Combined hepatocellular carcinoma and cholangiocarcinoma: pictorial review of Imaging findings and correlation with Clinicopathological features

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Learning objectives

The purposes of our educational exhibit are to:

1. describe radiological findings of combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC) at quadri-phasic multidetector computed tomography (4-MDCT) and magnetic resonance imaging (MRI);
2. correlate radiological findings with clinicopathological features;
3. differentiate 'mixed' cHCC-CC from HCC and peripheral CC.
Background

Combined hepatocellular-cholangiocarcinoma (cHCC-CC), is a rare (incidence among primary liver cancer ranges from 0.4% to 14%) but an increasingly recognized primary malignant neoplasm in the liver[1]. It is "a tumor containing unequivocal elements of both hepatocellular and cholangiocarcinoma that are intimately admixed" as defined by the World Health Organization (WHO) classification [2].

The first case of this neoplasm was reported in 1903 by Wells [3], but the first comprehensive description was published in 1949 by Allen and Lisa [4]. These authors classified cHCC-CC into three subtypes: type A, 'double cancer' (HCC and CC are present at different sites within the same liver); type B, 'combined type' (HCC and CC are present at adjacent sites and mingle with continued growth); type C, 'mixed type' (HCC and CC components are combined within the same mass).

Goodman subsequently examined 24 cases of combined HCC-CC using immunohistochemistry and classified these neoplasms into three types: Type I, 'collision tumor' (an apparently coincidental occurrence of HCC and CC within the same liver); Type II, 'transitional tumor' (in which there is transition from elements of HCC to elements typical of CC); Type III, 'fibrolamellar tumor' (which resembles the fibrolamellar subtype of HCC but which contains mucin-producing pseudoglands) [5].

The type consisting of intermixed components and transitional cells, classified as type C tumor by Allen and Lisa and as type II (transitional) neoplasms by Goodman et al, represents a true combination tumor whereas cases of separate HCC and CC coincidentally found in the same liver are generally considered as collision tumors and are excluded by the WHO classification of combined HCC-CC [2]. The HCC components of cHCC-CC consist of tumor cells that resemble hepatocytes and are immunohistochemically positive for HepPar1. The CC components are tubular or papillary or cord-like adenocarcinomas that are positive for CK7 and CK19. cHCC-CC was classified by WHO into 2 types: 'classical cHCC-CC, composed of typical HCC and CC components, with less than 5% of the area occupied by subtypes with stem cell features, and cHCC-CC with more than 5% stem cell-like areas [2].

The incidence of synchronous development of collision tumors is estimated to be 0.25% of the primary liver cancers [6]. Even though the biomolecular and clinicopathological features of this phenomenon have not been clarified, recent studies suggest a relationship between HCV and/or HBV infection and risk of double primary hepatic tumor [6-7].

The histogenesis of cHCC-CC is still debated. Overall three possibilities may be postulated regarding its cell of origin: (1) collision (double) tumor of HCC and CC that incidentally coexist in the same liver; (2) subsequent differentiation of HCC or CC into the other component; (3) the cancer derives from the hepatic progenitor cells that can
differentiate into hepatocytic and biliary lineages [8]. Recent data indicate common genomic traits between peripheral HCC and CC, supporting the hypothesis of common cell ancestors and common pathobiological pathways to all primary liver parenchymal tumours [9], and it has become clearer that hepatic progenitor cells are present also in cHCC-CC [10].

Asian case series suggest risk factors and patient demographics are similar for cHCC-CC, HCC, and CC and include advanced age, male predominance, hepatitis B and C viral infection, and chronic liver disease [11], whereas in a few US series underlying chronic liver disease is not a prerequisite for combined HCC-CC that may also arise in non-cirrhotic liver [12].

Close attention is required to differentiate HCC from CC in case of 'double cancer', and 'mixed' cHCC-CC from HCC and CC, because prognosis and treatment options differ significantly.

Given the rarity of mixed cHCC-CC, the prognosis and appropriate management of this tumor remain controversial; most studies show worse prognosis and a few showing intermediate survival than HCC and CC[13]. Surgical resection likely yields the greatest survival benefit in limited-stage patients with cHCC-CC [11].
Findings and procedure details

Distinct imaging features of HCC and peripheral CC are well documented in literature therefore accurate diagnosis of these two entities is possible in most cases [14-15].

