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ABOUT COVER

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World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

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CASE REPORT

Esophageal metastasis of stem cell-subtype hepatocholangio carcinoma: Rare presentation of a rare tumor

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Author contributions: Salimon M and Touchefeu Y designed the research; Salimon M, Chapelle N, Mosnier JF and Frampas E performed the research; Salimon M, Matysiak-Budnik T and Touchefeu Y wrote the paper.

Informed consent statement: This is a non-interventional report; the patient died before the writing of the report. The report is in accordance of the Declaration of Helsinki and its latter amendments.

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Abstract

Hepatocholangiocarcinoma (cHCC-ICC) is a rare primary hepatic tumor defined by the presence of histological features of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Its prevalence ranges from 1%-5% of all primary liver cancers. We report the case of a 55-year-old cirrhotic male patient admitted to our university hospital for dysphagia, revealing a 10 cm lower-third esophageal metastasis of an unresectable cHCC-ICC with stem-cell features. Computed tomography and abdominal magnetic resonance imaging scans revealed multiple hepatic lesions combining features of both HCC and ICC, associated with synchronous bone metastasis. Histological and immunohistochemical analyses of biopsies from the esophageal lesion and the hepatic tumor confirmed the diagnosis of cHCC-ICC with a stem cell-subtype, according to the World Health

Organization classification. After a multidisciplinary meeting, the patient was treated with chemotherapy. He received two cycles of a gemcitabine plus cisplatin regimen before bone progression, and he died 3 mo after the initial diagnosis.

Key words: Hepatocholangiocarcinoma; Stem cell-subtype; Esophageal metastasis; Chemotherapy; Gemcitabine plus platinum-based chemotherapy

Core tip: Hepatocholangiocarcinoma (cHCC-ICC) represents less than 5% of all hepatic tumors and remains an uncommon cancer, with no guidelines concerning its management. Esophageal metastasis is a rare presentation of hepatic tumors. To our knowledge, this case report is the first to describe an esophageal lesion revealing a metastatic stem cell-subtype cHCC-ICC.

Salimon M, Chapelle N, Matysiak-Budnik T, Mosnier JF, Frampas E, Touchefeu Y. Esophageal metastasis of stem cell-subtype hepatocholangiocarcinoma: Rare presentation of a rare tumor. *World J Gastroenterol* 2018; 24(7): 870-875 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i7/870.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i7.870

INTRODUCTION

Primary liver cancer is the sixth most common cancer worldwide[1]. The majority of intrahepatic cancers are hepatocellular carcinomas (HCCs) or intrahepatic cholangiocarcinomas (ICCs). The prevalence of hepatocholangiocarcinoma (cHCC-ICC), combining histological features of HCC and ICC, ranges from 1% to 5% of primary hepatic cancers[2]. In 1949, Allen and Lisa[3] were the first to describe and classify cHCC-ICC into three subtypes (A, B and C). The classification subsequently evolved until the latest World Health Organization classification, proposed in 2010 (Table 1)[4].

Here we report the case of a patient diagnosed with a cHCC-ICC of stem cell-subtype, presenting with dysphagia and revealing an esophageal metastasis.

CASE REPORT

A 55-year-old male was admitted to the University Hospital of Nantes, France, in January 2017 for investigation of a recent and elective dysphagia to solids associated with an alteration in general status (ECOG score 2) and weight loss of 14 kg.

The patient had a medical history of schizophrenia, alcoholic cirrhosis with Child-Pugh score A and a daily alcohol intake of 30 g, Barrett's esophagus C1M6, and heavy cigarette smoking.

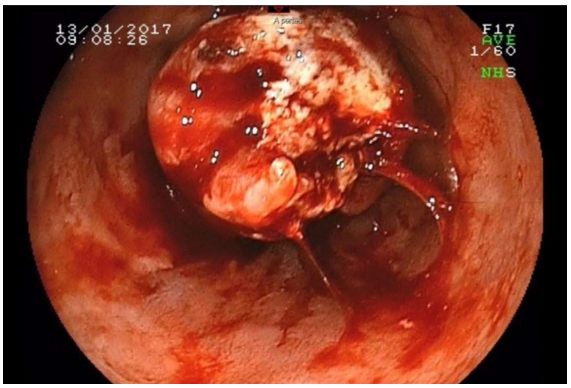

Figure 1 Endoscopic appearance of the elevated lesion in the esophagus. Upper digestive endoscopy showed a 10-cm polypoid tumor at 30 cm from incisors.

The first biological analyses showed isolated thrombocytopenia of 107 G/L, and normal renal and hepatic functions. The C-reactive protein level was 9.9 mg/L.

