Correspondence

DOI: 10.5582/irdr.2023.01094

Pathologic features and clinical treatment of sarcomatoid intrahepatic cholangiocarcinoma

Xiaoli Xie[1], Nannan Lai[2], Yuanyuan Yang[1], Jinwei Zhang[3], Jianmin Qin[3,*], Xia Sheng[1,*]

[1] Department of Pathology, Minhang Hospital, Fudan University, Shanghai, China;
[2] Key Laboratory of Whole-Period Monitoring and Precise Intervention of Digestive Cancer, Shanghai Municipal Health Commission (SMHC), Minhang Hospital, Fudan University, Shanghai, China;
[3] Department of General Surgery, The Third Hospital Affiliated to Naval Military Medical University, Shanghai, China.

SUMMARY The current study examined sarcomatoid intrahepatic cholangiocarcinoma (S-iCCA). S-iCCA was a more aggressive subtype of intrahepatic cholangiocarcinoma (iCCA). Early detection and complete resection of tumors are very important. Reported here is a case of S-iCCA, and the diagnosis and treatment of S-iCCA are discussed. The patient underwent a tumor resection and was treated with chemotherapy and molecularly targeted drugs after surgery. The clinical pathologic features and treatment of S-iCCA are discussed based on the literature. An immunohistochemical examination revealed positivity for cytokeratin 7 (CK7), CK-pan, vimentin, and CK19 and negativity for hepatocyte paraffin 1 (HepPar-1) in sarcomatoid cells. This case suggests that the particular molecular characteristics of sarcomatoid cells have great clinical diagnostic value, and comprehensive treatment of S-iCCA based on surgery is described.

Keywords sarcomatoid intrahepatic cholangiocarcinoma, diagnosis, molecular pathology, surgery/drug therapy

Sarcomatoid carcinoma has been reported in various sites, including the upper digestive tract, lungs, pancreas, skin, breasts, thyroid, uterus, urinary tract, and gallbladder, and the most common organs are the breasts and lungs (*1,2*). Sarcomatoid intrahepatic cholangiocarcinoma is defined by the World Health Organization as iCCA with sarcomatoid changes (*3*). The mechanism of its pathogenesis is still unknown. Primary liver sarcomatoid carcinoma is rare, and most cases are hepatocellular sarcomatoid carcinoma (*4-6*). S-iCCA is an aggressive carcinoma with a high mortality and poor survival rate (*7,8*). Macroscopic vascular invasion, positive surgical margins, and an advanced TNM stage are associated with a high recurrence rate and a poor prognosis (*9*).

Reported here is a case involving a 68-year-old Chinese man who was admitted to this Hospital for intermittent right upper abdominal pain and a fever for 14 days. Half a month ago, the patient developed right upper quadrant pain of unknown origin, chills, a high fever, and a peak body temperature of 39.5°C, accompanied by nausea, vomiting, and diarrhea. Routine blood work and liver function were checked, and a hepatobiliary B-ultrasound and enhanced MRI were performed at a local hospital. The man was diagnosed with "massive hepatocellular carcinoma in the right lobe of the liver with intrahepatic bleeding, necrosis, and infection and multiple hepatic cysts". The man was treated with anti-inflammatories, antidiarrheals, and nutritional support, and his symptoms improved. The man then visited this Hospital for further diagnosis and treatment. The patient had an unremarkable medical and family history, a physical examination revealed tenderness in the right upper abdomen, and a 4 × 6 cm mass was palpable under the right costal margin; the mass was hard and fixed. After admission, routine laboratory tests, including serum glutamic oxaloacetic transaminase (AST), glutamic pyruvic transaminase (ALT), and the bilirubin index, were normal. Viral serology tests for hepatitis B surface antigen (HBsAg), hepatitis B E antigen (HBeAg), hepatitis C antibody, and hepatitis C virus (HCV) were negative. However, hepatitis B surface antibody, hepatitis B E antibody, and hepatitis B core antibody were positive. Hepatitis B virus DNA was < 100 IU/mL (normal range: < 100 IU/ mL). A serum tumor biomarker test revealed that the cancer antigen 125 (CA125) level was 69 U/mL (normal range: < 35 U/mL), while alpha-fetoprotein (AFP) and cancer antigen 19-9 (CA19-9) levels were normal.

