

## CASE REPORT

# Combined hepatocellular and cholangiocellular carcinoma presenting with radiological characteristics of focal nodular hyperplasia

Inneke Willekens, Anne Hoorens, Caroline Geers, Bart Op de Beeck, Frederik Vandenbroucke, Johan de Mey

Inneke Willekens, Anne Hoorens, Caroline Geers, Bart Op de Beeck, Frederik Vandenbroucke, Johan de Mey, Department of Radiology and Pathology, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium

**Author contributions:** Willekens I, Hoorens A, Op de Beeck B and de Mey J designed research; Willekens I, Hoorens A, Geers C, Vandenbroucke F and Op de Beeck B performed research; Willekens I, Hoorens A and Geers C analyzed data; and Willekens I and Hoorens A wrote the paper.

**Correspondence to:** Inneke Willekens, MD, Department of Radiology, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium. [inneke.willekens@gmail.com](mailto:inneke.willekens@gmail.com)

Telephone: +32-24763645 Fax: +32-24775362

Received: March 20, 2009 Revised: June 19, 2009

Accepted: June 26, 2009

Published online: August 21, 2009

F, de Mey J. Combined hepatocellular and cholangiocellular carcinoma presenting with radiological characteristics of focal nodular hyperplasia. *World J Gastroenterol* 2009; 15(31): 3940-3943 Available from: URL: <http://www.wjgnet.com/1007-9327/15/3940.asp> DOI: <http://dx.doi.org/10.3748/wjg.15.3940>

## INTRODUCTION

The two major subtypes of primary liver cancer are hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). Combined hepatocellular and cholangiocellular carcinoma (cHCC-CC) is a rare tumor type containing unequivocal elements of both HCC and CC that are intimately mixed<sup>[1,2]</sup>. It accounts for 1.0%-14.2% of all primary liver carcinomas<sup>[3]</sup>. Initial misdiagnosis was reported in several patients. The main diagnostic techniques for cHCC-CC include serum markers, imaging and histological analysis.

## CASE REPORT

A 47-year-old woman, who was admitted to the radiology department of our hospital, presented with a 2 mo history of general illness, slight weight loss and a palpable mass in the right upper abdomen. Ultrasound and contrast-enhanced computed tomography (CT) of the abdomen were performed in another hospital. Ultrasound of the upper abdomen revealed a heterogeneous hypoechoic tumor in the liver. The CT scan showed a heterogeneous contrast-enhanced mass in segments 5 and 6 of the liver. Her past medical history included an appendectomy and hepatitis B positivity for more than 15 years. She was considered a so called healthy carrier of hepatitis B.

Magnetic Resonance Imaging (MRI) was performed in our hospital. On MRI a focal liver lesion inferior in the right lobe was visualized. The mass was homogeneous hypointense on T1 (Figure 1C and G) and slightly hyperintense on T2 (Figure 1A and B). The dynamic contrast-enhancement with gadolinium chelate (Magnevist®, Bayer HealthCare Pharmaceuticals, Düsseldorf, Germany) established a relatively hypervascular heterogeneous nature with late enhancement of the central scar (Figure 1D-H). The contrast-enhancement

