

Double primary hepatic cancer (hepatocellular carcinoma and intrahepatic cholangiocarcinoma) in a single patient: A case report

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Abstract. Double primary hepatic cancer, consisting of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) located separately within a single liver simultaneously, is extremely rare. The present study reports a case of double hepatic nodules, in which HCC and ICC occurred simultaneously in the right hepatic lobe. The 47-year-old male patient, who was a carrier of hepatitis B virus, was admitted to our hospital for physical examination, which revealed two liver masses. The results of initial laboratory tests, including liver function tests, were within normal limits, with the exception of mildly elevated aspartate aminotransferase and alanine aminotransferase, and decreased albumin levels. α -fetoprotein was in the normal range, while carbohydrate antigen 19-9 was marginally elevated. Abdominal ultrasonography and enhanced computed tomography revealed two tumors located in segments (S) VI and VII of the liver, respectively, with malignant behavior. Examination of the two masses following resection of S VI and VII confirmed a diagnosis of combined HCC and ICC. After 8 months of follow-up, no signs of recurrence have been observed with chemical therapy.

Introduction

Primary liver cancer (PLC) ranks as the 5th most common cancer worldwide and the 3rd most prevalent in China (1,2). The majority of PLCs are hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC); however, combined HCC and cholangiocarcinoma (CC) in a single liver (cHCC-CC) is reported to account for 0.4-14.2% of cases (3-7). Allen and Lisa (8) classified cHCC-CC into three subtypes: Type A,

separate nodules of HCC and CC; type B, contiguous masses of HCC and CC; and type C, individual masses intermingling, with components of HCC and CC. Type C is regarded to be the real cHCC-CC classification, and the majority of cases of cHCC-CC reported are type C (9). Types A or B, also known as double separate masses of HCC and ICC, are extremely rare in clinical practice, particularly type A. It has been reported that clinicopathological characteristics and surgical outcomes generally differ between types A, B and C, although this is poorly understood at present (10). The current study reports the case of a patient diagnosed with HCC and ICC occurring as two separate nodules.

Case report

A 47-year-old male was admitted to West China Hospital of Sichuan University (Chengdu, China) in February 2014 without any symptoms and tumor was discovered by physical examination. Physical examination revealed two nodules in the right lobe of the patient's liver. No history of drug or alcohol abuse was reported, however, the patient was positive for hepatitis B virus (HBV). Abdominal ultrasound, enhanced computed tomography (CT) and initial laboratory tests were scheduled. The laboratory test results revealed that the blood hemoglobin (HGB) levels and white blood cell and platelet counts were all within the normal range. However, a liver function test revealed that aspartate aminotransferase and alanine aminotransferase levels were mildly elevated, and albumin levels were found to be decreased, with a normal total bilirubin concentration. A HBV DNA titer of 5×10^3 copies/l was detected. Levels of the tumor markers α -fetoprotein (AFP; 2.1 $\mu\text{g}/\mu\text{l}$; normal range, 0-8 $\mu\text{g}/\mu\text{l}$), carcinoembryonic antigen (2.1 $\mu\text{g}/\text{ml}$; normal range, 0-5 $\mu\text{g}/\text{ml}$) and carbohydrate antigen (CA) 125 (16.2 U/ml; normal range, 0-35 U/ml) were all within the normal limits, however, the CA19-9 level was marginally elevated. The abdominal ultrasound revealed two tumors in segment (S) VII (tumor A) and S VI (tumor B), with liver echo enhancement. In addition, enhanced spiral CT scanning of the upper abdomen showed that the two masses, tumors A and B, were both located in the right posterior lobe and measured 4 cm and 1 cm in diameter, respectively (Fig. 1). Esophageal varices were also observed. Enhanced CT imaging revealed that tumor A was heterogeneously enhanced in the arterial phase, and enhancement decreased in the portal venous phase,