A color Doppler ultrasound revealed an irregular and slightly hyperechoic region in the right lobe of the liver. The tumor was 14.1 × 10.5 cm in size, it had

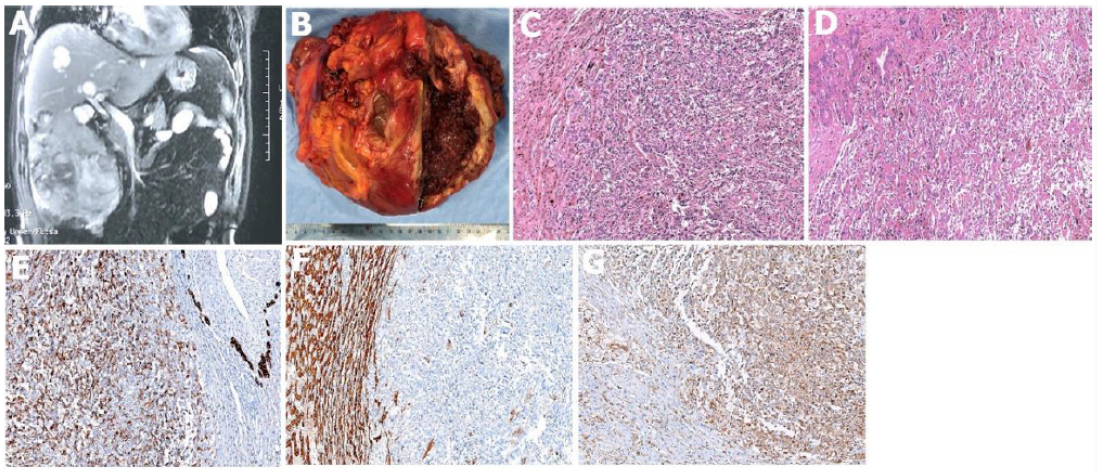

Figure 1. Clinical and pathologic findings of this study. (A) An enhanced MRI revealed an exophytic mass located in right liver segments 5 and 6, and mixed intensity lesions in the right lobe of the liver with uneven enhancement in the arterial phase. The tumor was about 15 × 13 × 11 cm in size. **(B)** Surgical specimen including the gallbladder, hepatic flexure, and tumor. It was about 23 × 17 × 16 cm, and grayish white, and hard. Intratumoral bleeding and necrosis were present. **(C)** A histopathological examination revealed sarcomatoid carcinoma (hematoxylin-eosin staining, ×10 original magnification). **(D)** A histopathological examination revealed the transition zone between sarcomatoid carcinoma and cholangiocarcinoma (hematoxylin-eosin staining, ×10 original magnification). **(E)** An immunohistochemical examination revealed positivity for CK19 in the cytoplasm of sarcomatoid cells (×10 original magnification). **(F)** An immunohistochemical examination revealed positivity for HepPar1 in the cytoplasm of paraneoplastic hepatocytes (×10 original magnification). (G) An immunohistochemical examination revealed positivity for vimentin in the cytoplasm of sarcomatoid cells (×10 original magnification).

distinct margins, and the internal echo was not uniform. A CDFI scan revealed obvious blood flow signals in the tumor. A contrast-enhanced MRI revealed signals of mixed intensity in the tumor in the right lobe of the liver, uneven enhancement in the arterial phase, and decreased enhancement in the delayed phase. The tumor was 14.1 × 9.6 cm in size. Several hyperintensities were noted in the liver, so primary liver cancer and multiple hepatic cysts were considered (Figure 1A).

