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Mixed Tumor Hepatocellular Carcinoma and Cholangiocarcinoma in a Cirrhotic Patient: Case Report and Review of the Literature

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ABSTRACT

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) is a rare primary hepatic neoplasm that presents simultaneous differentiation into hepatocytes and cholangiocytes, predominantly in patients with chronic liver disease. Its diagnosis continues to be a challenge due to its clinical and imaging presentation similar to other liver tumors, especially in cirrhotic patients. We present the case of a 61-year-old female patient with liver cirrhosis secondary to nonalcoholic fatty liver disease, who was diagnosed with cHCC-CCA after a hepatic bisegmentectomy. During her evolution, she presented tumor recurrence at hepatic and lymph node level, managed by salvage surgery and immunotherapy. However, he developed acute on chronic hepatic failure, which forced to suspend treatment and opt for palliative management. This entity stands out for its high recurrence rate, limited response to systemic therapies and lack of standardized guidelines. The present case emphasizes the importance of an accurate histopathologic diagnosis and individualized evaluation for therapeutic selection.

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Abbreviations

AFP: Alpha-Fetoprotein
CA 19-9: Carbohydrate Antigen 19-9
CCA: Cholangio Carcinoma
CHCC-CCA: Hepato-Colangiocellular Carcinoma
HCC: Hepatocellular Carcinoma
ICCA: Intrahepatic Cholangiocarcinoma
ICIs: Immune Checkpoint Inhibitors
MELD: Model For End-Stage Liver Disease
PET/CT: Positron Emission Tomography

Introduction

Hepato-colangiocellular carcinoma (cHCC-CCA) is a rare primary neoplasm of the liver, characterized by the coexistence of morphologic features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). According to the fifth classification of the World Health Organization (WHO), this tumor presents unequivocal differentiation of hepatocytes and cholangiocytes in the same lesion [1,2]. Its incidence is low, less than 2% of malignant liver neoplasms, and it predominates in male patients [2]. Its pathogenesis has been related to the transformation of hepatic progenitor cells capable of differentiating into both cell lineages [2]. It has been described to share risk factors with HCC and CCA, such as cirrhosis, hepatitis B and C, sclerosing cholangitis, non-alcoholic fatty liver disease, alcoholism and smoking [1,2]. Clinically, it is usually diagnosed in advanced stages with non-specific symptoms such as jaundice, weight loss and fatigue [1]. Preoperative diagnosis is challenging, since imaging and biomarkers lack specificity, although some patients present simultaneous elevation of alpha-fetoprotein (AFP) and carbohydrate antigen 19-9 (CA 19-9) [1]. Currently, hepatic resection with lymph node dissection is the only treatment with curative intent, although it presents high recurrence rates and limited survival [1,2,3]. There are no specific guidelines for its management, and it is frequently treated with strategies aimed at HCC or intrahepatic CCA [1,2,3]. This entity continues to represent a diagnostic and therapeutic challenge that requires further investigation.

Material and Methods

A literature review was conducted in various medical databases, such as PubMed and Cochrane, using controlled search terms. The keywords included were: "primary liver cancers" AND "cholangiocarcinoma" AND "hepatocellular carcinoma" AND "combined hepatocellular-cholangiocarcinoma" AND "diagnosis" AND "management" AND

"prognosis". This strategy allowed us to select relevant articles that provided information on the diagnosis, treatment and prognosis of this pathology.

Results / Clinical Case

We present the case of a 61-year-old female patient with a history of cholecystectomy and liver cirrhosis secondary to nonalcoholic hepatic steatosis. Her clinical history also includes the development of esophageal varices, treated by endoscopic approach. During her follow-up, a liver ultrasound was performed, in which a 4.5 cm mass was identified in the left hepatic lobe, specifically in segments II and III. Given this finding, extension studies were performed which reported a CA 19-9 level of 122, suggesting a possible diagnosis of intrahepatic cholangiocarcinoma.

The patient was classified with a Child-Pugh score of B7 and a Model for End-Stage Liver Disease (MELD) 3.0 of 12 points. As part of the therapeutic approach, a left lateral bisegmentectomy was performed. The histopathological study confirmed the diagnosis of hepatocellular carcinoma combined with cholangiocarcinoma, in addition to evidence of perineural invasion.

During postoperative follow-up, the patient started adjuvant treatment with capecitabine in combination with oxyplatin, however, she presented progressive deterioration of liver function, so platinum was suspended in May and she continued with capecitabine monotherapy, completing the scheme in June. Mild hypertensive gastritis was also documented in relation to portal hypertension.

