Case Report
Combined hepatocellular-cholangiocarcinoma with stem cell features, ductal plate malformation subtype: a case report and proposal of a new subtype

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Received January 4, 2013; Accepted February 17, 2013; Epub March 15, 2013; Published April 1, 2013

Abstract: In the current WHO blue book, combined hepatocellular-cholangiocarcinoma (C-HCC-CC) was classified into two types; classical type and type with stem cell features. The latter is extremely rare, and is subcategorized into the following three subtypes; typical subtype, intermediate cell subtype, and cholangiocellular subtype. Recently, intrahepatic cholangiocarcinoma (ICC) with features of ductal plate malformations (DPM) have been reported, and the ICC with DPM was proposed as a subtype of ICC. The author herein reports a case of C-HCC-CC with stem cell features. Characteristically, the CC element showed features of DPM. A 51-year-old man of HBV carrier was found to have high AFP. A laboratory test showed an elevated AFP (395 ng/ml, normal 9-10) and hepatitis B virus-related antigens and antibodies. Liver and ductal enzymes and PIVKAII were within normal ranges. Imaging modalities including CT identified a small liver tumor. Hepatocellular carcinoma (HCC) was suspected, and the resection of the hepatic tumor was performed. Grossly, the liver tumor is well-defined white solid tumor measuring 22x16x23 mm. Microscopically, the tumor was a C-HCC-CC, and was composed of following three elements: well differentiated HCC, well differentiated cholangiocarcinoma (CC), and intermediate tumor element. Characteristically, the CC cells formed tortuous markedly irregular tubules with intraluminal cell projections, bridge formations, intraluminal tumor biliary cells; such features very resembled the ductal plate (DP) and DPM. Immunohistochemically, the cells of CC element were positive for stem cell antigens (KIT (CD117), CD56, EMA, CD34), HepPar1, EpCAM, cytokeratin (CK) CAM5.2, AE1/3, CK34BE12 (focal), CK7, CK8, CK18, CK19, CA19-9, p53, MUC1, MUC2, MUC5AC, MUC6, and Ki-67 (labeling=25%). They were negative for CEA, CK5/6, CK20, NSE, chromogranin, synaptophysin, and p63. No mucins were found by histochemically. The background liver showed chronic hepatitis B (a1, f3). Very interestingly, many DPMs were scattered in the non-tumorous parenchyma. This type of C-HCC-CC with DPM features has not been reported. The author herein proposes that this tumor should be included or added in the C-HCC-CC subtype as C-HCC-CC with stem cell features, DPM subtype.

Keywords: Combined hepatocellular cholangiocarcinoma, liver stem cells, ductal plate, ductal plate malformation, histopathology, immunohistochemistry

Introduction
According to Nakanuma [1], intrahepatic cholangiocarcinoma (ICC) is an intrahepatic malignancy with biliary epithelial differentiation. ICC can arise in any portion of the intrahepatic biliary tree, from the segmental and area ducts and their major branches to the smallest bile ducts and ductules. He also classified ICC into hilar and peripheral ones [1]. Most ICCs are adenocarcinomas with variable differentiation and fibroplasia. ICC arising in non-biliary cirrhosis frequently presents with bile ductile differentiation, possibly arising from the hepatic progenitor or stem cells [1]. He proposed several rare variants of ICC such as squamous cell carcinoma, adenosquamous carcinoma, mucinous carcinoma, signet ring cell carcinoma, clear cell carcinoma, mucopidermoid carcinoma, lymphoepithelioma-like carcinoma, sarcomatous ICC, intraductal papillary carcinoma, and precursor lesions of BiliN [1, 2]. Very recently, Nakanuma [2, 3] proposed a new subtype of ICC; i.e, ICC with predominant “ductal plate malformation (DPM)” pattern. This new subtype of ICC is characterized by well differentiated adenocarcinoma whose carcinoma cells very resemble DPM. The ductal plate (DP) implies
progenitor biliary cells in the fetus livers characterized by a double-layered cylinder of precursor biliary cells with capacities of apoptosis and cell proliferation, and differentiation into fetal biliary cells, adult biliary cells, stem cells of fetus and postnatal livers, hepatoblasts, hepatocytes, pancreatic acinar cells, biliary cells with pancreatic digestive enzymes, and peribiliary glands [4-42]. DPM is the persistence of fetal DP in the postnatal liver, and DPM is characterized by markedly irregular tortuous tubules with bridge formations, biliary cell projections into the lumen, and intraluminal tumor cells somewhat reminiscent of fetal DP [4-42]. DMP is seen mainly in congenital hepatic fibrosis, polycystic liver and kidney diseases, congenital biliary atresia, von-Meyenburg complex, Caroli’s disease [43-49]. This condition is also called DPM disease [7, 46] or hepatobiliary fibropoly cystic disease [47, 49]. DPM is also seen in ductular reactions in various hepatobiliary diseases [44, 50-52]. DP is entirely different from DPM.