The preoperative diagnosis was right lobe liver cancer and hepatic cysts. An exploratory laparoscopy was performed and revealed an exophytic mass located in right liver segments 5 and 6. The tumor was about 15 ×13 ×11 cm in size. The tumor involved the adjacent gallbladder and hepatic flexure of the colon with indistinct margins. A small volume of ascites was found in the abdominal cavity; it was light yellow and transparent. Exfoliative cytology of the ascites revealed no tumor cells during surgery. No enlarged lymph nodes were found in the hilar and duodenal ligaments during surgery. Resection of the right liver tumor, gallbladder and hepatic flexure of the colon was performed. The resected tumor specimen was off-white, bleeding, and necrotic, and the tumor was very hard. The gallbladder and hepatic flexure of the colon were closely attached to the tumor and not well demarcated from the tumor. The specimen, including the gallbladder, colon, and tumor, was about 23 ×17 × 16 cm in size (Figure 1B).

A histological examination of the tumor using hematoxylin and eosin staining revealed the presence of poorly-moderately differentiated S-iCCA. Tumor cells were found in the mucosa and serosa of the gallbladder and the serosa of the colon. No metastasis was found in the hilar lymph nodes. No tumor cells were found at the resection margin of the liver. A separate inspection revealed emboli in the blood vessels of cancer tissue, while the microvascular invasion (MVI) grade was M1. The tumor stage was determined to be T4N0M0 based on the 8th edition of the American Joint Committee on Cancer TNM staging system (*10*).

The tumor tissue consisted of different amounts of cholangiocarcinoma and sarcomatoid components, with bleeding and necrosis. The adenocarcinoma portion of the cholangiocarcinoma was poorly to moderately differentiated, and the sarcomatoid portion had a spindle cell and pseudohemangiomatous morphology. The tumor cells displayed infiltrative growth involving the surrounding liver tissue, moderate inflammation in the portal area of the liver tissue around the tumor, and obvious hyperplasia or dysplasia of small bile ducts (Figure 1C, D). An immunohistochemical examination of the tumor tissue revealed positivity for cytokeratin (CK) 7, CK-pan, CK19, and vimentin in the cytoplasm of sarcomatoid cells, positivity for hepatocyte paraffin 1 (HepPar-1) in the cytoplasm of paraneoplastic hepatocytes, and negativity for HepPar-1 in tumor cells (Figure 1E, F, G). The Ki-67 proliferation index was approximately 70%. Based on these histopathological and immunohistochemical findings, the patient was definitively diagnosed with S-iCCA.

Six cycles of chemotherapy were performed with the GS regimen (Gemcitabine plus S-1) in the third week after surgery, combined with the tyrosine kinase inhibitor anlotinib hydrochloride (12 mg, once a day for 2 weeks, respite for 1 week). Nonetheless, the patient died of intrahepatic recurrence and metastasis 8 months after surgery.

S-iCCA is defined by the World Health Organization

(2010) as "cholangiocarcinoma with a spindle cell component, such as spindle cell sarcoma, fibrosarcoma, or malignant fibrous histiocytoma; scattered cancer foci, including squamous cell carcinoma, can be seen within the tumor" (*11*). Sarcomatoid transformation was found in 3.9-9.4% of hepatocellular carcinomas and 4.5% of intrahepatic cholangiocarcinomas (*5,12*). Studies have shown that tumors have epithelial and heterologous mesenchymal components and have a subtle transition. The mesenchymal component has characteristics of epithelial tissue, such as similar gene and protein phenotypes, through metaplasia into mesenchymal cells and other characteristics (*13*).

The early symptoms of S-iCCA patients lack specificity, hampering diagnosis. S-iCCA is highly malignant because most of the tumors have spread to the liver, invaded adjacent organs, or metastasized to distant organs at the time of diagnosis. The surgical resection rate is low, the postoperative tumor recurrence and metastasis rates are high, and patient prognosis is poor (*14,15*). The diagnosis of S-iCCA requires pathological and immunohistochemical analysis. The tumor cells of S-iCCA mainly consist of spindle cells, giant cells and atypical cells, and malignant epithelial bile duct cells; sarcomatoid biphasic components and mixed phenotypic regions usually coexist. The sarcomatoid components of spindle cells are arranged in sheets or bundles and mixed with heterogeneous polymorphic giant cells. Epithelial tumor markers (CK, Keratin, and EMA) and mesenchymal tumor markers (Vimentin, SMA, and CD68) are simultaneously positive. Intermediate keratin (CAM5.2 and CK19) is positive (*16*), which is consistent with the immunohistochemical results in the current case. The presence of malignant epithelial bile duct cells and sarcomatoid biphasic components, positivity for epithelial tumor markers and mesenchymal tumor markers, and the presence of desmosome junctions between sarcomatoid cells are the characteristic pathological manifestations of S-iCCA and the gold standard for the diagnosis of S-iCCA.

