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An unusual case of jaundice: Biliary tumor thrombus in fibrolamellar hepatocellular carcinoma



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ABSTRACT

BACKGROUND: Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare and unique variant of hepatocellular carcinoma (HCC) whose presentation remains inadequately described. We present a resectable case of FL-HCC which involved tumor thrombus of the common bile duct.

PRESENTATION: A 27 year-old male presenting with jaundice, abdominal pain, vomiting, hepatic dysfunction and hyperbilirubinemia was found to have a large liver mass and lymphadenopathy on preoperative imaging. A right hepatectomy with perihepatic lymph node dissection and cholecystectomy was performed. Intraoperative cholangiogram demonstrated common bile duct (CBD) obstruction. CBD exploration revealed biliary tumor thrombus relieved with biliary thrombectomy.

DISCUSSION: FL-HCC can initially present with invading obstructing biliary tumor thrombus of the CBD causing jaundice.

CONCLUSION: Preoperative surgical approach should consider CBD exploration on an individual basis for underlying obstructive biliary tumor thrombus.

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1. Introduction

First described in 1956 by HA Edmonson [1], FL-HCC is a relatively rare malignancy that affects healthy, non-cirrhotic, young adults. Afflicting only 0.02 people per 100,000 in the U.S., the disease represents 1–9% of primary liver tumors [2]. Though it shares a similar name, it does differ from HCC proper in that it often occurs in normal non-cirrhotic liver tissue. FL-HCC has a unique histopathological and molecular profile. The disease was initially considered to have a better prognosis than HCC, however recent data suggests that outcomes are comparable [3].

Demographically, patients are often young adults lacking classic risk factors for HCC. Liver enzymes are usually normal, and common tumor markers including alpha fetoprotein (AFP) are negative in 90% of patients [4]. Once diagnosed, resection appears to be the best option for survival [5] and has been associated with a 5-year overall survival of 58–82% [6]. FL-HCC is thought to be minimally responsive to chemotherapy [7]. Unfortunately, patients tend to present late in the disease course. Symptoms occur by mass effect allowing for substantial growth before initial presentation. In one study involving 35 patients undergoing hepatectomy, 27 had symptoms with cramping abdominal pain being the most common [8].

Previous case reports describe presentation with tumor thrombus in the portal veins [9].

2. Case presentation

A 27 year-old, previously healthy male, presented to our emergency department with several days of right upper quadrant abdominal pain, vomiting, and jaundice. He had no history of smoking, obesity, or known exposure to carcinogenic compounds. Physical exam was unremarkable except for jaundice. Laboratory results demonstrated hepatic dysfunction [alkaline Phosphatase (ALP) 406 IU/L, alanine aminotransferase (ALT) 280 IU/L, aspartate aminotransferase (AST) 121 IU/L] and hyperbilirubinemia (total bilirubin 7.9 mg/dL). An ultrasound of the gallbladder demonstrated an enlarged lymph node at the porta hepatitis with diffuse biliary tree dilatation. A magnetic resonance imaging/cholangiopancreatography (MRI/MRCP) revealed a large mass in the right lobe of the liver however did not show presence of biliary thrombus. Subsequent Triple Phase computed tomography scan and multiplanar magnetic resonance imaging (Fig. 1) with contrast further detailed a large 13 × 11 × 10 cm hepatic mass with central scarring in the right lobe of the liver, with associated porta hepatitis lymphadenopathy consistent with FL-HCC. Tumor markers, vitamin B12 and vitamin B12 binding capacity were obtained. Alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA) were normal (2.2 ng/mL and 2.8 ng/mL respectively). Vitamin B12 surpassed 2000 pg/mL, while B12 binding level was normal at 99 pg/mL.