Although the author is only a diagnostic solo-pathologist in a low-grade hospital, the author examined many cases of ICC in the author’s young era [53-56]. The author had noticed the presence of ICCs whose carcinoma cells resembled DP or DPM about 20 years ago, but the author did not report the findings because the author thought that such ICCs were not a single clinicopathological entity. The author also had noticed the presence of combined hepatocellular carcinomas (HCC) and ICC in which the ICC resembled DP or DPM. The author also had not reported them because of the same reasons.

Herein reported is a case of combined HCC and ICC, in which the ICC cells resembled DP or DPM. The author herein proposes that this tumor should be included or added in the combined HCC and ICC subtype as combined hepatocellular-cholangiocarcinoma with stem cell features, DMP subtype.

Case report

A 51-year-old man of HBV carrier was found to have high serum AFP in the periodical follow-up. A laboratory test showed elevated AFP (395 ng/ml, normal 9-10), mild anemia (385x10^4/μl, normal 450-550x10^4), and high glucose (228 mg/dl, normal 70-110). Liver and ductal enzymes were within normal ranges. HBV-related antigens and antibodies were positive. PIVKAII was within normal limits (20 mAU, normal 0-30). Imaging modalities including CT and MRI identified a small tumor (2cm in diameter) of the S6 of the liver right lobe (Figure 1). HCC was suspected, and the resection of the tumor was performed.

Grossly, the tumor is well-defined white solid tumor measuring 22x16x23 mm (Figure 2). Microscopically, the tumor was a combined HCC and ICC (Figure 3A-G). The tumor cells were composed of the following three elements: well differentiated HCC (Figure 3B), well differentiated ICC (Figure 3C), and intermediate

![Figure 1. CT of the hepatic tumor. A small tumor (arrow) of 3 cm in diameter is seen in the S6 of the liver right lobe.](image1)

![Figure 2. Gross features of the resected hepatic tumor. The tumor is well-defined, white, firm, and solid tumor measuring 22x16x23 mm.](image2)
The tumor element (Figure 3D). The HCC element was typical well-differentiated HCC of Edmondson’s grade II with compact and focally trabecular histologies without fibrous stroma (Figure 3B). The IHC element was well differentiated adenocarcinoma with abundant fibrous stroma (Figure 3C). Characteristically, all the IHC cells formed tortuous markedly irregular tubules with intraluminal projections of tumor cells, bridge formation of tumor cells, and intraluminal tumor cells islands, which were features of DP and DPM (Figure 3D-G). The intermediate tumor element had intermediate histological features of both HCC and ICC, and appeared a cancer stem cell population (Figure 3D). The intermediate tumor element showed frequent HCC differentiation and ICC differentiation (Figure 3D), thus compatible with cancer stem cells. There were gradual transitions between HCC element and intermediate tumor element, and between intermediate tumor element and ICC element (Figure 3A and 3D).

A mucin study was performed using mucicarmine stain, PAS stain, diastase-PAS (d-PAS) stain, Alcian blue (AB) stains at pH 2.5 and
The cholangiocarcinoma (CC) element of the present combined hepato-cellular-cholangiocellular carcinoma are positive for four liver stem cell markers; KIT (A), CD56 (B), CD34 (C), and CK14 (D). The CC cell are positive for antigens showing cholangiocyte lineage; CK AE1/3 (E), CK CAM5.2 (F), CK7 (G), CK8 (H), CK18 (I), CK19 (J), CEA (K), CA19-9 (L), MUC1 (M), MUC2 (N), MUC5AC (O), MUC6 (P), and EpCAM (Q). The cells of CC also show positive some antigens of hepatocellular lineage; HepPar1 (R), AFP (S) CK8 (H), CK18 (I) and CK CAM5.2 (F). The CC cells are positive for EMA (T), CK34BE12 (U), p53 (focal, V) and Ki67-antigen (W) (labeling index= 40%).

