

# Imaging-Negative Hepatocellular Carcinoma Presents as an Intrabiliary Mass

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## ABSTRACT

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death and one of the most prevalent cancers worldwide. HCC prognosis remains poor with an average survival rate between 6 and 12 months. Obstructive jaundice, as a main clinical feature, is uncommon in HCC. HCC with bile duct invasion is much rarer than HCC with vascular invasion. We present a case where a patient's HCC was diagnosed by endoscopic retrograde cholangiopancreatography and digital cholangioscopy because his HCC manifested as an obstructing lesion in the intrahepatic duct, but not in the liver.

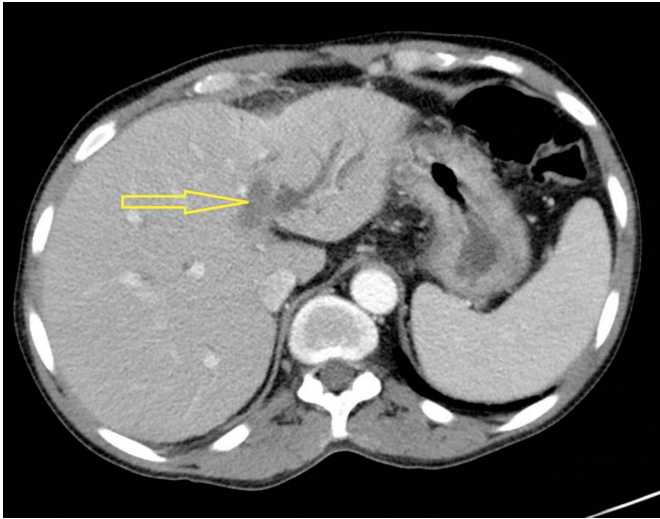
## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers globally. According to the World Health Organization, HCC is the second most common cause of cancer-related death worldwide, and the third in Western countries. In the United States, HCC incidence, hospitalization, and mortality rates are increasing, with a considerable shift toward younger ages.<sup>1</sup> In 2010, the annual incidence of HCC was at least 6 per 100,000 in the United States.<sup>2</sup> HCC prognosis remains poor with an average survival rate between 6 and 12 months.<sup>3</sup> The estimated worldwide annual death due to HCC is 500,000, with the highest rates being in Southeast Asia and sub-Saharan Africa.<sup>4</sup> HCC has a silent clinical course although it can present with nonspecific symptoms or with features of decompensated liver cirrhosis in patients with previously stable cirrhosis. HCC metastasis occurs by direct invasion, through hematogenous or lymphatic routes. Known sites of metastases include the lungs, lymph nodes, bone, adrenal glands, and brain. It is uncommon for HCC to present with obstructive jaundice as the main clinical feature. However, when it happens, a bile duct tumor thrombus is the likely cause. Despite the significant improvement in the imaging modalities, HCC with obstructive jaundice due to bile duct thrombus is still incorrectly diagnosed as cholangiocarcinoma or choledocholithiasis.<sup>5</sup>

