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A Case Report of Synchronous Double Primary Liver Cancers Combined with Early Gastric Cancer

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Combined hepatocellular carcinoma and cholangiocarcinoma is found at a frequency of 1.0~6.3% in resected primary hepatic tumors. However, the case of double cancers of hepatocellular carcinoma and cholangiocarcinoma that are discovered synchronously in different lobes of a liver is very rare. We experienced a case of a 74-year-old man who was found to have hepatocellular carcinoma and cholangiocarcinoma in different lobes of the liver, which were accompanied by early gastric cancer. To our knowledge, this is the first case report of double primary hepatic cancers accompanied with early gastric cancer. The pathogenesis and previous related reports of these lesions are discussed.

Key Words : Carcinoma, Hepatocellular; Cholangiocarcinoma; Stomach neoplasm; Double cancer; Triple cancer

INTRODUCTION

Among primary hepatic tumors, the rate of the combined type of hepatocellular carcinoma and cholangiocarcinoma is approximately 1.0~6.3%[1, 2], and the probability of double cancers found in different lobes of a liver is extremely rare. Furthermore, the cases of double hepatic cancer accompanying early gastric cancer have not yet been reported. Although the pathogenesis of these combined hepatocellular carcinoma and cholangiocarcinoma is not defined yet, it is embryologically supposed that hepatic stem cells independently differentiate into hepatocellular carcinoma and cholangiocarcinoma[3]. However, the relationship between these double cancers and early gastric cancer is unknown. Herein, the authors report a case of a 74-year-old male patient with triple cancer composed of hepatocellular carcinoma, cholangiocarcinoma and early gastric cancer.

CASE

A 74-year-old male patient came to the hospital for the evaluation of general weakness and headache that started 10 days ago. The patient drank approximately 350~700 mL (1~2 bottles) of *Soju*, a Korean spirit containing 25% of alcohol, per day for 50 years. Until recently, he had never experienced any chronic illness. In the family history, his younger brother died of hepatocellular carcinoma 20 years ago. His blood pressure was 100/60 mmHg, body temperature was 36.2℃, pulse was 72 per minute and his respiration rate was 20 times per minute. On physical examination, no abnormal finding including stigmata of chronic liver disease, was found.

In the complete blood cell count, hemoglobin was 13.1 g/dL, hematocrit was 35.6% and leucocytes and platelets increased to 16,400/mm^3 and 558,000/mm^3, respectively. Results of blood biochemical test were as follows: total bilirubin 0.38 mg/dL, albumin 3.3 g/dL, AST/ALT 48/54 IU/L, γ-GT 544 U/L (normal

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<50), alkaline phosphatase 316 IU/L (normal 39~117). Viral markers were HBsAg (-), anti-HBs (+), and anti-HCV (-). In tumor marker tests, α-FP and CEA were slightly higher than normal value, that is, 12.4 ng/mL (normal <8.4) and 5.4 ng/mL (normal <3.0), respectively, but CA 19-9 was within normal range, 2.8 U/mL.

Abdominal ultrasonography disclosed a 6.5 cm sized mass in the left medial segment of the liver. The mass was not enhanced in the arterial phase of abdominal CT and intrahepatic bile ducts of the left lobe were dilated to the peripheral portion from the mass (Figure 1). It was not visualized by endoscopic retrograde cholangiography suggesting obstruction of the bile duct branches by the tumor. In hepatic angiography, hypervascularity were demonstrated around the periphery of the tumor (Figure 2).

