【 CASE REPORT 】

Intrahepatic Cholangiolocellular and Cholangiocellular Carcinoma - Differences in the 18F-FDG PET/CT Findings

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Abstract:

Cholangiolocellular carcinoma is a minor primary cancerous tumor of the liver and its coexistence with intrahepatic cholangiocarcinoma in the liver is rare. We herein report a case of concurrent cholangiolocellular carcinoma and intrahepatic cholangiocarcinoma in the liver, in addition to a rectal G1 neuroendocrine tumor, a so-called carcinoid. The intrahepatic tumors showed a different uptake in the 18F-fluoro-2-deoxyglucose (FDG) positron-emission tomography (PET)/computed tomography (CT) findings. In addition to conventional dynamic contrast-enhanced CT, we concluded that FDG PET/CT could therefore be a helpful modality to identify the properties of both cholangiolocellular carcinoma and intrahepatic cholangiocarcinoma.

Key words: cholangiolocellular carcinoma, combined hepatocellular cholangiocarcinoma, with stem cell features, cholangiocellular carcinoma, neuroendocrine tumor, 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography

Introduction

First reported by Steiner and Higginson (1), cholangiolocellular carcinoma (CoCC) is a rare malignant liver tumor accounting for 1% of all primary liver cancers, and it is considered to originate from either hepatic progenitor or stem cells (2). The new classification presented in the 5th edition of the General Rules for Clinical and Pathological Study of Primary Liver Cancer in Japan, published in 2008 (3), proposes that CoCC is independent from intrahepatic cholangiocellular carcinoma (ICC). However, the findings obtained in imaging examinations remain controversial. Recently, we treated a patient with a rectal neuroendocrine tumor and double primary liver cancerous tumors, CoCC and ICC, with those latter two demonstrating contrasting findings obtained by 18F-fluoro-2-deoxyglucose (FDG) positron-emission tomography (PET)/computed tomography (CT).

Case Report

An 84-year-old Japanese male with an upper abdominal palpable mass was admitted to our hospital. He had diabetes mellitus and a history of hepatitis B virus (HBV) infection. Alcohol intake was 20 g/day and a smoking habit had been discontinued approximately 30 years prior to presentation. There were no remarkable physical findings, except for a palpable tumor in the right upper abdominal quadrant.

Laboratory results of samples obtained at admission showed a mild elevation of biliary enzymes (GGT 133 U/L, normal range 9-32 U/L) and renal dysfunction. As for Hepatic viral markers, hepatitis surface antigen and hepatitis C virus antibodies were negative, while hepatitis B surface and core antibody were positive. Tumor markers were within the normal ranges, [AFP 5.67 ng/mL (normal <20 ng/mL), des-gamma-carboxy prothrombin (DCP) 25 mAU/mL (normal <40 mAU/mL), CA19-9 4.9 U/mL (normal <37 U/mL),

