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Illuminating and Instructive Clinical Case

Sarcomatoid Intrahepatic Cholangiocarcinoma After Immunotherapy: A Case Report and Review of the Literature

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Abstract

Sarcomatoid carcinoma is a rare tumor that is composed of a mixture of malignant epithelial cells and mesenchymal cells. Many studies have reported that sarcomatoid carcinoma occurs in multiple organs including the liver. Sarcomatoid intrahepatic cholangiocarcinoma (S-iCCA) is an extremely rare tumor that primarily occurs in the liver. This case occurred in a middle-aged man who was admitted to our hospital with abdominal pain. Enhanced computed tomography of the abdomen showed a low-density mass in the upper right posterior lobe of the liver with enhancement in the periphery. Histological and immunohistochemical examination indicated that the tumor was malignant, with both cancer and sarcoma components, and was positive for cytokeratin and vimentin. The patient was diagnosed with S-iCCA. Metastases appeared in the liver and lung 4 months after surgery. Two cycles of chemotherapy were administered. Because of enlargement of the tumor, anti-angiogenic agents combined with immunotherapy were subsequently given to achieve disease control. To the best of our knowledge, this is the first reported case of a programmed cell death-1 inhibitor used in a S-iCCA patient. The purpose of this case report and literature review is to enhance clinician understanding of S-iCCA and to explore safe and effective treatment methods.

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Keywords: Sarcomatoid intrahepatic cholangiocarcinoma; Sarcomatoid degeneration; PD-1 inhibitors; Anti-angiogenic therapy.

Abbreviations: AAT, A-1-antitrypsin; AFP, alpha-fetoprotein; BTC, biliary tract cancer; CA125, carbohydrate antigen 125; CA19-9, carbohydrate antigen 19-9; CD, cluster of differentiation; CDX2, caudal type homeobox transcription factor 2; CEA, carcinoembryonic antigen; CHB, chronic hepatitis B; CHC, chronic hepatitis C; C-kit, receptor tyrosine kinase; CK-Pan, pan-cytokeratin; CK19, cytokeratin 19; CT, computed tomography; EMA, epithelial membrane antigen; F, female; HCC, hepatocellular carcinoma; Hep Par 1, hepatocyte paraffin 1; HSA, human serum albumin; ICIs, immune checkpoint inhibitors; IHCC, intrahepatic cholangiocarcinoma; KER, keratin; M, male; NA, not available; NSE, neuron-specific enolase; PAS, periodic acid–Schiff; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; S-iCCA, sarcomatoid intrahepatic cholangiocarcinoma; SMA, smooth muscle actin; TACE, transhepatic arterial chemotherapy and embolization.

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Introduction

Biliary tract cancer (BTC) is a malignant tumor that is composed of bile duct cells that may come from any part of the bile duct epithelium.[1] Sarcomatoid intrahepatic cholangiocarcinoma (S-iCCA) is a rare subtype of BTC that the World Health Organization 2010 classification defines as a BTC similar to spindle-cell sarcoma, fibrosarcoma, or malignant fibrous histiocytoma, with scattered lesions within the tumor, including squamous cell carcinoma. Epithelial tumors with sarcomatoid changes have been reported to occur in the lung, uterus, skin, kidney, esophagus, stomach, gallbladder, and thyroid, and account for 4.5% of BTC cases. However, the mechanism of S-iCCA pathogenesis is not known.[2] At present, the main treatment option for S-iCCA is surgical resection. Recurrent S-iCCA, is usually treated with a BTC chemotherapy regimen chemotherapy but the therapeutic effect is limited. Immune checkpoint inhibitors (ICIs) have achieved significant response in multiple tumor types in recent years. Preliminary evaluations of single-agent or combined chemotherapy and antivascular therapy have been carried out in patients with end-stage BTC.[3] However, the effectiveness of ICIs for treating BTC is still controversial.[4] We report a case with postoperative recurrence of S-iCCA treated by a combination of programmed cell death-1 (PD-1) inhibitor and anti-angiogenic drugs. We reviewed the published data on S-iCCA. And to the best of our knowledge, this is the first reported case of S-iCCA a treated with a PD-1 inhibitor.