## Abstract

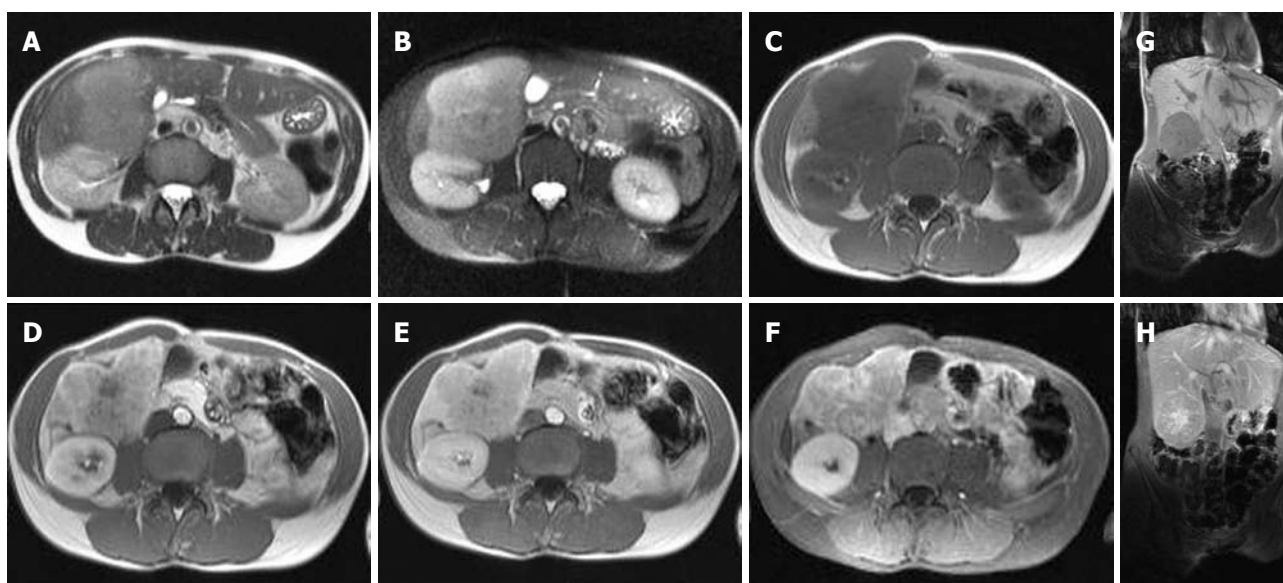
Combined hepatocellular and cholangiocellular carcinoma (cHCC-CC) is a rare tumor type containing unequivocal elements of both hepatocellular carcinoma and cholangiocarcinoma that are intimately mixed. Although these tumors are usually considered to be more related to hepatocellular carcinoma than to cholangiocarcinoma, they sometimes, in contrast to hepatocellular carcinoma, contain a significant amount of fibrous stroma. This might in some cases explain atypical radiological features. We report a case of a cHCC-CC in a 47-year-old female that resembled focal nodular hyperplasia on Magnetic Resonance Imaging. Correlation of imaging and serum levels of  $\alpha$ -fetoprotein and CA19.9 can help to make the correct diagnosis preoperatively.

© 2009 The WJG Press and Baishideng. All rights reserved.

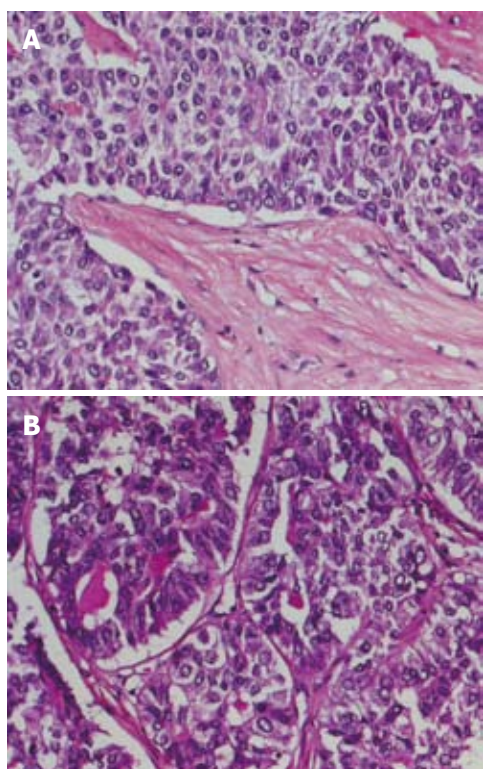
**Key words:** Combined hepatocellular; Cholangiocellular carcinoma; Magnetic resonance imaging

**Peer reviewer:** Hiroaki Nagano, MD, PhD, Associate Professor, Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of Surgery, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka E-2, Suita 565-0871 Osaka, Japan

Willekens I, Hoorens A, Geers C, Op de Beeck B, Vandenbroucke



**Figure 1** MRI images of combined hepatocellular and cholangiocellular carcinoma. Axial T2 (A) and T2 fat saturated (B) MRI images showed a slightly well circumscribed lesion. The mass is hyperintense in comparison to the normal liver. Axial T1 (C) MRI images demonstrated a hypointense lesion. Early arterial (D), late arterial (E) and venous (F) MRI images displayed a hypervascular heterogeneous enhancement with central scar. The coronal T1 (G) image showed a hypointense lesion, while the coronal T1 MRI image after Gadolinium contrast (H) demonstrated a heterogeneous early enhancement of the lesion with delayed uptake in the scar.