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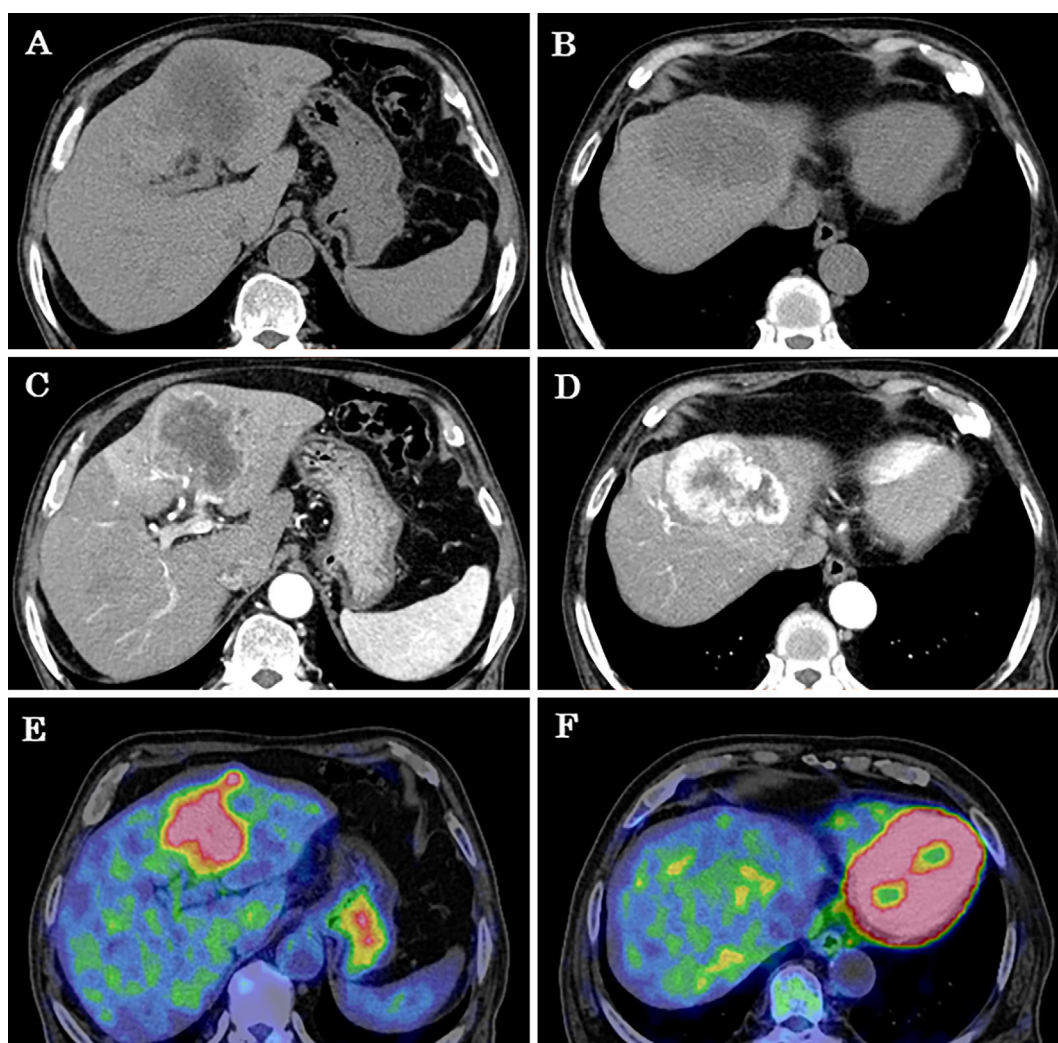
Figure 1. A plain CT scan image showing 6.5-cm low density masses in the (A) lateral and (B) medial segments. Dynamic CT images showing (C) the gradual enhancement of the mass in the lateral segment, and (D) a rapid and lobar enhancement of the masses in the medial segment in the arterial phase. FDG PET/CT images showing (E) the FDG uptake in the mass in the lateral segment, and (F) no uptake in the masses in the medial segment and segment 8.

urine 5-HIAA 3.2 mg/day (normal 1-6 mg/day)], except for an elevation of carcinoembryonic antigen (CEA) 72.89 ng/mL (normal <5 ng/mL). Ultrasonography revealed hypoechoic masses with a central hyperechoic area in the lateral and 8th segments, as well as a hypoechoic mass in the medial segment of the liver. Plain computed tomography (CT) showed 6.5-cm low density areas (LDAs) in the lateral (Fig. 1A) and medial (Fig. 1B) segments, and a 2-cm LDA in segment 8 of the liver. Early phase contrast enhanced CT scan images obtained following bolus contrast material injection revealed the peripheral enhancement of the mass in the lateral segment (Fig. 1C), and a rapid enhancement of the mass in the medial segment (Fig. 1D) and lobar enhancement of the mass in segment 8 (Fig. 2A and B). FDG PET/CT findings also showed an FDG uptake in the mass in the lateral segment, whereas there was no FDG uptake in the medial segment and segment 8 masses (Fig. 1E and F).

