Combined Hepatocellular Carcinoma - Cholangiocarcinoma Harboring a Metastasis of Colon Adenocarcinoma

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ABSTRACT

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CC) represents a rare form of primary hepatic neoplasia. We report an unusual case of tumor-to-tumor metastasis: a cHCC-CC harboring a metastasis of colon adenocarcinoma developed in a 59 year old patient with alcohol-related liver cirrhosis. To the best of our knowledge, this is the first case of such a simultaneous occurrence.

Key words: hepatocellular carcinoma – cholangiocarcinoma – combined hepatocellular carcinomacholangiocarcinoma – liver metastasis

INTRODUCTION

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CC) is a rare form of primary liver malignancy, with an upward diagnostic trend. In its more common counterparts, it is a highly vascularised tumor. We describe a rare, but biologically not fortuitous event that may involve cHCC-CC: housing of a colon cancer metastasis. Such a condition poses diagnostic and therapeutic challenges to clinicians and pathologists in terms of management.

CASE REPORT

A 59-year-old Caucasian man was admitted to the hospital complaining of abdominal discomfort, weakness and weight loss over the last month. Main features of the medical history were alcohol-related liver cirrhosis and more recently, i.e. 6 months before, a segmental resection of the transverse colon for a primary adenocarcinoma (pT3N0, G2, with elevated carcinoembryonic antigen – CEA level). At the time of colon surgery, no other thoracic or abdominal lesions were found on computed tomography (CT) and following the diagnosis no adjuvant chemotherapy was given.

At the current admission, the patient's laboratory analyses showed increased α -fetoprotein (AFP) level (321 µg/L, NV <20 µg/L) with normal levels of carbohydrate antigen 19-9 and CEA. Hepatitis B and C markers were negative and liver function tests were within the normal limits, except for a mild cholestasis: gamma-glutamyl transpeptidase 86 IU/l (NV < 50 IU/L) and alkaline phosphatase 215 IU/l (NV 145 < IU/L). The CT-scan performed for staging identified a 64 x 56 x 55 mm lesion in the VI-VII liver segments with heterogeneous arterial (Fig. 1A) and portal-phase (Fig. 1B) enhancement, and non dilated bile ducts. According to the past history of the patient, it was assumed that the lesion was a liver metastasis despite the laboratory findings (normal CEA, increased AFP) and an US-guided fine needle aspiration (FNA) evidenced malignant epithelial glandular cells, unlikely related to colon cancer.

As upper digestive endoscopy did not find any lesions and the patient had a well compensated cirrhosis (Child A), the resection of the tumor mass was performed. The postoperative recovery was without major complications and the patient was discharged 10 days after surgery.

The resected specimen showed a 6 cm sized heterogeneous and not encapsulated tumor mass and, in close proximity, 5 additional whitish nodular lesions ranging between 0.5 and 1.0 cm. The surrounding parenchyma was cirrhotic. Microscopically, the main tumor and 4 out of the 5 small nodules showed morphological features of cHCC-CC. The neoplasm was characterized by malignant glandular structures (Fig. 2A, right) staining positive for cytokeratin-19 (CK 19, Fig.



Fig. 1. CT-scan showing ringed-tumor enhancement in arterial-phase (A) and delayed enhancement in most of the central area (B).

2B), intermingled with more solid sheets of hepatocytes (Fig. 2A, left) highlighted by hepatocyte paraffin 1(HepPar1, Fig. 2C) immunostaining. The hepatocellular carcinoma (HCC) areas were also positive for the panel of immunomarkers: glypican 3 (GPC3), heat shock protein 70 (HSP70) and glutamine synthetase (GS). Conversely, one of the small nodules was composed by well defined glandular structures (Fig. 2D) staining positive with CK20 and CDX-2 (Fig. 2D, inset) consistent with the diagnosis of metastatic adenocarcinoma of the colon.

All these findings together confirmed the diagnosis of a cHCC-CC harboring a metastasis of colon adenocarcinoma.

DISCUSSION

Combined hepatocellular carcinoma-cholangiocarcinoma is a rare but increasingly recognized type of primary hepatic tumor, accounting for 0.4%-14.2% of primary liver cancers [1, 2]. It has been previously reported in the setting of hepatitis B or C chronic infection, long term alcohol abuse and liver cirrhosis. However, these etiological factors are strongly associated more with HCC than with cholangiocarcinoma (CC), assessed separately [2]. Despite awareness of this entity, a preoperative diagnosis can be extremely difficult. Indeed, at imaging, patients are often misdiagnosed as having either HCC or CC, depending on the predominant tumor component [3]. Even liver biopsy, if performed as in this case, can be misleading [4, 5]. By contrast, metastases of colorectal cancer to the liver are extremely common. However they are much more frequent in the normal liver than in the cirrhotic liver (37% vs. 10-13.7%) [6] as a consequence of distortion of liver architecture and vascularization, which prevents the grafting of metastatic cells.

We therefore present an unusual event of a tumor-totumor metastasis. This "tumor in tumor" effect is not likely to be biologically fortuitous, as it has been described in several tumors. Indeed in most of the cases the recipient tumor was a clear cell carcinoma of the kidney, i.e. a highly vascularised



Fig. 2. Microscopical features of combined hepatocellular carcinomacholangiocarcinoma (A-C) harbouring a metastasis of colon adenocarcinoma (D). A. Malignant glandular structures (left part) and solid sheets of hepatocytes (right part) merging one into another (H&E, 20X). B) Cytokeratin-19 (CK 19) immunostaining for billiary structures (20X). C) Hepatocyte paraffin 1 (HepPar1) immunostaing for hepatocytes (20X). D) Metastatic colon adenocarcinoma (H&E, 10X) and CDX-2 immunostain (inset).

tumor [7], as are most primary hepatic malignancies. A rare primary tumor of the liver (cHCC-CC) harboring a metastasis of adenocarcinoma of the colon has never been reported until now.

Although the cHCC-CC was incidentally discovered during the follow-up evaluation for colon cancer, hepatic resection remains the only effective treatment for cHCC-CC, when feasible [8-9]. Unfortunately, the mixed tumor displays aggressive behavior and a poor outcome, due to its CC component.

When simultaneous neoplasms are diagnosed, systemic treatment can be performed and this should target the tumor with the worst prognosis [2, 10]. Referring to our case, chemotherapy was timed according to the request of the patient.

CONCLUSION

Clinical, laboratory and radiological findings should be carefully considered for the diagnosis of classical versus combined HCC. In addition, it should be kept in mind that these highly vascularized tumors might harbor metastatic foci from other sites.

Conflicts of interest: None to declare.

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