## CASE REPORT

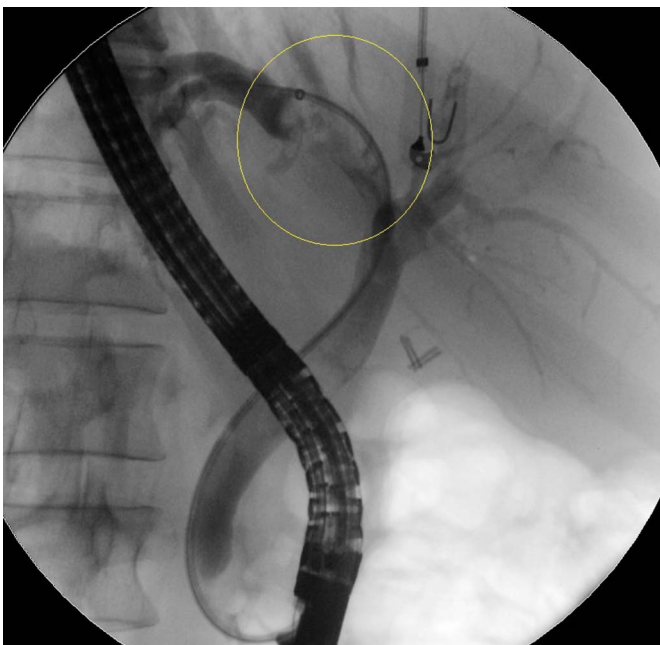
A 40-year-old African man, with a medical history significant for hepatitis B exposure with spontaneous clearance and aortic valve sclerosis, presented with intermittent right upper quadrant pain, 40 pounds unintentional weight loss, and hyperbilirubinemia. He had no history of hypertension, diabetes mellitus, or alcohol use. He was afebrile, and his vital signs were stable. Physical examination was remarkable for jaundice and moderate epigastric tenderness. His calculated body mass index was 22 kg/m<sup>2</sup>.

His laboratory workup was significant for total bilirubin 3.2 mg/dL (fractionated to indirect 2.3 mg/dL, direct 1 mg/dL), aspartate aminotransferase 39 U/L, alanine aminotransferase 36 U/L, alkaline phosphatase 117 U/L,  $\gamma$ -glutamyl transferase 97 U/L, positive hepatitis B total core antibody, negative hepatitis B core IgM, negative hepatitis B surface antigen, positive hepatitis B surface antibody, and negative hepatitis C virus antibody. Other laboratory results included a negative antimitochondrial antibody, F-actin (smooth muscle) antibody, and anti-nuclear antibody.



**Figure 1.** Axial view of an abdominal computed tomography scan showing the dilated biliary system (arrow), with a normal appearing liver (no cirrhotic morphology or masses identified).

Initial imaging including an abdominal ultrasound and a computed tomography (CT) scan showed dilated intrahepatic and extrahepatic bile ducts and a distended main pancreatic duct, with no evidence of cirrhosis (Figure 1). Magnetic resonance cholangiopancreatography showed a possible distal common bile duct (CBD) stone with mild intrahepatic dilatation. Subsequent laparoscopic cholecystectomy with intraoperative cholangiography showed a filling defect in the left intrahepatic duct (IHD). Endoscopic retrograde cholangiopancreatography showed a filling defect within the left intrahepatic bile duct with no CBD stones seen (Figure 2). When digital cholangioscopy was performed, a mass was seen in the left hepatic duct. Biopsy of the



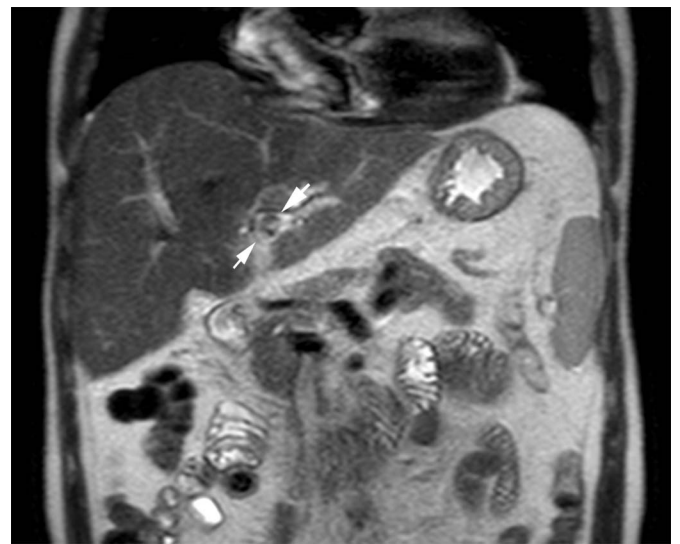
**Figure 2.** Endoscopic retrograde cholangiopancreatography showing a filling defect within the left intrahepatic bile duct.

mass showed poorly differentiated carcinoma, but its origin was inconclusive based on immunohistochemical stains.

