Case Report

DOI: 10.7860/JCDR/2026/84230.23251

Pathology Section

Combined Hepatocellular-Cholangiocarcinoma (cHCC-CCA): A Rare Case of Biphenotypic Primary Liver Carcinoma in a Post-Hemicolectomy Patient

DEVIKA VENUGOPAL[1], VEENA RAJA[2]

ABSTRACT

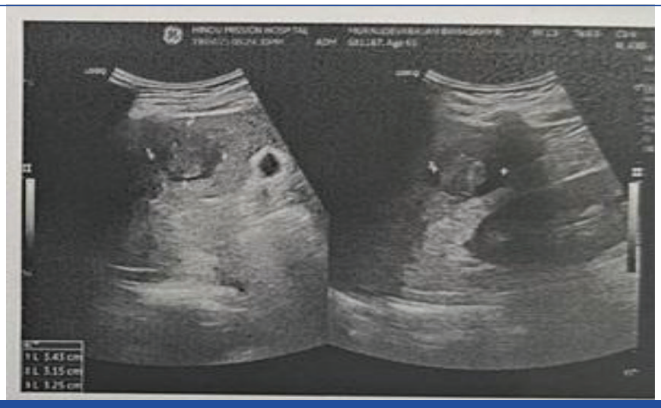
Combined Hepatocellular-Cholangiocarcinoma (cHCC-CCA) is a rare primary liver malignancy characterised by the presence of both hepatocytic and biliary epithelial differentiation within the same tumour and is associated with a poorer prognosis compared to Hepatocellular Carcinoma (HCC) or intrahepatic Cholangiocarcinoma (iCCA) alone. Accurate diagnosis is challenging, particularly in patients with a prior history of extrahepatic malignancy, where metastatic disease must be carefully excluded. We report the case of a 65-year-old male with a history of colonic adenocarcinoma treated by hemicolectomy and adjuvant chemotherapy in 2007, who remained disease-free for 18 years. In 2025, he presented with abdominal pain, and imaging revealed a solitary hepatic lesion in segment VI. Serum tumour markers demonstrated markedly elevated Alpha-Fetoprotein (AFP; 951 ng/mL), while Carcinoembryonic Antigen (CEA) and Carbohydrate Antigen 19-9 (CA19-9) levels were within normal limits. Given the prior history of Colorectal Carcinoma (CRC), metastatic disease was initially considered. Histopathological examination revealed a poorly differentiated malignant neoplasm with biphasic morphology. Immunohistochemical analysis showed hepatocytic differentiation with positivity for HepPar-1 and arginase-1, alongside cholangiocytic differentiation demonstrated by CK7 and CK19 expression. Markers associated with colorectal origin (CK20, CDX2, SATB2) were negative, effectively excluding metastatic CRC. Based on these findings, a final diagnosis of poorly differentiated classical combined hepatocellular–cholangiocarcinoma was rendered. This case underscores the critical role of comprehensive histopathological evaluation and targeted immunohistochemistry in establishing the diagnosis of cHCC-CCA. Early and accurate distinction from metastatic disease and other primary liver tumours is essential due to its distinct biology, aggressive behaviour, and adverse prognostic implications.

Keywords: Carbohydrate antigen 19-9, Carcinoembryonic antigen, Hepatocellular carcinoma

CASE REPORT

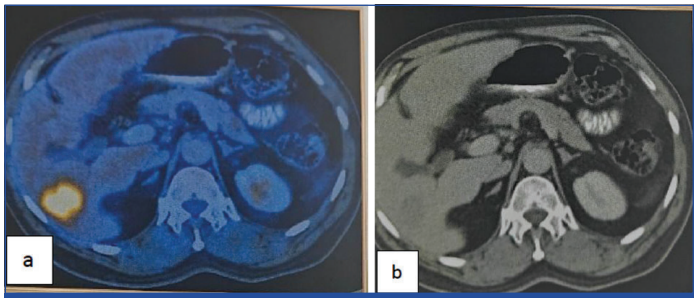
A 65-year-old male, known case of diabetes mellitus, with a history of a cerebrovascular accident, presented with abdominal pain of one-month duration. Past history revealed that he had colonic adenocarcinoma and was treated with right hemicolectomy and six cycles of chemotherapy in 2007. The patient remained clinically asymptomatic with no significant medical events until June 2025.