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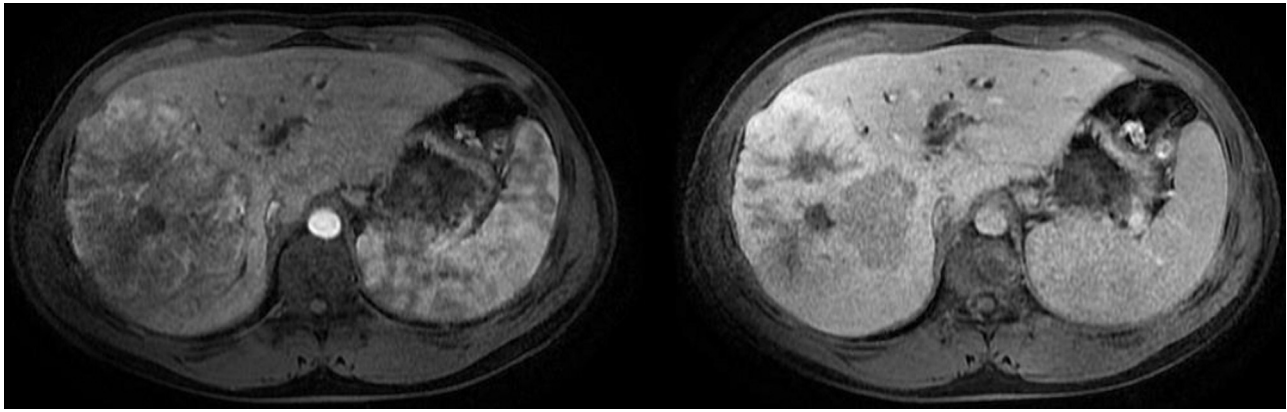


Fig. 1. MRI showing mass in R lobe of the liver with central scar.

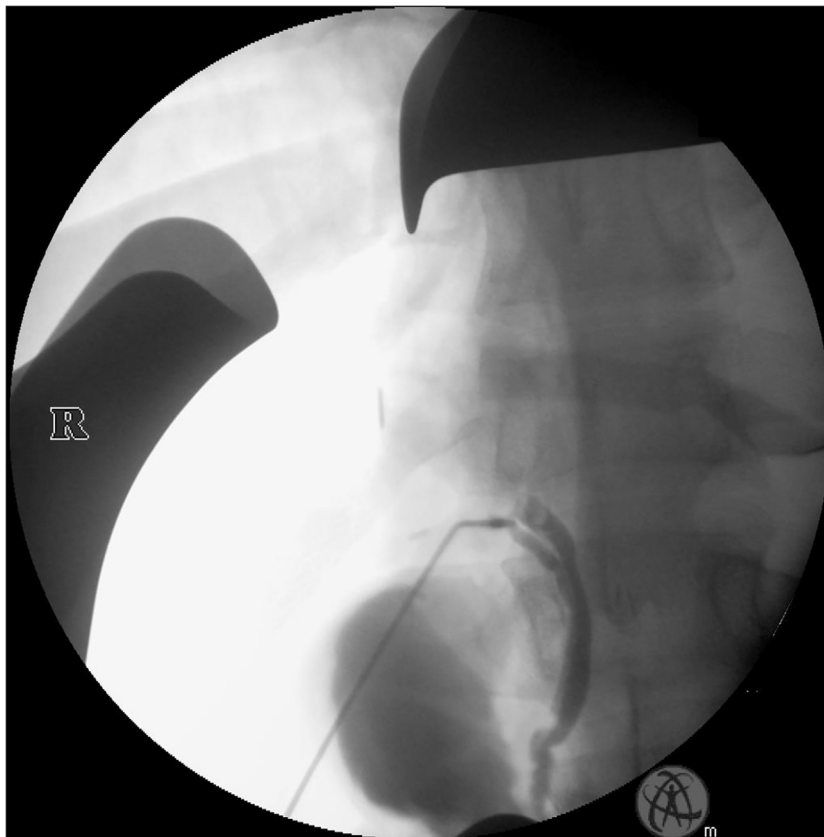


Fig. 2. An intraoperative cholangiogram demonstrating occlusive tumor thrombus in the proximal common bile duct.