Case report

A 54-year-old man was admitted to our hospital for intermittent upper abdominal pain. Physical examination revealed mild tenderness and rebound pain in the upper abdomen. Routine blood tests, liver function, kidney function, electrolytes, carbohydrate antigen 125 (CA125), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) levels were within the normal range. Enhanced abdominal computed tomography (CT) revealed a patchy, low-density lesion in the upper right posterior lobe, intrahepatic bile duct dilation, and multiple bile duct stones. A chest CT did not indicate tumor metastasis. The preoperative diagnosis was a space-occupying lesion of the right posterior lobe of the liver and intrahepatic bile duct stones. No involved lymph nodes or distant metastases were discovered. Right hepatic lobectomy, cholecystectomy, biliary exploration, T-tube drainage, and adhesiolysis were performed. Postoperative pathological evaluation found an enlarged bile duct with a cross sectional diameter of 0.5–1.0 cm, and filled with sand-like stones. Postoperative histology found a 6.0 × 4.5 × 3.3 cm liver tumor with unclear borders and gray nodules. The junction of some tumor cells and bile duct cells suggested high-grade intraepithelial neoplasia. No evidence of cancer invasion was found in the margins and nerves of hepatectomy tissue. but tumor invasion of the blood vessels of the liver was observed. Using the American Joint Committee on Cancer TNM Staging System, version 8, the tumor was T2N0M0 (Stage II). Immunohistochemical examination of the tumor revealed that vimentin and pan-cytokeratin (CK-Pan) were positive, while smooth muscle actin (SMA), S-100, cluster of differentiation (CD) 34, desmin, cytokeratin (CK)19, caudal type homeobox transcription factor 2 (CDX2), CD117 and hepatocyte paraffin 1 (Hep Par 1) were negative. The Ki-67 proliferation index was about 50% and the programmed death-ligand 1 (PD-L1) combined positive score was 60 (Fig. 1). Based on the above histopathological and immunohistochemical results, a definitive diagnosis of S-iCCA was confirmed. No subsequent chemotherapy or radiotherapy was administered. The patient was readmitted 4 months after surgery complaining of pain in the right upper abdomen. The patient's serum CA125 was elevated to 103.2 IU/ml (0–34.0 IU/ml), and CA199, CEA, and AFP were all in the normal range. CT of the chest (Fig. 2A, D, G) and abdomen (Fig. 2J, M, P) revealed that the tumor had metastasized to the liver and lung. According to the response evaluation criteria in solid tumors 1.1, the total diameter of all measurable target lesions was about 12.2 × 11.7 × 10.7 cm. We treated the patient with 2 cycles of gemcitabine and cisplatin chemotherapy. Follow-up chest (Fig. 2B, E, F) and abdominal CT (Fig. 2K, N, Q) showed that the target lesions had enlarged from 34.6 to 39.8 cm, which was an increase of 15% compared with baseline. The patient achieved stable disease with a significant weight decrease of 3 kg. CA125 decreased briefly and then continued to increase. The patient was switched to carrelizumab, a PD-1 inhibitor, 200 mg every 3 weeks combined with anlotinib, an anti-angiogenic drug, 8 mg every day. After 4 cycles of the combination regimen, the pain in the right upper abdomen was significantly improved, the patient's weight had increased by 2.5 kg, and his CA125 was reduced to 8.7 IU/ml compared with the previous period. Treatment response was evaluated on the basis of the findings of chest (Fig. 2C, F, I) and abdominal CT (Fig. 2L, O, R) in accordance with response evaluation criteria in solid tumors 1.1. The total diameter of measurable target lesions was about 9.1 × 8.7 × 8.0 cm, which was a 35% reduction from baseline. The patient achieved partial response. The drugs were well tolerated, with development of some cutaneous capillary endothelial proliferation in the facial skin that resolved spontaneously within 1 week. The overall follow-up time was 12 months.

Discussion

S-iCCA is a rare but an aggressive variant of BTC with a very poor prognosis.[5] S-iCCA pathogenesis is not yet clear, but it has been reported to be associated with hepatitis B virus infection and preoperative anticancer treatment, such as transcatheter arterial chemoembolization, radiofrequency ablation, and percutaneous ethanol injection.[1,6,7] Clinical manifestations of S-iCCA are determined by its location, mode, and speed of tumor growth. Abdominal pain is the most common clinical symptom.[8]

Serum CA125, CA19-9, CEA, and AFP may not be sensitive for the diagnosis of S-iCCA. The imaging features of S-iCCA are also nonspecific and usually appear as hypoattenuated or mixed-echoic masses on ultrasonography.[9] CT shows low-density lesions with peri-enhancement regions occasionally accompanied by intratumor hemorrhage.[7,10] Because of the lack of specificity in serology and imaging, the diagnosis of S-iCCA mainly depends on pathological confirmation. The pathology of S-iCCA has both carcinoid and sarcomatoid manifestations.[1,6]

To understand the known characteristics of S-iCCA, we searched PubMed and Google using the keywords "liver," "sarcomatous," "sarcomatoid," and "cholangiocarcinoma." After analysis of the retrieved publications, 51 unrepeated S-iCCA cases were identified in 20 published studies.[1,2,5–22] Table 1 summarizes the clinical characteristics of 52 patients (including this case). Thirty-five were male (67.3%), 17 were female (32.7%), and the average age was 61 (range: 37–87) years. Nineteen patients (36.5%) had a history of liver disease or surgery, including 11 (21.2%) with chronic hepatitis B virus infection, three (5.8%) with hepatitis C, three (5.8%) with hepatolithiasis, one (1.9%) with biliary tract roundworm, and one (1.9%) with cholecystectomy. It is conceivable that chronic inflammation of the biliary tract may be related to the onset of S-iCCA. Thirty-four patients had obvious symptoms at the first visit. The main clinical manifestations were abdominal discomfort including pain and fever in 21 (65.4%) and eight (15.4%) patients. There were 24 cases with confirmed liver location reported, mostly located at the left lobe (15 cases, 62.5%), followed by the right lobe (seven cases, 29.2%), and anus (two cases, 8.3%). A total of 42 patients (80.8%) had one tumor and 10 (19.2%) had multiple tumors. Most of the tumors were single lesions in the left lobe of the liver. The tumors ranged from 2.0–22.0 cm, with an average size of 8.4 cm.

The findings of the first laboratory examination and preliminary imaging characteristics are shown in Table 2. CA199 was elevated in 17 cases and normal in 23. CEA was elevated in three cases and normal in 25. AFP was elevated in six cases and normal in 28. CA125 was elevated in one case and normal in three. Compared with CEA, AFP, and CA125, CA199 may be more significant in the diagnosis and follow-up of S-iCCA. However, CA125 was elevated in our patient during the follow-up period, but with no concurrent increase in CA199. Meanwhile, the change in CA125 was consistent with the degree of tumor control identified by imaging, which suggests that CA125 may be a useful indicator of diagnosis and follow-up of S-iCCA. In general, the serological markers were not unique. Preliminary imaging findings in 28 patients included 10 (35.7%) with hepatocellular carcinoma, nine (32.1%) with cholangiocellular carcinoma, one (3.6%) with lymphoma, four (14.3%) with hepatic abscess, three (10.7%) with hepatic space-occupying lesions, and one (3.6%) with intrahepatic cholangiolithiasis.