Immunohistochemically, the ICC cells were positive for all four liver stem cell markers, i.e, KIT (Figure 4A), CD56 (Figure 4B), CD34 (Figure 4C), and CK14 (Figure 4D). They were also positive for antigens showing cholangiocyte lineage; CK AE1/3 (Figure 4E), CK CAM5.2 (Figure 4F), CK7 (Figure 4G), CK8 (Figure 4H), CK18 (Figure 4I), CK19 (Figure 4J), CEA (Figure 4K), CA19-9 (Figure 4L), MUC1 (Figure 4M), MUC2 (Figure 4N), MUC5AC (Figure 4O), MUC6 (Figure 4P), and EpCAM (Figure 4Q). The cells of ICC also showed positive some antigens of hepatocellular lineage; HepPar1 (R), AFP (S) CK8 (H), CK18 (I) and CK CAM5.2 (F). They were positive for EMA (Figure 4T), CK34BE12 (Figure 4U), p53 (focal, Figure 4V) and Ki67-antigen (Figure 4W) (labeling index= 40%). The cells of ICC element were negative for CK AE1/3, CK34BE12, CK5/6, CK20, p63, chromogranin, synaptophysin and NSE. Mucins were negative histochemically.

The cells of HCC element were positive for three liver stem cell markers, i.e, KIT, CD34, and CK14, but were negative for CD56. They were positive for antigens of hepatocellular lineage; HepPar1, AFP, CK8, CK18, and CK CAM5.2. They were also positive for same antigens showing cholangiocyte lineage; CK7, MUC1, MUC2, MUC5AC, MUC6, and EpCAM. They were also positive for p53 and Ki-67 (labeling index= 37%). They were negative for CK AE1/3, CK34BE12, CK5/6, CK19, CK20, EMA, CEA, CA19-9, p63, chromogranin, synaptophysin and NSE. Mucins were negative histochemically.

Immunohistochemically, the ICC cells were positive for all four liver stem cell markers, i.e, KIT (Figure 4A), CD56 (Figure 4B), CD34 (Figure 4C), and CK14 (Figure 4D). They were also positive for antigens showing cholangiocyte lineage; CK AE1/3 (Figure 4E), CK CAM5.2 (Figure 4F), CK7 (Figure 4G), CK8 (Figure 4H), CK18 (Figure 4I), CK19 (Figure 4J), CEA (Figure 4K), CA19-9 (Figure 4L), MUC1 (Figure 4M), MUC2 (Figure 4N), MUC5AC (Figure 4O), MUC6 (Figure 4P), and EpCAM (Figure 4Q). The cells of ICC also showed positive some antigens of hepatocellular lineage; HepPar1 (R), AFP (S) CK8 (H), CK18 (I) and CK CAM5.2 (F). They were positive for EMA (Figure 4T), CK34BE12 (Figure 4U), p53 (focal, Figure 4V) and Ki67-antigen (Figure 4W) (labeling index= 40%). The cells of ICC element were negative for CK AE1/3, CK34BE12, CK5/6, CK20, p63, chromogranin, synaptophysin and NSE. Mucins were negative histochemically.
The cells of intermediate tumor element showed intermediate immunophenotype. They were positive for all the four liver stem cell markers, i.e., KIT, CD56, CD34, and CK14. They were positive for antigens of hepatocellular lineage; HepPar1, AFP, CK8, CK18, and CK CAM5.2. They were also positive for same antigens showing cholangiocyte lineage; CK AE1/3, CK7, CK19, MUC1, MUC2, MUC5AC, MUC6, and EpCAM. They were also positive for EMA, p53 and Ki-67 (labeling index=32%). They were negative for CK34BE12, CK5/6, CK20, CEA, CA19-9, p63, chromogranin, synaptophysin and NSE. Mucins were negative histochemically.