The patient underwent right hepatectomy, perihepatic lymph node dissection, hepatic and celiac artery lymphadenectomy, cholecystectomy, intra-operative cholangiogram, and CBD exploration. CBD exploration demonstrated invading tumor thrombus which was removed from the bifurcation of the hepatic duct. Subsequent thrombectomy was performed with repeat cholangiogram confirming no additional obstructive thrombus (Figs. 2 & 3) with contrast flow reconstituted within the right intrahepatic biliary tree. Pathology of the right hepatic lobe confirmed Edmonson and Steiner Grade II, unifocal, HER-2 negative FL-HCC with American Joint Committee on Cancer stage T2N1Mx, R0. There was microscopic vascular invasion without involvement of large vessels. Parenchymal and vascular margins were negative. 1/1 periportal lymph node, 1/2 celiac axis nodes, and 2/2 pericaval nodes

were positive for metastatic disease. 1/1 hepatic artery nodes were negative for disease. Pathological staining of the biliary thrombus confirmed direct invasion of FL-HCC (Fig. 4). The patient was taken to the surgical intensive care unit postoperatively for observation and transferred to the surgical floor on postoperative day one. He recovered without incident and was discharged home on postoperative day 11 in stable condition. Postoperative positron emission tomography scan at 1 month showed no evidence of disease. Case was discussed at multidisciplinary gastrointestinal cancer conference attended by surgeons, medical oncologist and radiation oncologist and the recommendation was for biannual surveillance liver MRI and no role for adjuvant chemotherapy or radiation therapy. Last follow up MRI at 1 year showed NED.

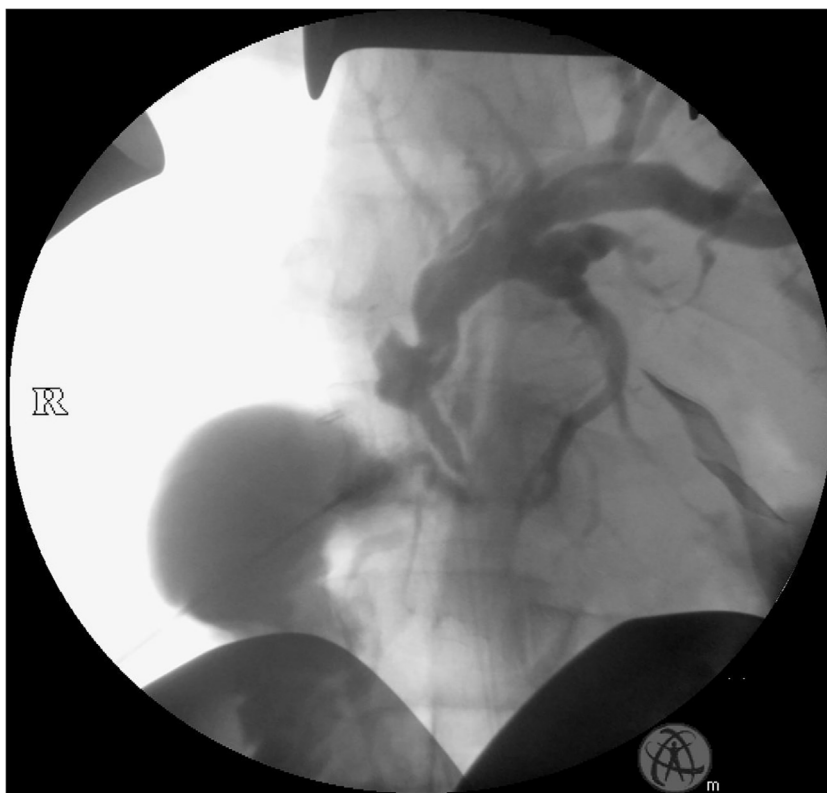


Fig. 3. Intraoperative cholangiogram demonstrating filling of the left hepatic duct after tumor thrombectomy.

