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Fibrolamellar Hepatocellular Carcinoma: A Case Report

Fibrolamellar hepatocellular carcinoma is a relatively rare condition that occurs in non-cirrhotic livers, most frequently in adolescents or young adults with no gender predominance. The prognosis is more favorable than that of the usual hepatocellular carcinoma.

Here is the case of an eighteen-year-old male patient with history of right upper quadrant abdominal pain, and no hepatomegaly. Liver function tests and serological markers for viral B and C hepatitis and tumor markers were normal. CT scan demonstrated a large hypervascular lesion in the liver and the histological examination was reported as a typical fibrolamellar hepatocellular carcinoma. Intra-arterial chemotherapy and embolization have been done for the patient. In his recent imaging the mass seems to become smaller and is considered operable. After 2.5 years he does not have any complaint and has gained some weight.

Keywords: fibrolamellar, carcinoma, hepatocellular

Introduction

Fibrolamellar hepatocellular carcinoma (FLHC) occurs in non-cirrhotic livers, most frequently in adolescents or young adults with no gender predominance, with a more favorable prognosis than the usual hepatocellular carcinoma (HCC).[1]

It is a relatively rare condition accounting for less than 1% of primary liver cancers. Therefore, studies especially on the clinical course and epidemiology of FLHC are either individual case reports or small case series, mostly from western countries. Studies from eastern Asian countries are restricted to some case reports. Reviewing the literature, we could not find any similar report of FLHC from our region.[2-4]

Herein, we report an Iranian young patient with definite diagnosis of FLHC.

Case Report

An 18-year-old boy with history of right upper quadrant abdominal pain 2.5 years ago, which had been relieved spontaneously in 2 days and then relapsed 3 months later, was presented with a probable diagnosis of renal problems.

Lab studies, which included serum aminotranspherases, alkalaine phosphatase, bilirubin (total and direct), BUN and creatinine were all in the normal range. Ultrasonography reported a huge ill-defined mixed echogenicity, heterogeneous structure in the posterior aspect of the right lobe of liver extending from subdiaphragmatic region to the upper pole of the right kidney measuring about 135 x 124 mm. The lesion seemed to be hepatic in origin. The rest of liver parenchyma was normal in echogenicity pattern. Intra- and extrahepatic billiary ducts and the portal vein were normal in diameter. The gallbladder showed normal wall thickness without stone, sludge or space-occupying lesions. Kidneys, ureters, and the bladder were normal in ultrasonography.

He was treated with the diagnosis of hepatic abscess, and the pain was tempo

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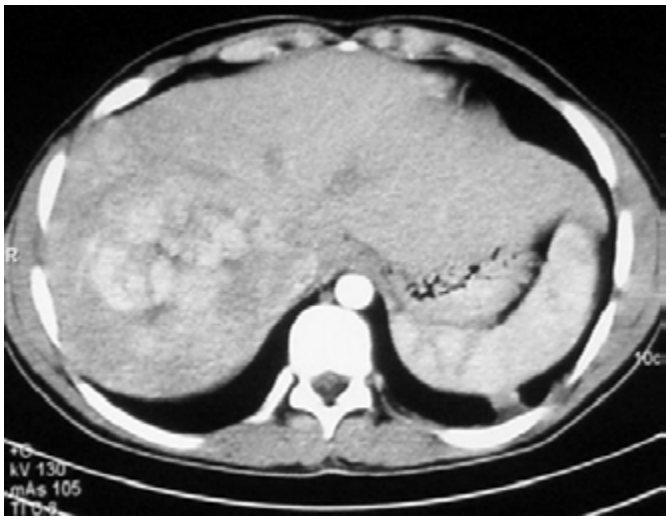

Fig 1a. Liver CT scan before embolization in portal phase showed significant enhancing mass lesion in right liver lobe.