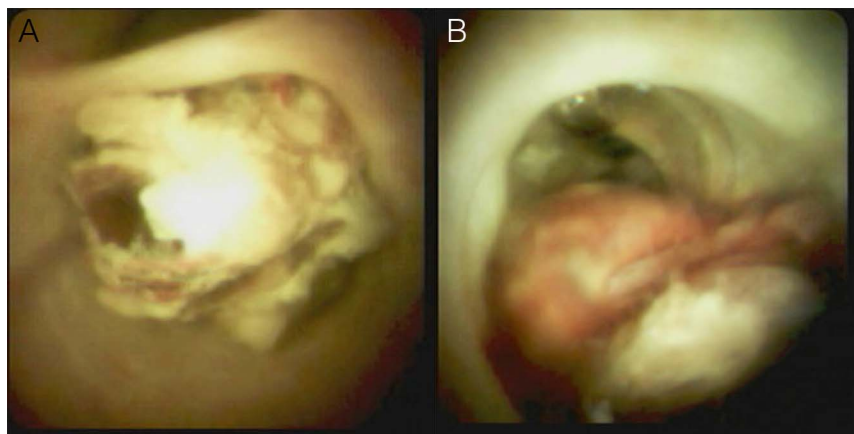
The patient was then lost to follow-up for 3 months, when he presented with right upper quadrant pain and fever and was diagnosed with ascending cholangitis. Laboratory work was significant for aspartate aminotransferase 115 U/L, alanine aminotransferase 130 U/L, alkaline phosphatase 261 U/L, total bilirubin 7.3 mg/dL (fractionated to indirect 2.5 mg/dL, direct 2.9 mg/dL, and  $\delta$  1.9 mg/dL),  $\alpha$ -fetoprotein (AFP) 73.95 ng/mL, cancer antigen 19-9 1 U/mL, and cancer antigen 125 59.70 U/mL.

Abdominal CT scan showed intrahepatic and extrahepatic biliary duct dilation. Magnetic resonance imaging with contrast demonstrated a low-level enhancing material in the left IHD, concerning for malignancy (Figure 3). A second endoscopic retrograde cholangiopancreatography was performed with DC, which showed an obstructing polypoid mass in the left IHD (Figure 4). The polypoid lesion was rebiopsied, and immunohistochemical stains were positive for hepatocyte antigen, Arginase 1, and glypican and negative for Melan-A, HMB45, CK7, and CK20. The diagnosis of HCC was made.

The patient was referred for left hepatectomy. Histology, using hematoxylin and eosin stain, revealed a poorly differentiated HCC with infiltration of the large hilar bile ducts and extension into the peripheral soft tissue (Figure 5). Other associated pathological features included marked inflammation and fibrosis of the hilar tissue with cholangitic abscesses. It was noted from the surgical specimen that the patient had background liver cirrhosis which was not described by all previous imaging studies. No clear etiology for cirrhosis could be identified through immunohistochemical stains.



**Figure 3.** Abdominal magnetic resonance imaging showing the left intrahepatic ductal mass, without a hepatic mass.



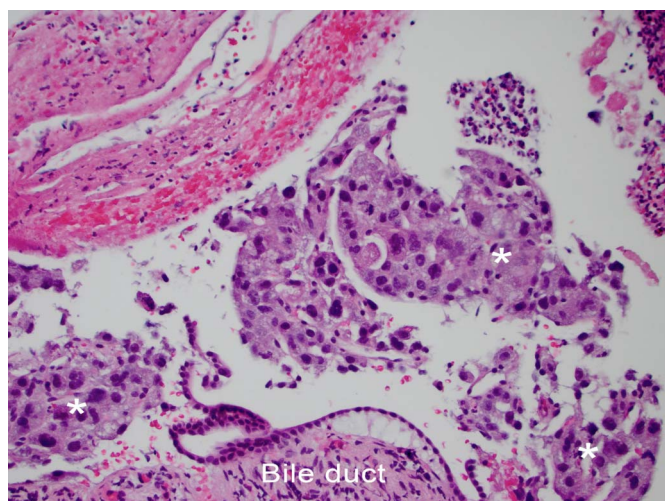
**Figure 4.** Digital cholangioscopy showing the (A) villous appearance of the intrahepatic ductal mass and the (B) polypoid left intrahepatic ductal hepatocellular carcinoma.

