



## Case Report



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

Zheng Zeng<sup>1</sup>, Yu Liu<sup>1</sup>, Jing Yu<sup>1</sup>, Qiang Xu<sup>1</sup>, Yong Wang<sup>1</sup>, Chang Zhao<sup>2</sup> and Ou Jiang<sup>1</sup>

<sup>1</sup>Department of Abdominal Oncology, The Second People's Hospital of Neijiang, Neijiang, Sichuan, China; <sup>2</sup>Department of Pathology, The Second People's Hospital of Neijiang, Neijiang, Sichuan, China

Received: 7 September 2021 | Revised: 14 December 2021 | Accepted: 29 January 2022 | Published: 2 March 2022

## 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.

**Citation of this article:** Zeng Z, Liu Y, Yu J, Xu Q, Wang Y, Zhao C, et al. Sarcomatoid Intrahepatic Cholangiocarcinoma After Immunotherapy: A Case Report and Review of the Literature. J Clin Transl Hepatol 2022. doi: 10.14218/JCTH.2021.00395.

**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.

**Correspondence to:** Ou Jiang, Department of Abdominal Oncology, The Second People's Hospital of Neijiang, Neijiang, Sichuan 641000, China. ORCID: <https://orcid.org/0000-0002-6615-8068>. Tel: +86-13990570757, E-mail: [jiangou318@163.com](mailto:jiangou318@163.com)

## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> However, the effectiveness of ICIs for treating BTC is still controversial.<sup>4</sup> 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  $6.0 \times 4.5 \times 3.3$  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  $12.2 \times 11.7 \times 10.7$  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  $9.1 \times 8.7 \times 8.0$  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.<sup>5</sup> 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.<sup>1,6,7</sup> Clinical manifestations of S-iCCA are determined by its location, mode, and speed of tumor growth. Abdominal pain is the most common clinical symptom.<sup>8</sup>

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.<sup>9</sup> CT shows low-density lesions with peri-enhancement regions occasionally accompanied by intratumor hemorrhage.<sup>7,10</sup> 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.<sup>1,6</sup>