The results of immunohistochemical staining of the 52 patients are shown in Table 2. Thirty cases (96.8%) were positive for cytokeratins, 27 (84.4%) were positive for vimentin, 16 (94.1%) were negative for AFP, four (100%) were negative for Hep Par 1, and nine (100%) were negative for human serum albumin (HSA). Immunohistochemical staining indicated that epithelial tumor markers (cytokeratins) and mesenchymal tumor markers (vimentin), that are related to S-iCCA epithelial bile duct tumors, were positive, and that HSA, AFP, and Hep Par 1 were negative as hepatocyte markers, which provided valuable information for the differential diagnosis of hepatocellular carcinoma, cholangiocarcinoma, and metastatic liver cancer.[5] That approach was helpful in arriving at the final diagnosis of S-iCCA.

Table 1 also summarizes the stage, treatment, and prognosis of the 52 patients. Fifteen patients were staged. Thirteen were stage IVA or IVB and the remaining two were both stage II. of the 52 patients with S-iCCA, 26 (50.0%) had surgery, 17 (32.7%) received chemotherapy or ra-

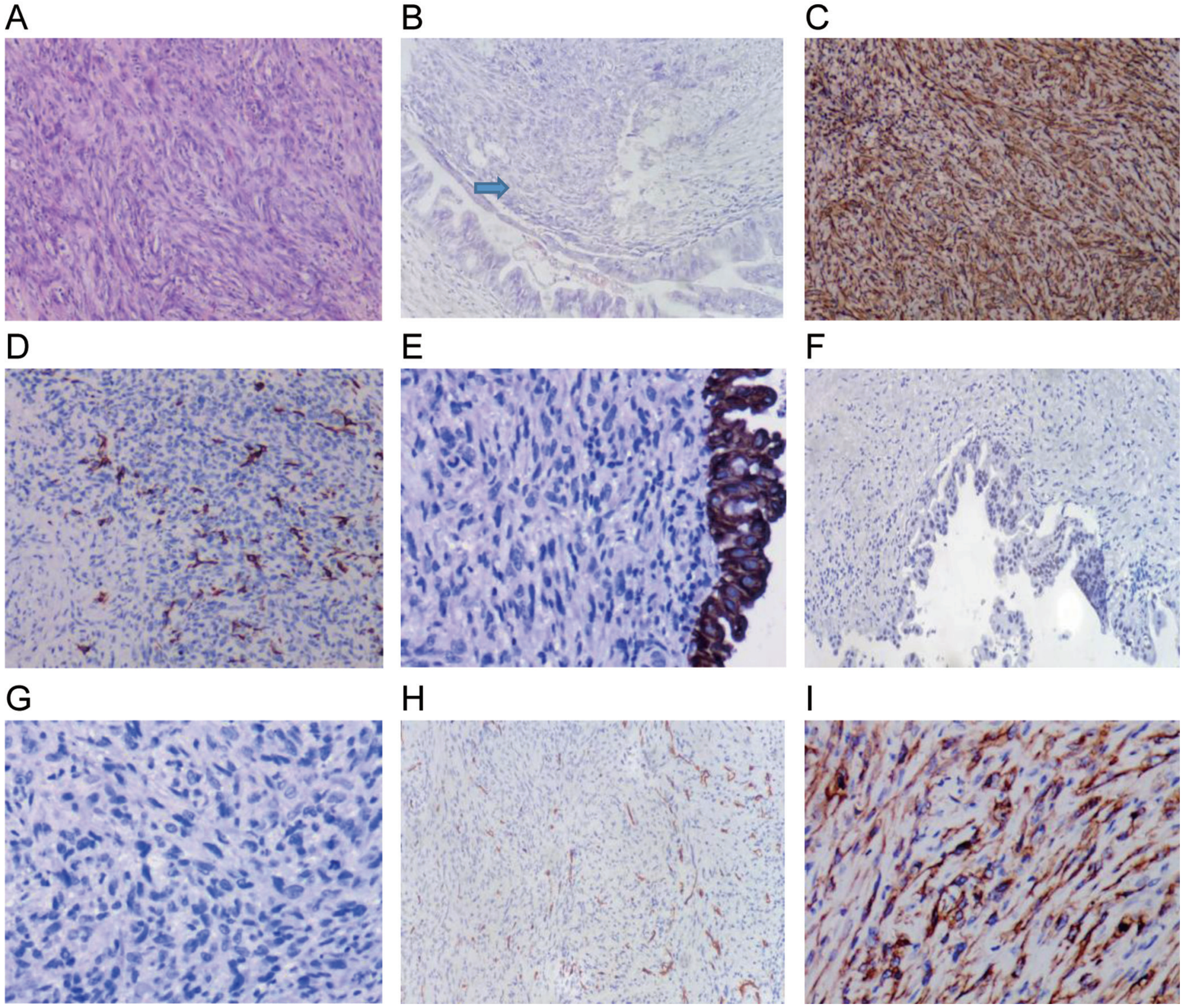
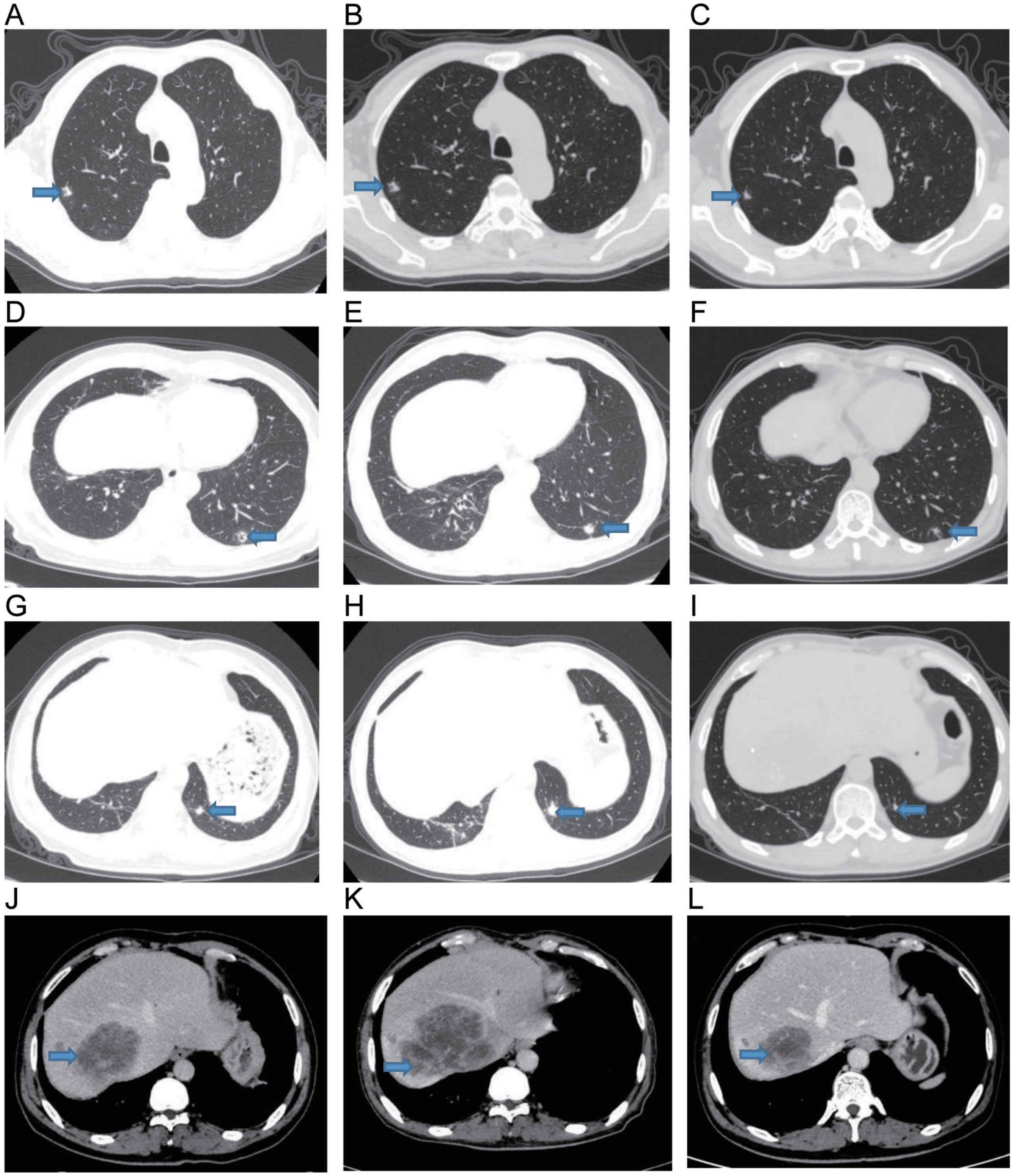