The background liver showed chronic hepatitis B (a1, f3) (Figure 5A). Very interestingly, many DPMs were scattered in the non-tumorous parenchyma (Figure 5B).

Discussion

Combined HCC and ICC is a relatively rare condition. According to Theise [61], most cases of combined HCC and ICC (C-HCC-CC) are derived from liver progenitor cells or stem cells. According to Theise [61], C-HCC-CC is defined as a tumor containing unequivocal, intimately mixed elements of both HCC and ICC. The C-HCC-CC should be distinguished from separate HCC and ICC arising in the same liver [61].

Such a tumor may be separated or intermixed (“collision tumor”). The present tumor is a single tumor composed of mixing HCC, ICC and intermediate tumor elements, thus fulfilling the criteria of C-HCC-CC of Theise [61].

Theise [61] classified C-HCC-CC into that of classical type and that of subtypes with stem-cell features. The latter was further categorized into the following three subtypes: CC-HCC-CC with stem cell features, typical subtype, CC-HCC-CC with stem cell features, intermediate subtype, and CC-HCC-CC with stem cell features, cholangiocellular subtype [61].

Most of the C-HCC-CC is C-HCC-CC of classical type [61]. This classical type of C-HCC-CC is characterized by the presence of ordinary HCC and ICC cells. The HCC element was immunohistochemically positive for HepPar1, CD10, rabbit polyclonal CEA, and AFP [61]. The ICC element is typical adenocarcinoma, shows fibrosis, and is positive for mucins [61]. It is immunohistochemically positive for biliary type CK (CK7 and CK19). In many cases of this classical type of C-HCC-CC there are foci of intermediate morphology at the interface of the HCC and ICC element. Immunohistochemistry often provides confirmatory evidence of mixed phenotypes in these regions. Cells having phenotypical and immunophenotypical features of stem cells/progenitor cells may be present [61]. However, if these predominate, C-HCC-CC of with stem cell feature type should be considered. The present case is not C-HCC-CC classical type, because the ICC element showed features of stem-cell type, as described later, and also because the present tumor showed stem cell features such as positive KIT, CK14, CD34 and CD56 (liver stem cell markers).

The C-HCC-CC of stem-cell type is very rare. A PubMed search could not detect such a case in the English literature. The present case belongs to this type of C-HCC-CC, because the tumor cells showed stem cells phenotypes and immunophenotypes positive KIT, CD34, CD56 and CK14. According to Theise [61], the current case may belong to C-HCC-CC with stem-cell features, cholangiocellular subtype. However, the ICC element of the present case resembles DP or DPM, and showed stem-cell antigens. The ICC element of the present case is very similar to ICC of DPM type of Nakanuma [2, 3]. In the present case, the tumor cells showed liver stem cell phenotypes o Thus, the present tumor belong to Thus, the author believes that the biliary elements of the present C-HCC-CC show DMP. The author wants to emphasize that the present case is a new subtype of C-HCC-CC with stem cell features, DPM subtype, and the author want that the WHO adds this C-HCC-CC with stem cell features, DPM subtype in the list of variants of C-HCC-CC.

The C-HCC-CCC with stem-cell features, cholangiocellular subtype of Theise [61], the pictures of which is available in the WHO blue book [61], is somewhat similar to the bile duct structures [DPM] of the present case and to the DPM type of ICC of Nakanuma [2, 3]. Therefore, there seems to be a strong association of these three entities proposed by different researchers. In the literature, ductular reactions of various chronic liver disease and focal nodular hyperplasia (FNH) have been recognized to have DPM features by Desmet [50-52] and by the author [44]. The first description of DPM was
A significant percentage of C-HCC-CC, in particular that with stem-cell feature type, is thought to arise from liver stem cells or progenitor cells [61, 68-70]. This is also thought to be true in cases of other liver carcinomas such as HCC and ICC [61]. However, HCC usually arises from hepatocytes or dysplastic nodules [71-73], and cholangiocarcinoma from cholangiocytes [53-56]. Liver stem cells/progenitor cells are located in the ductules and Herring ducts next to liver parenchyma [61, 74, 75]. The antigens or markers of these liver stem cells are KIT (CD117), CD34, CD56, OV6, Thy-1 (CD90), CK14, CD133, ALDH, and M2PK [14-16, 69, 70, 74, 75]. In the current study, the author used KIT, CK14, CD34, and CD56 as markers of liver stem cells/liver progenitor cells. CK7, CK8, CK19, EMA, CEA, CA19-9, EpCAM, mucins, MUC apomucins are markers of cholangiocytes. The expression of CD8, CK18, AFP, and HepPar1 shows the hepatocellular lineage.