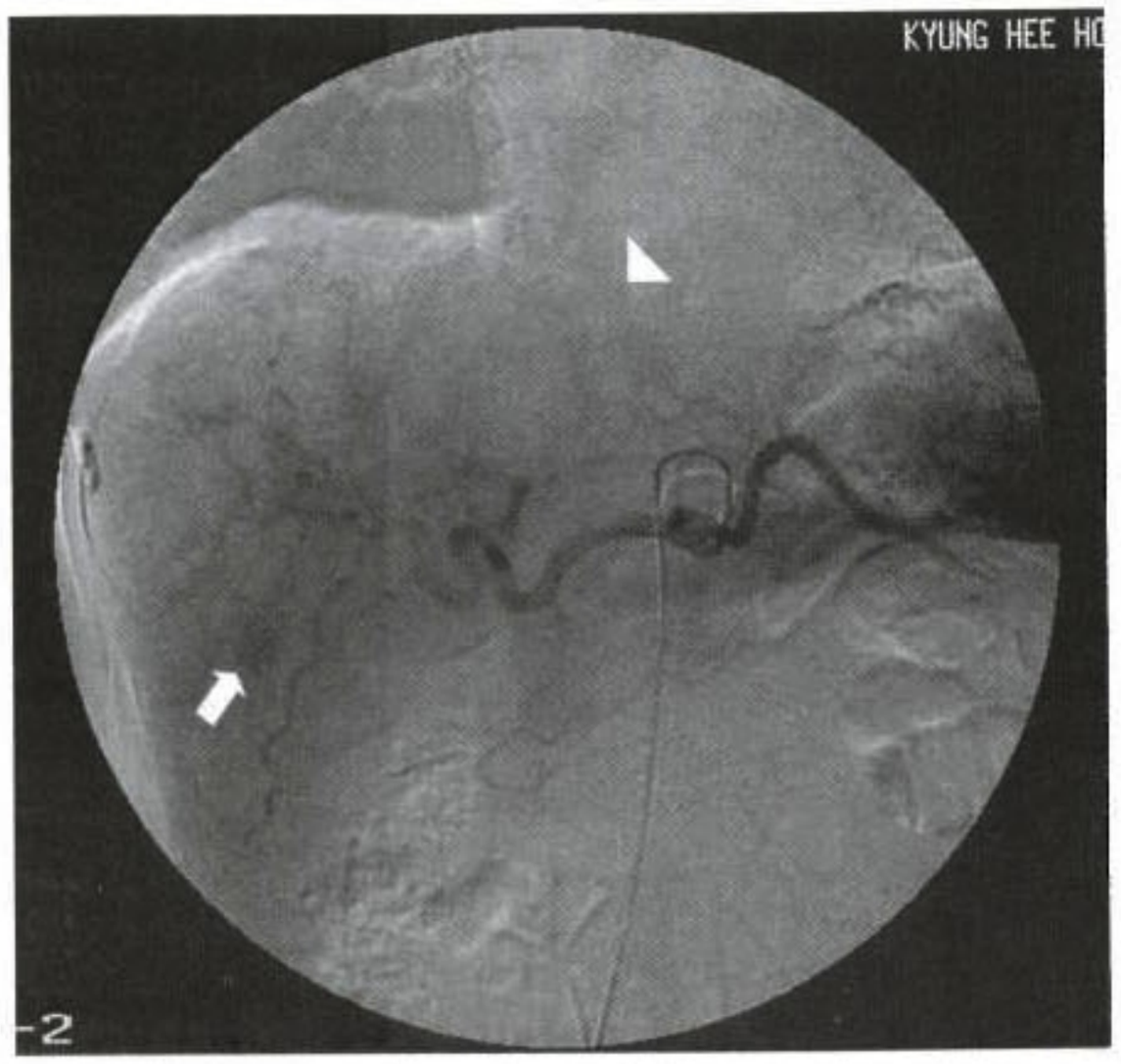

Figure 2. Hepatic angiography. It shows a large hypovascular mass in the left lobe (arrowhead) and some dot-like small nodular staining lesions around the left lobe. A small nodular hyper staining mass is noted in the right posteroinferior segment (arrow).