HCC

- **Pathological features:** classic macroscopic classification proposed by Eggle in 1901, still used today, divides HCC into three forms: nodular (encapsulated and smaller than massive lesions), massive (one large lesion occupying almost entire liver or composed of confluent small tumors) and diffuse (multiple infiltrating lesions occupying large part of liver); microscopically HCC may show increased fat and glycogen in cytoplasm.
- **Imaging findings:** typical HCC commonly occurs in setting of chronic liver disease and frequently results as final manifestation in continuum of nodular liver disease. Key imaging features are arterial hypervascularity with washout on delayed phase, presence of a capsule and the evidence of venous invasion (portal vein > hepatic vein), but we can found also satellite lesions and regional lymphadenopathy.
- **Ultrasound findings:** small lesions (< 5 cm) are usually hypoechoic with thin hypoechoic halo corresponding to fibrous capsule, whereas larger lesions (≥ 5 cm) show mixed echogenicity with hyperechoic areas in setting of intratumoral fat and hyperechoic regions in setting of necrosis (Fig.1).
- **Unenhanced CT findings:** HCC appears as a hypodense mass, with fat, necrosis or calcifications (Fig.2).
- **Unenhanced MRI findings:** it may be hyperintense (fat, hemorrhage or glycoproteins) at T1-weighted, and generally hyperintense at T2-weighted images.
- **Dynamic imaging (CEUS, MDCT and MRI) findings:** typically this tumor enhances more intensely than the surrounding liver in the arterial phase (AP) while it enhances less than the surrounding liver in the equilibrium phase (EP); the presence of arterial uptake followed by washout is highly specific for HCC and this dynamic pattern is the current non-invasive diagnostic criteria for HCC proposed by the American Association for the Study of Liver Disease (AASLD) [16] and by the European Association for the Study of the Liver and the European Organisation for Research and Treatment of Cancer (EASL-EORTC) [17] (Fig.2-3). However several studies have demonstrated that 27% to 34% of the small HCCs are hypovascular with a risk of misdiagnosis with other hypovascular hepatic lesions, therefore these guidelines should be reconsidered (Fig.4).

CC

- **Pathological features:** the morphologic classification system for primary liver cancer proposed by the Liver Cancer Study Group of Japan divides
intrahepatic CC into three types: mass-forming (exophytic/nodular), periductal infiltrating (sclerosing), and intraductal growing type (polypoid/papillary) [18]. Mass-forming CC, the most common type, is a large, white tumor with dense fibrosis, irregular margins and capsular retraction; it shows a radial growth pattern, invading into the adjacent hepatic parenchyma.

- **Imaging findings:** a typical intrahepatic CC appears as an infiltrative mass with capsular retraction, parenchymal atrophy of liver segments peripheral to tumor, "satellite" nodules, bile duct dilatation (focal around the lesion or diffuse) and lymph node metastasis. Mass-forming CC appears as well circumscribed, large mass with lobulated margins and progressive, gradual and centripetal enhancement.

- **Ultrasound findings:** mass-forming tumor show variable echogenicity (Fig.5).

- **Unenhanced CT findings:** it is hypodense with punctate, stippled or chunky calcifications (18% of cases) (Fig.2-3).

- **Unenhanced MRI findings:** it may show hyperintense periphery (cellular tumor) and large central hypointensity (fibrosis) or hyperintense foci in center (necrosis or mucin) at T2-weighted images.

- **Dynamic imaging (CEUS, MDCT and MRI) findings:** peripheral CC typically shows initial rim enhancement, followed by progressive and concentric filling with contrast material at dynamic 4-MDCT and MRI; this effect may reflect fibrosis which is slow to enhance but retains the intravenous contrast agent (Fig.6). Recent guidelines for the diagnosis and management of intrahepatic CC proposed by EASL [19], established that a pathological diagnosis is required for a definitive diagnosis of intrahepatic CC, while a presumed radiographic diagnosis of intrahepatic CC is sufficient in the absence of other extrahepatic primary malignancies and cirrhosis if a decision has been made to proceed with surgical resection; currently radiological studies cannot reliably differentiate between scirrhous HCC and intrahepatic CC, or metastatic adenocarcinoma (Fig.7) and CC [20]. On the other hand, recent studies showed that peripheral CC in cirrhosis patients can also display intense contrast uptake during the AP followed by washout on liver contrast enhanced ultrasonography [21-22], therefore only 4-MDCT and MRI are recommended for non-invasive diagnosis of HCC [14-15]. However, several recent reports demonstrated that peripheral CC, particularly the small (<3 cm in diameter) and the histologically well-differentiated lesions in chronic liver disease could show an atypical enhancement pattern as an arterially hyperenhancing lesion with/without washout on CT and MRI (Fig.8-10), mimicking HCC [23-28].

