

# A Case with Intrahepatic Double Cancer: Hepatocellular Carcinoma and Cholangiocarcinoma Associated with Multiple von Meyenburg Complexes

Youn Wha Kim<sup>1</sup>, Yong-Koo Park<sup>1</sup>, Jae Hoon Park<sup>1</sup>, Juhie Lee<sup>1</sup>, Sang Mok Lee<sup>2</sup>, Sung Wha Hong<sup>2</sup>, and Moon Ho Yang<sup>1</sup>

## Abstract

Combined hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) is sometimes found in resected livers, however, cases with double cancer of HCC and CC are very rare. As well, the rarity of CC arising in von Meyenburg complexes (VMCs) is appreciated. We report the case of a 74-year-old man found to have intrahepatic double cancer composed of well-differentiated HCC and CC which exhibited a histologic progression from VMCs to adenomatous lesions and CC. To our knowledge, this is the first case report published in the literature of a double HCC and CC associated with multiple VMCs. The pathogenesis and previous associated reports of these lesions are discussed.

**Key Words:** Double cancer, hepatocellular carcinoma, cholangiocarcinoma, von Meyenburg complex

## INTRODUCTION

Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC) is the preferred term for a tumor containing both hepatocellular carcinoma (HCC) and distinct or separate cholangiocarcinoma (CC).<sup>1</sup> Allen and Lisa classified cHCC-CC into three categories: 1) separate tumors, 2) contiguous but independent tumors, and 3) an intimate intermingling of both components.<sup>2</sup> Intrahepatic double carcinoma may be defined as two separate carcinomas without direct contact and histological transition between HCC and CC components.<sup>3</sup> The incidence of cHCC-CC among primary liver cancer has been reported to be 1.0% to 6.3%.<sup>1,4,5</sup> However, the simultaneous occurrence of double HCC and CC is extremely rare.<sup>6-8</sup>

Bile duct hamartoma or von Meyenburg complex (VMC) is a developmental defect which is characterized by dysgenetic intrahepatic bile ducts within a

dense collagenous stroma.<sup>9</sup> To date, six cases of CC associated with VMCs have been reported.<sup>9-13</sup> We experienced a case with intrahepatic double cancer composed of HCC and CC associated with multiple VMCs. The pathogenesis of these tumors is discussed.

## CASE REPORT

A 74-year-old Korean man was admitted to hospital for the evaluation of a hepatic mass. He had had hypertension for 8 years and he had undergone an aorto-bifemoral bypass graft due to atherosclerosis. On admission the patient's general condition was good, and on examination the abdomen was soft and flat, and no abdominal mass was felt. The laboratory data was normal with the exception of a high serum alkaline phosphatase level (204 IU/l, normal; 39–117 IU/l). Hepatitis B surface antigen and antibody to hepatitis C were negative. The serum alpha-fetoprotein level was 7.5 ng/ml (normal <8.4 ng/ml), carcinoembryonic antigen level was 0.4 ng/ml (normal <3.5 ng/ml), and CA19-9 level was 11.6 U/ml (normal <35 U/ml). Computed tomography and a magnetic resolution image of the liver revealed two relatively well-defined round masses on the right lobe separated from each other. A hepatic angiogram

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Departments of <sup>1</sup>Pathology and <sup>2</sup>General Surgery, College of Medicine, Kyung Hee University, Seoul, Korea.

Address reprint request to Dr. Y. W. Kim, Department of Pathology, College of Medicine, Kyung Hee University, #1 Hoiki-dong, Dongdaemun-gu, Seoul 130-701, Korea. Tel: 82-2-961-0543, Fax: 82-2-962-5278, E-mail: kimyw@nms.kyunghee.ac.kr

revealed a large hypervascular mass which was supplied by the antero-inferior segmental branch of the right hepatic artery, while another small hypervascular mass was noted at the anterior segment just right to the left medial segment. Under the impression of double HCC, an anterior bisegmentectomy was performed.