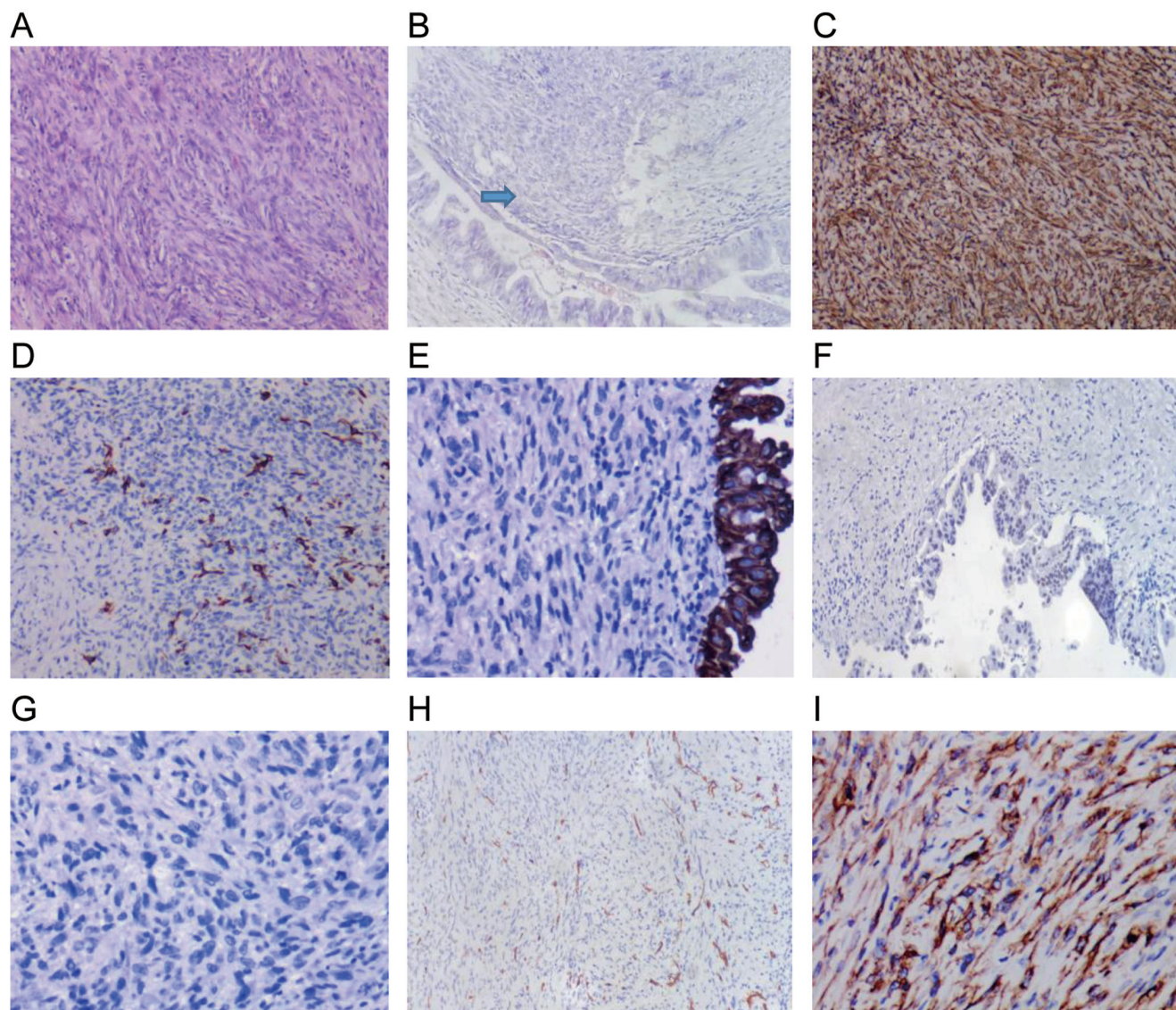
To understand the known characteristics of S-iCCA, we searched PubMed and Google using the keywords "liver," "sarcomatous," "sarcomatoid," and "cholangiocarcinoma." After analysis of the retrieved publications, 51 unrepeated S-iCCA cases were identified in 20 published studies.<sup>1,2,5–22</sup> Table 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.<sup>5</sup> 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-