**cHCC-CC** The histologic composition and relative ratio of cholangiocarcinoma and HCC components within combined hepatocellular cholangiocarcinoma tumors appear to dictate the imaging appearance. Tumors may show features typical of HCC, such as arterial enhancement, washout, and pseudocapsule, whereas other regions within the tumor show progressive or delayed enhancement, necrosis, and possible ductal dilation more akin to cholangiocarcinoma [12, 29-31]. cHCC-CC can shows also
characteristics of both portal vein invasion of HCC and lymph node metastasis of CC too (Fig.11-12). The combination of imaging features and tumor markers may be helpful in preoperative diagnosis of combined hepatocellular cholangiocarcinoma tumors [12]. The main tumor markers of interest are carbohydrate antigen (CA) 19-9 and \( \alpha \) fetoprotein (AFP), which are associated with CC and HCC respectively. Although neither marker alone is sensitive or specific for cHCC-CC, simultaneous elevation of both CA 19-9 and AFP has been suggested as highly concerning for cHCC-CC tumors [27]. Other reports suggest that when there is discordance between tumor marker elevation and imaging features (i.e., elevated AFP with imaging findings of CC, or elevated CA 19-9 with imaging findings of HCC), cHCC-CC should at least considered [12].
Fig. 1: Well differentiated HCC in 70-years old man with HCV related cirrhosis. A. Transabdominal ultrasound shows a mass of 5.8 cm in diameter with mixed echogenicity and thin hypoechoic halo within the left lobe of the liver. B. Color Doppler ultrasound shows scattered areas of arterial blood flow within the mass.
Fig. 2: Synchronous well differentiated HCC (left lobe of the liver) and moderately differentiated CC (right lobe of the liver) in 89-years old man with HCV related cirrhosis. Ca19-9 value = 173,4 U/ml, alpha-fetoprotein value = 215 ng/ml. A-F CE pattern at CEUS. A, D: Precontrast transabdominal ultrasound shows a hypoechoic mass (CC) of 5 cm in diameter in the right lobe of the liver (A) and a mass of 4.5 cm in diameter with mixed echogenicity and thin hypoechoic halo (HCC) within the left lobe of the liver (D). B-C, E-F: US images after contrast agent administration. CC nodule shows peripheral rim hyperenhancement on (B) arterial phase with washout in delayed phase (C), whereas HCC lesion is globally hyperenhancing on (E) arterial phase with wash-out in delayed phase (F). G-I CE pattern at MDCT. G: Precontrast axial CT image shows a hypodence CC nodule of 5 cm in diameter in the right lobe of the liver and a isodense HCC nodule of 4.5 cm in diameter in the left lobe of the liver. H-I: Axial CT images after non-ionic contrast agent administration. CC nodule is peripherally hyperenhancing on (H) arterial and (I) equilibrium phases with stable dynamic enhancement pattern, while HCC
nodule is typically globally hyperenhancing on (H) arterial phase and shows wash-out enhancement pattern on equilibrium phase (I).

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Fig. 3: Microscopic examinations of same HCC and CC nodules illustrated in Fig.2. A-B Hematoxylin and eosin stained section shows well differentiated HCC with macrotrabecular growth pattern (A) and moderately differentiated CC with desmoplastic reaction of hepatic parenchyma (B). C-D Immunohistochemical findings: immunohistochemical stain with antibody against Hep Par 1 shows tumor cells staining positively, supporting the diagnosis of HCC (C) whereas immunohistochemical stain with antibody against cytokeratin 7 shows tumor cells staining positively, supporting the diagnosis of CC (D).