The present study is the first case using very wide ranges of antigens in the human combined HCC and ICC. It is very interesting in the current case that all the HCC, ICC and intermediate tumor elements in a single C-HCC-CC with stem cell features showed immunoreactive liver stem cell markers (KIT, CD34 and CK14) strongly suggesting that the current tumor is entirely derived from liver stem cells. The other one stem cell marker CD56 was positive in ICC and intermediate tumor elements but negative in HCC element. Taken together, it is suggested that the whole tumor of the present case are derived from liver stem cells. Thus, the present tumor is liver stem cell malignancy.

The MUC apomucins’ expression in the combined HCC and ICC has not been studied. The present study for the first time demonstrated the distribution of MUC1, MUC2, MUC5AC, and MUC6. Of very interest, these four MUC apomucins were expressed in the HCC element and intermediate tumor element in addition to ICC element. These are novel findings. These data suggest the homogenous natures of the current tumor, and imply that HCC and intermediate tumor elements had features of cholangiocytes in current tumor.

made by Jorgenson in 1977 [62]. The definition of DP is clear [10-39], but the definition of DPM is unclear. In the pioneer works of Jorgenson and Desmet of DPM [7-10, 50-52, 62], they showed that the DPM denotes simple tortuous tubules reminiscent of DP of fetal life. DPM is generally considered to be an aberrant biliary structures in the postpartum livers resembling fetal DP [7-10, 43-48, 50-52, 62], and is considered to result from lack of DP remodeling during human intrahepatic bile duct development [7-39, 43-48, 50-52, 62, 63]. Recently, the pathogenesis of DMP has been studied, and it was found that the development of DPM is involved the molecular deficiencies or emergency of hepatocyte nuclear factor-6 (HNF6), HNF1β, cystin-1, and HNF1β/TCF2 mutation, and a new classification of DPM was proposed [64, 65]. Immunohistochemically, DPM expresses CK7, CK8, CK19, but not CD34 [66]. The DPM of Nakanuma [2, 3, 48] seems to be an extreme examples of DPM showing very marked biliary cells abnormality. The author thinks, like Desmet and Jorgenson, that the ICC component of the present tumor is a DPM rather than cholangiocellular phenotype. Therefore, the author reported this case as C-HCC-CC with stem cell features, DMP subtype rather than C-HCC-CC with stem cell features, cholangiocellular subtype. The author also want to stress that there is a strong similarity between the C-HCC-CC with stem cell features cholangiocellular subtype of Theise [61] and ICC of DPM subtype of Nakanuma [2, 3]. The tumor is equivalent for hepatic “stem cell malignancy” reported by Theise et al [67]. The author think that the C-HCC-CC with stem cell features, cholangiocellular subtype of Theise [61] may contain cases of C-HCC-CC with stem cell features, DPM subtype, because the picture of C-HCC-CC with stem cell features, cholangiocellular subtype of Theise in the WHO blue book somewhat resembles the present case of C-HCC-CC with stem cell features, DPM subtype. Much more studies of C-HCC-CC with stem cell features should be required. These confusions may result from the unclear definition of DPM. The DPM of Nakanuma showed marked irregularities of the DPM [2, 3, 48], while The DPM of Desmet [7-9, 50-52], Jorgenson [62], Summerfield [49] and the author [43-47] includes biliary cell abnormalities with mild irregularities including bile ductular reactions and von-Meyenburg complex. Thus, the definition of DPM is different among researchers. The strict definition of DPM is need.
In the current case, CK expression was examined in a wide range of CKs. The expression of biliary type CK (CK7, 8, 18 and 19) and hepatocellular type CK (CK8, 18) was the same of previous studies [10, 19, 28]. The new findings of the present study were that CK34BE12, a high molecular weight CK, was expressed in the ICC element of the current case. The negative expression of CD5/6, a high molecular weight CK in combined HCC and ICC is also a new finding. The negative CK20 in ICC and HCC is well recognized, and this negative CK20 is useful for differentiation from metastatic carcinomas of the liver.