Ultrasound of the abdomen revealed a liver of normal size, showing increased and slightly heterogeneous echotexture with nodular outline. An irregular heterogeneously hypoechoic lesion measuring 3.4×3.1×3.2 cm was seen in segment VI of the liver, with features of liver parenchymal disease, with a space-occupying lesion in the right lobe of the liver, likely malignant [Table/Fig-1].



[Table/Fig-1]: USG abdomen showing a normally sized liver with increased and slightly heterogeneous echotexture, with nodular outline. An irregular heterogeneously hypoechoic lesion measuring 3.4×3.1×3.2 cm was seen in V/VI of the liver.

Positron-Emission Tomography-Computed Tomography (PET-CT) subsequently demonstrated an ill-defined metabolically active hypodense lesion measuring 31×34 mm in segment VI of the liver, with a differential diagnosis of metastasis versus primary hepatic malignancy. The lesion showed a T2 hyperintense signal with restricted diffusion on MRI screening [Table/Fig-2a,b].



[Table/Fig-2]: (a): PET-CT shows a metabolically active hypodense lesion in segment VI of the liver; (b) FDG-avid hypodense lesion in segment VI of the liver.

The patient's liver function test was deranged, while viral markers for Hepatitis B, HIV, and Hepatitis C were negative.

Tumour marker evaluation showed normal CEA and CA19-9 levels, but a markedly elevated AFP (951 ng/mL), raising the suspicion of a primary hepatocellular neoplasm. Patient's tumour markers and reference range are depicted in the [Table/Fig-3].

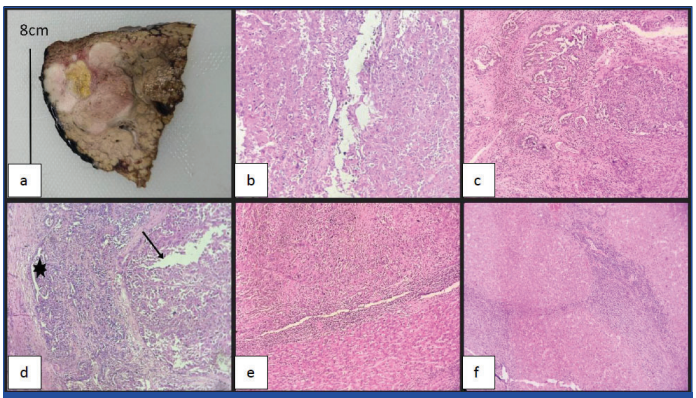
Resection was performed, and a segment of liver measuring 8×6.5×6 cm was received. External surface shows nodularity, cut surface revealed an ill-defined lesion measuring 3.8×3.4×2.8 cm without margin involvement, close to the inferior aspect of the

Tumour marker	Patients value	Reference range
AFP (ng/mL)	951	10-40
CA-19.9 (GI tract) (U/mL)	24.6	0-28
CEA (ng/mL)	2.84	0-3

[Table/Fig-3]: Tumour markers.

liver. The lesion showed a variegated appearance with grey-white, yellowish, and haemorrhagic areas [Table/Fig-4a].

Microscopy showed liver parenchyma with infiltrating neoplasm exhibiting two distinct tumour components, one component arranged in sheets having abundant eosinophilic cytoplasm, pleomorphic vesicular nuclei, some with prominent nucleoli, and intranuclear inclusions. Also, a few binucleated and multinucleated giant cells were noted [Table/Fig-4b,d]. The second component was arranged in a glandular pattern and in sheets with pleomorphic vesicular nuclei and with prominent nucleoli [Table/Fig-4c-e]. Mitotic figures were noted 4-5/20 high-power fields (HPF). Focal areas of necrosis and haemorrhage were noted. Adjacent liver parenchyma showed cirrhosis with regenerated nodules separated by fibrous septae (ISHAK stage 6) [Table/Fig-4f].