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Fig. 4: Moderately differentiated HCC in 61-years old man with chronic hepatitis due to B-viral infection A Precontrast axial fat-suppressed T1w 3D SPGR MR image of a 2.5 cm in diameter nodule in liver III segment: the nodule is hypointense compared with the surrounding liver parenchyma. B-D T1w dynamic 3D SPGR MR images after gadobenate dimeglumine administration. The lesion is peripherally hyperenhancing on (B) arterial, (C) portal venous and (D) equilibrium phases with stable dynamic enhancement pattern.

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**Fig. 5:** Moderately differentiated CC in 80-years old man with HBV related cirrhosis. A Transabdominal ultrasound shows a hypoechoic mass of 6.5 cm in diameter within the right lobe of the liver. B Color Doppler ultrasound shows scattered areas of peripheral blood flow.

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Fig. 6: Moderately differentiated IMCC in 74-year old man with cryptogenetic cirrhosis. A Precontrast axial fat-suppressed T1w 3D SPGR MR image of a 5 cm in diameter nodule in liver segments III and IV: the nodule is hypointense compared with the surrounding liver parenchyma. B-D T1w dynamic 3D SPGR MR images after gadobenate dimeglumine administration. The lesion is peripherally hyperenhancing on arterial phase (B), it is partially hyperenhancing on portal venous phase (C), and equilibrium phase (D) with centripetal and progressive dynamic enhancement pattern.

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Fig. 7: Metastasis in 70-years old man with rectal cancer. A Precontrast axial CT image of multiple hepatic lesions: the lesions are hypodense relative to surrounding liver parenchyma. B-D Axial CT images after non-ionic contrast agent administration. The lesions are hypoenhancing on (B) arterial, (C) portal venous and (D) equilibrium phase with stable dynamic pattern

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**Fig. 8:** Well differentiated peripheral CC in 64-years old woman with chronic hepatitis due to B-viral infection A Precontrast axial fat-suppressed T1w 3D SPGR MR image of a 2 cm in diameter nodule in liver III segment: the nodule is hypointense compared with the surrounding liver parenchyma. B-D T1w dynamic 3D SPGR MR images after gadobenate dimeglumine administration. The lesion is globally hyperenhancing on (B) arterial, (C) portal venous and (D) equilibrium phases with stable dynamic enhancement pattern.

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**Fig. 9:** Poorly differentiated IMCC in 85-years old man with metabolic cirrhosis. A Precontrast axial CT image of a 7.5 cm in diameter nodule in liver V and VI segments: the nodule is hypodense relative to surrounding liver parenchyma. B-D Axial CT images after non-ionic contrast agent administration. The lesion is partially hyperenhancing on (B) arterial and (C) portal venous phases and shows wash-out enhancement pattern on equilibrium phase (D).

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**Fig. 10:** Microscopic examinations of same CC nodule illustrated in Fig.9. A Hematoxylin and eosin stained section shows infiltrative poorly CC cells arranged in formed glands invading into and replacing the liver parenchyma with surrounding fibrosis. B Immunohistochemical stain with antibody against cytokeratin 7 shows tumor cells staining positively, supporting the diagnosis of CC.

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**Fig. 11:** Poorly differentiated cHCC-CC in 64-years old man with alcohol cirrhosis. Ca19-9 value = 10.1 U/ml, alpha-fetoprotein value = 339 ng/ml. A Precontrast axial CT image of a 6.5 cm in diameter nodule in liver IV and VIII segments: the nodule is hypodense relative to surrounding liver parenchyma. B-D Axial CT images after non-ionic contrast agent administration. The lesion is peripherally hyperenhancing on (B) arterial phase and (C) portal venous phases, and it is partially hyperenhancing on (D)

Fig. 12: Microscopic examinations of same cHCC-CC nodule illustrated in Fig.11. A Hematoxylin and eosin stained section shows HCC component with typical trabecular and pseudo-acinar pattern and CC component with typical desmoplastic stroma surrounding the neoplastic glands. B-D Immunohistochemical findings: immunohistochemical staining for hepatocytic differentiation show the positive staining for alpha-fetoprotein (B) and Hep Par 1 (C), but not the CC component, whereas cytokeratin 7 immunostain are positive for the CC component, but not the HCC component (D).
Conclusion

imaging findings, serum tumour markers levels and biopsy are essential for cHCC-CC detection, proper diagnosis and treatment choice.
Personal information

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