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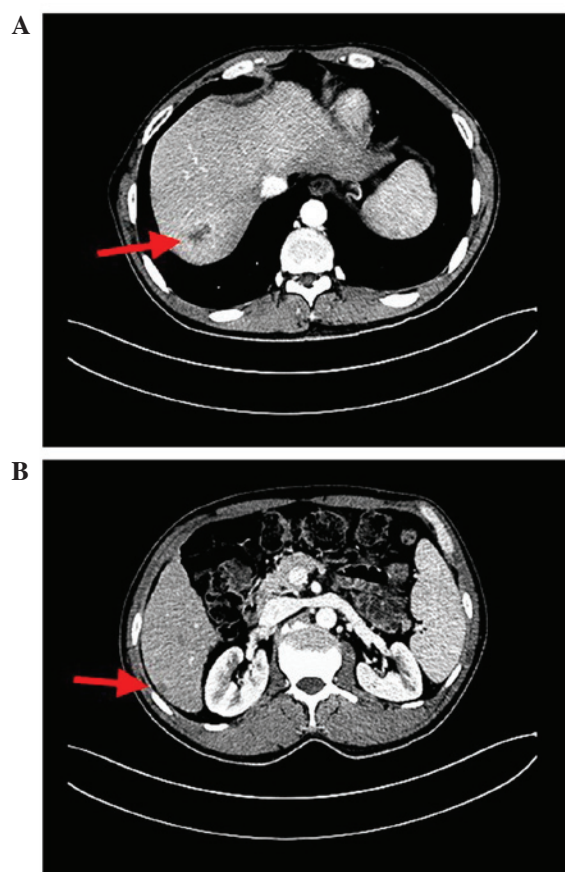


Figure 1. Computed tomography scan of the liver in the venous phase. Red arrows indicate (A) tumor A (hepatocellular carcinoma) in segment VII and (B) tumor B (intrahepatic cholangiocarcinoma) in segment VI.

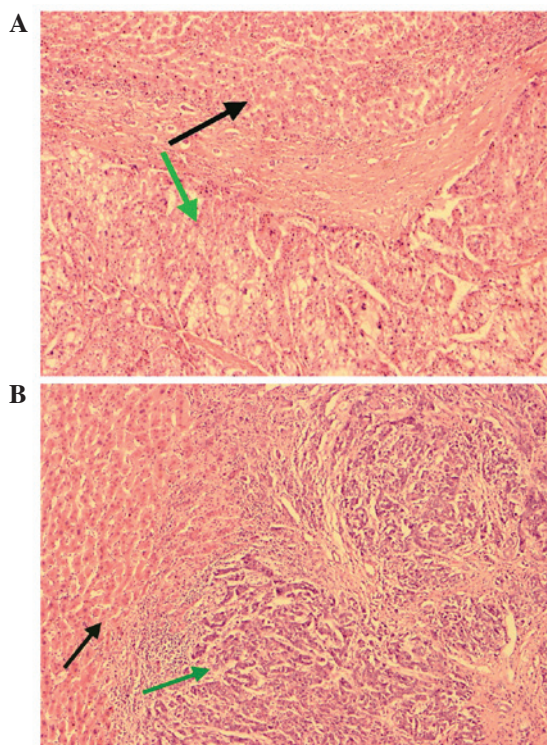


Figure 2. Light microscopy of (A) tumor A (hepatocellular carcinoma) and (B) tumor B (intrahepatic cholangiocarcinoma). Black arrows indicate normal liver tissue, while green arrows indicate carcinoma tissue (hematoxylin and eosin staining; magnification, x100).

