Combined Hepatocellular-Cholangiocarcinoma in Extrahepatic Bile Duct with Co-existing of Scirrhous Type of Hepatocellular Carcinoma

Sang Hoon Lee¹, Moon Jae Chung¹,²

Departments of ¹Internal Medicine, ²Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

We report a patient with combined hepatocellular-cholangiocarcinoma confined in the common hepatic duct and scirrhous type of hepatocellular carcinoma in the caudate lobe of liver simultaneously. The patient was a 55-year-old Korean man with hepatitis B virus (HBV) carrier who was referred from a local hospital due to detected liver mass on abdominal computed tomography (CT). He has presented jaundice and weight loss for the previous 3 weeks. Laboratory examination showed AST/ALT elevation and hyperbilirubinemia, HBsAg was positive. The tumor marker study showed elevated AFP and DCP, not CEA and CA 19-9. Abdominal CT disclosed an about 2.1×0.9 cm sized soft tissue density in hilum with both intrahepatic duct (IHD) dilatations and an about 3×2.1 cm sized arterial enhancing lesion at segment 8 of the liver. Patient received 15 cycles of Gemcitabine/Carboplatin chemotherapy from February 27, 2013 to December 31, 2013. Caudate lobectomy of liver, segmental resection of bile duct and Roux-en-Y hepaticojejunostomy was performed on February 10, 2014. The final pathologic report showed double primary liver cancer, combined hepatocellular-cholangiocarcinoma in common hepatic bile duct and scirrhous type of hepatocellular carcinoma in segment 1 of the liver. This is a very unusual case in which combined hepatocellular-cholangiocarcinoma confined in the large bile duct and two rare hepatic cancers coexisted.

Key Words: Combined hepatocellular-cholangiocarcinoma, Scirrhous type, Hepatocellular carcinoma, Large bile duct, Multicentric liver cancer

INTRODUCTION

Combined hepatocellular-cholangiocarcinoma is relatively rare form of primary liver cancer, showing features of both hepatocellular and biliary epithelial differentiation in same tumor.¹ The pathogenesis of combined hepatocellular-cholangiocarcinoma has remained unclear for many years. However, recent advances in hepatic progenitor cell (HPC) research have provided new concepts. Liver cancers, including hepatocellular carcinoma (HCC), combined hepatocellular-cholangiocarcinoma, and cholangiocarcinoma, are considered to originate from HPCs (also referred as oval cells, tumor-initiating stem-like cells).² HPCs are liver-specific adult stem cells that are activated when mature hepatocytes and/or cholangiocytes are damaged. HPCs have bipotential; they are capable of differentiation into either hepatocytes or cholangiocytes.³,⁴ The hypothesis that combined hepatocellular-cholangiocarcinoma is derived from HPCs is easily acceptable.⁵

The concept that combined hepatocellular-cholangiocarcinoma originates from HPCs is adopted in the chapter “combined hepatocellular-cholangiocarcinoma” of the latest World Health Organization (WHO) classification of digestive system. According to the WHO classification,⁴ combined hepatocellular-cholangiocarcinoma is divided into classical type and subtype with stem cell features. In addition, the latter is subdivided into typical subtype, intermediate subtype and cholangiocellular subtype.

Generally, HPCs were considered to locate in the bile ducts and canals of Hering,³ and almost combined hepatocellular-cholangiocarcinoma exist anatomically in intrahepatic area. Only few cases were previously reported which extended
to the extrahepatic area such as common hepatic duct. We report a unique case in which the combined hepatocellular-cholangiocarcinoma confined in common hepatic duct with separately co-existing of scirrhous type of hepatocellular carcinoma in caudate lobe of liver, as double primary liver cancer.

