Combined hepatocellular-cholangiocarcinoma: a rare biphenotypic primary liver cancer

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Abstract
Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) is a fascinating and rare primary liver cancer. This biphenotypic neoplasm is characterized by the unequivocal presence of hepatocellular and cholangiocytic histomorphology. Here, we report a case of cHCC-CCA in a 64-year-old man with risk factors for HCC treated with segmentectomy.

Keywords cHCC-CC; cHCC-CCA; combined hepatocellular carcinoma and cholangiocarcinoma; hepatobiliary carcinoma; mixed hepatocellular-cholangiocarcinoma; primary liver cancer

Case report
A 64-year-old male patient with a background of cirrhosis underwent a left lateral segmentectomy for a screening detected liver tumour. On CT scan, a 30 mm poorly circumscribed lesion was identified. It showed arterial enhancement with washout on the venous phase, characteristic of a hepatocellular carcinoma (HCC). On MRI scan, a solitary lesion was confirmed in segment II showing irregular, increased enhancement in the arterial phase and inconspicuous washout on portal venous phase (Figure 1). At the multidisciplinary team meeting, these appearances were felt not entirely typical of an HCC. AFP was markedly elevated at 1494 ng/mL (Reference value <8.4 ng/mL).

Grossly, a single hard white irregular lesion was identified. Macroscopic findings were also not entirely characteristic of an HCC, which typically shows a well circumscribed mass with yellow to green colour, depending on the proportion of fat and bile content of the tumour. Microscopically, the neoplasm demonstrated heterogenous appearances. The majority of malignant cells showed cytoarchitectural features of hepatocellular differentiation; they were moderately differentiated and arranged in a mixed trabecular/solid and pseudoglandular growth pattern. In contrast, a focal region of the neoplasm comprised malignant cells with cholangiocytic morphology. They were arranged in irregular angular tubules and strands. The cells had scant cytoplasm, pleomorphic vesicular nuclei and prominent nucleoli. An abundant desmoplastic stroma was conspicuous. Overall, this primary liver tumour demonstrated both hepatocellular and cholangiocytic cytomorphology. The background liver parenchyma showed marked bridging fibrosis, in keeping with the known cirrhosis. Immunohistochemistry supported the morphological impression. The majority of tumour cells with hepatocellular morphology stained with HepPAR1 and Arginase-1, while the minority of tumour cells with cholangiocytic morphology stained with CK7, CK19 and CA19-9 (Figure 2). The morphological and immunohistochemical features lent support to the final diagnosis of a combined hepatocellular-cholangiocarcinoma (cHCC-CCA).

Discussion
Primary liver carcinoma (PLC) is undoubtedly leading cause of cancer death globally with 782,000 cancer deaths per year and 5-year survival of 19%. While more prevalent in Eastern countries, an increasing incidence of PLC is observed in Western countries. By far, the two most common PLCs are a hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). It is thought that they represent two ends of the differentiation spectrum of PLC. shorts...
Here we present a neoplasm which does not fit diagnostic criteria for either classic HCC or iCCA: Combined hepatocellular-cholangiocarcinoma (cHCC-CCA). This is a rare form of PLC which comprises malignant cells of both hepatocellular and cholangiocyctic differentiation within the same tumour.\(^2\)\(^3\)\(^4\) The diagnosis is based on the unequivocal histomorphology of both HCC and iCCA.\(^2\)\(^3\)\(^4\) The 2019 WHO Classification of Digestive system tumours emphasises the biphenotypic histomorphology on haematoxylin and eosin as the essential diagnostic criteria. There is no strict cut-off for each component to diagnose cHCC-CCA. Both components can be either close or intermixed. Interestingly, the tumour can show either both HCC and iCCA or individual components upon metastasis.\(^5\)