Fig. 1. The patient's hepatic biopsy pathology was intrahepatic sarcomatoid cholangiocarcinoma. (A) Hematoxylin and eosin stain of the tumor specimen. (B) High-grade intraepithelial neoplasia at the junction of bile duct cells and tumor cells; (C, D) Positive vimentin and pan-cytokeratin staining supported the diagnosis of S-iCCA. (E, F) Tumor tissue was cytokeratin 19 and CDX2 negative, but bile duct epithelial cells were partially positive. (G) Tumor cells were Hep Par 1 negative, which denied an origin of liver cells. (H) Tumor cells were CD34 negative and vascular endothelial cells were positive. (I) Tumor tissue stained with the PD-L1 clone 22C3. shows a high level of PD-L1 expression with a combined positive score of 60 (× 200). CD34, cluster of differentiation 34; CDX2, caudal type homeobox transcription factor 2; Hep Par 1, hepatocyte paraffin 1; PD-L1, programmed death-ligand 1; S-iCCA, sarcomatoid intrahepatic cholangiocarcinoma.

diotherapy, three (5.8%) received transcatheter arterial embolization, 10 (19.2%) received symptomatic and supportive therapy, and one (2.0%) received immunotherapy and antivascular therapy. Currently, there are no relevant guidelines for the treatment of S-iCCA patients. Surgery is currently considered the most effective treatment. In previous cases, the median survival of patients with S-iCCA who were treated without surgery was 3 months. The median survival of S-iCCA patients with surgical resection was 11 months, which is comparable to the median survival of 8 months in patients with ordinary intrahepatic cholangiocarcinoma who did not undergo surgery.[5,11] The prognosis of S-iCCA are worse than those of ordinary intrahepatic cholangiocarcinoma. The former is not sensitive to radiotherapy and chemotherapy, and the survival rate is extremely low, with 1-year overall survival at almost zero.[8,22] Based on this context, more treatment options urgently need to be developed and updated.