Differential diagnosis can be made by carefully looking for epithelial components and the transition between epithelial components and sarcomatoid components. Histologically, S-iCCA needs to be differentiated from the following tumors: *(i)* S-iCCA is mainly associated with hepatocellular differentiation of sarcomatoid carcinoma and mixed hepatocellular-biliary sarcomatoid carcinoma. With the former, the level of positivity for HepPar1 differs and it occasionally has hepatoblastoma features, which increases the difficulty of diagnosis (*6*); with the latter, HepPar 1 and CK19 are simultaneously positive (*17*). *(ii)* S-iCCA needs to be differentiated from primary sarcoma (including angiosarcoma, undifferentiated embryonal sarcoma, and malignant teratoma). Angiosarcoma is positive for CD31 and CD34 and negative for CK. In addition to the characteristic histological morphology, malignant teratoma can express various markers of mesenchymal differentiation at different levels. Residual hepatocytes and bile duct components can be seen in the tumor, but primitive cells expressing high and low molecular weight CK, which may be differentiated from primitive stem cells are also observed (*18*). *(iii)* S-iCCA needs to be distinguished from epithelioid or exotic angiomyolipomas, angiomyolipomas with significant atypia, which are positive for HBM45 and SMA. *(iv)* S-iCCA needs to be differentiated from metastatic carcinoma and metastatic mesenchymal tumors, which usually have a clear medical history of a primary tumor. The corresponding epithelial markers may be expressed in metastatic carcinoma, and metastatic mesenchymal tumor are mainly positive for characteristic markers of gastrointestinal stromal tumors and melanoma.

Although there are few treatments for S-iCCA and their effectiveness is limited, surgical resection is still the preferred treatment. For inoperable tumors, chemotherapy, molecularly targeted drugs, and immunotherapy (such as PD-1/PD-L1) are still in the clinical exploratory stage.

In conclusion, S-iCCA is too difficult to diagnose early through a clinical examination and imaging studies, and it can easily be misdiagnosed as a liver abscess, liver metastasis, or the like. Assuming that it could be diagnosed early and treated surgically, the patient a better clinical prognosis. The determination of S-iCCA is based on some important findings: *(i)* a history of intrahepatic bile duct stones and recurrent bile duct infections, *(ii)* imaging studies and blood tumor markers heavily suggest sarcoma and require a pathological biopsy, *(iii)* positivity for epithelial tumor markers (CK, Keratin, and EMA) and mesenchymal tumor markers (Vimentin, SMA, and CD68) in the cytoplasm of sarcomatoid cells, *(iv)* positivity for intermediate keratin (CAM5.2) in the cytoplasm of sarcomatoid cells, and positivity for HepPar1 in the cytoplasm of paraneoplastic hepatocytes.

Acknowledgements

The authors would like to thank Dr. Han Wang (Department of Pathology, The Third Hospital Affiliated with Naval Military Medical University, Shanghai, China) for helpful advice and discussion.

