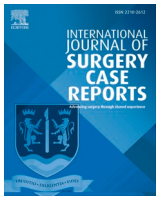
International Journal of Surgery Case Reports 129 (2025) 111165

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr



Case report

Combined hepatocellular-cholangiocarcinoma in a middle-aged patient: A case report and review of therapeutic approaches

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ARTICLE INFO

Keywords:
Combined hepatocellular-cholangiocarcinoma
Diagnostic imaging
Pathology diagnosis
Neoplasm recurrence
Case report

ABSTRACT

Introduction: Combined hepatocellular cholangiocarcinoma (cHCC-CCA) is a rare hepatic malignancy featuring both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) components, often leading to poor prognosis owing to its clinical complexity.

Case presentation: A middle-aged man presented with sudden abdominal pain and unexplained weight loss, leading to an initial diagnosis of CCA. The patient underwent laparoscopic left hepatectomy and lymph node dissection, and postoperative pathology confirmed cHCC-CCA with lymph node metastasis. Despite initial recovery, the disease recurred at 2 months and progressed to lung metastasis and multi-organ involvement by 7 months. Immuno-combination targeted therapy was ineffective, and the patient succumbed to the disease eight months after surgery.

Discussion: This case highlights the diagnostic and therapeutic challenges of cHCC-CCA, including its histological complexity, high recurrence rate, and limited treatment efficacy. Despite surgical resection, early recurrence and rapid progression to pulmonary metastasis were observed, emphasizing the need for improved treatment strategies for this condition. The failure of immune checkpoint inhibitors and targeted therapy suggests the need for alternative or combined therapeutic approaches.

Conclusion: Future research should focus on integrating molecular profiling into treatment selection, optimizing adjuvant therapies, and exploring novel targeted or immunotherapy combinations to improve the long-term outcomes. This report contributes to the growing evidence on cHCC-CCA and underscores the urgency of developing precise diagnostic tools and personalized treatment strategies.

1. Introduction

Combined hepatocellular cholangiocarcinoma(cHCC-CCA)is a rare primary liver tumor, accounting for 0.4 %–14 % of all primary liver cancers, disease exhibits characteristics of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) components, with a more aggressive nature than HCC, poorer treatment response, and a lower overall survival rate [1,2]. Overall, cHCC-CCA presents significant challenges in diagnosis and treatment because of its unique histological features and diverse treatment responses. This case report aims to provide a comprehensive account of the treatment process of a middle-aged man with cHCC-CCA, including laboratory findings, imaging characteristics, and pathological features, offering valuable insights into clinical decision making. Through an in-depth analysis of cHCC-CCA, we aim to enhance the understanding of this complex tumor type and provide guidance for future research and clinical practice. This case report was prepared in accordance with the SCARE 2023 criteria [3].

2. Case presentation

A middle-aged man with no significant medical history, 30-year history of smoking, or history of alcohol abuse or familial genetic disease. He was admitted with a sudden onset of severe right upper abdominal pain, accompanied by a bitter taste and bloating for two weeks prior. The patient reported a weight loss of approximately 5 kg after symptom onset. Physical examination revealed diffuse tenderness in the right upper abdomen, without signs of bowel obstruction, nausea, or vomiting. Pre-admission ultrasonography of the liver, gallbladder, pancreas, spleen, and kidneys revealed multiple solid lesions in the left lobe of the liver and a solid nodule at the hepatic hilum. Laboratory tests revealed negative results for HBV, HCV, and novel coronavirus, while tumor markers CA125, CA19-9, and AFP were elevated. Other

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https://doi.org/10.1016/j.ijscr.2025.111165
Received 5 February 2025; Received in revised form 11 March 2025; Accepted 15 March 2025
Available online 17 March 2025

laboratory tests, including blood cell count, liver and kidney function, and coagulation profiles, showed no significant abnormalities. Contrast-enhanced CT of the portal vein, inferior vena cava, and hepatic arteries revealed multiple lesions in the left lobe of the liver, with the largest tumor measuring approximately 5.1 × 4.0 cm. The scan also indicated intrahepatic bile duct dilatation and enlarged lymph nodes in the hepatic region, raising suspicion of cholangiocarcinoma (Fig. 1).

The surgery was well prepared before the operation, which was performed by laparoscopic left hepatectomy with lymph node dissection. The resected specimen showed a hard texture of the left liver tumor with a grayish-white cut surface (Fig. 2). Liver, gallbladder, and lymph node specimens were sent to the pathology department for further examinations. The pathology report revealed the following findings: the gallbladder showed chronic inflammatory changes, with no evidence of cancerous involvement; the resected liver tissue was diagnosed as cHCC-CCA, with the hepatocellular carcinoma component accounting for 90 % and poorly differentiated (Fig. 3a), whereas the cholangiocarcinoma component accounted for 10 % and was moderately to poorly differentiated (Fig. 3b). Immunohistochemical tests showed that the tumor cells (Fig. 3c) did not express CD56, CgA, Syn, Glypican-3, CDX-2, or CK20, whereas they were positive for P40, P63, Hepa, CK19, CK18, CK8, CK7, Villin, and focal CEA. All examined lymph nodes showed metastasis.