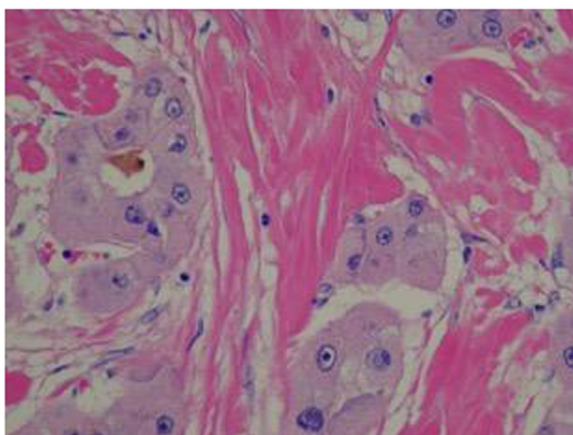


Fig. 4. The sections from the liver tumor show a neoplasm composed of polygonal, large cells with abundant eosinophilic, granular cytoplasm and enlarged, ovoid, vesicular nuclei with conspicuous nucleoli. Throughout the majority of the tumor, dense hyalinized collagenous stroma arranged in parallel lamellae with separate tumor cells occasionally forming small canaliculi containing bile. Invasion is identified: tumor deposits within portal and central veins are seen within the background hepatic parenchyma.

3. Discussion

Current literature emphasizes cramping, abdominal pain being the most common presenting complaint of FL-HCC with a multitude of various nonspecific symptoms such as nausea, weight loss and night sweats [8]. Interestingly, Liu et al. describes that up to 40% of cases involving FL-HCC may present with jaundice [10]. Case reports dated back to the 20th century have documented obstructive jaundice secondary to mass extrinsic compression as a presenting symptom for FL-HCC [11,12]. A 2012 review of FL-HCC argues that biliary obstruction is more common than it is reported

in the literature. Understanding that patients with FL-HCC often do not have concomitant liver cirrhosis, clinical presentation with jaundice should raise suspicion for intraluminal thrombus. As many as 40% of documented cases of FL-HCC demonstrate dilated intrahepatic bile ducts on diagnostic imaging [4,13]. To the best of our knowledge, there is only one documented case in 1988 attributing obstructive jaundice in FL-HCC due to intrinsic tumorous permeation of the left hepatic duct with extension into the CBD [14].

Alternative causes of jaundice may be attributed to hepatic failure with diffuse tumor involvement. However, external compression and/or intrinsic tumor involvement should be entertained in patients with FL-HCC.

FL-HCC is readily identified by radiology. A CT scan may be useful as it is 84% sensitive and 94% specific for non FL-HCC. FL-HCC is readily visible on triple phase CT scan, where it appears as a hypodense, well demarcated mass with a central scar that enhances with contrast. Eighty-percent have a lobulated surface and calcifications are found in 35–68% [15,16]. On magnetic resonance imaging (MRI), FL-HCC appears as a mass with a low intensity central scar [18]. It is isointense on T1 weighted images and hypointense to hyperintense on T2 weighted images [15]. Technetium 99 sulfur colloid does not uptake into this tumor because it lacks metabolically active Kupffer cells, making it phosphopenic on imaging [15]. Tc-99 RBC scan however will show increased uptake on arterial phase [15].

In a meta-analysis involving 206 patients with a median age of 21 years, the median survival was 39 months overall (including surgical and non-surgical candidates). Survival is increased dramatically by 18.5 years for those in whom surgical resection was performed [3]. Negative prognostic factors associated with worsened overall survival after resection are multiple tumors, vascular invasion, and lymphatic metastasis [19].

Optimal management for FL-HCC involves resection. In considering surgical intervention, it is important to emphasize that unlike HCC, FL-HCC is rarely associated with cirrhosis, often occurring in

younger otherwise healthy adults. As a result, patients with FL-HCC are commonly better surgical candidates and can readily undergo more aggressive liver resections. Our patient underwent a right hepatectomy, cholecystectomy, and lymphadenectomy of the hepatic hilum, celiac axis, and hepatic artery. Although there are few modern surgical series for FL-HCC resection, the most recent 2006 series reported the results of 28 patients who underwent resection [21]. They report a 5-year survival of 76% and 113 month median survival [21]. In contrast, Kakar et al. reported 20 patients undergoing liver resection for FL-HCC in comparison to those with typical HCC [22]. Although there appears to be discrepancy in the literature, patients undergoing resection for FL-HCC have higher five-year survival rates after resection than those patients with HCC and concomitant cirrhosis [22].