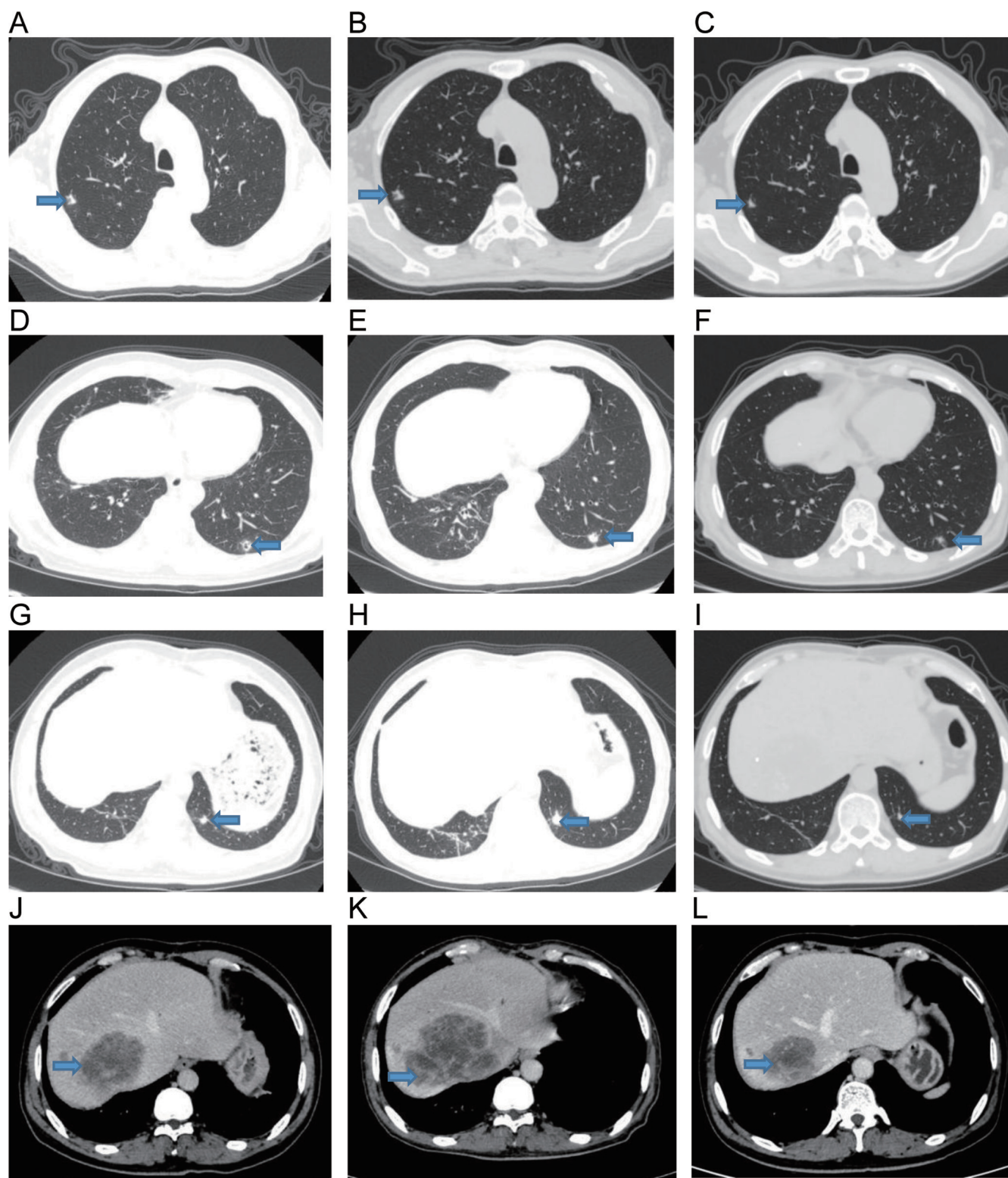
**Fig. 1. The patient's hepatic biopsy pathology was intrahepatic sarcomatoid cholangiocarcinoma.** (A) Hematoxylin and eosin stain of the tumor specimen. (B) High-grade intraepithelial neoplasia at the junction of bile duct cells and tumor cells; (C, D) Positive vimentin and pan-cytokeratin staining 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 ( $\times 200$ ). 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.<sup>5,11</sup> 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.<sup>8,22</sup> Based on this