At the one-month follow-up, imaging and laboratory tests showed no signs of disease recurrence. However, two months postoperatively, new intrahepatic lesions were detected, and the tumor markers increased. Despite receiving sintilimab and bevacizumab therapy, the disease progressed, with pulmonary metastases confirmed at seven months. A full abdominal CT scan revealed that the tumor had metastasized to the lungs, the residual liver had multiple enlarging nodules, the hepatic venous system was compressed and narrowed (Fig. 4a), the retroperitoneal lymph nodes were enlarged with necrosis, and the pancreas was compressed (Fig. 4b). Laboratory tests showed that the tumor markers had increased again since the last admission, with decreased albumin levels and a significant increase in the D-dimer levels. Therefore, we discontinued immunotherapy and targeted drug treatments and opted for supportive care. The patient succumbed to the disease eight months after surgery.

3. Discussion

cHCC-CCA exhibits dual histological characteristics of both HCC and CCA [4]; however, no standardized threshold has been established to determine the proportion of HCC and CCA components within the tumor [5]. Owing to its distinct clinical presentation, biological behavior, diagnostic challenges, and therapeutic complexity, surgical resection remains the primary treatment modality for localized lesions [6–8], utilized for tumors measuring 2.0–3.2 cm, while TACE is preferred for lesions of 4.8–6.0 cm. However, for tumors of 4.8 cm and 6.0 cm, surgical resection is often favored by surgeons, with more than half also considering liver transplantation a viable treatment option for patients with cHCC-CCA [9].

This case involved a middle-aged man who presented with abdominal pain and liver discomfort. Except for a significant increase in tumor markers CA125, CA19-9, and ferritin, AFP levels were not notably elevated, and the results of other laboratory tests showed no abnormalities. Notably, in liver malignancies, particularly those associated with HBV and HCV, these viruses are widely recognized as the primary etiological factors [10]. However, the hepatitis virus test results were negative.

Given the absence of jaundice, nausea, vomiting, or other gastrointestinal symptoms in the early stage, further imaging was conducted, which suggested the imaging features of cholangiocarcinoma, and the "pseudocapsule" sign suspected to be HCC was found (Fig. 5). This increases the complexity of diagnosis. Typically, biopsy is employed for pathological confirmation when CT or MRI images are atypical or when there is uncertainty regarding the diagnosis [11]. However, liver tumors frequently exhibit obvious heterogeneity, and a solitary biopsy may merely reflect the local situation, resulting in a false-negative outcome when the sampling area does not encompass the typical lesions and the pathological features have not been collected. In certain instances, inflammatory or other benign changes may also be pathologically false-positive for malignant lesions. Given the invasive nature of the biopsy procedure, which carries the inherent risks of bleeding and infection, we elected to forgo this approach in the present case. Instead, we made a preliminary diagnosis of CCA based on imaging results.

Subsequent postoperative pathology reports indicated that immunohistochemical detection revealed the tumor cells to be sensitive to neuroendocrine markers (CD56, CgA, Syn) as well as typical hepatocyte markers (Glypican-3).) Markers of intestinal origin and differentiation (CDX-2, CK20) were not expressed, whereas P40 and P63 were positive, suggesting local squamous or basal-like differentiation. Positive expression of Hepa, CK18, and CK8 indicated that the tumor was characterized by hepatocellular differentiation, whereas positivity for Villin, CK7, and CK19 supported biliary epithelial differentiation. In addition, a Ki-67 proliferation index of up to 60 % showed high proliferative activity of the tumor cells, focal CEA positivity suggested the presence of adenocarcinoma-like differentiation, and capillarization staining of CD34 reflected abundant microangiogenesis. In conclusion, the immunohistochemical results confirmed that the tumor possessed both hepatocellular and biliary epithelial differentiation features, which was highly consistent with the diagnosis of cHCC-CCA. A rare disease cohort study indicated that owing to its rarity, cHCC-CCA is often misdiagnosed as either HCC or CCA before pathological examination is performed [12], the imaging features are atypical, and the sensitivity is low [13]. The present case supports these findings. In addition, lymph node