Esophageal endoscopy (Figure 1) revealed a significant, quasiobstructive lesion of the lower third of the esophagus. Histological analysis confirmed an esophageal localization of an undifferentiated carcinoma, with immunohistochemical analysis indicating HCC with positive hepatocyte antigen.

Thoraco-abdomino-pelvic computed tomography (CT) and abdominal magnetic resonance imaging (MRI) scans were performed. CT scans were performed before and after injection of contrast media, including arterial, portal and delayed phase at 5 min. MRI scan included T1-weighted sequence with fat suppression before and after injection of gadolinium chelates at the same phases. CT and MRI scan analyses (Figure 2) revealed the esophageal lesion and multiple hepatic nodules, mainly located in the right liver. Hepatic tumors exhibited atypical imaging features for classic HCC but showed combined imaging features of both HCC with peripheral arterial enhancement and delayed wash out, and ICC with delayed central fibrous enhancement. The tumors more closely resembled ICC. Metastases were present in adrenal glands (33 mm on the right adrenal gland and 17 mm on the left adrenal gland) and lymph nodes of the celiac region, associated with a bony lesion of the right iliac branch invading the pubic symphysis.

All tumor markers were normal: alpha fetoprotein (αFP): 1.8 ng/mL (normal range: 0.8-8.8 ng/mL); carbohydrate antigen 19-9 (CA19-9): 4.5 U/mL (normal range: < 37 U/mL); and, carcinoembryonic antigen: 2.4 μg/L (normal range: < 5 μg/L).

A liver biopsy was performed. Histological and immunohistochemical analyses showed cHCC-ICC with stem cell features (small cells) and an intermediate cell subtype, as described in Table 1. The tumor consisted

Table 1 World Health Organization 2010 classification of combined hepatocholangiocarcinoma

World Health Organization 2010[4]
cHCC-ICC classical: Typical HCC and typical ICC
cHCC-ICC-SC
cHCC-ICC-SC-typical: Nests of mature-looking hepatocytes with peripheral clusters of small cells that have a high nucleus:cytoplasm ratio and hyperchromatic nuclei.
cHCC-ICC SC-int: Tumor cells show features intermediate between hepatocytes and cholangiocytes. These tumor cells show strands, solid nests and/or trabeculae of small, uniform cells with scant cytoplasm and hyperchromatic nuclei.
cHCC-ICC-SC-CLC: Admixtures of small monotonous glands, antler-like anastomosing patterns. Each tumor cell is cuboidal, smaller in size than normal hepatocytes, with a high nucleus: cytoplasm ratio, and distinct nucleoli.

cHCC-ICC: Combined hepatocholangiocarcinoma; cHCC-ICC-SC-typical: Combined hepatocholangiocarcinoma, stem cell features, typical subtype; cHCC-ICC-SC-int: Combined hepatocholangiocarcinoma, stem cell features, intermediate cell-subtype; cHCC-ICC-SC-CLC: Combined hepatocholangiocarcinoma, stem cell features, cholangiolocellular subtype; HCC: Hepatocellular carcinoma; ICC: Intrahepatic cholangiocarcinoma; SC: Stem cell.