**Figure 2** Histopathological images of combined hepatocellular and cholangiocellular carcinoma. A: Nests of tumor cells with trabecular architecture, reminiscent of hepatocellular differentiation, separated by bands of fibrous tissue; B: Focally tumor cells formed glandular structures with mucinous secretory material, compatible with cholangiocellular differentiation.

and morphologies were consistent with focal nodular hyperplasia. Laboratory results, however, revealed an elevated  $\alpha$ -fetoprotein level of 154 000 ng/mL.

Right hepatectomy was performed. A white firm tumoral mass of 8.5 cm in diameter and one satellite

nodule of 1 cm were identified during macroscopic examination of the resection specimen. The non-tumoral liver did not display signs of cirrhosis macroscopically. Microscopically, the tumor consisted of nests of tumor cells separated by broad bands of fibrous tissue, focally resembling a fibrous scar (Figure 2A). In most tumor cell nests, tumor cells displayed a trabecular growth pattern. Trabecular structures were several cell layers thick, in contrast to normal liver tissue in which trabeculae are only 1 to 2 layers in thickness. Focally, however, glandular structures containing secretory material were observed (Figure 2B). Tumor cells arranged in trabecular structures displayed positivity for HepPar1 and  $\alpha$ -fetoprotein and immunohistochemistry with a polyclonal anti-CEA antibody revealed the presence of canalicular structures. These features are consistent with hepatocellular differentiation. Where tumor cells formed glandular structures, the presence of neutral mucin could be demonstrated. The secretory material displayed alcian blue positivity and was positive in a PAS-diastase reaction, compatible with cholangiocellular differentiation. Moreover, areas of glandular differentiation displayed positivity for CA19.9 and MUC1, while areas of hepatocellular differentiation were negative. In addition, positivity for CK7 and CK19 was observed in areas of glandular growth pattern, while areas with trabecular growth pattern displayed most often only positivity for CK8 and CK18. These histological features together with the immunohistochemical profile are consistent with a diagnosis of CHCC-CC.

## DISCUSSION

CHCC-CC is a rare primary liver tumor type containing unequivocal elements of both hepatocellular carcinoma and cholangiocarcinoma<sup>[1,2]</sup>. It accounts for 1.0%-14.2% of

all primary liver carcinomas<sup>[3]</sup>. In 1949, the first description of cHCC-CC was reported by Allen *et al*<sup>[4]</sup>. Some studies found that this tumor type is more frequently diagnosed in patients with chronic hepatitis and liver cirrhosis<sup>[5]</sup>, although this could not be confirmed in other studies<sup>[1]</sup>. Most studies report that patients with cHCC-CC show similar clinical and pathological features as hepatocellular carcinoma patients, including a mean age onset in the sixth decade, male predominance, a high incidence of hepatitis B virus infection, underlying chronic liver disease and elevated serum  $\alpha$ -fetoprotein levels<sup>[6]</sup>. Several reported patients were initially misdiagnosed<sup>[7]</sup>. Various factors, such as an atypical enhancing pattern on imaging, the small size of one of the components, and the presence of a tumor composed of intermediate tumor cells, were found to be the causes of misdiagnosis<sup>[8]</sup>. The tumor remains usually generally clinically silent and patients present with advanced illness<sup>[9]</sup>. A simultaneous elevation of serum levels of CA 19-9 and  $\alpha$ -fetoprotein in patients with a liver mass on imaging may suggest the presence of cHCC-CC<sup>[7]</sup>. Ultrasound usually demonstrates a round or ovoid hypoechoic mass with a central hyperechoic area<sup>[9]</sup>. On contrast-enhanced CT, cHCC-CC lesions are divided into 3 classes of enhancement patterns. The first group of lesions, namely cHCC-CC resembling hepatocellular carcinoma, shows hyperenhancement in the early phase and hypoenhancement in the late phase due to washout of contrast (Type I lesions). The second group, Type II lesions, demonstrates peripheral enhancement in the early as well as in the late phase. Type III lesions present an area of hyperenhancement in the early phase and an area of slight delayed enhancement in the late phase<sup>[10]</sup>. The cHCC-CC lesions resembling cholangiocarcinoma, however, enable low attenuation in the arterial phase and low, iso- or high attenuation in the venous phase<sup>[11]</sup>. Preoperatively cHCC-CC is, however, usually only considered when a liver tumor has CT features of both hepatocellular carcinoma and cholangiocellular carcinoma<sup>[12]</sup>. In addition, Toh *et al*<sup>[13]</sup> reported a hypodense tumor with vague contrast enhancement associated with elevation of  $\alpha$ -fetoprotein levels and multiple regional lymphadenopathies as a cHCC-CC. Finally, cHCC-CC has also been reported as presenting as a hypervascular tumor associated with increased serum CEA and CA 19-9<sup>[14]</sup>.