A systemic screening examination was performed, because both primary and metastatic tumors of the liver were suspected. Colonoscopy showed an elevated yellowish lesion in the rectum (Fig. 3). We performed a total endoscopic biopsy and the histological findings showed a neuroendocrine tumor, which was graded as G1 based on positive synaptophysin staining and a Ki67 index of less than 2%. To examine whether a metastatic neuroendocrine tumor of the liver or primary liver malignancy was present, a liver biopsy was performed, and samples of the masses in the lateral and medial segments were obtained. The histological findings of the mass in the lateral segment (Fig. 4) were positive for cytokeratin 7, 19, and 20, while mucus production revealed by alcian blue staining was also detected. However, in the specimen from the medial segment of the liver, no mucus production was detected and immunostaining for cytokeratin 20 was weak. In addition, the tumor cells were found to be much smaller than normal liver cells and showed proliferation as if they were replacing the surrounding hepatocyte cords at the tumor-non-tumor boundaries (Fig. 5). Based on the histological findings, our diagnosis of this case was ICC
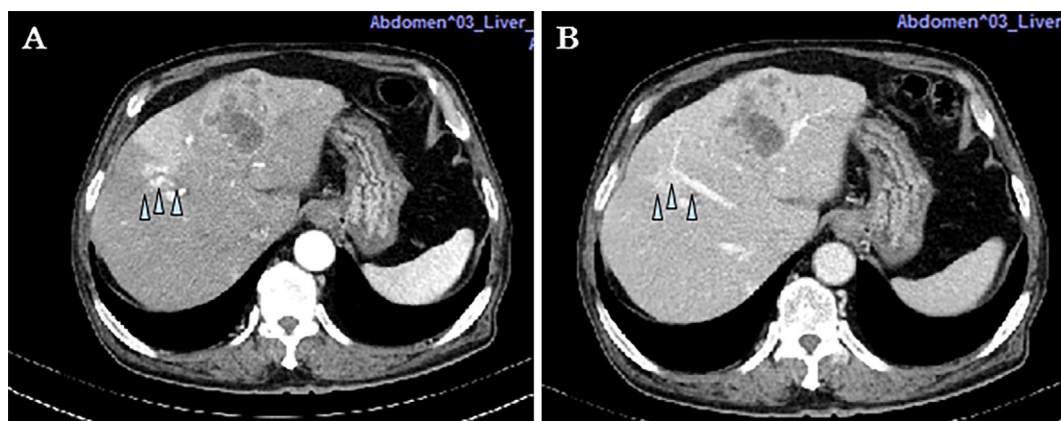
Figure 2. Dynamic CT imaging revealed a portal vessel penetrating the mass in segment 8. (A) A vessel is shown without enhancement (arrowheads) penetrating the masses in the arterial phase. (B) A vessel is shown with enhancement (arrowheads) penetrating the masses in the portal phase.
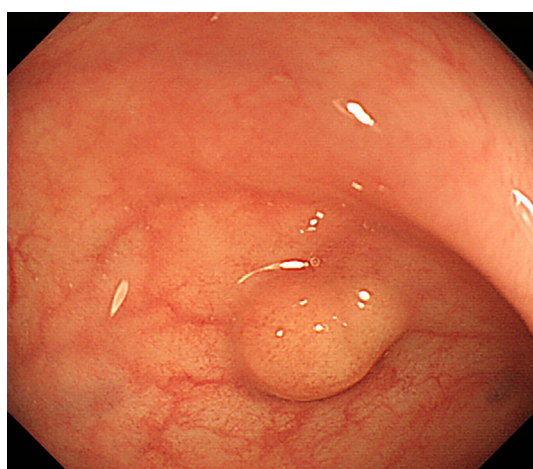

Figure 3. A colonoscopy image showing a yellow-colored elevated lesion coverd with a normal mucosa located in the rectum.

in the lateral segment and CoCC in the medial segment.

Discussion

CoCC, first reported by Steiner and Higginson (1), is a rare malignant liver tumor that accounts for 1% of all primary liver cancer cases, while its occurrence rate among primary liver cancer cases in Japan is 0.57% (4). That initial report described the distinct pathological characteristics of CoCC, which is derived from the cholangioles, or the smallest and most peripheral branches of the biliary tree (canals of Hering). The tumor has been categorized as a subtype of ICC by the World Health Organization (WHO) (5) as well as in the 4th edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan (6).