The resected liver was measured  $16 \times 14 \times 5$  cm and weighed 480 gm. There was a round rubbery mass measuring  $4 \times 5$  cm which was located in the antero-inferior segment. On section, the larger appeared well encapsulated and green and felt firm (Fig. 1). Surrounding liver parenchyma showed normal appearance without cirrhotic changes. Microscopically, the tumor was a well differentiated hepatocellular carcinoma (Fig. 2). Another hard mass was located in the antero-superior segment measuring  $2 \times 2$  cm. Cut

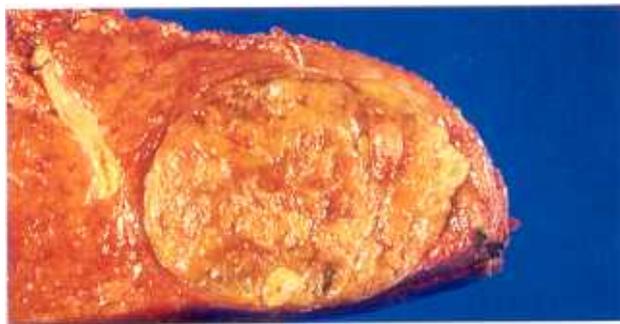


Fig. 1. The cut-section shows a well-encapsulated firm, greenish mass with normal adjacent hepatic parenchyma.

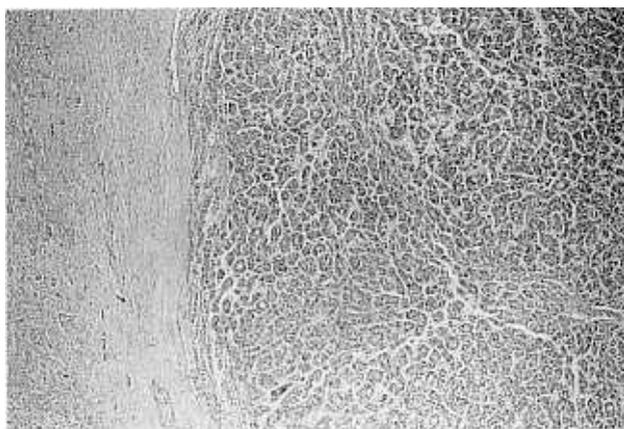


Fig. 2. The tumor shows microglandular type of hepatocellular carcinoma (H&E,  $\times 40$ ).

section revealed an ill-demarcated mass that was brown to green, firm and variegated in appearance (Fig. 3). The liver parenchyma between the two masses seemed grossly normal. Microscopically, most of the tumor was composed of proliferating bile ductules. These ductules were irregularly dilated and admixed with histiocytes, bile and some cellular debris (Fig. 4A). Foci of dysplastic epithelium was found along the dilated bile ducts. Also noted was a proliferation of small well-formed glands lined by a single layer of low cuboidal cells without bile, which were reminiscent of bile duct adenoma. In the general area, scattered neoplastic glands were found which were lined by anaplastic epithelial cells surrounded by dense fibrous connective tissue with lymphocyte infiltration and occasionally lymphoid follicles (Fig. 5). Foci of the transitional zone from bile duct dysplasia to bile duct carcinoma were identified in the tumor.

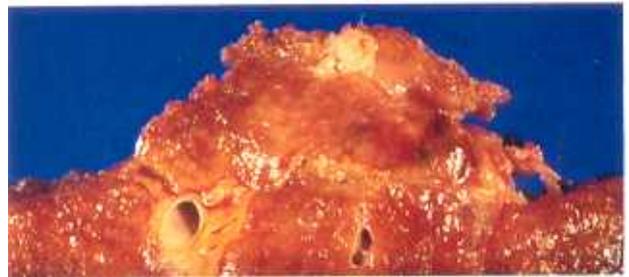


Fig. 3. The cut-section shows ill-demarcated brownish firm variegated appearance.

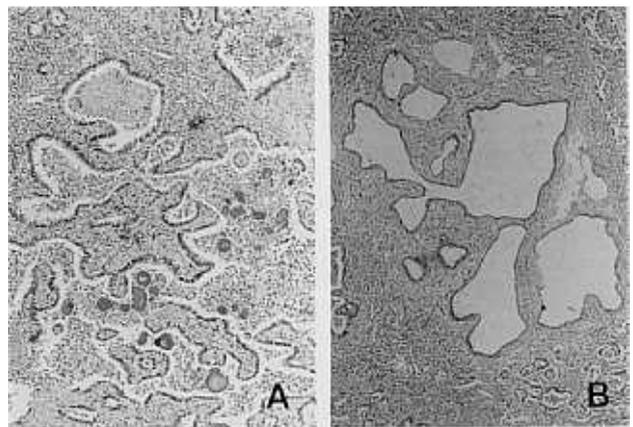


Fig. 4. In some areas, bile ductules were irregularly dilated and contained histiocytes, bile and some cellular debris (A); while von Meyenburg complex and surrounding proliferation of bile ductules were seen (B) (H&E,  $\times 40$ ).