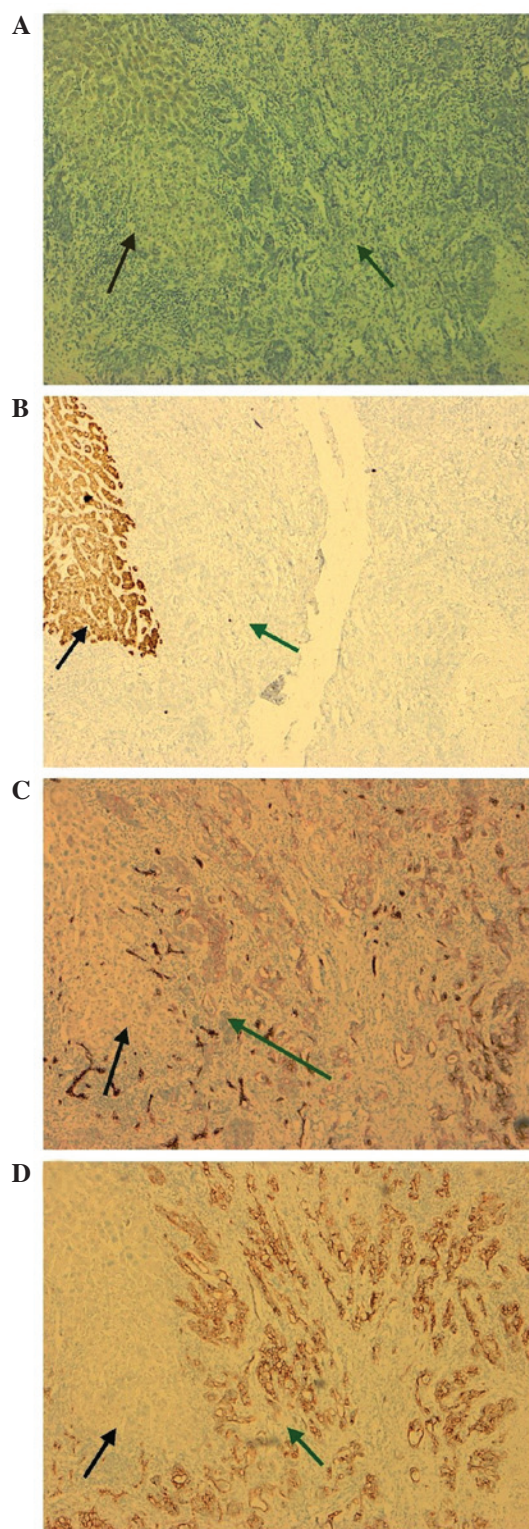


Figure 3. Immunohistochemical analysis of tumor B (intrahepatic cholangiocarcinoma). Black arrows indicate normal liver tissue, and green arrows indicate adenocarcinoma tissue. Figures show negative staining of adenocarcinoma tissue for (A) α -fetoprotein and (B) hepatocyte antigen, and positive staining for (C) CK7 and (D) CK19 (magnification, x100). CK, cytokeratin.

while tumor B was heterogeneously enhanced in these two phases.

Based on these findings, primary HCC with intrahepatic metastasis was the initial diagnosis; there was no evidence of extrahepatic lesions on enhanced brain and chest CT imaging

and bone scanning. Therefore, surgical resections of liver S VI and VII were performed under full anesthesia within 110 min. The patient experienced ~200 ml blood loss during surgery, and no blood transfusion was required. Following an uneventful recovery, the patient was discharged on the 7th day after surgery. The biopsy of the liver revealed cirrhosis with an Ishak score of 6 (11). Tumor A was found to be moderately differentiated HCC with a complete capsule and without tumor thrombus. By contrast, tumor B was a poorly differentiated adenocarcinoma with liver capsule violation (Fig. 2). In order to elucidate the source of tumor B, an immunohistochemical analysis of the tumor was performed. The cells of tumor B stained positively for cytokeratins (CKs) 7 and 19, and negatively for hepatocyte antigen (Hepa) and AFP (Fig. 3). Thus, these findings indicated that tumor B had a biliary origin, confirming a diagnosis of ICC. During the 8 months of follow-up, the patient has undergone liver ultrasonography and tumor marker tests at 3-month intervals, and no signs of recurrence have been observed. No further treatment has been administered.

The patient provided written informed consent for the publication of this report.