The present case is the first that examine CEA and CA19-9 immunoreactivities in C-HCC-CC with stem cell features. CEA and CA19-9 expression was seen in the ICC element but not seen in HCC element and intermediate tumor element. The data suggest that CEA and CA19-9 may be present only in ICC element of this C-HCC-CC with stem cell features, DPM subtype.

The expression of EMA was different in the current tumor. EMA was expressed in the ICC element and intermediate tumor element, but not in HCC element. The lack of EMA immunoreactivity in hepatocytes and HCC is well known. The findings of the present study shows the expression of EMA in C-HCC-CC with stem cell features, DPM subtype is not different from other liver malignancies. The presence of EMA in the intermediate tumor element may suggest that EMA expression disappears from HCC during ICC transition to HCC process.

It is very interesting that AFP and HepPar1, both of which are antigens of hepatocytes and neoplastic hepatocytes, were expressed in ICC cells in the current case. This fact suggest that the tumor is derived from liver stem cells, and that ICC element of C-HCC-CC with stem cell features express hepatocellular lineage, i.e, AFP and HepPar1.

Chromogranin, synaptophysin, and NSE have not been investigated in C-HCC-CC with stem cell features. Expression of these molecules were not seen in the present case, suggesting that neuroendocrine characteristics or neuroendocrine differentiation were absent in C-HCC-CC with stem cell features. CD56 (NCAM) which is an antigen for both liver stem cells and neuroendocrine cells was expressed in the ICC and intermediate tumor elements but not in HCC element. In this case, the positive CD56 expression may not reflect the neuroendocrine features but demonstrate the liver stem cell nature of the tumor cells.

P53 and Ki-67 expression has not been examined in C-HCC-CC with stem cell features. In the present study, tumor cells of all the three elements were positive for p53 and Ki-67. The labeling index of Ki-67 was high. These findings suggest positive p53 gene mutations and high cell proliferative fraction in C-HCC-CC with stem cell features.

Morphologically, there were gradual transition between HCC element and intermediate tumor element and also between ICC element and intermediate tumor element in the current C-HCC-CC. Positive liver stem cell antigens strongly suggest that the present tumor is derived from liver stem cells/progenitor cells. It is very interesting; if one considers that the intermediate tumor element of the current case is composed of tumor cell stem cell. If so, it is conceivable that the cancer stem cells (intermediate tumor cells) may give rise to the HCC cells and ICC cells in the current C-HCC-CC. This concept seems to be supported by the present board immunohistochemical data. In the current study, the intermediate tumor cell element frequently showed HCC differentiation and ICC differentiation, strongly suggesting that the intermediate tumor cells element is a cancer stem cell population. Further studies of cancer stem cells in C-HCC-CC remain to be elucidated.

Interestingly, the present C-HCC-CC with stem cell features, DPM subtype was seen in chronic hepatitis B. Hepatitis B virus (HBV) is known to give rise to ICC in addition to HCC [1, 61, 76], though the reason is unclear with regard to ICC. However, the author previously suggested the role of hepatitis virus in the development of ICC [77], and showed that chronic hepatitis and cirrhosis may facilitate the development of ICC [77]. Therefore, the present tumor my be associated with chronic hepatitis B and HBV infection.

Of particular interest in the current study is that many benign DPM were seen in the non-tumorous parenchyma. Some DPMs, in particular
von-Meyenburg complex, are known to show malignant transformation or associated with ICC [78] and HCC [79]. Therefore, there is a possibility that the present combined HCC and ICC was derived from the DPM.

In summary, the author reported a case of apparent C-HCC-CC with stem cell features. The ICC element showed apparent features of DPM. The author wants that this tumor should be included or added in the C-HCC-CC subtype as C-HCC-CC with stem cell features, DMP subtype. These statements were very strengthened by the broad immunohistochemical study done in the current tumor.

Conflict of interest statement

The author has no conflict of interest.

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