Recent advancements in our understanding of hepatic progenitor cells (HPCs) (7), which exist in the canals of Hering, have suggested that CoCC originates from those cells. Thus, this tumor has been classified as a combined hepatocellular-cholangiocarcinoma with stem-cell features in the latest version of WHO classification of tumors of the digestive system 2010 (8), while the new classification in the 5th edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan, published in 2008 (3), proposes that CoCC is independent from ICC.

Although no specific imaging findings for CoCC have yet been determined, two patterns of enhanced CT findings have been reported. Early overall enhancement with a delayed washout and persistent peripheral enhancement with concentric delayed filling in the tumor has been noted (9), which may make a diagnosis difficult when using CT or magnetic resonance imaging results. In a recent case, persistent peripheral enhancement was observed in the early arterial phase of CT scanning. On the other hand, some tumors present with the same enhancement pattern (e.g., sclerosing cholangioma, mixed typed hepatoma, sclerosing hemangioma). Additionally, signs of penetration of intrahepatic vessels by the tumor are sometimes observed in patients with CoCC (10) which is a characteristic of cell proliferation to maintain the structure of the liver. However, this finding is rarely observed in ICC, metastatic tumors or hepatocellular carcinoma cases (11, 12).

According to the results of several studies, the sensitivity of FDG PET for intrahepatic ICC was relatively higher than that for perihilar and extrahepatic lesions without mucinous adenocarcinomas. (13-16), thus ICC without an FDG uptake is very rare. A weak production of mucin in an ICC, histologically observed in a recent case, may not disturb the abnormal uptake of FDG. We performed a systemic search of the PubMed database for the English-language literature up to September 2016 using the search term 'cholangiolocellular cholangiocarcinoma', and found only 2 cases of CoCC that included FDG PET/CT images (17, 18). Mori et al. reported a case of CoCC of the liver that exhibited a high FDG uptake and noted that malignant CoCC cells show significant alterations in their metabolism during the process of transformation from normal cells. The different uptakes by different tumors revealed by FDG PET/CT might
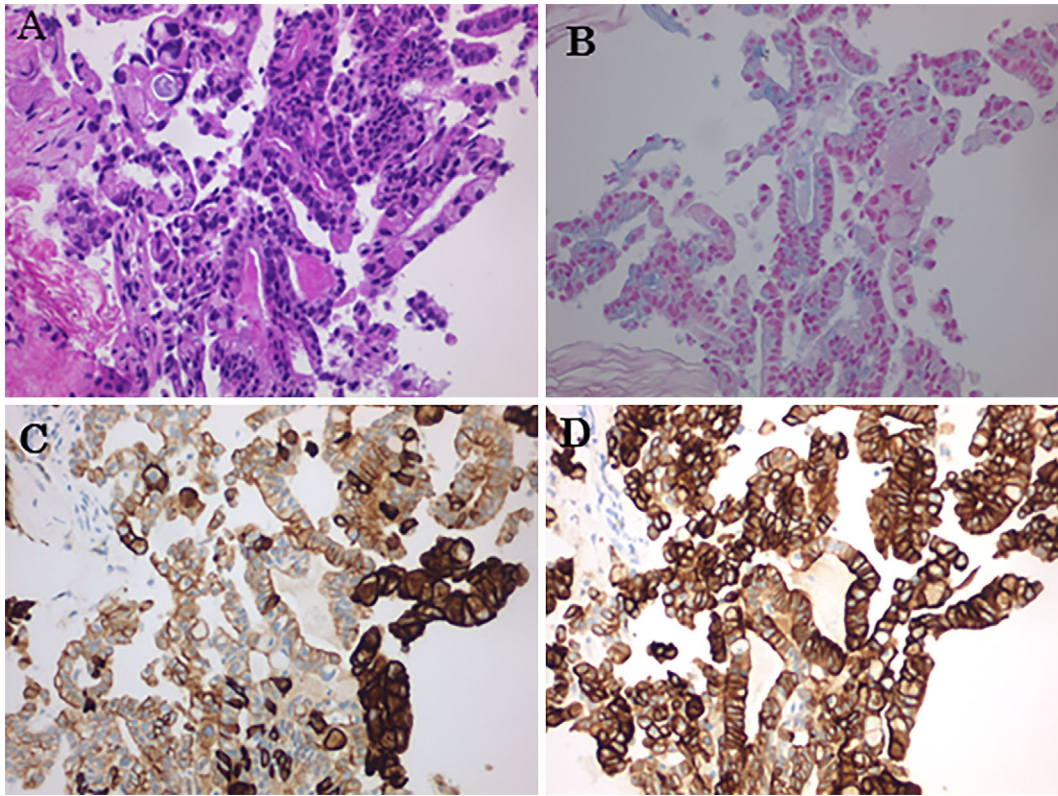
Figure 4. Histological findings obtained from the lateral segment. (A) Hematoxylin and Eosin staining, (B) alcian blue staining, (C) cytokeratin 20 immunostaining, and (D) cytokeratin 7 immunostaining.
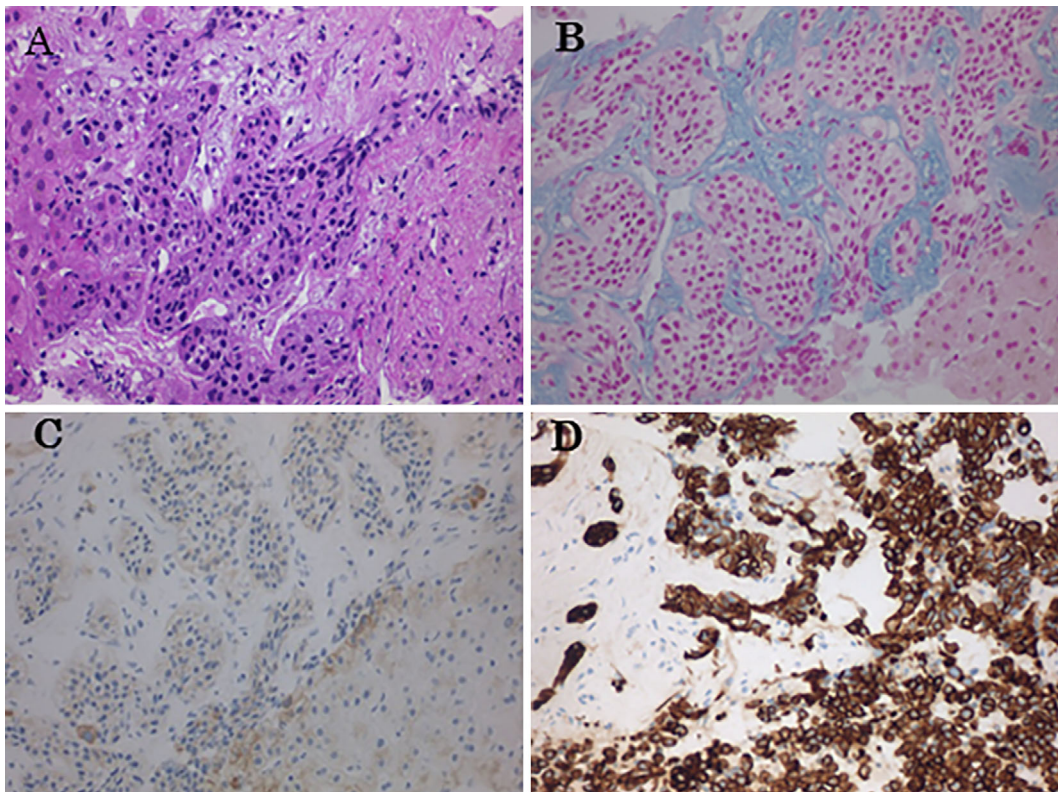

Figure 5. Histological findings obtained from the medial segment. (A) Hematoxylin and Eosin staining, (B) alcian blue staining, (C) cytokeratin 20 immunostaining, and (D) cytokeratin 7 immunostaining.

be caused by the malignant potential and/or tumor characteristics, and findings suggesting a disordered carbohydrate metabolism in CoCC may vary. There are few reports regarding the FDG uptake in CoCC and further studies are thus needed in order to examine this issue.

In conclusion, in addition to conventional dynamic enhanced CT findings, FDG PET/CT may be a useful modality for differentiating between ICC and CoCC.

The authors state that they have no Conflict of Interest (COI).

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