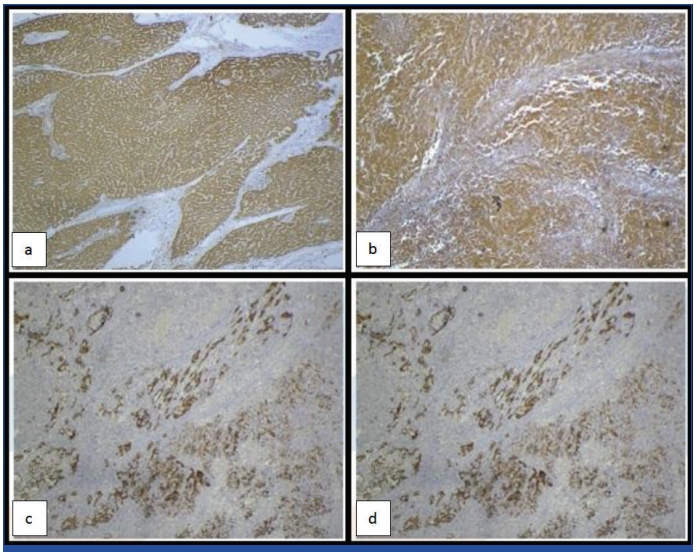
[Table/Fig-4]: a) The liver showing an ill-defined variegated lesion with grey-white, yellowish, and haemorrhagic areas; b) Tumour component resembling Hepatocellular Carcinoma (HCC) (20x); c) Tumour component resembling cholangiocarcinoma(20x); d) Highlights both cholangiocarcinoma (indicated by an asterisk in the figure) and HCC (indicated by an arrow in the figure) components (20x); e) Adjacent liver parenchyma (20x); f) Adjacent liver parenchyma with cirrhosis (20x).

The histopathological differential diagnoses included HCC, cholangiocarcinoma, and metastatic adenocarcinoma of gastrointestinal origin. Accordingly, an immunohistochemical panel comprising markers of hepatocytic differentiation (HepPar-1 and arginase-1), cholangiocytic differentiation (CK7 and CK19), and gastrointestinal origin (CK20, CDX2, SATB2, and ERG) was employed.

According to TNM staging, this tumour falls under the pT1a stage, which is a solitary tumour less than or equal to 5 cm without vascular invasion. Histological grade is poorly differentiated. Tumour extent was confined to the hepatic parenchyma. No vascular invasion was identified, and no lymph nodes were submitted for evaluation. The closest resection margin was the inferior margin, with a microscopic clearance of 0.5 mm.

Immunohistochemistry confirmed dual differentiation, with hepatocellular areas positive for HepPar-1 and arginase-1 [Table/Fig-5a,b], and glandular areas showing CK7 and CK19 positivity [Table/Fig-5c,d], while CK20, CDX2, SATB2, and ERG were negative, thereby excluding a metastatic colonic adenocarcinoma.

Thus, the final diagnosis was classical cHCC-CCA, poorly differentiated, arising in a cirrhotic liver, a rare and aggressive primary liver tumour. As the tumour was completely resected with no evidence of vascular invasion, the patient was managed with active surveillance. On follow-up in October 2025, serum AFP levels had decreased to 4.10 IU/mL, which was within the normal reference range (< 6.05 IU/mL).



[Table/Fig-5]: a): HepPar-1 IHC Positive in HCC component (40X); b) Arginase-1 IHC positive in HCC component (40x); c) CK-7 positivity in glandular areas (40x); d) CK-19 positivity in glandular areas (40x).

This case underscores the importance of integrating imaging, tumour markers, histomorphology, and immunohistochemistry for accurate diagnosis, particularly in patients with a prior history of extrahepatic malignancy.

DISCUSSION

The cHCC-CCA is an uncommon form of primary liver cancer, representing approximately 0.4% to 14% of all cases. This tumour type is characterised by the co-existence of both hepatocytic and cholangiocytic features, making it biologically and clinically distinct from HCC or CCA alone [1,2]. cHCC-CCA tends to demonstrate a more aggressive clinical course, often associated with limited treatment efficacy and reduced overall survival compared to HCC. Its diagnosis and management remain challenging due to its mixed histology and variable therapeutic response [1,3].

This case report aims to deliver an in-depth examination of cHCC-CCA by detailing laboratory results, radiological findings, and histopathological characteristics. Through comprehensive analysis, the report seeks to contribute to a better understanding of this rare malignancy and support more informed clinical decisions and future investigative efforts.

The cHCC-CCA is characterised by its dual histological composition, exhibiting features of both HCC and CCA [1,2]. Despite recognition of these biphenotypic features, there is currently no universally accepted criterion for quantifying the proportion of HCC and CCA components within the tumour mass [2,3]. The disease is distinguished by its unique clinical manifestation, aggressive biological behaviour, diagnostic ambiguity, and therapeutic challenges [4].