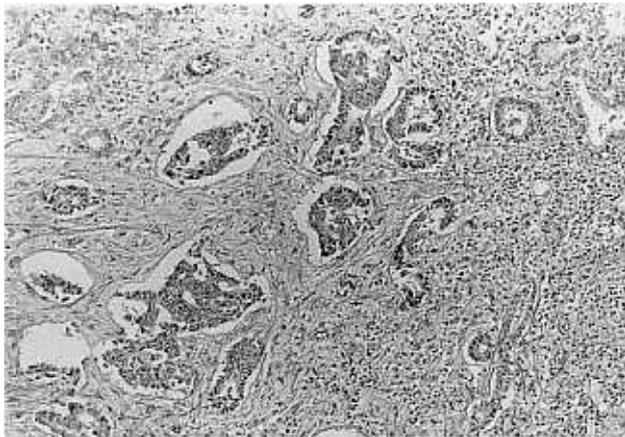


Fig. 5. Areas of adenocarcinoma with desmoplasia are noted (H&E,  $\times 100$ ).

Multiple foci of von Meyenburg complexes were scattered in the center of the tumor, surrounded by liver parenchyma (Fig. 4B). Immunohistochemically, these bile duct-like glands were positive for cytokeratin, but negative for alpha-fetoprotein and carcinoembryonic antigen.

Two years after the operation, a follow-up computed tomography showed metastatic lesions in the left scapula. A left intraarticular total scapulectomy was performed. The mass measured  $10 \times 15$  cm. Microscopically, the tumor was a metastatic, well-differentiated hepatocellular carcinoma. At present, the patient is approximately 6 months out of left scapulectomy and is doing well without evidence of metastatic lesions.

## DISCUSSION

In the surgically-resected liver of the presenting case, a well-differentiated HCC was located in the antero-inferior segment and a CC was located in the antero-superior segment without any connection between them. Large parts of tumor containing CC were composed of a proliferation of small bile ductules containing bile admixed with irregularly dilated ducts which had foci of varying degrees of dysplastic epithelium. Foci of transitional zone from dysplasia to carcinoma were found in the mass with desmoplasia and lymphocytic infiltration. Multiple foci of VMCs were scattered within the mass and in adjacent hepatic parenchyma. So it was assumed that this CC

arose from the dysgenetic bile duct epithelium of VMCs.

Until recently, there has been no universally-accepted criteria for the diagnosis of cHCC-CC. Craig et al. used the term cHCC-CC only when the HCC and CC were present separately, but not in cases of collision or intermingled tumors.<sup>1</sup> Haratake and Hashimoto defined intrahepatic double carcinoma as two separate tumors which lacked direct contact and any histological transition between HCC and CC elements.<sup>3</sup> The histogenesis of double HCC and CC is still unclear. Embryologically the hepatoblasts that constitute the early embryonic liver are bipotential progenitor cells, which can give rise to cholangiocytes or to hepatocytes.<sup>14</sup> We believe double HCC and CC may have originated from embryonic hepatoblasts, later differentiating into HCC and CC independently and separately.

Multiple bile-duct hamartoma or von Meyenburg complexes are developmental bile duct defects and not true neoplasms, which may be seen alone or in association with congenital liver disorders such as hepatic fibrosis or polycystic liver disease. VMC is a rare disorder comprising 0.6% and 0.7% in a series of surgical cases and autopsies respectively.<sup>9</sup> Neoplastic transformation within VMCs was first reported by Homer, along with two cases of adenomatous transformation and a case of frank adenocarcinoma.<sup>10</sup> There have been several reports suggesting that VMCs could be the source of CC; A bile duct carcinoma arising from ductal epithelium of multiple VMCs,<sup>11</sup> two cases of VMCs with foci of atypical changes,<sup>9,12</sup> and two cases of multiple VMCs with multifocal adenomatous lesions and CC.<sup>13</sup>

The etiology and pathogenesis of CC in a patient with VMCs is speculative. VMCs represent ductal plate malformations of smaller interlobular ducts.<sup>15</sup> Various degrees of epithelial dysplasia as shown in this case have been identified in cases of VMCs, which is similar to precancerous changes in the carcinogenesis of bile duct cancer where bile duct hamartoma is not present. Burns et al. observed ubiquitous bile inspissation within dilated ducts, often in association with nuclear pleomorphism and atypia of the dilated duct. They then speculated that long-standing cholestasis, dilatation, and hepatotoxin might play a role in the bile duct carcinogenesis.<sup>12</sup>

In conclusion, we report a case with intrahepatic double cancer consisting of HCC and CC, the latter

arising from the ductal epithelium of multiple VMCs.

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