Following the milestone results of the ABC-02 phase III trial, the standard first-line treatment for advanced BTC was based on a combination of cisplatin and gemcitabine, with a median progression-free survival of only 8.0 months.[23] The limited survival benefit provided by systemic chemotherapy highlighted the need for more effective treatments of metastatic BTC. ICIs promote the activation of T lymphocytes by blocking PD-1/PD-L1 proteins on tumor cells and/or immune cells, thereby restoring normal antitumor immunity to achieve treatment of the target tumor.[24] There are currently a number of preclinical and clinical studies investigating the application of ICIs in BTC, and the role of immunotherapy in BTC remains to be determined.[4] However, studies have shown that the expression of PD-L1 in tumors or tumor-



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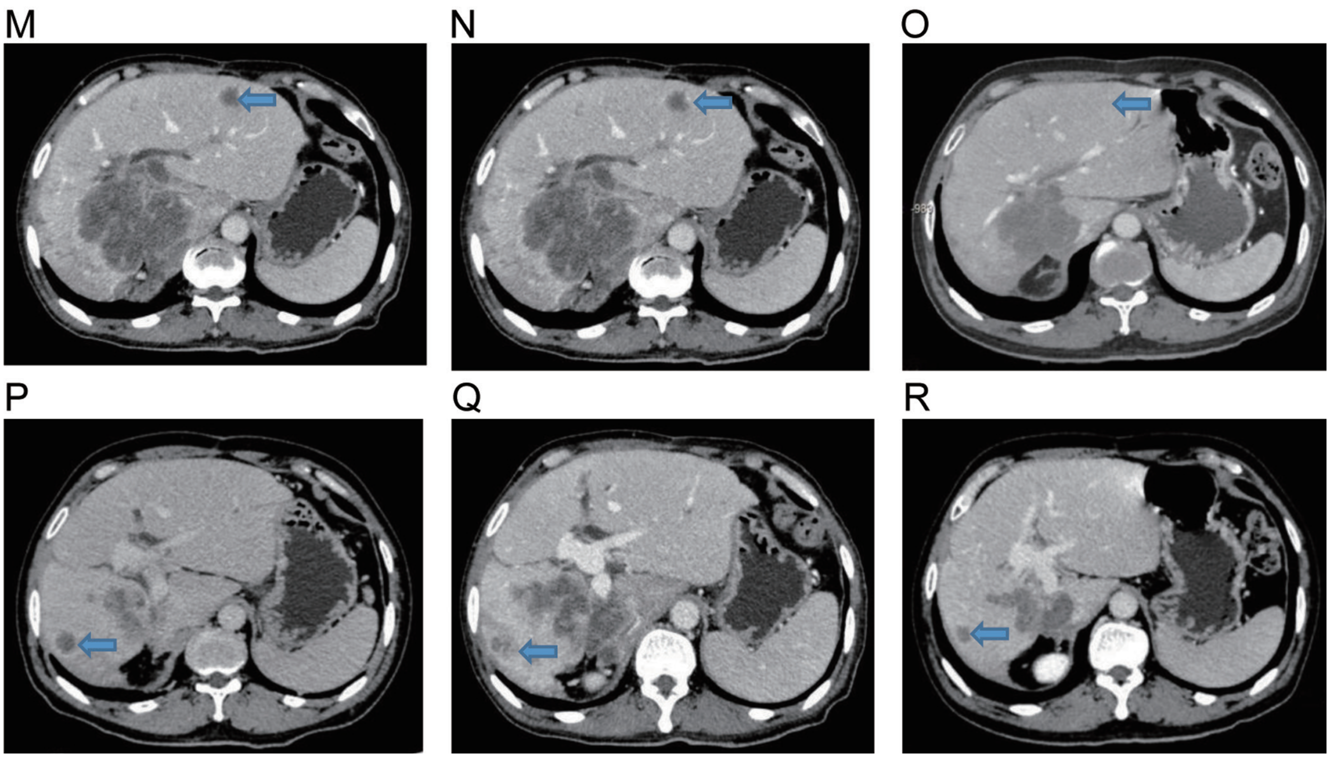

Fig. 2. Computed tomography of the chest and abdomen before and after treatment. (A, D, G) Four months after surgery, nodules were scattered in both lungs. The largest were located in the posterior basal segment of the lower lobe of the left lung, about 1.0 × 0.8 cm. The boundary was not clear and small bubbles were seen in the nodules. (J, M, P) Four months after surgery, partial loss of the right posterior lobe of the liver, multiple nodules, and masses in the residual liver with annular enhancement are seen. (B, E, H) After chemotherapy, scattered nodules in both lungs were larger than before. (K, N, Q) After chemotherapy, partial loss of the right posterior lobe of the liver with multiple nodules in the residual liver that had enlarged. (C, F, I) After four cycles of treatment with carilizumab and anlotinib, scattered nodules in both lungs were smaller than before. (L, O, R) After four cycles of treatment with carilizumab and anlotinib, the right posterior lobe of the liver was partially missing and the number and size of multiple nodules and masses in the residual liver were reduced. CT, computed tomography.

related immune cells is closely related to the clinical efficacy of ICIs in BTC. BTC patients with PD-L1 expression of 1% or higher were more likely to respond to ICIs.[24]

The patient's PD-L1 combined positive score reached 60 and the use of PD-1 inhibitors may achieve better results. The PD-1 inhibitor carrelizumab that used in this case has shown good anticancer activity and controllable toxicity against BTC in recent studies.[25] Although ICIs alone have had a certain promise in the treatment of advanced BTC, the overall effectiveness for treating metastatic BTC is limited, which has led to the exploration of different combinations of ICIs, including in combination with antivascular agents.[3,4] Preclinical evidence indicates that the use of a combination of anti-angiogenic agents and ICIs enhanced the activity of the immune system.[3] The anti-angiogenic drug anlotinib, which is also used in this case, has been shown to significantly improve the prognosis of patients with relapsed advanced soft tissue sarcoma. China has approved it as the standard treatment for advanced or unresectable soft tissue sarcoma. The above studies suggest that combined therapy may have achieve a better response than single-agent therapy.