Naturally, immunohistochemistry (IHC) for hepatocellular and cholangiocyctic markers can corroborate the morphological findings of biphenotypic differentiation, as in the present case. Commonly used markers for a HCC component includes HepPar1, Arginase-1, polyclonal CEA (canalicular), CD10 (canalicular) and BSEP (bile salt export pump, canalicular). Markers of biliary differentiation including CK7 and CK19 positivity can help confirming a CCA component.\(^6\) However, one should be mindful of general caveats of IHC including sensitivity and specificity of each IHC markers and overlapping immunophenotypes. Importantly, histomorphology takes precedence over immunophenotypes; one should not diagnose cHCC-CCA solely based on IHC. There is no diagnostic molecular signature specific to cHCC-CCA.\(^4\) Recent genomic studies demonstrated that it is enriched with oncogenic driver mutations of both HCC and iCCA (e.g. TPS3), HCC (e.g. CTNNB1) or iCCA (e.g. IDH1).\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) The pathogenesis of cHCC-CCA has yet to be elucidated.\(^4\)

Unfortunately, cHCC-CCA still remains a challenge in diagnostics and research. Although it was first described a century ago, accumulation of a sufficient number of cases for systematic study has been challenging.\(^2\)\(^3\) The main reason for this is inconsistent nomenclature which may be attributed to the heterogeneous morphological and immunohistochemical profile of cHCC-CCA. With the limited data, cHCC-CCA is considered a rare form of PLC (<5%).\(^3\)\(^6\) It has overlapping clinical features (incidence and predisposing factors such as hepatitis) and imaging features as HCC and iCCA.\(^1\)\(^4\) Prognosis is worse than HCC and similar to iCCA.\(^2\) Surgical resection with lymph node dissection leads to a significant improvement of survival and is considered the only curative measure.\(^2\)\(^6\) Optimal therapeutic approaches remain to be determined.\(^2\) With standardized nomenclature and advancing molecular technologies, it is hoped that this enigmatic cancer is better understood in future.

**REFERENCES**

Practice points

- cHCC-CCA is defined by the unequivocal histomorphological features of both cholangiocytic and hepatocellular differentiation.
- The diagnosis of cHCC-CCA is based on the morphological features on routine H&E. Immunohistochemical evidence of HCC and iCCA can corroborate the morphological diagnosis but are not sufficient by themselves.
- cHCC-CCA shares similar risk factors as HCC and iCCA. There are no specific clinical, serological and radiological features. It confers worse prognosis than conventional HCC but is comparable to one of iCCA. Currently, surgical resection with lymph node dissection is the only curative option for selected patients. No standard systematic treatment regime has been established.

Self-assessment MCQs

1. What is the essential criterion for diagnosis of cHCC-CCA?
   - a. Immunohistochemical profile with positive hepatocellular and cholangiocytic stains
   - b. The presence of TP53 and KRAS mutation
   - c. The morphological features of unequivocal HCCA and iCCA within the same tumour on H&E

Correct answer: c

2. Which immunophenotype is most helpful for the diagnosis of cHCC-CCA?
   - a. Absence of HepPAR1 and arginase immunostaining in tumour cells with hepatocellular morphology
   - b. Presence of CK7, CK19 and CA19-9 immunostaining in tumour cells with hepatocellular morphology
   - c. Presence of CK7 and CK19 in tumour cells with cholangiocytic morphology
   - d. Absence of EpCAM in tumour cells with cholangiocytic morphology
   - e. Presence of diffuse AFP positivity throughout the tumour

Correct answer: c

3. Which tumour type can cHCC-CCA show when it metastasizes?
   - a. HCC
   - b. CCA
   - c. Both HCC and CCA
   - d. Either HCC or CCA as an individual component
   - e. C or D (both HCC and CCA or as a solitary component)

Correct answer: e

d. The serological and pathological evidence of background chronic liver disease

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   b. Presence of CK7, CK19 and CA19-9 immunostaining in tumour cells with hepatocellular morphology
   c. Presence of CK7 and CK19 in tumour cells with cholangiocytic morphology
   d. Absence of EpCAM in tumour cells with cholangiocytic morphology
   e. Presence of diffuse AFP positivity throughout the tumour

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   a. HCC
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   e. C or D (both HCC and CCA or as a solitary component)

Correct answer: e