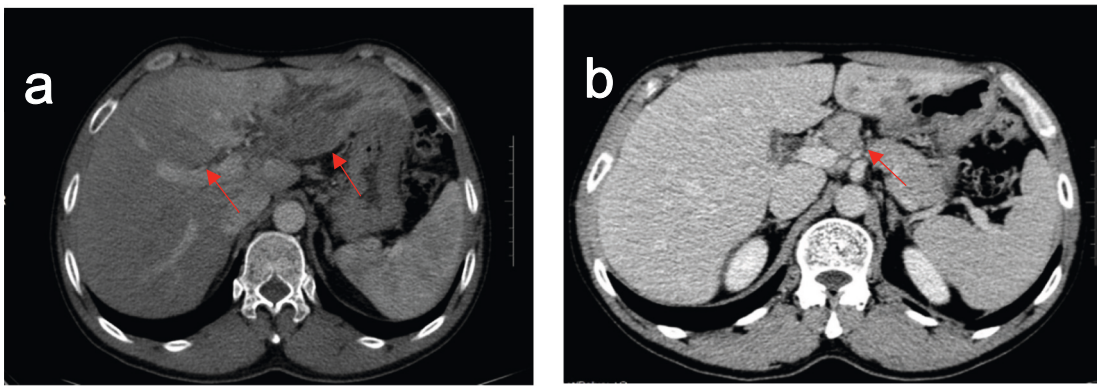

Fig. 1. A CT scan of the portal vein, inferior vena cava, and hepatic artery was performed, revealing the presence of multiple tumors in the left lobe of the liver images were obtained to document dilated intrahepatic bile ducts (a) and enlarged lymph nodes in the liver region (b).

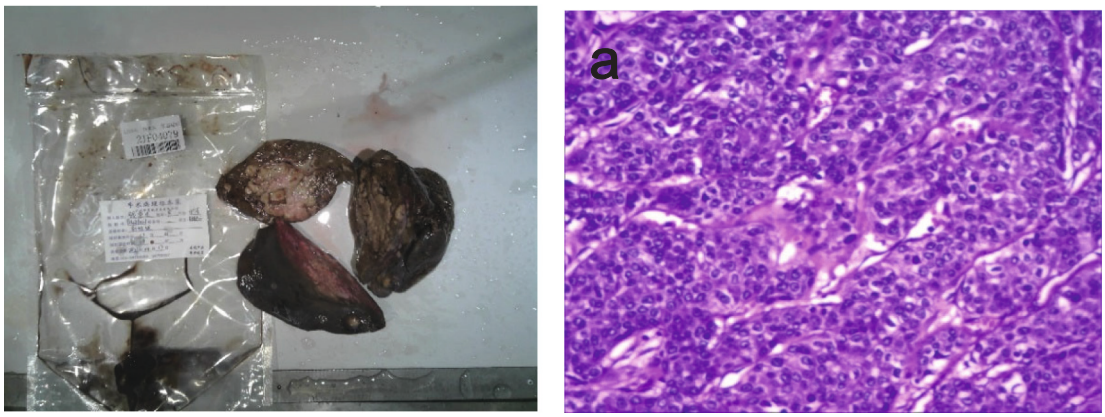

Fig. 2. Tumor specimen after left hepatic surgery.

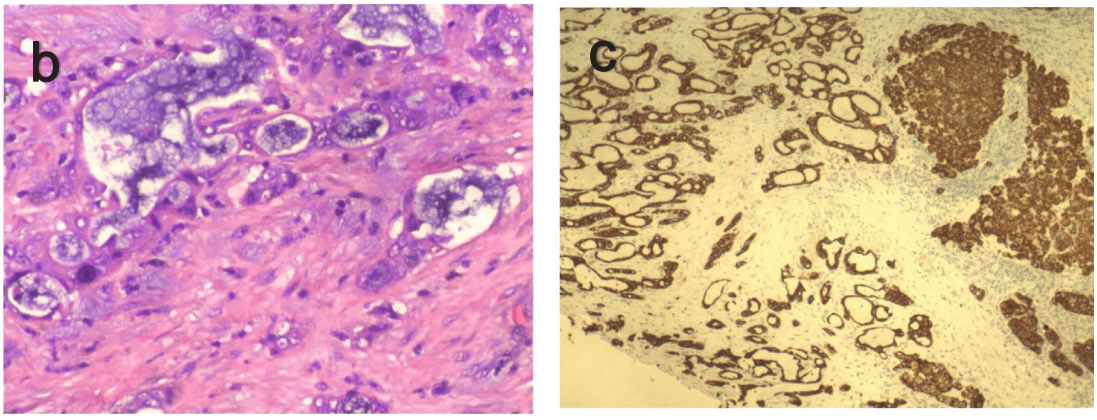

Fig. 3. Hepatocellular carcinoma cells stained with hematoxylin and eosin (a), cholangiocarcinoma (b), immunohistochemical staining of hepatocellular carcinoma and cholangiocarcinoma (c).