In July 2024, a follow-up positron emission tomography (PET/CT scan with 18F-FDG) was performed, which showed a hypodense nodular image in the hepatic segment VI, with peripheral enhancement, venous washout and increased radiotracer uptake (SUV max 4.61), findings compatible with tumor recurrence. Also, two portal and intercavoaortic lymph nodes were identified with hypermetabolism (SUV max 6.77) suggestive of lymph node dissemination. The complementary imaging study by magnetic resonance with hepatobiliary contrast confirmed a 2.1 cm solid lesion in segment VI, with radiological characteristics compatible with hepatocarcinoma (LI-RADS 5), and corroborated the presence of pathological mesenteric and periportal adenopathies, in addition to chronic changes due to hepatopathy and portal hypertension.

In view of the recurrence, it was decided to perform a new surgical intervention; a non-anatomic hepatic resection of segment VI and lymphadenectomy were performed. During the procedure, firm adhesions to major vascular structures were found in the hepatoduodenal ligament, which prevented complete portal dissection. Para-aortic lymph node resection was performed without complications.

Given the progression of the disease, systemic treatment with immunotherapy was established under a combined scheme of durvalumab, atezolizumab and bevacizumab, however, the patient presented a rapid functional deterioration with development of acute on chronic liver failure (according to the CLIF classification) in December 2024, which required a new hospitalization, in which, after a multidisciplinary assessment, it was determined to definitively suspend immunotherapeutic treatment and establish measures aimed at palliative management in January 2025. At the moment he is in his 7th postoperative month with neoplastic disease without progression and without further deterioration of liver function. Splanchnic nerve ablation was performed for pain control in May 2025 with a prolonged recovery period due to hepato renal disease, completing his recovery 7 hours after the procedure, he was discharged without complications.

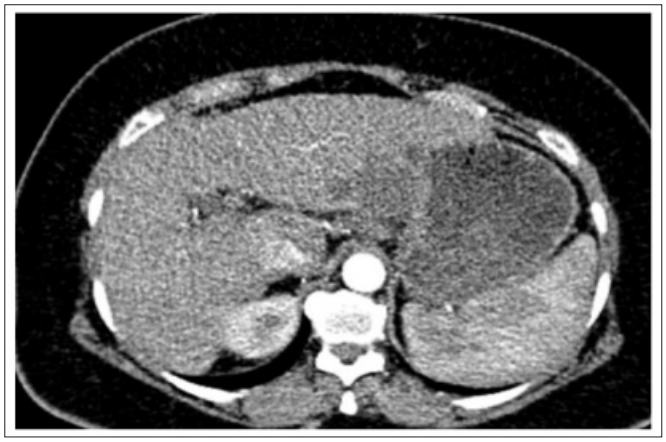

Figure 1: Computed tomography (CT) of the abdomen with contrast. Axial section in portal phase showing a hypodense and heterogeneous lesion in the left hepatic lobe, located in segments II and III. The lesion has poorly defined borders, with no clear evidence of arterial enhancement or washout in this phase

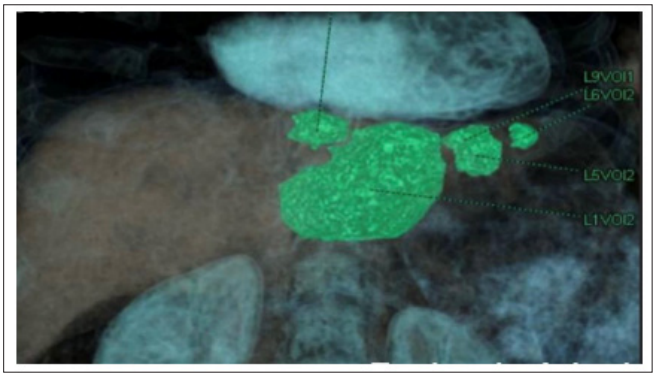

Figure 2: Three-dimensional reconstruction of positron emission tomography (PET/CT scan with 18F-FDG). Multiple areas of radiotracer (FDG) hyperuptake highlighted in green, including a hepatic lesion located in segment VI