CASE REPORT

A 55-year-old Korean male was referred to our hospital for evaluation of a liver mass that was detected in abdominal computed tomography (CT) at a local hospital on February 18, 2013. He had experienced jaundice and weight loss for the previous 3 weeks. The patient has history of hypertension, type 2 diabetes mellitus, and was carrier of hepatitis B virus (HBV). He was a current smoker with history of 30 pack-years, and has no history of alcohol drinking. He has a family history of intrahepatic cholangiocarcinoma (mother and older sister of the patient). On admission, the blood pressure was 138/90 mmHg, the pulse rate was 76 per minute, the respiratory rate 18 per minute and the body temperature was 36.5°C. Physical examinations showed mild icteric sclera with non-anemic conjunctive and no cervical lymphadenopathy. Abdominal palpation revealed no palpable mass and no tenderness over the whole abdomen. In laboratory examinations, the complete blood count was 4,730/mm³ for the white cell count, 16.2 g/dL for the hemoglobin level, and 142,000/mm³ for the platelets count. The blood chemistry showed 15.0 mg/dL of urea nitrogen, 0.53 mg/dL of creatinine, 6.3 g/dL of total protein, 3.7 g/dL of albumin, 67 IU/L of AST, 127 IU/L of ALT, 146 IU/L of alkaline phosphatase, 3.9 mg/dL of total bilirubin, and normal prothrombin time. HBsAg was positive and anti-HCV was negative. The tumor marker study showed elevated AFP of 1,141.05 ng/mL and DCP of 36 mAU/mL. CEA and CA 19-9 were normal. Abdominal CT disclosed an about 2.1×0.9 cm sized soft tissue density in hilum with both intrahepatic duct (IHD) dilatations (Fig. 1A) and an about 3.1×2.1 cm sized arterial enhancing lesion at segment 8 of the liver (Fig. 1B). Pancreatobiliary magnetic resonance imaging (MRI) revealed a lobulated mass at the center of the liver (S8, S7 and S1 invasion) with invasion to hilar bile duct (type IIIA pattern) and abutting to the middle hepatic vein and IVC. The lesion exhibited arterial enhancing and early washout pattern after intravenous contrast medium administration. Endoscopic retrograde cholangio-pancreatography (ERCP) showed significant both IHD dilatations with abruption of hilar bile duct. The biopsy was done at hilar common bile duct (CBD) and two endoscopic retrograde bile drainages (ERBD) to right and left IHD were inserted to reduce obstructive jaundice. The pathologic report of hilar CBD biopsy suggested poorly differentiated adenosquamous carcinoma. Patient received 15 cycles of Gemcitabine/Glipatin chemotherapy from February 27, 2013 to December 31, 2013. Caudate lobectomy of liver, segmental resection of bile duct and Roux-en-Y hepaticojejunostomy was performed on February 10, 2014.

Pathological examination determined that there were two distinct tumors in common hepatic duct and caudate lobe of liver, regarded as double primary tumor. The aforementioned tumor, grossly located in common hepatic duct was reddish polyloid mass measuring 2.1 cm in the greatest diameter (Fig. 2A). Microscopically, the tumor was classical type of poorly differentiated combined hepatocellular-cholangiocarcinoma, which was confined to the bile duct with extension only up to the muscle layer or fibrous tissue (Fig. 2B). The most tumor cells showed trabecular growth pattern, resembling hepatocellular carcinoma, but some tumor cells formed glandular structures with desmoplastic stroma, regarded as cholangiocarcinoma portion (Fig. 2C). They showed negative resection margin (distal common bile duct, left hepatic duct, right hepatic duct and circumferential margin). Immunohistochemically, the tumor cells were focal positive for anti-hepatocyte (Fig. 3A) and diffuse positive for alpha 1-fetoprotein (Fig. 3B). They were diffuse positive for CK 19 with mainly cytoplasmic expression (Fig. 3C). The study for Alcian blue-PAS was focal weak positive (Fig. 3D), but that of Mucicarmine was negative. The another tumor was grossly well-defined whitish solid tumor measuring 2.8×2.4 cm in the resected liver (Fig. 4A). This tumor was diagnosed as scirrhous type of hepatocellular carcinoma (Fig. 4B, C, D) with positive surgical margin; however invasion to bile duct or vessel was not detected. The immunohistochemical stain revealed positive for anti-hepatocyte (Fig. 5A) and alpha 1-fetoprotein (Fig. 5B). About half of tumor cells were positive for CK19 with cytoplasmic and membranous expression (Fig. 5C). Mucicarmine and Alcian blue-PAS were negative immunohistochemically (Fig. 5D).

Fig. 1. Abdominal CT. A 2.1×0.9 cm sized soft tissue density in hilum with both intrahepatic duct dilatations (A) and a 3×2.1 cm sized arterial enhancing lesion at segment 8 of the liver (B)
Fig. 2. Gross feature and histologic findings of the combined hepatocellular-cholangiocarcinoma. The tumor, grossly located in common hepatic duct was reddish polypoid mass measuring 2.1 cm in the greatest diameter (A). Microscopically, the tumor cells were confined to the bile duct with extension only up to the muscle layer or fibrous tissue (B). The most tumor cells showed trabecular growth pattern (Upper), resembling hepatocellular carcinoma, but some tumor cells formed glandular structures with desmoplastic stroma (Thick white arrow), suggesting cholangiocarcinoma portion (C).

Fig. 3. Immunohistochemical findings of the combined hepatocellular-cholangiocarcinoma. The tumor cells were focal positive for anti-hepatocyte (A) and diffuse positive for alpha 1-fetoprotein (B). They were diffuse positive for CK19 with mainly cytoplasmic expression (C). The study for Alcian blue-PAS was focal weak positive (D).

Fig. 4. Gross feature and histologic findings of the scirrhous type of hepatocellular carcinoma. The tumor was grossly well-defined whitish solid tumor measuring 2.8×2.4 cm in the resected liver (A). Microscopically, neoplastic hepatocytes proliferated in an infiltrative growth pattern along the abundant fibrous stroma (B, C). The tumor cells were arranged in a trabecular pattern with irregular nuclear membrane and condensed chromatin (D).