On MRI, cHCC-CC has been reported to show low signal intensities on T1-weighted images and high signal intensities on T2-weighted images<sup>[15]</sup>. In the arterial phase, it has been described that the T1-weighted images describe an enhancing mass nearly isointense to the surrounding parenchyma with a central necrotic non-enhancing zone<sup>[16]</sup>.

Final diagnosis of cHCC-CC can only be made by histological examination. Extensive sampling of tissue is required in order not to miss the diagnosis in case one of the tumor compounds represents only a minor component of the tumor. Surgery is the only effective treatment for this tumor. The median survival time following cHCC-CC surgery has been reported to be 48 mo<sup>[17]</sup>. Partial hepatectomy with lymph node dissection can result in 5-year survival rates exceeding 50% in

patients with early stage disease<sup>[18]</sup>. Prognostic factors of poor outcome of cHCC-CC are distant metastasis, major vascular branch invasion, regional lymph node involvement, bilobar distribution, multiple tumors, tumor necrosis and ascites<sup>[19]</sup>.

In conclusion, preoperative diagnosis of cHCC-CC remains difficult. It is of great importance to choose appropriate imaging, such as MRI, in combination with serum  $\alpha$ -fetoprotein and CA 19.9 levels. In addition, extensive tissue sampling is required in order to not miss this diagnosis in cases where one of the two components is of small size. Most studies show that this tumor type has similar geographical distribution and age and sex distribution as hepatocellular carcinoma. Some authors, however, have reported a worse prognosis as compared to patients with pure hepatocellular carcinoma.