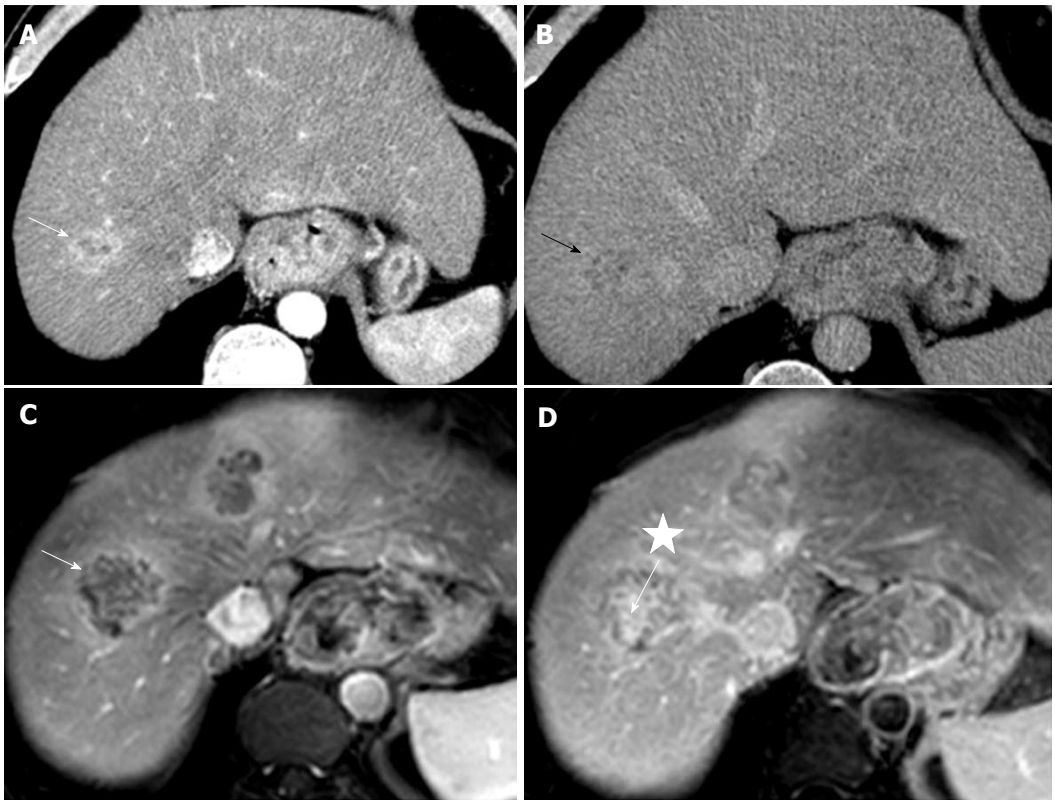

Figure 2 Computed tomography scan and magnetic resonance imaging scan imaging. Axial-enhanced computed tomography scans with arterial (A) and 5-min delayed times (B). Corresponding axial enhanced MRI in T1-weighted sequence with fat suppression (C and D). Tumor of the junction of the segments Ⅷ-Ⅶ combined the double imaging features with peripheral arterial contrast enhancement (white arrow) and secondary wash out (black arrow) (HCC part) and a late fibrous contrast enhancement of the central part (white asterisk) (ICC part). MRI was performed at 2-mo intervals and demonstrated a second tumor with comparable behavior in segment Ⅳ. CT: Computed tomography; MRI: Magnetic resonance imaging.

of small cuboidal cells arranged in a ductal pattern at the borders of nodules, in continuity with a trabecular pattern at the center. Tumor cells concomitantly expressed hepatocyte antigen HepPar1 and cytokeratin 19, normally expressed by biliary cells (Figure 3). The tumor cells appeared to be growing within and replacing regenerative nodules of cirrhosis.

The patient was treated with systemic intravenous gemcitabine and cisplatin combined chemotherapy (gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 every week for 2 wk, with 1 wk of rest before a new cycle). He received two cycles of chemotherapy. During the follow-up, the patient showed a progressive alteration in general condition, with an ECOG score of 3, associated with the appearance of diffuse bone pain. A bone scintigraphy was performed 2 mo after the beginning of chemotherapy, and revealed a multifocal metastatic spread over the entire axial and peripheral skeleton with right ilio-pubic and voluminous right humeral lesions. The patient was then managed with