## DISCUSSION

Early diagnosis and effective treatment of HCC remains a challenge. Early diagnosis of an HCC less than 2 cm in size usually leads to favorable outcome either through liver transplant or through resection.

Diagnosis of HCC is usually made by a combination of serological testing and various imaging modalities. AFP concentration increases with tumor size but still has a questionable diagnostic accuracy because of low sensitivity to small-size tumors. AFP sensitivity decreases from 50% in tumors larger than 3 cm to 25% in tumors smaller than 3 cm, which are potentially resectable.<sup>4</sup>

Ultrasound sensitivity in detecting HCC increases with tumor size (50%–70% to 90% when the tumor increases from 1 to 5 cm).<sup>4</sup> The sensitivity and specificity of a triple-phase helical CT scan approach 89% and 99%, respectively.<sup>6</sup> MRI has a sensitivity of 72%, which decreases to as low as 47% for lesions less than 2 cm.<sup>7</sup>



**Figure 5.** Hematoxylin and eosin stain showing hepatocellular carcinoma (\*) in the bile duct.

According to the Barcelona criteria, HCC can be diagnosed when a 2-cm liver mass is associated with an AFP level of more than 400 ng/mL and the classic “early washout” pattern on contrast-enhanced cross-sectional imaging studies. Extrahepatic spread is present at the time of diagnosis in only 5%–15% of HCC cases. This occurs mainly with primary tumors >5 cm or when there is a large vascular invasion. HCC can present with obstructive jaundice in 0.5%–13% of cases, and the leading cause here is usually bile duct tumor thrombus.<sup>8</sup> Other rare causes include a growing distal CBD tumor or a migrated fragment of a necrotic tumor.

Twenty-two autopsies and 2 surgical cases of HCC with macroscopic tumor growth within the bile ducts, collected from 238 autopsies and 21 surgical cases (a frequency of 9%), were described by Kojiro et al in 1982.<sup>9</sup> In this study, approximately half of the patients presented with obstructive jaundice, whereas the other half developed obstructive jaundice throughout the disease course. The authors concluded that the development of obstructive jaundice may lead to early diagnosis of HCC. They also found that the survival rate is significantly lower when there is intraductal tumor growth.

HCC is usually associated with background liver cirrhosis. HCC presenting as an intraductal mass, without imaging evidence of parenchymal involvement, is extremely rare and was only reported in case reports. The absence of bile duct thrombus makes it further rarer. Philips et al reported a case of an isolated intraductal variant of HCC diagnosed using DC.<sup>10</sup> Ramakrishna et al reported a similar case which was initially misdiagnosed as cholangiocarcinoma but was found to be an intraductal HCC.<sup>11</sup> Tsushimi et al and Makino et al also reported a case of ectopic HCC arising in the bile duct and a case of anicteric ductal HCC with no evidence of liver mass, respectively.<sup>12,13</sup>

In our case, we observed a rare presentation of HCC as an intrahepatic ductal mass, causing biliary obstruction. No other mass lesions were observed in the rest of the liver. Although

the patient did not have typical cirrhotic morphology on imaging studies, background cirrhosis was subsequently observed on histology from the gross specimen obtained from the curative hepatectomy. Interestingly, obstructive jaundice, in our case, was caused by the unique isolated biliary metaplasia, not by the more frequently observed bile duct tumor thrombus.

## DISCLOSURES

Author contributions: A. Alshati wrote the manuscript, and is the article guarantor. S. Bellapravalu, I. Srinivasan, A. Nadir, and K-Y Chuang revised the manuscript.

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Informed consent was obtained for this case report.

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