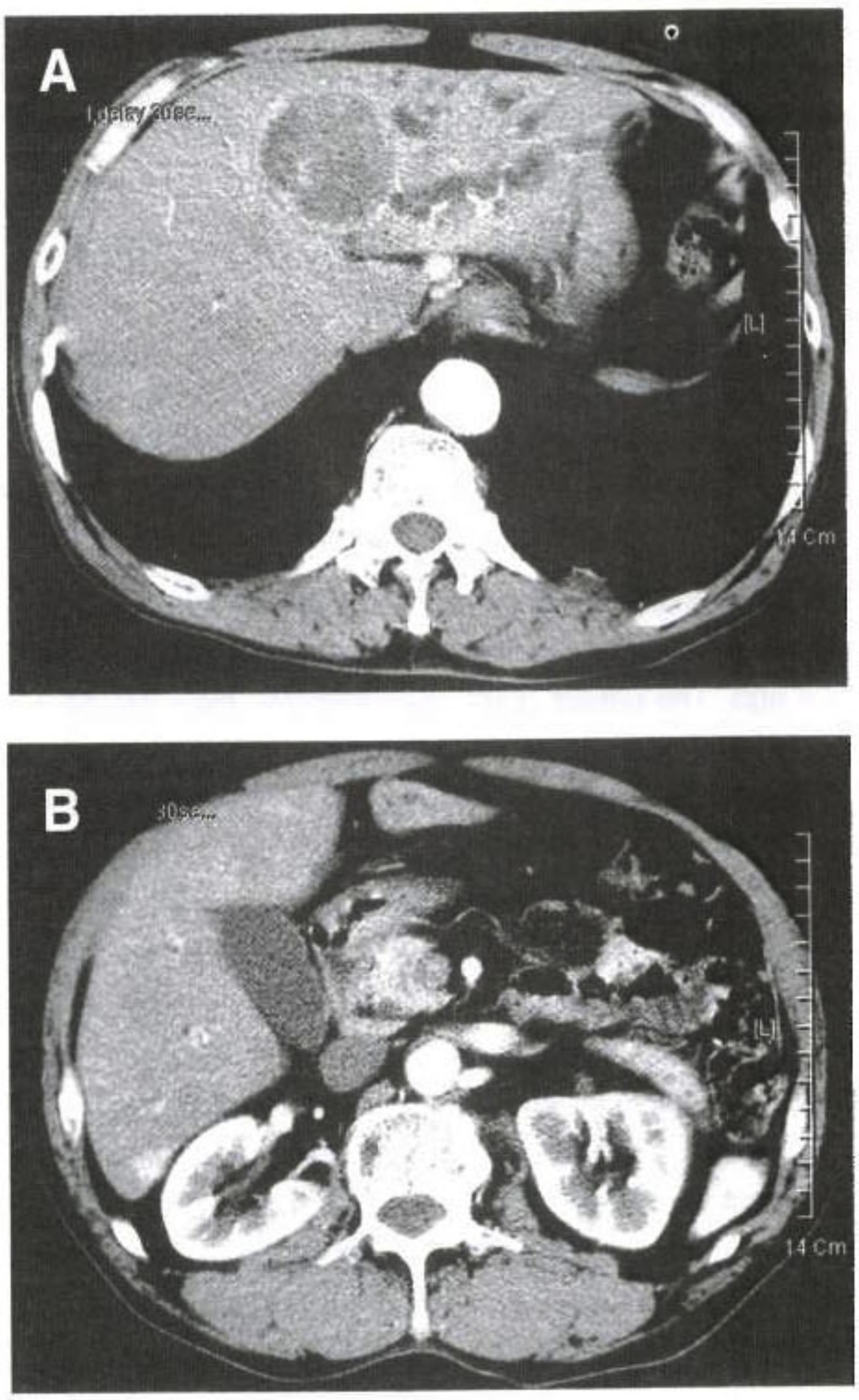

Figure 1. Abdominal CT finding. (A) Arterial phase. It shows a 6×5 cm mass with relatively discrete margin in the left medial segment of the liver. The left hepatic duct was encased by the mass and there was diffuse dilatation of intrahepatic bile ducts in the left lobe. (B) Arterial phase. It shows a small early enhanced mass in right posteroinferior segment.

All of these findings were compatible with cholangiocarcinoma. In abdominal CT, another 1.5 cm sized mass was found in the right posteroinferior segment of the liver, which was enhanced in the early arterial phase, but washed out in the early portal phase (Figure 1). In angiography, it appeared as a small nodular hyperstaining mass and was suspected to be hepatocellular carcinoma. However, intrahepatic metastasis from cholangiocarcinoma of the left lobe could not be excluded (Figure 2).

On gastroscopic examination, a 2×1.5 cm sized well-demarcated lesion was found at the greater curvature of the proximal antrum (Figure 3A). The well-differentiated adenocarcinoma of early gastric cancer type IIb was confirmed by pathologic examination (Figure 3B).

