Breast Metastasis From a Combined Hepatocellular–Cholangiocarcinoma

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ABSTRACT
Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a unique entity that contains mixed elements of both hepatocellular carcinoma and cholangiocarcinoma. We report a 62-year-old woman with alcoholic cirrhosis with elevated α-fetoprotein of 25.3 ng/mL. Abdominal computed tomography showed a poorly defined subcapsular nodular lesion in the VIII segment, showing enhancement during the arterial phase and washout in the delayed phase. Histological examination of hepatic segmentectomy revealed a malignant epithelial neoplasia constituted by 2 distinct components, consistent with the diagnosis of cHCC-CC, classical type. One year after surgical resection, the patient noticed a nodule in the right breast. Histological examination of core needle biopsy was compatible with a metastasis in the breast of the previously diagnosed liver cancer. To our knowledge, this is the first report of breast metastases from a cHCC-CC, denoting disseminated metastatic disease and poor prognosis.

INTRODUCTION
Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a unique entity that contains mixed elements of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC).1 This rare form of primary liver cancer accounts for 1%–5% of all primary liver cancers and has a poor prognosis.1 cHCC-CC was described for the first time in 1949 by Allen and Lisa.2 However, its diagnosis, biological behavior, prognosis, and treatment remain poorly understood compared with HCC or CC. Nonetheless, cHCC-CC has been increasingly recognized, partly because of the extensive sampling of explants and surgical resection specimens.1 cHCC-CC is currently defined as the presence of unequivocal mixed components of both HCC and CC according to the recent WHO definition and is divided into 2 subcategories: classic cHCC-CC and cHCC-CC with "stem cell features" when morphological and/or immunophenotypical features of stem/progenitor cells within the tumor predominate.3

Aggressive multimodal treatment is strongly recommended for recurrent CHCC-CC tumors. The current therapeutic management is based on surgical resection.3 Liver transplant, transarterial chemoembolization, radiofrequency ablation, and percutaneous ethanol injection are other available management options. However, the response to treatment is often poor, especially in patients with multiple or extrahepatic metastases.

CASE REPORT
A 62-year-old woman with alcoholic cirrhosis was regularly observed for 10 years in the Hepatology Department of Centro Hospitalar de São João. She denied alcohol consumption; she was not taking any medications, and there was no family history of liver disease.

In the biochemical screening, a slight elevation of α-fetoprotein (AFP) of 25.3 ng/mL (normal range, 1–8 ng/mL) was observed, without other abnormalities in liver function test analysis. Abdominal ultrasound was normal. Therefore, abdominal computed
tomography (CT) was performed, which showed a poorly defined subcapsular nodular lesion (4.7 × 4.6 cm) in the VIII segment, showing enhancement during the arterial phase and washout in the delayed phase (Figure 1). There was no evidence of distant or nodal metastasis in staging thoraco-abdominopelvic CT and neither in bone scintigraphy.

The case was discussed in a multidisciplinary meeting, and it was decided to perform hepatic segmentectomy VIII. Grossly, the surgical specimen measured 10.0 × 8.5 × 5.0 cm, weighed 133 g, and was partially covered by the liver capsule. On the cut surface, a well-circumscribed, heterogeneous nodule (4.2 cm in diameter) was seen. Histological examination revealed

**Figure 1.** Computed tomography images displaying a 4.7 × 4.6 cm tumor, showing enhancement during the arterial phase and washout in the delayed phase.

**Figure 2.** Pathological features of the liver tumor. The tumor displayed 2 distinct components: hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). (A) HCC component showing a trabecular growth pattern and polygonal cells (hematoxylin and eosin (H&E), 200×). (B) Expression of HepPar-1 and (C) CD34 (sinusoidal pattern) in the HCC component of the tumor. (D) CC component with glandular growth pattern and desmoplastic stroma (H&E, 200×). (E) Expression of CK7 and (F) CK19 in the CC component of the tumor.
A malignant epithelial neoplasia constituted by 2 distinct components: one with HCC-like features and the other with adenocarcinomatous pattern, displaying desmoplastic stroma. In the latter, cellular atypia was prominent, and mitoses were frequent. Phenotypical features of stem cells were not identified. Immunohistochemical studies revealed, in the HCC component, expression of HepPar-1 (focal), arginase-1 (focal), glypican-3 (diffuse), glutamine synthetase (diffuse), and CD34 (sinusoidal pattern). In the adenocarcinomatous component, there was diffuse expression of cytokeratins 7 (CK7) and 19 (CK19), in keeping with biliary differentiation. On the basis of these findings, the diagnosis of cHCC-CC, classical type, was made (Figure 2). Imagiological revaluation was performed at 3 months with abdominal CT, without showing evidence of residual disease/recurrence.