DISCUSSION

Combined hepatocellular-cholangiocarcinoma was first reported in 1903 by Wells, but the first detailed description of combined hepatocellular-cholangiocarcinoma was in 1949 by Allen and Lisa. They subclassified combined hepatocellular-cholangiocarcinoma into three groups. In 1985, Goodman et al. suggested a third new system of classification: collision, transitional and fibrolamellar tumors. Although these classifications have been proposed, the histogenesis of combined hepatocellular-cholangiocarcinoma had remained unclear for many years. However, recent advances of HPDs investigations have provided new possible explanation for development of combined hepatocellular-cholangiocarcinoma.

HPDs are thought to differentiate into both biliary epithe-
lium and hepatocytes and identified in several pathologic liver conditions, such as hepatitis, cirrhosis, and hepatocellular adenoma. In cases of combined hepatocellular-cholangiocarcinoma, Fuji et al. showed that the tumor is originated from a single clone, and the histological diversity is a phenotypic expression of divergent differentiation. Yano et al. established a primary cell line derived from resected combined hepatocellular-cholangiocarcinoma and showed that it differentiated not only the characteristics of HCC but also those of cholangiocarcinoma under different growth conditions, suggesting that combined hepatocellular-cholangiocarcinoma arise from stem cells. The new explanation that combined hepatocellular-cholangiocarcinoma is derived from HPCs is widely accepted.

The diagnosis of combined hepatocellular-cholangiocarcinoma depends on demonstration of hepatocellular and biliary epithelial features in the same tumor. The HCC-like features include trabecular or pseudoglandular growth pattern, bile in the canaliculi, and carcinoma cells with intracellular inclusions similar to those found in hepatocytes (i.e. fat, Mallory-Denk bodies and alpha-1 antitrypsin). Features suggestive of cholangiocarcinoma differentiation include a desmoplastic stroma, and carcinoma cells forming glandular structures and producing mucus. Practically, a definitive diagnosis always requires the use of immunohistochemical and special stains to demonstrate both hepatocytic and biliary phenotypes. Generally used stains include Hep Par 1, polyclonal carcinoma-embryonic antigen or CD10 for hepatocytic differentiation, and mucin, CK7, and CK19 stains for the biliary differentiation. Combined hepatocellular-cholangiocarcinoma often expresses both biliary cytokeratins and markers of HCC, and is important diagnosis to consider when there is an apparently conflicting or overlapping immunophenotype.

Most interesting point in this case was location of combined hepatocellular-carcinoma, which confined in common hepatic duct. There was few case report that described about combined hepatocellular-cholangiocarcinoma growing to the common hepatic duct. In the report by Liver Cancer Study Group of Japan, the frequency of growth into the common hepatic bile duct was low with only 2 cases (2.4%) confirmed out of 84 operative and autopsy cases. However, combined hepatocellular-cholangiocarcinoma confined in only common hepatic duct has not been reported. Because hypothesis that combined hepatocellular-cholangiocarcinoma may be derived from HPCs is generally accepted, this is a conflicting report that combined hepatocellular-cholangiocarcinoma was confined in common hepatic duct, where the HPCs does not exist.

Embryologically, the extrahepatic bile duct and the ventral pancreas arise from the diverticulum of the posterior ventral foregut. In adult, biliary tree stem/progenitor cells, which are located in the peribiliary glands, have been recently reported to be multipotent and also express transcription factors and cell markers of stem/progenitor cells of the liver, pancreas and endoderm. Their descendants undergo a maturational lineage process giving rise to hepatocytes, cholangiocytes, and pancreatic endocrine cells. Besides the well-known HPCs at the level of the canals of Hering, biliary tree stem/progenitor cells within peribiliary glands of the large intrahepatic bile ducts both in fetal and adult life could become a newly identified reservoir of stem cells for the renewal of the large bile duct epithelium. In addition, some studies demonstrated about correlation between cholangiocarcinoma and biliary tree/progenitor cells. Therefore, our observation can provide the new possibility that combined hepatocellular-cholangiocarcinoma could derive from cells within peribiliary glands, instead of HPCs. Further studies for origin of combined hepatocellular-cholangiocarcinoma will be needed in future.

Scirrhous type of hepatocellular carcinoma is also a rare primary liver cancer, which features proliferation of fibrous bundles in sinusoids, resulting in a thick fibrous stroma dividing the tumor cell nest characteristics of tumor cells and the fibroitic stroma. It has been reported in only 1% of HCC patients in Japan and the frequency of the combination of scirrhous HCC and combined hepatocellular-cholangiocarcinoma...
was extremely low. To our knowledge, one case report was published for this combination of multicentric liver cancer.29

In conclusion, we reported a double primary liver cancer, combined hepatocellular-cholangiocarcinoma and scarboius HCC. This is a very unusual case in which combined hepatocellular-cholangiocarcinoma confined in the large bile duct and two rare hepatic cancers coexisted. Further studies for pathophysiologic characteristics of each tumor are necessary.

REFERENCES