Left lobectomy for the removal of the main mass, wedge resection of the nodular lesion in the right lobe and subtotal gastrectomy were performed. The cut surface of the left lobe showed a 6×5 cm sized gray white tumor tissue with multiple small nodules. However, there was no sign of cirrhotic change in the parenchyma of the liver. Pathologic examination revealed moderately differentiated cholangiocarcinoma with severe fibrosis and necrosis (Figure 4A). From the specimen obtained through the wedge resection of the right lobe, a 2.5×2 cm sized rather well-circumscribed tumor was observed. Microscopic examination showed a well-differentiated hepatocellular carcinoma with solid or trabecular pattern and occasional acinar differentiation (Figure 4B). A well-differentiated adenocarcinoma was confirmed on the mucosal layer of the stomach specimen. The patient is now under follow-up observation.

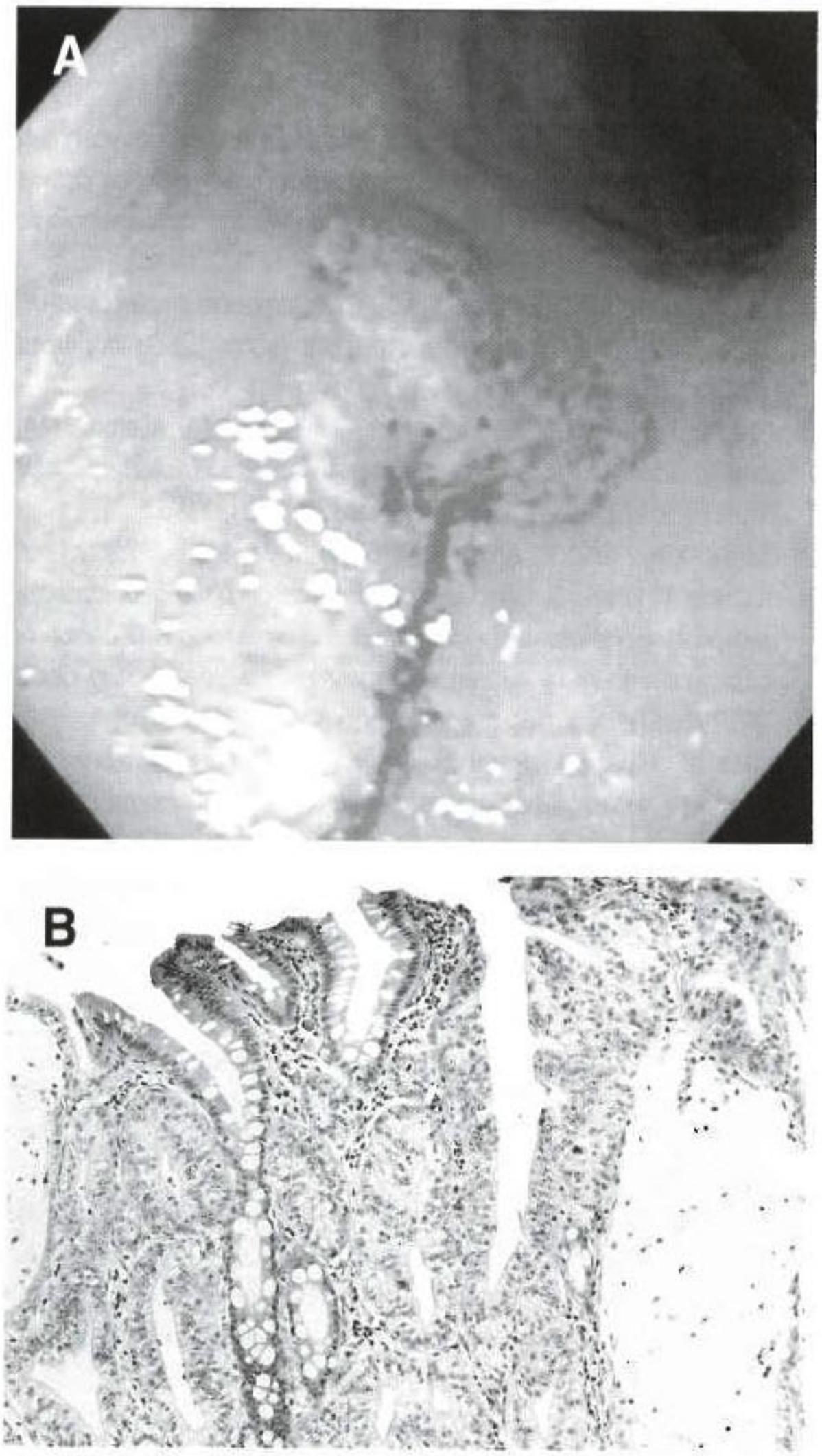

Figure 3. Gross and microscopic findings of the stomach lesion. (A) A 2×1.5 cm sized and well-demarcated flat lesion is noted at the proximal antrum of the greater curvature on gastroscopic examination. (B) Moderate to well-differentiated neoplastic epithelial cells with glandular differentiation are noted on microscopic examination (HE stain, ×100).