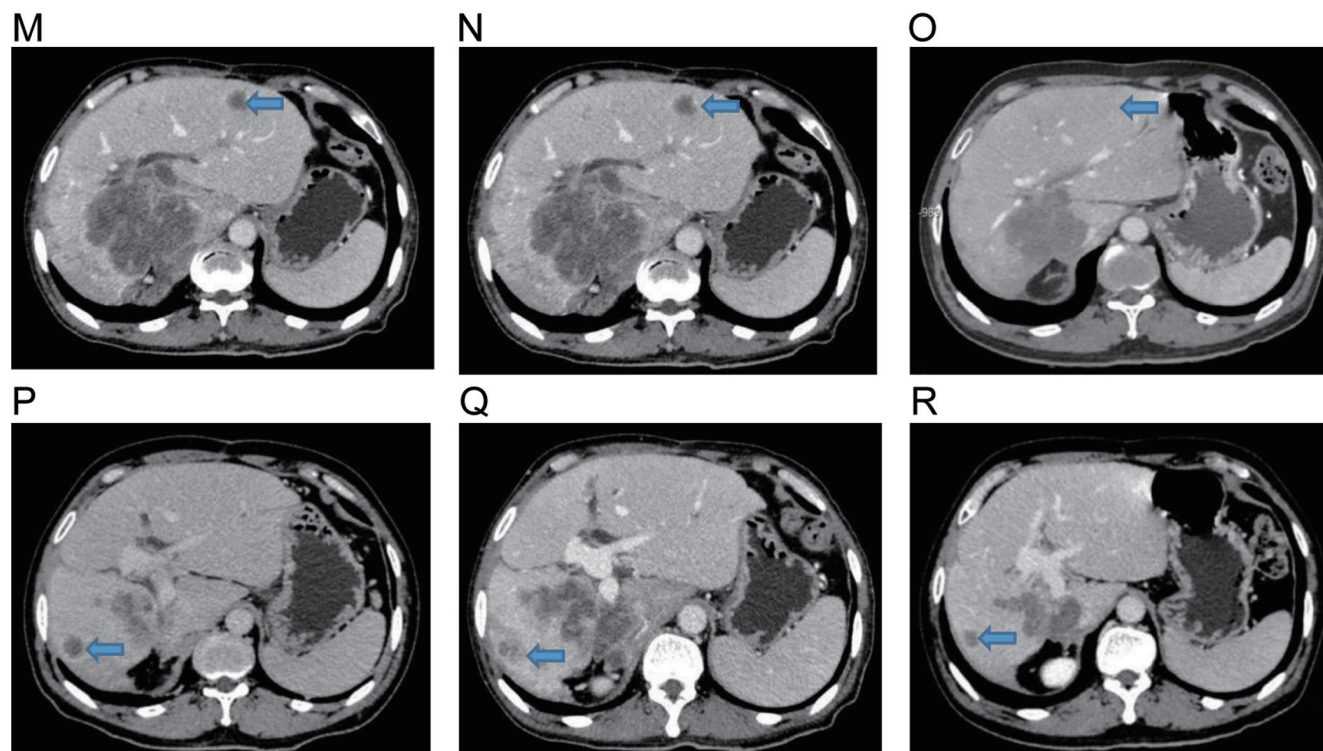
context, more treatment options urgently need to be developed and updated.

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.<sup>23</sup> 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.<sup>24</sup> 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.<sup>4</sup> However, studies have shown that the expression of PD-L1 in tumors or tumor-





(continued)



**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  $1.0 \times 0.8$  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 cariluzumab and anlotinib, scattered nodules in both lungs were smaller than before. (L, O, R) After four cycles of treatment with cariluzumab 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.<sup>24</sup>

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.<sup>25</sup> 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.<sup>3,4</sup> Preclinical evidence indicates that the use of a combination of anti-angiogenic agents and ICIs enhanced the activity of the immune system.<sup>3</sup> 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.

## Acknowledgments

We would like to acknowledge with gratitude the contribution of Pathology, West China Hospital of Sichuan University.

## Funding

This work was supported by grants from State Project for Essential Drug Research and Development of the People's