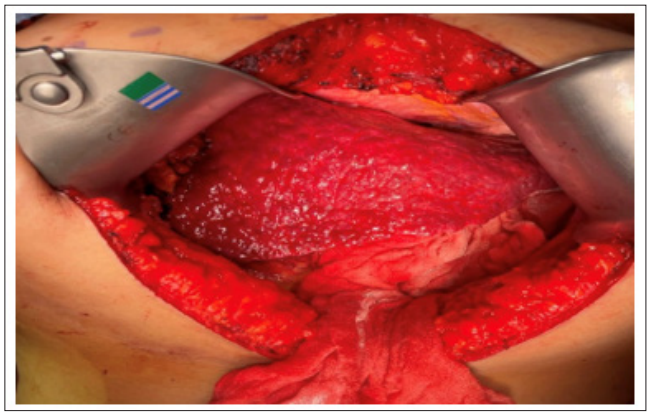

Figure 3: Intraoperative image. Open surgical field during the second operation. The cirrhotic liver is evident, with exposure of segment VI, in which a non-anatomic liver resection was performed due to tumor recurrence. The exploration showed firm adhesions to major vascular structures in the hepatoduodenal ligament, which limited the complete lymphadenectomy

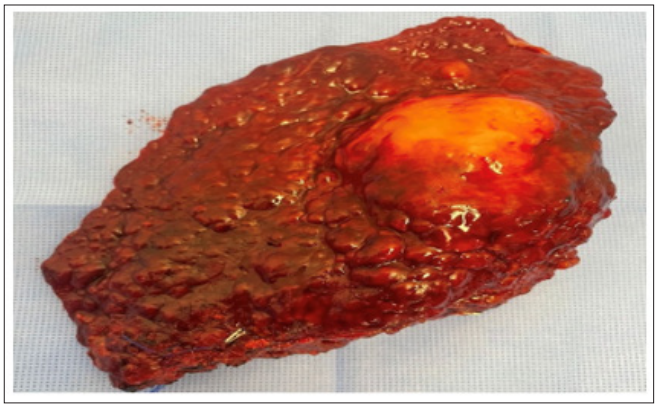

Figure 4: Hepatic surgical specimen. Specimen of the resected hepatic segment VI, showing a prominent nodular lesion, with a firm appearance and yellowish capsule, delimited from the surrounding cirrhotic liver parenchyma

Discussion and Conclusion

Hepatocellular carcinoma combined with cholangiocarcinoma is a rare entity, whose identification represents a challenge for both diagnosis and treatment. Its presentation in patients with liver cirrhosis may make the characterization of the lesion even more difficult, since its clinical and imaging manifestations may overlap with other types of primary hepatic neoplasms.

In this case, the initial diagnosis was oriented towards an intrahepatic cholangiocarcinoma due to imaging findings and CA 19-9 elevation. However, the histopathological study was key to establish the definitive diagnosis of hepatocellular carcinoma combined with cholangiocarcinoma. The perineural invasion identified in the resected specimen highlights the aggressiveness of this entity and suggests a poor prognosis.

On the other hand, cHCC-CCA is associated with a high recurrence rate after curative surgical resection. A study analyzing data from the Taiwan Cancer Registry found that the local recurrence rate for cHCC-CCA was 65.3%, compared with 74.6% for HCC and 88.4% for iCCA [4]. Risk factors associated with recurrence of cHCC-CCA include positive surgical margins, vascular invasion, and lymph node metastases. In addition, the presence of liver cirrhosis and elevated preoperative CA19-9 levels have been identified as predictors of early recurrence [5]. In the literature, recurrence of iCCA occurs predominantly at the intrahepatic level, either at the surgical margin (23.9%) or in other hepatic regions distant from the resection site (29.3%), accounting for about 47% of recurrences. Extrahepatic recurrences are less frequent (14.8%). In addition, a median time to recurrence of 10 months has been reported, with a three-year survival after relapse of approximately 28.6% [6].

Moreover, the administration of chemotherapy and immunotherapy presents significant clinical challenges, chemotherapy can lead to hepatic decompensation in patients with already impaired liver function, susceptibility to this damage may be influenced by factors such as the presence of cirrhosis, hepatic viral infections and malnutrition. Immune checkpoint inhibitors (ICIs), such as anti-CTLA-4 and anti-PD-1/PD-L1 antibodies, have shown efficacy in the treatment of HCC, however, their use may be associated with immune-mediated hepatotoxicity; a meta-analysis identified risk factors for the development of ICI-induced hepatotoxicity in cancer patients, underscoring the importance of close monitoring of liver function during treatment [7].

In addition, clinical studies have shown that the combination of atezolizumab and bevacizumab is effective in patients with HCC and compensated liver disease; however, in those with compromised liver function (Child-Pugh B and C), the efficacy of the treatment is limited, which suggests the need for careful patient selection for this type of therapy [8].

Therefore, the low incidence of this type of carcinoma and the absence of specific management guidelines make it difficult to make therapeutic decisions; consequently, it is essential to continue investigating the prognostic factors and the most effective therapeutic strategies to improve the survival of these patients [9-12].

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this case report.

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