Funding: This study was supported in part by a grant-in-aid for a Minhang Project of the Shanghai Science and Technology Commission (2021MHZ065, 2022MHZ089), the Minhang District of Shanghai Commission to Create Medical Specialties (2020MWFC03), and the Shanghai Minhang Hospital Project to Create Departments (YJXK-2021-09-003).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Mochizuki T, Ishii G, Nagai K, Yoshida J, Nishimura M, Mizuno T, Yokose T, Suzuki K, Ochiai A. Pleomorphic carcinoma of the lung: Clinicopathologic characteristics of 70 cases. Am J Surg Pathol. 2008; 32:1727-1735.
2. Carter MR, Hornick JL, Lester S, Fletcher CD. Spindle cell (sarcomatoid) carcinoma of the breast: A clinicopathologic and immunohistochemical analysis of 29 cases. Am J Surg Pathol. 2006; 30:300-309.
3. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020; 76:182-188.
4. Haratake J, Horie A. An immunohistochemical study of sarcomatoid liver carcinomas. Cancer. 1991 ;68: 93-97.
5. Kakizoe S, Kojiro M, Nakashima T. Hepatocellular carcinoma with sarcomatous change. Clinicopathologic and immunohistochemical studies of 14 autopsy cases. Cancer. 1987; 59:310 -316.
6. Cho MS, Lee SN, Sung SH, Han WS. Sarcomatoid hepatocellular carcinoma with hepatoblastoma-like features in an adult. Pathol Int. 2004; 54:446-450.
7. Aishima S, Oda Y. Pathogenesis and classification of intrahepatic cholangiocarcinoma: different characters of perihilar large duct type versus peripheral small duct type. J Hepatobiliary Pancreat Sci. 2015; 22:94-100.
8. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol. 2014; 60:1268-1289.
9. Jiang BG, Sun LL, Yu WL, Tang ZH, Zong M, Zhang YJ. Retrospective analysis of histopathologic prognostic factors after hepatectomy for intrahepatic cholangiocarcinoma. Cancer J. 2009; 15:257-261.
10. Amin MB, Edge SB, Greene FL, Brierley JD. AJCC Cancer Staging Manual. 8th ed. New York: Springer. 2017.
11. Dosman FT, Carneiro F, Hruban RH. WHO classification of tumours of the digestive system. 4th ed. Lyon: IARC Press. 2010; 211-249.
12. 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; 72:1872-1877.
13. Lao XM, Chen DY, Zhang YQ, Xiang J, Guo RP, Lin XJ, Li JQ. Primary carcinosarcoma of the liver: clinicopathologic features of 5 cases and a review of the literature. Am J Surg Pathol. 2007; 31:817-826.
14. Kaibori M, Kawaguchi Y, Yokoigawa N, Yanagida H, Takai S, Kwon AH, Uemura Y, Kamiyama Y. Intrahepatic sarcomatoid cholangiocarcinoma. J Gastroenterol. 2003; 38:1097-1101.
15. Lee DH, Han KH, Sun YA, Sang SK, Kim SB. Sarcomatoid intrahepatic cholangiocarcinoma: A rare case of primary liver cancer. J Liver Cancer. 2016; 16:139-1344.
16. Wang T, Kong J, Yang X, Shen S, Zhang M, Wang W. Clinical features of sarcomatoid change in patients with intrahepatic cholangiocarcinoma and prognosis after surgical liver resection: A propensity score matching analysis. J Surg Oncol. 2020; 121:524-537.
17. Aishima S, Kuroda Y, Asayama Y, Taguchi K, Nishihara Y, Taketomi A, Tsuneyoshi M. Prognostic impact of cholangiocellular and sarcomatous components in combined hepatocellular and cholangiocarcinoma. Hum Pathol. 2006; 37:283-291.
18. Zheng JM, Tao X, Xu AM, Chen XF, Wu MC, Zhang SH. Primary and recurrent embryonal sarcoma of the liver: Clinicopathological and immunohistochemical analysis. Histopathology. 2007; 51:195-203.

Received October 2, 2023; Revised November 5, 2023; Accepted November 8, 2023.

*Address correspondence to:
Jianmin Qin, Department of General Surgery, The Third Hospital Affiliated to Naval Military Medical University, Shanghai, China.
E-mail: jianminqin68@hotmail.com

Xia Sheng, Department of Pathology, Minhang Hospital, Fudan University, No.170, Xinsong Road,Minhang District, Shanghai 201199, China.
E-mail: shengxia_021@fudan.edu.cn

Released online in J-STAGE as advance publication November 10, 2023.