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

| Study                                | Case (no.) | Age/sex | Hepatic disease                          | Clinical symptom                    | Location      | Tumor size (cm) | Number of tumors | TNM | Treatment                     | Outcome, months |
|--------------------------------------|------------|---------|--|-------------------------------------|---------------|-----------------|------------------|-----|-------------------------------|-----------------|
| Sasaki <i>et al.</i> <sup>13</sup>   | 1          | 79/M    | (-)                                      | NA                                  | Left          | 7               | Multiple         | NA  | Supportive                    | NA              |
|                                      | 2          | 59/M    | Hepatolithiasis                          | Fever, icterus, abdominal mass      | Right         | Fist-sized      | Multiple         | NA  | Supportive                    | 1, dead         |
|                                      | 3          | 37/M    | NA                                       | Abdominal discomfort, epigastralgia | Left          | 10              | Single           | NA  | Supportive                    | 2.5, dead       |
| Nakajima <i>et al.</i> <sup>15</sup> | 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         |
| Sasaki <i>et al.</i> <sup>13</sup>   | 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 <i>et al.</i> <sup>16</sup>    | 10         | 77/M    | NA                                       | Liver tumor                         | Left          | 6               | Single           | NA  | Surgery                       | 11, alive       |
|                                      | 11         | 61/F    | (-)                                      | Back pain                           | Left          | NA              | Multiple         | IVB | Supportive                    | 3.8, dead       |
|                                      | 12         | 70/M    | CHC                                      | Fatigue, fever                      | Right         | 8               | Single           | NA  | TACE and Surgery              | 9, alive        |
| Matsuo <i>et al.</i> <sup>19</sup>   | 13         | 77/F    | (-)                                      | Abdominal pain                      | Left          | 7.7             | Single           | NA  | Surgery                       | 5, dead         |
|                                      | 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         |
| Shimada <i>et al.</i> <sup>11</sup>  | 16         | 74/F    | NA                                       | NA                                  | NA            | 4               | Single           | NA  | Surgery                       | 19, dead        |
|                                      | 17         | 64/F    | NA                                       | NA                                  | NA            | 8               | Single           | NA  | Surgery                       | 29, dead        |
|                                      | 18         | 69/F    | NA                                       | Fever, abdominal pain               | Left          | 22              | Single           | NA  | Surgery                       | 3, dead         |
| Kaibori <i>et al.</i> <sup>12</sup>  | 19         | 41/F    | (-)                                      | Palpable epigastric mass            | Left          | 17              | Single           |     | Surgery                       | 2, alive        |
|                                      | 20         | 87/M    | (-)                                      | Elevated ductal enzyme levels       | Left          | 4               | Single           | NA  | Supportive                    | 3, dead         |
|                                      | 21         | 60/F    | NA                                       | Abdominal pain, abdominal mass      | Left          | 20              | Single           | NA  | Surgery and Chemotherapy      | 29, alive       |
| Bilgin <i>et al.</i> <sup>10</sup>   | 22         | 48/M    | A laparoscopic cholecystectomy operation | Abdominal pain, fatigue             | Left          | 13              | Single           | NA  | Surgery and chemotherapy      | 12, alive       |
|                                      | 23         | 62/M    | (-)                                      | Liver tumor, jaundice               | Hepatic hilum | 5               | Multiple         | NA  | Surgery and chemotherapy      | 11, dead        |
|                                      | 24         | 65/M    | CHB                                      | NA                                  | NA            | NA              | Single           | NA  | Chemotherapy and Radiotherapy | 3, progress     |
| Watanabe <i>et al.</i> <sup>5</sup>  | 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  | Radiotherapy  | 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 <i>et al.</i> <sup>6</sup>    | 37         | 63/M    | Biliary ascariasis | Right upper abdominal pain | Left     | 8               | Multiple         | NA  | Surgery   | 1, alive        |
| Kim <i>et al.</i> <sup>1</sup>     | 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 <i>et al.</i> <sup>7</sup>    | 49         | 43/M    | CHB                | Abdominal discomfort       | Right    | 7               | Single           | NA  | Surgery   | 2.5, dead       |
| Li <i>et al.</i> <sup>9</sup>      | 50         | 64/M    | NA                 | Right upper abdominal pain | Left     | 2               | Single           | II  | Surgery   | 3.0, dead       |
| Sintra <i>et al.</i> <sup>23</sup> | 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, choledocholithiasis, 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          | 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, cytotome; 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.

Republic of China (No. 2018ZX09303014) and the Health and Family Planning Commission of Sichuan Province (No. 18PJ194).