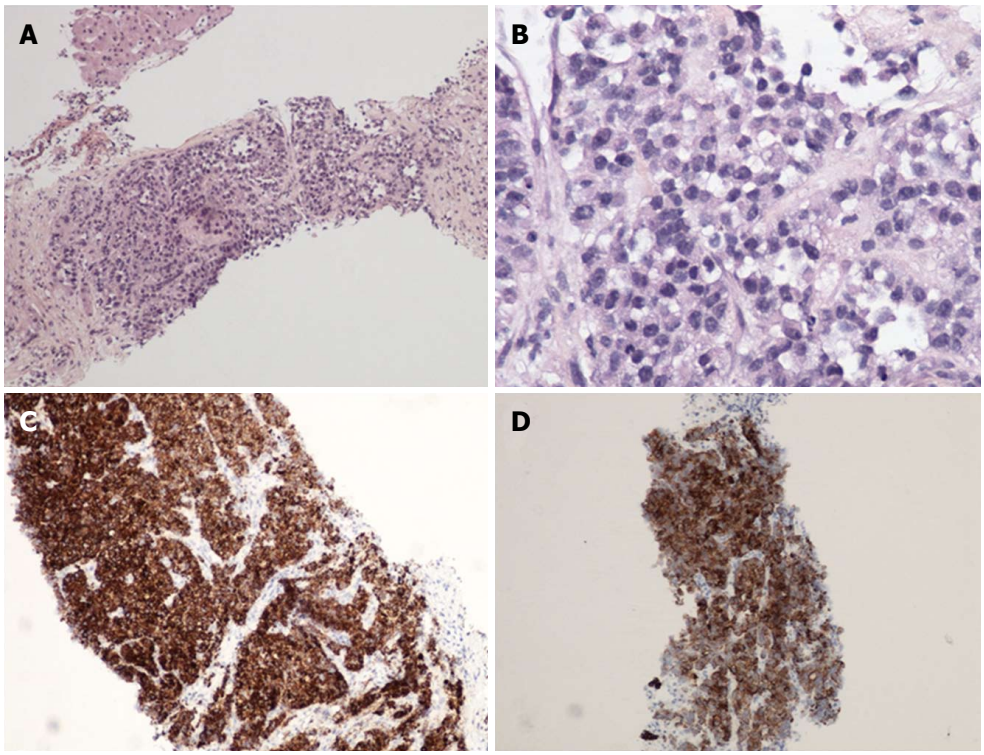

Figure 3 Histological and immunohistochemical appearance of hepatic lesions. A: Combined hepatocellular cholangiocarcinoma, stem cell features, intermediate cell-subtype with underlying cirrhosis; B: The tumor is composed of small tumor cells arranged in bays, with some ill-defined glands; C: Cells express both markers of hepatocyte cells (Her Par1); D: Markers of biliary cells (cytokeratin 19).

best supportive care and died 87 d after the beginning of treatment.

DISCUSSION

To our knowledge, this is the first report of an esophageal metastasis of a cHCC-ICC. Esophageal metastases are uncommon. In HCC, the incidence of metastatic esophageal tumors is low, accounting for less than 0.4%[5]. Few case reports have described the presence of esophageal metastases from HCC or ICC[6-14]. These metastases could develop by the spread of tumor cells infiltrating the portal system[15]. The dissemination by hepatofugal portal flow to the esophagus seems to be one possible route for esophageal metastasis[8].

There are no current guidelines for the treatment of unresectable, locally advanced or metastatic cHCC-ICC. We recently described the first series of patients with unresectable cHCC-ICC treated with gemcitabine plus platinum-based chemotherapy. In that retrospective study, including 30 patients, according to RECIST criteria, the partial response rate was 28.6%, stable disease rate 50% and progressive disease rate 21.4%. Median progression-free survival and overall survival were 9.0 mo and 16.2 mo, respectively[16].

The diagnosis of cHCC-ICC is challenging. The radiological diagnosis is difficult due to the high frequency of cHCC-ICC mimicking HCC, from 30% to 50% when considering the major features of HCC (arterial phase hyperenhancement, wash out and capsule appearance)[17,18]. However, the addition of non-HCC features in the radiologic assessment could improve the diagnostic accuracy[18]. Histological diagnosis is the gold standard, but is difficult to obtain in the absence of surgical specimens. The conduct of liver biopsies to sample both components of cHCC-ICC is infrequent. In a series of 23 resected cHCC-ICC, all of the tumors were misdiagnosed at preoperative histology, with 20 considered to be HCC and three classed as ICC[19].

As in the case presented here, criteria for identifying cHCC-ICC have been proposed previously[20]. The combination of elevated serum tumor markers and enhancement patterns on imaging should strongly suggest the diagnosis of cHCC-ICC in the following circumstances: imaging features of both ICC and HCC, regardless of marker levels; elevation of both αFP and CA19-9, regardless of imaging appearance; or discordance between imaging and tumor marker elevation (typical HCC enhancement pattern with elevated CA19-9 or typical ICC enhancement pattern with elevated αFP)[20].

The combination of histological, radiological and biological criteria is important to identify cHCC-ICC patients. Even in patients with cirrhosis and liver tumor with typical enhancement patterns of HCC, biopsies should be advocated in the presence of biological or imaging features suggesting a cHCC-ICC, as the

prognosis and the management of these tumors could be different[21].

ARTICLE HIGHLIGHTS

Case characteristics
A 55-year-old cirrhotic male patient was admitted for dysphagia.

Clinical diagnosis
Elective dysphagia for solids associated with an alteration in general status and a weight loss of 14 kg.

Differential diagnosis
Primary esophageal cancer.

Laboratory diagnosis
Normal renal and hepatic functions. Normal carbohydrate antigen 19-9, carcinoembryonic antigen and alpha fetoprotein.

Imaging diagnosis
Thoraco-abdomino-pelvic computed tomography and abdominal magnetic resonance imaging scans were performed and revealed hepatic lesions combining imaging features of both hepatocellular carcinoma, and intrahepatic cholangiocarcinoma.

Pathological diagnosis
Stem cell-subtype hepatocholangiocarcinoma.

Treatment
Chemotherapy: gemcitabine - cisplatin.

Term explanation
Hepatocholangiocarcinoma is a primary hepatic tumor representing less than 5% of all hepatic tumors. This is the first report of an esophageal metastasis of a hepatocholangiocarcinoma.

Experiences and lessons
The diagnosis of hepatocholangiocarcinoma is challenging. The addition of non-HCC features in the radiologic assessment could improve the diagnostic accuracy.

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