At present, there are no guidelines for determining the prognosis and survival of patients with S-iCCA. Because the patient in our case had enlarged lesions and weight loss after receiving gemcitabine plus cisplatin chemotherapy, the follow-up systemic treatment adopted carrelizumab combined with anlotinib. A relatively good short-term effect was achieved. At present, the patient's survival period has reached 12 months, with an Eastern Cooperative Oncology Group score of 0 and no reported adverse events above grade 2. It is expected that the patient can achieve long-term survival benefits.

Conclusion

S-iCCA is a rare malignant tumor for which laboratory tests, and radiologic examinations were not specific. The diagnosis of S-iCCA was made by pathology and immunohistochemical analysis because of the nonspecific clinical manifestations. Surgical resection is currently the main treatment for S-iCCA, but there is little evidence in the literature to support postoperative adjuvant radiotherapy and chemotherapy for treatment. Furthermore, overall survival is poor following surgery. In view of the low response rate of single-agent ICIs, combined anti-angiogenic drugs are not only the current standard regimen for advanced liver cancer but may also be a treatment option for S-iCCA.

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Table 1. Clinical characteristics of S-iCCA reported in English-language publications

Study	Case (no.)	Age/ sex	Hepatic disease	Clinical symptom	Loca- tion	Tumor size (cm)	Number of tumors	TNM	Treatment	Outcome, months
Sasaki *et al.*[13]	1	79/M	(−)	NA	Left	7	Multiple	NA	Supportive	NA
Haratake *et al.*[14]	2	59/M	Hepatolithiasis	Fever, icterus, abdominal mass	Right	Fist-sized	Multiple	NA	Supportive	1, dead
Nakajima *et al.*[15]	3	37/M	NA	Abdominal discomfort, epigastralgia	Left	10	Single	NA	Supportive	2.5, dead
	4	43/F	NA	Fever, icterus, abdominal mass	Right	14	Single	NA	Surgery	4.5 dead
	5	73/F	NA	Abdominal mass	Left	7	Single	NA	Chemotherapy	5.0, dead
	6	64/M	NA	Abdominal discomfort, nausea	Left	7.5	Single	NA	TACE	1, dead
	7	84/F	NA	Anorexia, jaundice, abdominal pain	Hepatic hilum	3.5	Single	NA	Supportive	3, dead
	8	52/M	NA	Right hypochondralgia	Right	7.5	Single	NA	TACE	2, dead
	9	69/M	NA	Fever	Left	10	Single	NA	Surgery	36, alive
Imazu *et al.*[16]	10	77/M	NA	Liver tumor	Left	6	Single	NA	Surgery	11, alive
Honda *et al.*[17]	11	61/F	(−)	Back pain	Left	NA	Multiple	IVB	Supportive	3.8, dead
Itamoto *et al.*[18]	12	70/M	CHC	Fatigue, fever	Right	8	Single	NA	TACE and Surgery	9, alive
Matsuo *et al.*[19]	13	77/F	(−)	Abdominal pain	Left	7.7	Single	NA	Surgery	5, dead
Shimada *et al.*[11]	14	70/M	NA	NA	NA	3.4	Single	NA	Surgery	6, dead
	15	55/M	NA	NA	NA	6.7	Single	NA	Surgery	7, dead
	16	74/F	NA	NA	NA	4	Single	NA	Surgery	19, dead
	17	64/F	NA	NA	NA	8	Single	NA	Surgery	29, dead
Kaibori *et al.*[12]	18	69/F	NA	Fever, abdominal pain	Left	22	Single	NA	Surgery	3, dead
Lim *et al.*[20]	19	41/F	(−)	Palpable epigastric mass	Left	17	Single		Surgery	2, alive
Sato *et al.*[21]	20	87/M	(−)	Elevated ductal enzyme levels	Left	4	Single	NA	Supportive	3, dead
Malhotra *et al.*[2]	21	60/F	NA	Abdominal pain, abdominal mass	Left	20	Single	NA	Surgery and Chemotherapy	29, alive
Bilgin *et al.*[10]	22	48/M	A laparoscopic cholecystectomy operation	Abdominal pain, fatigue	Left	13	Single	NA	Surgery and chemotherapy	12, alive
Watanabe *et al.*[5]	23	62/M	(−)	Liver tumor, jaundice	Hepatic hilum	5	Multiple	NA	Surgery and chemotherapy	11, dead
Gu *et al.*[22]	24	65/M	CHB	NA	NA	NA	Single	NA	Chemotherapy and Radiotherapy	3, progress
	25	70/M	CHB	NA	NA	NA	Single	NA	Surgery	3, recurrence
	26	48/F	Hepatolithiasis	NA	NA	NA	Single	NA	Surgery	35, recurrence

(continued)