Data from the National Cancer Registry showed that in the 133 patients in which nodal biopsies were obtained, approximately 46% had positive lymph node metastasis [20]. There appears to be a higher rate of lymph node involvement in FL-HCC compared to HCC and therefore a regional lymphadenectomy is often warranted [17]. FL-HCC commonly involves regional lymph nodes including celiac, gastric, and *para*-aortic nodes and metastatic extension into the pancreas, diaphragm, and stomach have all been reported [10]. One study found that a 5-year survival was 100% in those without nodal metastasis, but only 45% in those with positive nodes [21]. Positive nodal metastasis was associated with a median overall survival of 46 months versus 117 months without metastasis [20]. For regional disease, resection has been shown to improve overall survival to 52–82% [6].

The prognostic significance of tumor thrombus in the biliary system in FL-HCC is unclear. However, for HCC this has been found to impart a poorer outcome. In HCC, a study of 426 patients, those with a bile duct thrombus had poorer outcomes compared to those without (28.6 months vs 39.2 months median survival) [17]. In addition, 46% of those patients with bile duct thrombus presented with jaundice, whereas only 1.5% of those without bile duct thrombus developed jaundice. While it is unclear whether this data can be extrapolated to FL-HCC, it does give important grounding for future research. The management of malignant biliary thrombus involves either bile duct resection or CBD exploration and thrombectomy. Both of these techniques have been found to be effective in the management of biliary thrombus in HCC [17].

The role for adjuvant therapy for FL-HCC is unclear. However there are scattered reports of chemotherapy being used in population based on a few prominent studies. Data from the National Cancer Registry recorded 14% of patients with FL-HCC undergoing adjuvant chemotherapy although this was not associated with improved overall survival [23]. Various chemotherapy regimens have been proposed. Doxorubicin, oxaliplatin, cisplatin, fluoropyrimidines, gemcitabine, irinotecan have been used, as has interferon [3]. In addition, bevacizumab and sorafenib in combination or as a separate regimen has also been proposed [3]. In a case report by Fonseca, gemcitabine in combination with oxaliplatin (GEMOX) was used to downstage an otherwise unresectable tumor, allowing an extended right hepatectomy, segment 2 wedge resection with partial inferior vena cava resection, and hepatic hilar lymphadenectomy [3]. Platinum based systemic chemotherapy has been used in pediatric FL-HCC cases, with radiographic partial response in 31% of patients [7]. Currently, there are no effective treatments for metastatic disease. Surgical resection has been used in regional metastasis and in recurrent distant metastasis [17]. Chemotherapy often fails to elicit a satisfactory response. FL-HCC malignant hepatocytes are indolent in nature and often have decreased mitotic index and normal growth factor receptors [24].

4. Conclusion

FL-HCC is an aggressive, unique subtype of primary hepatic carcinoma affecting children and young adults without underlying cirrhotic disease. Presenting symptoms are often indicative of mass involvement with extrinsic and/or intrinsic tumor progression. Jaundice can be a prominent physical finding with multifactorial etiology. Intrinsic involvement of the biliary system with obstruction should be entertained and may require formal CBD exploration in addition to resection.

Conflict of interest

We have no conflict of interest to report.

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Ethical approval

Approval has been given by the Western Michigan Cancer Center ethics committee. WMCC IRB approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Alex Merlo Jr., MD – Writing of paper.
Mohamed Arafeh, MD – Editing of paper, data analysis.
Jairo Espinosa, MD – Editing of paper, data collection.
Gitonga Munene, MD – study concept, design, main author.

Registration of research studies

Researchregistry2484.

Guarantor

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