One year after surgical resection, the patient noticed a nodule in the right breast (1.5 cm in diameter), localized in the upper inner quadrant, characterized as hard and irregular. Mammography revealed a single nodule (1.1 cm), which showed characteristics compatible with BI-RADS 5. Core needle biopsy of the breast nodule displayed a solid neoplasia with necrosis, composed of polygonal cells with prominent nucleoli and marked anisocariosis. The cells were immunoreactive for glypican-3 and glutamine synthetase, with no expression of estrogen receptor, progesterone receptor, HER-2, GATA-3, GCDFP-15, mammaglobin, arginase-1, and HepPar-1. These findings were compatible with a metastasis in the breast of the previously diagnosed liver cancer (Figure 3). At the time, another abdominal CT was performed, which showed 2 new hepatic lesions (4.3 and 3.7 cm), associated with many smaller nodules, suggesting multifocal cHCC-CC. The patient was referred to best supportive care and died 2 months later because of disease progression.

DISCUSSION

Combined HCC-CC (variously referred to as mixed HCC-CC or biphenotypic hepatobiliary carcinoma) clearly represents a distinct subtype of liver carcinoma, histologically characterized by
intermingling of both HCC and CC elements. According to the WHO classification, cHCC-CC is classified into 2 subtypes: the classical type and cHCC-CC with stem cell features. The latter is additionally subcategorized into the following 3 subtypes: typical, intermediate, and cholangiocellular. Furthermore, in some cHCC-CCs, there are foci of intermediate morphology at the interface of the HCC and CC components, showing biphenotypic differentiation; cells that have phenotypic or immunophenotypical features of stem/progenitor cells may also be present. The presence of these stem/progenitor cells is believed to be the reason why these tumors exhibit aggressive biological behavior and poor prognosis with 5-year survival of 36%.

Although the histopathological characteristics of cHCC-CC are well known, its risks factors, imagiological characteristics, and clinical behavior are still poorly understood. Few studies have demonstrated that some risk factors are similar to those for HCC and CC, such as liver cirrhosis, chronic hepatitis B and C, alcohol intake, or dioxin exposure. Our patient had alcoholic liver cirrhosis; cHCC-CC was diagnosed 10 years after the initial diagnosis of cirrhosis, during a regular follow-up screening. The diagnosis was suspected because of a slight elevation of AFP levels; Yano et al observed that the AFP level >400 IU/L is an independent prognostic factor in cHCC-CC. Other authors reported that the AFP level in cHCC-CC was lower than that in HCC (not reaching the threshold of statistical significance). cHCC-CC is characterized by an aggressive biological behavior and dismal prognosis comparing to HCC or CC, and extrahepatic metastases commonly occur, with the stomach being the most common metastatic site. In our case, distant metastases were detected 1 year after surgery, localized in the breast, in keeping with the aggressiveness of these tumors, as described in the literature.

To our knowledge, this is the first report of breast metastases from cHCC-CC, denoting disseminated metastatic disease and poor prognosis. The accurate diagnosis, differentiating primary from metastatic breast carcinoma, is important for appropriate treatment to avoid unnecessary or even harmful therapy. In the literature, there are 5 cases of breast metastasis from HCC, and no cases have been described of combined HCC-CC.

DISCLOSURES

Author contributions: M. Silva and R. Coelho contributed equally to this work. M. Silva collected data, wrote the manuscript, and is the article guarantor. R. Coelho collected data and wrote the manuscript E. Rios performed the histopathologic examination and wrote the manuscript S. Gomes collected data and revised the manuscript. F. Carneiro performed the histopathologic examination and approved the manuscript. G. Macedo revised and approved the manuscript.

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Informed consent was obtained for this case report.

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