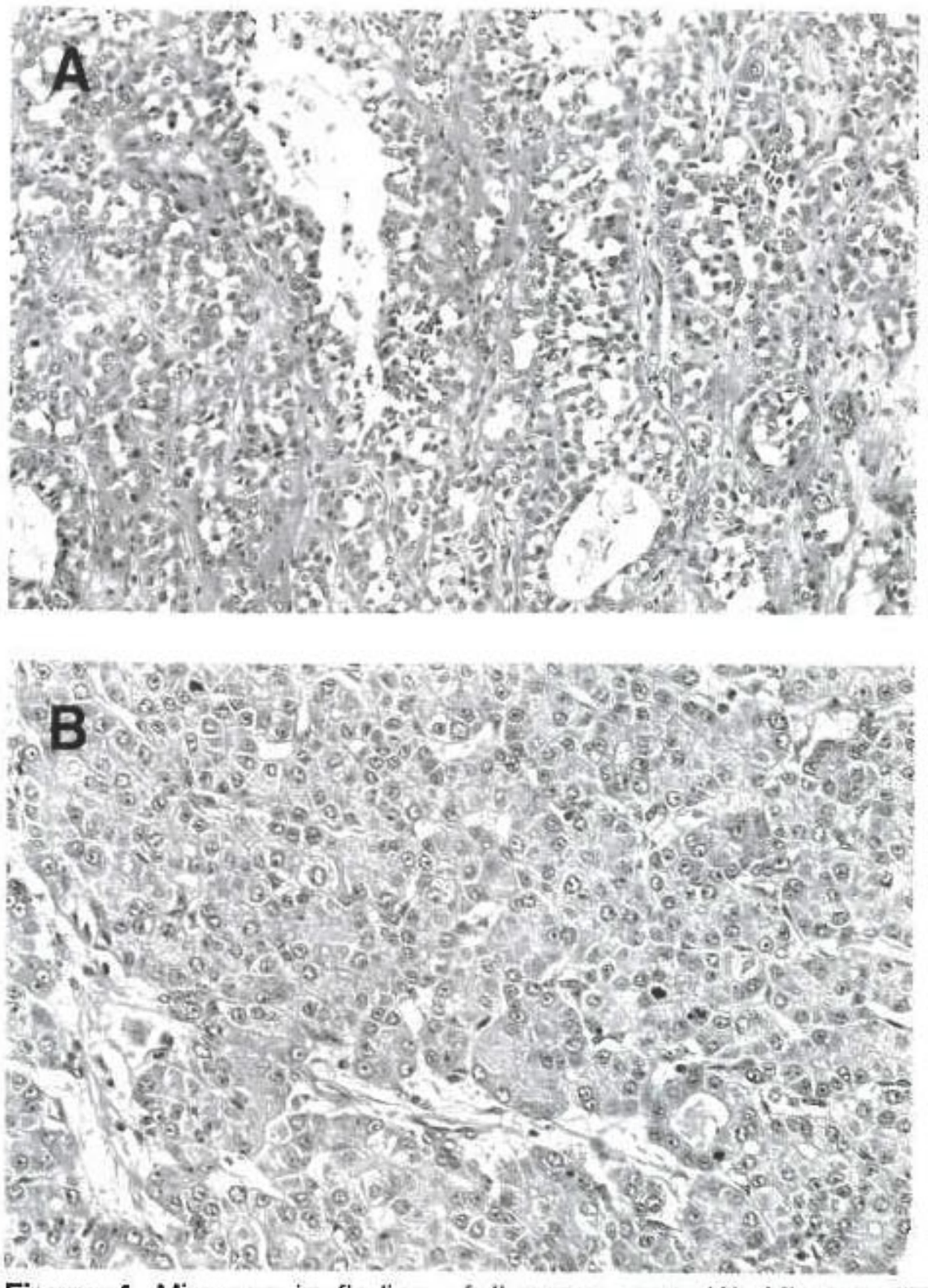

Figure 4. Microscopic finding of liver cancers. (A) Microscopic examination of the main mass revealed moderately-differentiated neoplastic epithelial cells with glandular differentiation which is compatible with cholangiocarcinoma (HE stain, ×100). (B) Microscopic examination of another small mass disclosed neoplastic hepatocytes with solid or trabecular pattern and occasional acinar differentiation which is compatible with hepatocellular carcinoma (HE stain, ×200).