In the present case, metastatic CRC was initially considered a strong differential diagnosis despite an 18-year disease-free interval following hemicolectomy and chemotherapy. This is because the liver is the most common site of CRC metastasis and in patients with a prior history of colorectal cancer, any new hepatic lesion-particularly a metabolically active lesion on PET-CT- is often presumed metastatic until proven otherwise. Although very late metastases are rare, they have been reported, and radiologically metastatic lesions can closely mimic primary hepatic malignancies. The normal serum CEA and CA19-9 levels, along with a markedly elevated AFP, favoured a primary hepatic process; however, tumour markers alone are insufficiently specific, reinforcing the need for histopathological confirmation.

Histopathological evaluation was pivotal in establishing the diagnosis. The tumour demonstrated biphasic morphology with distinct hepatocellular (trabecular and nested) and cholangiocytic

(glandular and alveolar) patterns. Immunohistochemistry confirmed true biphenotypic differentiation, with hepatocytic marker positivity (HepPar-1, arginase-1) and biliary marker expression (CK7, CK19), while markers of gastrointestinal origin (CK20, CDX2, SATB2) were negative, excluding metastatic CRC. These findings fulfil the WHO diagnostic criteria for classical cHCC-CCA. Other important differential considerations include collision tumours- where separate HCC and iCCA arise independently and abut each other- and synchronous or metachronous double primary malignancies. Unlike cHCC-CCA, these entities lack intimate histologic admixture and unified bi-phenotypic differentiation within a single tumour mass [5]. The comparison features of HCC, iCCA and cHCC-CCA are depicted in the [Table/Fig-6] [5].

Feature	HCC	iCCA	cHCC-CCA
Cell lineage	Hepatocytic	Biliary epithelial	Mixed hepatocytic and biliary
Common markers	HepPar-1, Arginase-1, Glypican-3	CK7, CK19	HepPar-1/Arginase-1 and CK7/CK19
Tumour markers	AFP often elevated	CA19-9 may be elevated	AFP ± CA19-9
Morphology	Trabecular/ pseudoglandular	Glandular with desmoplastic stroma	Biphasic or intermixed patterns
Prognosis	Better than cHCC-CCA	Variable, often poor	Worse than HCC; similar to or worse than iCCA
Main curative option	Resection/ transplant (selected)	Resection	Resection

[Table/Fig-6]: Comparison of HCC, iCCA, cHCC-CCA [5].

An important feature in this case was the presence of underlying cirrhosis (Ishak stage 6). Cirrhosis is a recognised risk factor for primary liver malignancies, particularly HCC and cHCC-CCA. Although the aetiology of cirrhosis was not definitively established in this patient, potential causes include cryptogenic cirrhosis, metabolic dysfunction- associated steatotic liver disease, alcohol-related liver disease, or chronic viral hepatitis. Identifying the aetiology is clinically relevant, as it impacts long-term liver function, recurrence risk, and overall survival. Cirrhosis also plays a crucial role in determining surgical candidacy, as reduced hepatic reserve significantly increases the risk of post-hepatectomy liver failure. In this case, successful complete resection without postoperative decompensation suggests preserved functional reserve, but the presence of cirrhosis necessitates close surveillance.

Surgical resection with negative margins remains the mainstay and only potentially curative treatment for localised cHCC-CCA. However, there is no established standard adjuvant therapy due to the rarity of the disease and lack of randomised trials. In higher-risk cases, many centers extrapolate adjuvant systemic therapy from iCCA treatment protocols, such as gemcitabine-based or fluoropyrimidine-based regimens, although evidence remains limited. Liver transplantation is generally not recommended because outcomes are inferior compared to HCC. Locoregional therapies and systemic chemotherapy are typically reserved for unresectable or recurrent disease [6]. The following table shows a comparison of HCC, iCCA, and cHCC-CCA.

The diagnostic ambiguity observed in this case is consistent with findings from prior cohort studies, which indicate that cHCC-CCA is frequently misclassified as either HCC or CCA prior to pathological examination. This is largely due to its non-specific imaging characteristics and the low sensitivity of radiological modalities in identifying biphenotypic tumours [6,7].

This case underscores the importance of a multimodal diagnostic approach. In patients with prior extrahepatic malignancy, hepatic lesions are frequently presumed metastatic; however, primary mixed liver tumours must also be considered. Tumour markers, while useful, are not definitive- AFP elevation is more common in HCC and combined tumours, whereas CEA and CA19-9 may remain normal. Immunohistochemistry is therefore essential in confirming biphenotypic differentiation [7,8]. Clinically, cHCC-CCA carries higher recurrence rates and poorer survival than either HCC or iCCA, with surgical resection remaining the mainstay of therapy. Emerging genomic studies identifying TP53, TERT, and PTEN alterations may eventually offer opportunities for targeted therapies [3].