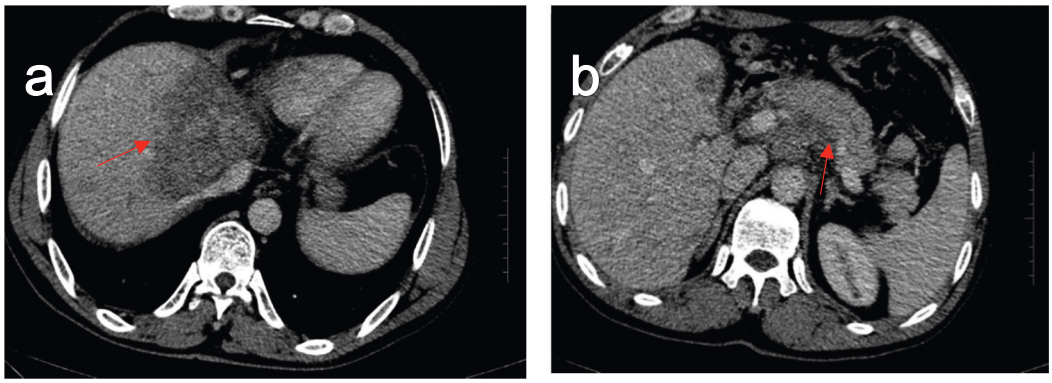

Fig. 4. CT scan of the entire abdomen showing fusion and enlargement of multiple nodules in the residual liver (a) and enlarged necrotic retroperitoneal lymph nodes with compression of the pancreas (b).

enlargement and metastasis were observed both before and after surgery in this patient, which aligns with the findings of KW et al., indicating that cHCC-CCA has a high incidence of lymphatic metastasis [14].

Throughout the treatment process, traditional surgical resection may be effective for localized lesions; however, its efficacy is often limited in cases of extensive metastasis or recurrence. For patients with cHCC-CCA who meet the Milan criteria, liver transplantation has demonstrated superior outcomes compared to resection alone [15]; whereas systemic chemotherapy, despite its ability to slow disease progression in advanced-stage patients, is associated with poor overall prognosis [16]. Several studies suggest that TACE may provide a meaningful survival benefit for patients with cHCC-CCA, although its efficacy in stabilizing tumor growth remains limited [17,18].

The recurrence rate following cHCC-CCA is high, with studies indicating a range of 81 % to 95 % of cases, primarily manifesting in the residual liver and, to a lesser extent, in lung metastases [19]. The key factors influencing distant metastasis include tumor necrosis, lymphovascular invasion, and perineural invasion [20]. The patient was treated with the immune checkpoint inhibitor sindilizumab in combination with the targeted drug bevacizumab, in accordance with the guidelines for

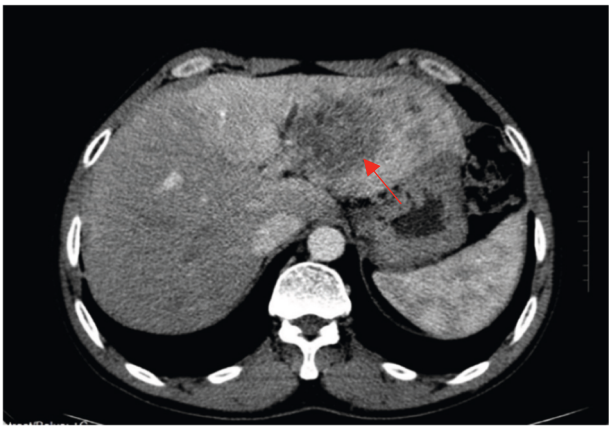

Fig. 5. Spiral CT scan of the portal vein, inferior vena cava, and hepatic artery showing "pseudocapsule" features suspicious for hepatocellular carcinoma.

the management of HCC and CCA. However, the disease progressed rapidly, and lung metastasis eventually occurred. During postoperative follow-up, the patient died of the disease after eight months.

4. Conclusion

This case highlights the diagnostic and therapeutic challenges of cHCC-CCA, emphasizing the need for improved early detection, risk stratification, and personalized treatment strategies. Given its high recurrence rate and poor response to immunotherapy, future research should focus on refining the diagnostic criteria, optimizing multimodal treatment approaches, and identifying reliable biomarkers to guide precision therapy. Enhanced molecular profiling and tailored therapeutic strategies may improve patient outcomes and inform clinical decision making.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Ethical approval

We adhered to the case report policy, including obtaining written informed consent from the patient for the publication of this case report and the accompanying images. Patient privacy was maintained throughout the reporting process.

Guarantor

Lin Wang

Research registration number

Not applicable.

Funding

This research has been funded.

Author contribution

Conceptualization: Yutao He, Data collection: Chen Guo, Investigation: Zhitian Shi, Writing - Original draft: Chen Guo. Writing - Review & Editing: Lin Wang.

Conflict of interest statement

The authors declare that they have no competing interests relevant to the content of this article.

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