Discussion

The simultaneous occurrence of HCC and ICC in a single liver, in the form of separated nodules, is extremely rare. To the best of our knowledge, there have been no previous reports about the incidence of the type A cHCC-CC, and only several English language case reports are available in the literature (12).

It is well-established that HCC is closely associated with HBV or hepatitis C virus (HCV) infections (2,13), while HBV or HCV infections are also risk factors for ICC (14). In the present report, the patient had a long history of HBV infection, including increasing HBV DNA titers, and no standard antiviral treatments were administered.

Tumor markers are intrinsically linked to certain tumors, however, tumor markers cannot necessarily be used to confirm an exact final diagnosis (15). For example, the level of blood CA19-9, a tumor marker of ICC, may also increase when HCC invades the biliary tract; therefore, elevated levels cannot conclusively diagnose a liver mass as ICC, but may suggest the possibility of ICC. In the present report, the AFP level of the patient, which is regarded to be the most significant tumor marker of HCC (16), was within the normal limits, however, CA19-9 was marginally elevated. Thus, whilst they provide some information, tumor markers cannot be used as the sole foundation of the diagnosis, and the final diagnosis depends on pathological assessment of biopsied specimens.

The pathological characteristics of HCC and ICC also differ from one another: According to the consensus of pathological immunohistochemical examinations, Hepa and AFP are reliable markers for HCC (17), while CK7 and CK19 are valuable markers for differentiating ICC from HCC (18). In the present report, tumor A was a typical HCC mass, and tumor B cells stained positively for CK7, CK19 and CK20, and negatively for Hepa and AFP. Negative AFP and Hepa staining indicated that the tumor did not originate from hepatocytes, while the CK7 and CK19 positive staining suggested that the tumor arose from cholangiocytes (19,20).

The use of abdominal ultrasound to detect liver masses is common for screening and follow-up; however, the characterization of a malignant tumor by ultrasound often leads to ambiguity due to the variable and non-specific features observed using this modality, and is limited to the experience of the sonologist (21). HCC and ICC masses may perform differently on enhanced CT imaging: ICC typically appears with peripheral enhancement on the early phase, and mild centripetal progression of enhancement in the venous phase, while HCC generally exhibits enhancement in the whole tumor during the hepatic arterial phase and negative enhancement during the portal venous phase ('fast in and out') (22). The biomolecular mechanism of enhancement differences on spiral CT between HCC and ICC is related to the differential expression of vascular endothelial growth factor (23). However, it remains difficult to characterize tumors of small diameter or with atypical features by CT imaging. In the present report, the diameter of the ICC nodule in S VI was ~1 cm, and the CT image revealed irregular enhancement in the arterial and venous phases; thus, it could not be fully distinguished from certain metastatic tumors (24). Therefore, even combining the tumor marker and imaging findings, correctly diagnosing the double primary hepatic masses as HCC and ICC preoperatively was still challenging.

Hepatectomy is the primary treatment option for all malignant liver tumors, however, different approaches to lymph node dissection are usually taken between HCC and ICC (25). It is essential to dissect lymph nodes for ICC, but not for HCC (26). In the present case, the patient only underwent liver resection and not lymph node dissection, due to the misdiagnosis of tumor B preoperatively. Despite this, the patient has experienced disease-free survival to date, owing to the small diameter of the tumor and absence of lymph node metastasis. It may be possible to avoid uncertainty regarding the necessity for lymph node dissection by implementing frozen section biopsy intraoperatively, when the evidence from preoperative tests is unable to fully eliminate the possibility of ICC (10).

In summary, the present study reported an extremely rare case of PLC consisting of double hepatic tumors, with HCC and ICC occurring simultaneously at separate locations within a single liver. In such cases, it is difficult to determine a diagnosis preoperatively due to uncharacteristic performances on tumor marker analysis and imaging studies; the final diagnosis depends on pathological and immunohistochemical examination of biopsy specimens. Surgery remains the primary treatment option. The present case highlights the potential value of frozen section biopsy performed intraoperatively that may alert surgeons to the necessity for lymph node dissection.

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