Table 1. *(continued)*

Study	Case (no.)	Age/sex	Hepatic disease	Clinical symptom	Location	Tumor size (cm)	Number of tumors	TNM	Treatment	Outcome, months
	27	45/M	CHB	NA	NA	NA	Single	NA	Chemotherapy and Radiotherapy	5, progress
	28	46/F	(−)	NA	NA	NA	Single	NA	Chemotherapy and Radiotherapy	2, progress
	29	69/M	NA	NA	NA	NA	Single	NA	Chemotherapy and Radiotherapy	1, recurrence
	30	54/F	CHB	NA	NA	NA	Single	NA	Surgery	26, recurrence
	31	74/M	CHC	NA	NA	NA	Single	NA	Surgery	12, recurrence
	32	57/M	(−)	NA	NA	NA	Single	NA	Chemotherapy and Radiotherapy	2, progress
	33	51/M	CHB	NA	NA	NA	Single	NA	Surgery	3, recurrence
	34	69/M	(−)	NA	NA	NA	Single	NA	Surgery	2, recurrence
	35	61/F	(−)	NA	NA	NA	Single	NA	Surgery	4, recurrence
	36	53/M	CHB	NA	NA	NA	Single	NA	Surgery	3, recurrence
Ning *et al*.[6]	37	63/M	Biliary ascariasis	Right upper abdominal pain	Left	8	Multiple	NA	Surgery	1, alive
Kim *et al*.[1]	38	45/M	CHB	Abdominal pain	NA	7.5	Multiple	IVB	Chemotherapy	1.6, dead
	39	67/M	CHC	Abdominal pain	NA	2.5	Single	IVB	Chemotherapy	4.9, dead
	40	55/M	(−)	Abdominal pain, fever	NA	6.5	Multiple	IVA	Chemotherapy	4.3, dead
	41	66/M	(−)	Abdominal pain	NA	10	Single	IVB	Supportive	0.7, dead
	42	56/M	CHB	Abdominal pain, fatigue	NA	8	Single	IVB	Chemotherapy	2.4, dead
	43	66/F	(−)	Abdominal pain	NA	7.5	Single	IVB	Chemotherapy	4.2, dead
	44	68/F	(−)	BWL, fatigue	NA	6	Single	IVB	Supportive	0.6, dead
	45	55/F	(−)	Abdominal pain, fever	NA	8.5	Multiple	IVA	Chemotherapy	1.6, dead
	46	49/M	CHB	Abdominal pain, fever	NA	9.5	Multiple	IVA	Chemotherapy	NA
	47	65/M	(−)	Abdominal pain	NA	9.5	Multiple	IVA	Supportive	0.5, dead
	48	61/M	(−)	Abdominal pain	NA	5	Single	IVB	Viscum album	12.7, alive
Wang *et al*.[7]	49	43/M	CHB	Abdominal discomfort	Right	7	Single	NA	Surgery	2.5, dead
Li *et al*.[9]	50	64/M	NA	Right upper abdominal pain	Left	2	Single	II	Surgery	3.0, dead
Sintra *et al*.[23]	51	NA/M	CHB	Head trauma	Right	10	Single	IVB	Supportive	1.5, dead
Our case	52	54/M	Hepatolithiasis	Right upper abdominal pain	Right	6	Single	II	Surgery, Chemotherapy, immunotherapy, and anti-angiogenic	12.0, alive

CHB, chronic hepatitis B; CHC, chronic hepatitis C; F, female; M, male; NA, not available; S-iCCA, sarcomatoid intrahepatic cholangiocarcinoma; TACE, transhepatic arterial chemotherapy and embolization.

Table 2. First laboratory findings, initial radiologic impression, and immunohistochemistry reported in English-language publications

Case (no.)	CEA (ng/mL)	CA19-9 (U/mL)	AFP (ng/mL)	CA125 (U/mL)	Initial radiologic impression	Positive result	Negative result
1	Normal	Normal	Normal	NA	Hepatic mass	KER, EMA, vimentin, CEA	AFP S-100, AAT
2	NA	NA	NA	NA	Hepatic abscess	Low molecular cytokeratin, vimentin	UEA-1, desmin
3	NA	NA	NA	NA	NA	PAS, KER, EMA, vimentin	CEA, CA199, AFP, actin, desmin, S-100, NSE
4	NA	NA	NA	NA	NA	KER, EMA, vimentin	PAS, CEA, AFP, CA199, actin, desmin, S-100, NSE
5	NA	NA	NA	NA	NA	/	PAS, CEA, AFP, CA199, actin, desmin, S-100, NSE, KER, EMA, vimentin
6	NA	NA	NA	NA	NA	KER, EMA	PAS, CEA, AFP, CA199, actin, desmin, S-100, NSE, vimentin
7	NA	NA	NA	NA	NA	KER, EMA, CA19-9	PAS, CEA, AFP, vimentin, actin, desmin, S-100, NSE
8	NA	NA	NA	NA	NA	PAS, KER, EMA, CEA	vimentin, CA199, AFP, actin, desmin, S-100, NSE
9	NA	NA	NA	NA	NA	/	PAS, CEA, AFP, CA199, actin, desmin, S-100, NSE, KER, EMA, vimentin
10	<0.5	17	Normal	NA	Cholangiocarcinoma	KER, vimentin, CEA	actin, AAT, S-100, AFP
11	9	13,394	<10	NA	IHCC	vimentin	S-100, desmin, AFP, albumin, myoglobin
12	Normal	2,634	293	NA	HCC	KER, EMA, vimentin	AFP, CEA, CA199, actin, desmin, S-100
13	Normal	Normal	Normal	NA	Hepatic abscess	AAT, vimentin, F13a	desmin, EMA, CYT, SMA, CEA, AFP
14	2.4	44.7	NA	NA	NA	NA	NA
15	3.2	170	NA	NA	NA	NA	NA
16	2.9	21.6	NA	NA	NA	NA	NA
17	0.5	16.0	NA	NA	NA	NA	NA
18	Normal	3,665	Normal	251	Hepatic carcinoma	vimentin, EMA, CK	S-100, CEA, AFP
19	Normal	Normal	Normal	NA	Hepatic mass	CK-pan, vimentin, CEA	CK7, CK20, S-100, HMB-45, AMA, CD34, AFP, C-kit
20	16.2	2,894	Normal	NA	IHCC	CK19, vimentin, CD44s	b-catenin
21	NA	NA	NA	NA	Hepatic carcinoma	EMA, AE1/AE3, CK7, CK19, CEA	HepPar-1
22	NA	39	NA	NA	Hepatic carcinoma	NA	NA
23	1.4	1,109.9	NA	NA	IHCC	CK, vimentin	N/A
24	NA	11.25	3.6	NA	NA	NA	NA
25	NA	22.44	NA	NA	NA	NA	NA
26	NA	7.28	1.8	NA	NA	NA	NA
27	NA	10,384	2.8	NA	NA	NA	NA