### 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.

### References

- [1] Kim DK, Kim BR, Jeong JS, Baek YH. Analysis of intrahepatic sarcomatoid cholangiocarcinoma: Experience from 11 cases within 17 years. *World J Gastroenterol* 2019;25(5):608–621. doi:10.3748/wjg.v25.i5.608, PMID: 30774275.
- [2] Malhotra S, Wood J, Mansy T, Singh R, Zaitoun A, Madhusudan S. Intrahepatic sarcomatoid cholangiocarcinoma. *J Oncol* 2010;2010:701476. doi:10.1155/2010/701476, PMID:20454704.
- [3] Rizzo A, Ricci AD, Brandi G. Recent advances of immunotherapy for biliary tract cancer. *Expert Rev Gastroenterol Hepatol* 2021;15(5):527–536. doi:10.1080/17474124.2021.1853527, PMID:33215952.
- [4] Fostea RM, Fontana E, Torga G, Arkenau HT. Recent Progress in the Systemic Treatment of Advanced/Metastatic Cholangiocarcinoma. *Cancers (Basel)* 2020;12(9):2599. doi:10.3390/cancers12092599, PMID:32932925.
- [5] Watanabe G, Uchinami H, Yoshioka M, Nanjo H, Yamamoto Y. Prognosis analysis of sarcomatous intrahepatic cholangiocarcinoma from a review of the literature. *Int J Clin Oncol* 2014;19(3):490–496. doi:10.1007/s10147-013-0586-x, PMID:23824556.
- [6] Zhang N, Li Y, Zhao M, Chang X, Tian F, Qu Q, *et al*. Sarcomatous intrahepatic cholangiocarcinoma: Case report and literature review. *Medicine (Baltimore)* 2018;97(39):e12549. doi:10.1097/md.00000000000012549, PMID: 30278551.
- [7] Bilgin M, Toprak H, Bilgin SS, Kondakci M, Balci C. CT and MRI findings of sarcomatoid cholangiocarcinoma. *Cancer Imaging* 2012;12(3):447–451. doi:10.1102/1470-7330.2012.0036, PMID:23092855.
- [8] Li X, Li J, Liu K, Tan L, Liu Y. Sarcomatoid intrahepatic cholangiocarcinoma in a patient with poor prognosis: a case report and literature review. *J Int Med Res* 2020;48(11):300060520969473. doi:10.1177/0300060520969473, PMID:33161814.
- [9] Wang Y, Ming JL, Ren XY, Qiu L, Zhou LJ, Yang SD, *et al*. Sarcomatoid intrahepatic cholangiocarcinoma mimicking liver abscess: A case report. *World J Clin Cases* 2020;8(1):208–216. doi:10.12998/wjcc.v8.i1.208, PMID:31970189.
- [10] Shimada M, Takenaka K, Rikimaru T, Hamatsu T, Yamashita Y, Kajiyama K, *et al*. Characteristics of sarcomatous cholangiocarcinoma of the liver. *Hepato-gastroenterology* 2000;47(34):956–961. PMID:11020857.
- [11] Kaibori M, Kawaguchi Y, Yokogawa N, Yanagida H, Takai S, Kwon AH, *et al*. Intrahepatic sarcomatoid cholangiocarcinoma. *J Gastroenterol* 2003;38(11):1097–1101. doi:10.1007/s00535-003-1203-y, PMID:14673730.
- [12] Sasaki M, Nakanuma Y, Nagai Y, Nonomura A. Intrahepatic cholangiocarcinoma with sarcomatous transformation: an autopsy case. *J Clin Gastroenterol* 1991;13(2):220–225. doi:10.1097/00004836-199104000-00022, PMID:1851775.
- [13] Haratake J, Yamada H, Horie A, Inokuma T. Giant cell tumor-like cholangiocarcinoma associated with systemic cholelithiasis. *Cancer* 1992;69(10):2444–2448. doi:10.1002/1097-0142(19920515)69:10<2444::aid-cnrc2820691010>3.0.co;2-r, PMID:1314689.
