis. QQ was helped in surgical treatments of some of those patients. XH was the correspondence author in this article. He was in charge of the surgical treatments and the whole team, and guided this research program.

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Investigation: Yatong Li, Xiaodong He.
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