## REFERENCES

- 1 Jarnagin WR, Weber S, Tickoo SK, Koea JB, Obiekwe S, Fong Y, DeMatteo RP, Blumgart LH, Klimstra D. Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors. *Cancer* 2002; **94**: 2040-2046
- 2 Hamilton SR, Aaltonen LA. The WHO Classification of tumours. Pathology & Genetics of tumours of the Digestive System. Lyon: IARC Press, 2000: 204
- 3 Koh KC, Lee H, Choi MS, Lee JH, Paik SW, Yoo BC, Rhee JC, Cho JW, Park CK, Kim HJ. Clinicopathologic features and prognosis of combined hepatocellular cholangiocarcinoma. *Am J Surg* 2005; **189**: 120-125
- 4 Allen RA, Lissa JR. Combined liver cell and bile duct carcinoma. *Am J Pathol* 1949; **25**: 647-655
- 5 Shin CI, Lee JM, Kim SH, Choi JY, Lee JY, Han JK, Jo SY, Choi BI. Recurrence patterns of combined hepatocellular-cholangiocarcinoma on enhanced computed tomography. *J Comput Assist Tomogr* 2007; **31**: 109-115
- 6 Kassahun WT, Hauss J. Management of combined hepatocellular and cholangiocarcinoma. *Int J Clin Pract* 2008; **62**: 1271-1278
- 7 Tang D, Nagano H, Nakamura M, Wada H, Marubashi S, Miyamoto A, Takeda Y, Umeshita K, Dono K, Monden M. Clinical and pathological features of Allen's type C classification of resected combined hepatocellular and cholangiocarcinoma: a comparative study with hepatocellular carcinoma and cholangiocellular carcinoma. *J Gastrointest Surg* 2006; **10**: 987-998
- 8 Nishie A, Yoshimitsu K, Asayama Y, Irie H, Aibe H, Tajima T, Shinozaki K, Nakayama T, Kakihara D, Shimada M, Aishima S, Yoshida K, Honda H. Detection of combined hepatocellular and cholangiocarcinomas on enhanced CT: comparison with histologic findings. *AJR Am J Roentgenol* 2005; **184**: 1157-1162
- 9 Choi BI, Han JK, Kim YI, Kim HC, Park JH, Kim CW, Han MC. Combined hepatocellular and cholangiocarcinoma of the liver: sonography, CT, angiography, and iodized-oil CT with pathologic correlation. *Abdom Imaging* 1994; **19**: 43-46
- 10 Sanada Y, Shiozaki S, Aoki H, Takakura N, Yoshida K, Yamaguchi Y. A clinical study of 11 cases of combined hepatocellular-cholangiocarcinoma. Assessment of enhancement patterns on dynamics computed tomography before resection. *Hepatol Res* 2005; **32**: 185-195
- 11 Fukukura Y, Taguchi J, Nakashima O, Wada Y, Kojiro M. Combined hepatocellular and cholangiocarcinoma: correlation between CT findings and clinicopathological features. *J Comput Assist Tomogr* 1997; **21**: 52-58
- 12 Ebied O, Federle MP, Blachar A, Brancatelli G, Grazioli L, Cazals-Hatem D, Dondero F, Vilgrain V. Hepatocellular-cholangiocarcinoma: helical computed tomography findings

- in 30 patients. *J Comput Assist Tomogr* 2003; **27**: 117-124
- 13 **Toh CH**, Cheung YC, Ng SH, Lin CY, Chan SC, Ng KK. Combined hepatocellular-cholangiocarcinoma: a case report. *Int J Clin Pract* 2004; **58**: 1170-1173
- 14 **Uenishi T**, Hirohashi K, Shuto T, Yamamoto T, Kubo S, Tanaka H, Ikebe T, Kinoshita H. Surgery for mixed hepatocellular and cholangiocellular carcinoma. *Hepatogastroenterology* 2000; **47**: 832-834
- 15 **Hashimoto T**, Nakamura H, Hori S, Tomoda K, Mitani T, Murakami T, Kozuka T, Monden M, Wakasa K, Sakurai M. MR imaging of mixed hepatocellular and cholangiocellular carcinoma. *Abdom Imaging* 1994; **19**: 430-432
- 16 **Huppertz A**, Haraida S, Kraus A, Zech CJ, Scheidler J, Breuer J, Helmberger TK, Reiser MF. Enhancement of focal liver lesions at gadoxetic acid-enhanced MR imaging: correlation with histopathologic findings and spiral CT--initial observations. *Radiology* 2005; **234**: 468-478
- 17 **Lee WS**, Lee KW, Heo JS, Kim SJ, Choi SH, Kim YI, Joh JW. Comparison of combined hepatocellular and cholangiocarcinoma with hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Surg Today* 2006; **36**: 892-897
- 18 **Sasaki A**, Kawano K, Aramaki M, Ohno T, Tahara K, Takeuchi Y, Yoshida T, Kitano S. Clinicopathologic study of mixed hepatocellular and cholangiocellular carcinoma: modes of spreading and choice of surgical treatment by reference to macroscopic type. *J Surg Oncol* 2001; **76**: 37-46
- 19 **Lin G**, Toh CH, Wu RC, Ko SF, Ng SH, Chou WC, Tseng JH. Combined hepatocellular cholangiocarcinoma: prognostic factors investigated by computed tomography/magnetic resonance imaging. *Int J Clin Pract* 2008; **62**: 1199-1205

S- Editor Li LF L- Editor Lutze M E- Editor Lin YP