From a prognostic perspective, cHCC-CCA generally behaves more aggressively than either HCC or iCCA. Reported five-year survival rates after surgical resection are lower, recurrence is more frequent, and outcomes are typically poor even with curative-intent therapy [3,7]. Tumour size, poor differentiation, vascular invasion, and underlying cirrhosis are recognised adverse prognostic factors [7,8].

Future research should prioritise the integration of comprehensive molecular and genomic profiling to uncover actionable mutations and distinct molecular signatures that can guide precision medicine. Additionally, optimising multimodal treatment strategies combining surgery, systemic therapy, and locoregional interventions may offer improved disease control. The identification and validation of reliable biomarkers will also be essential to tailor therapeutic approaches to individual patients, enhancing treatment efficacy while minimising unnecessary toxicity.

CONCLUSION(S)

This case highlights the diagnostic complexity of combined hepatocellular-cholangiocarcinoma, particularly in patients with a prior history of malignancy. A comprehensive approach integrating imaging, tumour markers, histopathology, and immunohistochemistry was essential in establishing the diagnosis and excluding metastatic colonic adenocarcinoma. Awareness of the rare entity is crucial, as accurate identification has important implications for prognosis and management.

REFERENCES

[1] Guo C, He Y, Shi Z, Wang L. Combined hepatocellular-cholangiocarcinoma in a middle-aged patient: A case report and review of therapeutic approaches. Int J Surg Case Rep. 2025;129:111165. Epub 2025 Mar 17.Doi: 10.1016/j.ijscr.2025.111165. PMID: 40106944; PMCID: PMC11964574.

[2] Brunt E, Aishima S, Clavien PA, Fowler K, Goodman Z, Gores G, et al. cHCC-CCA: Consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentiation. J Hepatol. 2021;75(2):274-91. Doi: 10.1016/j.jhep.2021.03.035.

[3] Vij M, Veerankutty FH, Rammohan A, Rela M. Combined hepatocellular cholangiocarcinoma: A clinicopathological update. World J Hepatol. 2024;16(5):766-75. Doi: 10.4254/wjh.v16.i5.766.

[4] Roßner F, Sinn BV, Horst D. Pathology of combined hepatocellular carcinoma-cholangiocarcinoma: An update. Cancers (Basel). 2023;15(2):494. Doi: 10.3390/cancers15020494. PMID: 36672443; PMCID: PMC9856551.

[5] Song P, Midorikawa Y, Nakayama H, Higaki T, Moriguchi M, Aramaki O, et al. Patients' prognosis of intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma after resection. Cancer Med. 2019;8(13):5862-71. Doi: 10.1002/cam4.2495. Epub 2019 Aug 13. PMID: 31407490; PMCID: PMC6792494.

[6] Beaufrère A, Calderaro J, Paradis V. Combined hepatocellular-cholangiocarcinoma: An update. J Hepatol. 2021;74(5):1212-24. Doi: 10.1016/j.jhep.2021.01.035. Epub 2021 Feb 3. PMID: 33545267.

[7] Choi JH, Ro JY. Combined hepatocellular-cholangiocarcinoma: An update on pathology and diagnostic approach. Biomedicines. 2022;10(8):1826. Doi: 10.3390/biomedicines10081826. PMID: 36009374; PMCID: PMC9405224.

[8] Kim TH, Kim H, Joo I, Lee JM. Combined hepatocellular-cholangiocarcinoma: Changes in the 2019 World Health Organization Histological Classification System and potential impact on imaging-based diagnosis. Korean J Radiol. 2020;21(10):1115-25. Available from: https://doi.org/10.3348/kjr.2020.0091.

PARTICULARS OF CONTRIBUTORS:
1. Consultant Pathologist, Department of Pathology, Hindu Mission Hospital, Chennai, Tamil Nadu, India.
2. Professor, Department of Pathology, Bharath Medical College and Hospital, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Veena Raja,
No. 146-147, Sree Sai Nagar 4th Main Road West Tambaram, Chennai-600045, Tamil Nadu, India.
E-mail: drveenaraja88@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 06, 2025
- Manual Googling: Jan 17, 2026
- iThenticate Software: Jan 19, 2026 (2%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Nov 05, 2025**
Date of Peer Review: **Dec 15, 2025**
Date of Acceptance: **Jan 21, 2026**
Date of Publishing: **May 01, 2026**