(continued)

Table 1. *(continued)*

Case (no.)	CEA (ng/mL)	CA19-9 (U/mL)	AFP (ng/mL)	CA125 (U/mL)	Initial radiologic impression	Positive result	Negative result
28	NA	NA	1.9	NA	NA	NA	NA
29	NA	NA	NA	NA	NA	NA	NA
30	NA	11.34	1.6	NA	NA	NA	NA
31	NA	6.07	1.8	NA	NA	NA	NA
32	NA	2	6.17	NA	NA	NA	NA
33	NA	11.71	5.1	NA	NA	NA	NA
34	NA	NA	NA	NA	NA	NA	NA
35	NA	886.51	1.6	NA	NA	NA	NA
36	NA	10.55	93.8	NA	NA	NA	NA
37	Normal	100.5	Normal	NA	Hepatolithiasis, choledocho-lithiasis, and cholecystolithiasis	AE1/AE3, STAT6, SOX10, CD34, CK19, Desmin, MUC1, Vimentin, SMA, S-100	NA
38	0.74	>1,200	131.67	NA	HCC	CK19, vimentin	HSA, CD10
39	1.45	3.38	66.45	NA	HCC	CK, vimentin, CEA, AFP	CK7, CK19, HSA, C-kit, CD117
40	0.1	3	2.54	NA	IHCC	CK, CK19, vimentin	CK8, desmin, EMA, CEA, C-kit, S-100
41	2.35		1.73	NA	Hepatic abscess	CK, CK8, CK19, vimentin, CEA, EMA	HSA, AFP, TTF-1
42	1.81	2.33	2.31	NA	HCC	CK, CK8, CK19, vimentin, SMA	HSA, CD5, CD68, HMW-CK
43	12.7	710.38	3.92	NA	IHCC	CK7, CK8, CK19, vimentin, CEA	HSA
44	1.18	12.59	2.70	NA	HCC	CK7, CK8, CK19, vimentin, CD34	HSA, CEA, HMW-CK
45	3.15	>1,200	1.71	NA	IHCC	CK19, vimentin, CEA, p53	CD31, CD34
46	1.08	<2.00	1.52	NA	Lymphoma	CK19, vimentin, CEA	CK7, desmin, HSA, SMA, C-kit, S-100
47	3.56	599.14	1.02	NA	IHCC	CK, CK19, vimentin, CEA	HSA, CD31
48	1.81	5.77	3.02	NA	IHCC	CK7, CK19, vimentin, MUC1	HSA, CD10
49	Normal	Normal	66.91	26.3	HCC	CD34, CK19 and AE1/AE3	CA19, hepatocytes, AFP, HMBE-1, G3, TG, TTF-1, and CK5/6.
50	Normal	351.74	Normal	NA	Hepatic mass	CK-pan, CK8, vimentin	CK7, CK20, HepPar-1
51	NA	Normal	1,753	Normal	Hepatic carcinoma	CK7, vimentin	CK20, HepPar1
52	Normal	Normal	Normal	Normal	Hepatic mass, Hepatolith	Vimentin, CK-Pan	SMA, S-100, desmin, CD34, CK19, CDX2, CD117, HepPar1

AAT, A-1-antitrypsin; AE1/AE3, CK-pan, pan-cytokeratin; AFP, a-fetoprotein; AMA, antimitochondrial autoantibodies; C-kit, receptor tyrosine kinase; CA19-9, carbohydrate antigen 19-9; CD10, cluster of differentiation 10; CEA, carcinoembryonic antigen; CK, cytokeratin; CYT, cytochrome; EMA, epithelial membrane antigen; F13a, factor XIIIa; HCC, hepatocellular carcinoma; Hep Par1, hepatocyte paraffin 1; HMB-45, human melanoma black 45; HMW-CK, high molecular weight cytokeratin; HSA, human serum albumin; IHCC, intrahepatic cholangiocarcinoma; KER, keratin; MUC1, mucin-1; NA, not available; NSE, neuron-specific enolase; PAS, periodic acid–Schiff; SMA, smooth muscle actin; SOX-10, SRY-related HMG-BOX Gene 10; STAT-6, signal transducer and activator of transcription 6; TTF-1, thyroid transcription factor-1; UEA-1, ulex europaeus agglutinin-1.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Patient management (ZZ, JY), drafting of the manuscript (ZZ, YL), statistical analysis (ZZ, OJ), data collection (ZZ, JY, QX, YW, CZ), and revision of the manuscript for important intellectual content (ZZ, OJ).

Ethical statement

Prior written informed consent was provided by the patient and the study was approved by the Ethics Review Board of the Second People's Hospital of Neijiang.

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