DISCUSSION

The majority of primary liver cancers are hepatocellular carcinoma, followed by cholangiocarcinoma. According to the classification of WHO[4] and the Liver Cancer Study Group of Japan[5], the case where hepatocellular carcinoma and cholangiocarcinoma co-exist is designated as the combined hepatocellular carcinoma-cholangiocarcinoma. Among combined type primary liver cancer, 1.2% are found during the operation and 1.6% are found during autopsy, according to the Liver Cancer Study Group of Japan[5]. In Western countries, 2.4% of them are found during autopsy[6].

The combined hepatocellular carcinoma-cholangio-carcinoma is classified into 3 histological categories; separate tumors, contiguous but independent tumors and intermingling of both components[7]. The Liver Cancer Study Group of Japan also classifies carcinoma into three different categories; double cancer, combined type and mixed type[8]. The double cancer, where the carcinoma is separated in the same segment or same lobe, was only found in 3 cases of 376 primary liver cancer operations[9]. In the West, there was only one case out of 393 autopsies[10]. There are no reports concerning its frequency but only one case of double cancer has been reported in Korea[11].

In most of the double hepatic cancer cases, tumors are found at the same lobes. The case in which they are found in two different lobes of the liver is extremely rare, and only one case has been reported in Japan[12]. This case had cholangio-carcinoma in the left medial segment of the left lobe and hepatocellular carcinoma in the right posteroinferior segment.

In addition to this rare condition, our case had early gastric cancer as well, which made it a case of synchronous triple cancer that has not yet been reported.

The pathogenesis for the development of double cancers is unknown. Embryologically, hepatoblasts that constitute the early embryonic liver are bipotential progenitor cells, which can give rise to cholangiocytes or hepatocytes. Thus, this combined hepatocellular carcinoma-cholangiocarconoma can be originated from the embryonic hepatoblast, and later it can be independently differentiated into hepatocellular carcinoma and cholangiocarcinoma[3]. However, the relationship between early gastric cancer and double primary liver cancers is uncertain. Since gastric cancer is very common in Korea and our patient was on sustained excessive drinking, the possibility that the triple cancer is originated from environmental factors cannot be excluded.

Cholangiocarcinoma arises in the biliary lining epithelial cells, intrahepatic peribiliary glands and also Hering's ductule[13], and is associated with bile duct anomalies such as gallstones, liver flukes, Caroli's disease, choledochal cyst and primary sclerosing cholangitis[12]. Our case had no history or evidence of biliary tract disease. Moreover, hepatocellular carcinoma was incidentally found as well during the evaluation of cholangiocarcinoma. Hepatocellular carcinoma is frequently associated with liver cirrhosis or chronic hepatitis virus infection. However, this patient had no liver cirrhosis or viral hepatitis. The patient had a history of excessive drinking but there was no significant liver parenchymal disease. According to various researches, alcohol itself is not a carcinogen but liver cirrhosis caused by excessive drinking can increase the risk of hepatocellular carcinoma[14]. Therefore, the relationship between alcohol and the development of hepatoma, in this case, is uncertain.

Metastatic cancer and primary cancer of the liver can be identified using ultrasonography, computed tomography and angiography with over 80% accuracy[15]. In general, metastasis to the liver occurs frequently but the possibility of metastasis of cholagiocarcinoma to the stomach is not very high[16]. Considering that gastric cancer is an early cancer, it is much more persuasive that both tumors are independently developed. It has also been reported that if primary liver cancer occurs in patients with old age, they have a greater chance to have malignancies in extrahepatic organs[16]. However, the relationship between the primary liver cancer and malignancies in the extrahepatic organs is uncertain and more studies should be required.

In conclusion, we report a case of synchronous triple cancers that comprised double primary hepatic cancers of hepatocellular carcinoma and cholagiocarcinoma developed in different lobes and early gastric cancer.

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