CLINICAL VIGNETTE

A 19-Year-Old Female with a Rare Form of Liver Cancer

Ara Kardashian, MD and Daniel Eshtiaghpour, MD

Case Presentation

A 19-year-old female presented to the gastroenterology with two weeks of jaundice. She was initially told by a friend who noted a yellow hue to her eyes. She subsequently noted dark urine, light yellow color stools and a yellow skin tint. She reported subjective fevers but denied itching, hematemesis, melena, rectal bleeding, or easy bruising. There was no abdominal pain, nausea, vomiting, change in bowel habits or confusion. She had taken an oral contraceptive for eighteen months and recently switched to a new formulation after noticing jaundice. There were no other new medications and she denied use of acetaminophen, alcohol, and intravenous drugs. She had no history of blood transfusions or tattoos. Her only drug use was daily marijuana smoking, and there was no personal or family history of liver disease. She was healthy without significant past medical or surgical history, drug allergies, and taking no medications other than the oral contraceptive pill.

Physical examination included normal vital signs other than a mild tachycardia. She was jaundiced with scleral icterus. Her abdominal exam and remainder of the physical exam were normal. Labs and imaging studies were ordered.

Labs showed a total bilirubin of 11.6 mg/dL (normal 0.1-1.2), direct bilirubin of 8.3 mg/dL, alkaline phosphatase of 1081 U/L (normal 37-113), aspartate aminotransferase (AST) of 46 U/L (normal 13-62) and alanine aminotransferase (ALT) of 60 U/L (normal 8-70). Gamma-glutamyltransferase (GGT) was 174 U/L (normal 7-68), alpha-fetoprotein (AFP) was <1 ng/mL (normal), carbohydrate antigen 19-9 (CA 19-9) was elevated at 108 U/mL (normal 0-35), and carcinoembryonic antigen (CEA) was 0.5 ng/mL (normal).

Labs three years prior included normal total bilirubin of 0.6 mg/dL and alkaline phosphatase of 88 U/L.

Abdominal ultrasound showed liver heterogeneous echogenicity, moderate intrahepatic biliary dilation, with normal common bile duct and bulky lymphadenopathy in the porta hepatis. Subsequent magnetic resonance cholangiopancreatography (MRCP) showed a large infiltrative mass (11.3 x 15.1 x 16.4 cm) in the right hepatic lobe with associated soft tissue thickening along the common bile duct. There was moderate, multifocal intrahepatic biliary duct dilatation in both lobes as well as multiple enlarged lymph nodes.

Chest and neck computed tomography (CT) scans showed numerous enlarged lymph nodes consistent with nodal metastases.

Liver mass biopsy was performed by interventional radiology with pathology revealing carcinoma with a differential including hepatocellular and fibrolamellar variants. Additional testing showed abnormal rearrangement involving *PRKACA* gene region, which is associated with fibrolamellar carcinoma.

Initial management included decompression of the biliary system with placement of a percutaneous biliary drain. Treatment included radioembolization with yttrium-90 (Y-90) along with clinical trial chemotherapy (two cycles of gemcitabine, oxaliplatin and sorafenib). She was then treated with six cycles of peginterferon, nivolumab, and capecitabine and later treated with lenvatinib. Her disease was complicated by a cholangitic abscess (requiring hospitalization) and extensive tumor thrombus in the right and main portal veins with cavernous transformation. She also required repeated biliary drain exchange. Eventually all chemotherapy was stopped due to side effects and she was placed on hospice care and died at home.

Discussion

Fibrolamellar hepatocellular carcinoma (FLC) is a rare hepatic malignancy. Initially classified as a variant of hepatocellular carcinoma (HCC), FLC is now considered a distinct entity due to advances in genomics. It typically affects late adolescents or young adults,[1,2] with equal gender distribution.[3,4] FLC tumors represent less than 1% of primary hepatic malignancies. The majority (95%) occur in patients without history of liver disease.[1,2,5]

Presentation of FLC includes symptoms such as abdominal pain, weight loss, nausea, and abdominal fullness. Less commonly, the disease can present with fulminant liver failure, ascites, anemia, and encephalopathy.[1,2] Biliary obstruction and jaundice can be reported in up to 40% of patients.[6]

Laboratory findings can include elevated beta-human chorionic gonadotropin (β-HCG). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase may or may not be elevated. The tumor marker α-fetoprotein (AFP), which is typically elevated in traditional hepatocellular carcinoma (HCC), is frequently normal in FLC.[1,2]

Ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are all used to diagnose and characterize FLC. Typically, lesions are seen in a non-cirrhotic liver. On ultrasound, the lesions are typically large isoechoic or hyperechoic masses, sometimes with a central scar. Doppler imaging can show enhanced vascular flow in the tumor. The central scar is not pathognomonic for FLC and can be seen in other liver lesions. On CT, FLC appears as a heterogeneously enhancing mass. In the portal venous phase, around 50% become isointense while others may appear hypoattenuating or hyperattenuating. A central stellate scar may also be seen on CT. MRI findings are similar to CT characteristics with heterogeneous enhancement in the arterial phase followed by isointense or washout during the subsequent portal venous and delayed phases. Positron emission tomography (PET-CT) has been used in identifying metastatic disease.[1,2,5]

Definitive diagnosis is made via biopsy, though lesions highly suspicious for FLC on imaging can occasionally avoid biopsy. Pathologic examination and immunohistochemical staining distinguish FLC from HCC. Genetic differences have also been established. FLC tumors have a *DNAJB1-PRKACA* fusion and result in activation of protein kinase A.[1,2,5]

Treatment can include surgery, radiation, locoregional and systemic therapies. Surgical resection is the only opportunity for cure with regional lymph node dissection recommended. Patients with unresectable primary lesions without distant metastatic disease can be considered for liver transplantation. Stereotactic body radiotherapy (SBRT) is effective for local control of unresectable disease. Transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) with yttrium-90 can also treat FLC. Systemic therapies include various chemotherapies. Other studies are underway to evaluate additional systemic therapies including chemotherapy regimens, immunotherapies and targeted agents.[1,2,7]

Overall survival is better for patients with FLC than with HCC. Five-year survival is 70% in patients amenable to surgical resection. Patients not candidates for resection have median survival under 12 months and 5-year survival is 0-5%.[1,2,8]

REFERENCES

1. **Aziz H, Brown ZJ, Panid Madani S, Kamel IR, Pawlik TM**. Fibrolamellar Hepatocellular Carcinoma: Comprehensive Review of Diagnosis, Imaging, and Management. *J Am Coll Surg*. 2023 Feb 1;236(2):399-410. doi: 10.1097/XCS.0000000000000476. Epub 2022 Nov 4. PMID: 36648268.
2. **Abdelhamed W, El-Kassas M**. Fibrolamellar hepatocellular carcinoma: A rare but unpleasant event. *World J Gastrointest Oncol*. 2022 Jun 15;14(6):1103-1114. doi: 10.4251/wjgo.v14.i6.1103. PMID: 35949219; PMCID: PMC9244987.
3. **Eggert T, McGlynn KA, Duffy A, Manns MP, Greten TF, Altekruse SF**. Epidemiology of fibrolamellar hepatocellular carcinoma in the USA, 2000-10. *Gut*. 2013 Nov;62(11):1667-8. doi: 10.1136/gutjnl-2013-305164. Epub 2013 May 25. PMID: 23708586; PMCID: PMC4145809.
4. **El-Serag HB, Davila JA**. Is fibrolamellar carcinoma different from hepatocellular carcinoma? A US population-based study. *Hepatology*. 2004 Mar;39(3):798-803. doi: 10.1002/hep.20096. PMID: 14999699.
5. **Frenette C, Mendiratta-Lala M, Salgia R, Wong RJ, Sauer BG, Pillai A**. ACG Clinical Guideline: Focal Liver Lesions. *Am J Gastroenterol*. 2024 Jul 1;119(7):1235-1271. doi: 10.14309/ajg.0000000000002857. Epub 2024 Jan 26. PMID: 38958301.
6. **Liu S, Chan KW, Wang B, Qiao L**. Fibrolamellar hepatocellular carcinoma. *Am J Gastroenterol*. 2009 Oct; 104(10):2617-24; quiz 2625. doi: 10.1038/ajg.2009.440. Epub 2009 Jul 28. PMID: 19638962.
7. **Smith M, Tomboc PJ, Markovich B**. Fibrolamellar Hepatocellular Carcinoma. 2022 Sep 26. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 31971753.
8. **Ang CS, Kelley RK, Choti MA, Cosgrove DP, Chou JF, Klimstra D, Torbenson MS, Ferrell L, Pawlik TM, Fong Y, O'Reilly EM, Ma J, McGuire J, Vallarapu GP, Griffin A, Stipa F, Capanu M, Dematteo RP, Venook AP, Abou-Alfa GK**. Clinicopathologic characteristics and survival outcomes of patients with fibrolamellar carcinoma: data from the fibrolamellar carcinoma consortium. *Gastrointest Cancer Res*. 2013 Jan;6(1):3-9. PMID: 23505572; PMCID: PMC3597938.