- [14] Nakajima T, Tajima Y, Sugano I, Nagao K, Kondo Y, Wada K. Intrahepatic cholangiocarcinoma with sarcomatous change. Clinicopathologic and immunohistochemical evaluation of seven cases. *Cancer* 1993;72(6):1872–1877. doi:10.1002/1097-0142(19930915)72:6<1872::aid-cnrc2820720614>3.0.co;2-n, PMID:7689920.
- [15] Imazu H, Ochiai M, Funabiki T. Intrahepatic sarcomatous cholangiocarcinoma. *J Gastroenterol* 1995;30(5):677–682. doi:10.1007/bf02367798, PMID:8574344.
- [16] Honda M, Enjoji M, Sakai H, Yamamoto I, Tsuneyoshi M, Nawata H. Case report: intrahepatic cholangiocarcinoma with rhabdoid transformation. *J Gastroenterol Hepatol* 1996;11(8):771–774. doi:10.1111/j.1440-1746.1996.tb00330.x, PMID:8872777.
- [17] Itamoto T, Asahara T, Katayama K, Momisako H, Dohi K, Shimamoto F. Double cancer - hepatocellular carcinoma and intrahepatic cholangiocarcinoma with a spindle-cell variant. *J Hepatobiliary Pancreat Surg* 1999;6(4):422–426. doi:10.1007/s005340050144, PMID:10664295.
- [18] Matsuo S, Shinozaki T, Yamaguchi S, Takami Y, Obata S, Tsuda N, *et al*. Intrahepatic cholangiocarcinoma with extensive sarcomatous change: report of a case. *Surg Today* 1999;29(6):560–563. doi:10.1007/bf02482354, PMID:10385374.
- [19] Lim BJ, Kim KS, Lim JS, Kim MJ, Park C, Park YN. Rhabdoid cholangiocarcinoma: a variant of cholangiocarcinoma with aggressive behavior. *Yonsei Med J* 2004;45(3):543–546. doi:10.3349/ymj.2004.45.3.543, PMID:15227745.
- [20] Sato K, Murai H, Ueda Y, Katsuda S. Intrahepatic sarcomatoid cholangiocarcinoma of round cell variant: a case report and immunohistochemical studies. *Virchows Arch* 2006;449(5):585–590. doi:10.1007/s00428-006-0291-5, PMID:17033799.
- [21] Gu KW, Kim YK, Min JH, Ha SY, Jeong WK. Imaging features of hepatic sarcomatous carcinoma on computed tomography and gadoxetic acid-enhanced magnetic resonance imaging. *Abdom Radiol (NY)* 2017;42(5):1424–1433. doi:10.1007/s00261-016-1038-7, PMID:28078380.
- [22] Sintra S, Costa R, Filipe C, Simão A. Intrahepatic sarcomatoid cholangiocarcinoma. *BMJ Case Rep* 2018;2018:bcr2018225017. doi:10.1136/bcr-2018-225017, PMID:30244221.
- [23] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, *et al*. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362(14):1273–1281. doi:10.1056/NEJMoa0908721, PMID:20375404.
- [24] Kim RD, Chung V, Alese OB, El-Rayes BF, Li D, Al-Toubah TE, *et al*. A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer. *JAMA Oncol* 2020;6(6):888–894. doi:10.1001/jamaoncol.2020.0930, PMID:32352498.
- [25] Mo H, Huang J, Xu J, Chen X, Wu D, Qu D, *et al*. Safety, anti-tumour activity, and pharmacokinetics of fixed-dose SHR-1210, an anti-PD-1 antibody in advanced solid tumours: a dose-escalation, phase 1 study. *Br J Cancer* 2018;119(5):538–545. doi:10.1038/s41416-018-0100-3, PMID:29755117.