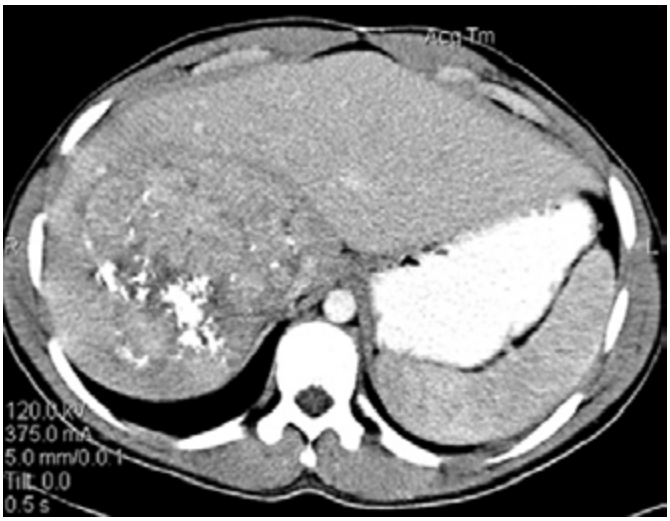

Fig 1b. Liver CT scan after embolization in portal phase showed minimal enhancement (Lipiodole drops made round dense area).

rarily relieved.One month later, the pain relapsed and he was admitted in our hospital. Hehad nocturnal sweating, weight loss of about 10 kg within last 4 months. He mentioned no pruritus, frequency, urgency, melena, hematochesia or hematemesis. He had no history of discoloration of feces, or changes in urine color. Vital signs were stable except for an oral temperature of 39.5 °c. In physical examination, the conjunctiva was not pale, sclera was not icteric, and lymphadenopathy was detectable in axillary and inguinal regions. Lungs were clear; there was no abnormal heart sounds on auscultation. The abdomen was soft with no tenderness, rebound tenderness or guarding— no palpable mass was detected. Extremities were normal.

On CT scan, there was a 10cm diameter mass that showed heterogeneous enhancement in the arterial and portal phases. Incomplete obliteration of the IVC was also visible (Figure 1A). Both kidneys were of mildly prominent size—measuring about 123 × 47 mm (right) and 122 × 56 mm (left) — with normal parenchymal echogenicity and cortical thickness. There was no evidence of stone or hydronephrosis. Spleen was 132 mm in diagonal diameter (mildly prominent) with homogenous parenchyma.

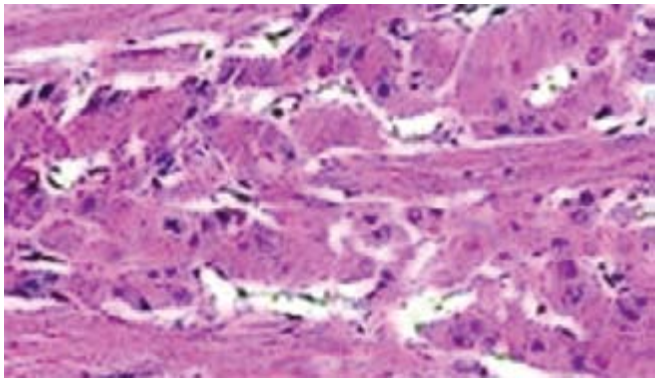

Fig 2. Biopsy finding of patient compatible with diagnosis of fibrolamellar hepatocellular carcinoma.

Ultrasonography-guided liver biopsy was performed. Biopsy reported large pleomorphic polygonal neoplasmic cells with eosinophilic cytoplasm and hyperchromic nuclei with mild to moderate mitotic activity that has been separated with lamellar hyalinized connective tissue. It was compatible with fibrolamellar hepatocellular carcinoma (Figure 2).

Due to the large tumor size and non-sufficient normal liver tissue, the patient was considered inoperable.

Intraarterial chemotherapy was done for the patient when the diagnosis was confirmed, then tumor embolization was performed for 5 times at different phases. For this purpose, after preparing the patient using the sterile setting, femoral puncture with super selective catheterization of the proper hepatic artery was done. Under fine fluoroscopy, controlled infusion of lipiodole suspension was done (10cc lipiodole + 50mg adriablastine). Post- embolization angiography showed complete cessation of blood flow through the proper hepatic artery and its branches (Figures 3A and 3B). After first embolization, control CT scan showed droplets of lipiodole in the tumor and previous enhancement did not appear coincided the significant reduction of blood flow through the tumor

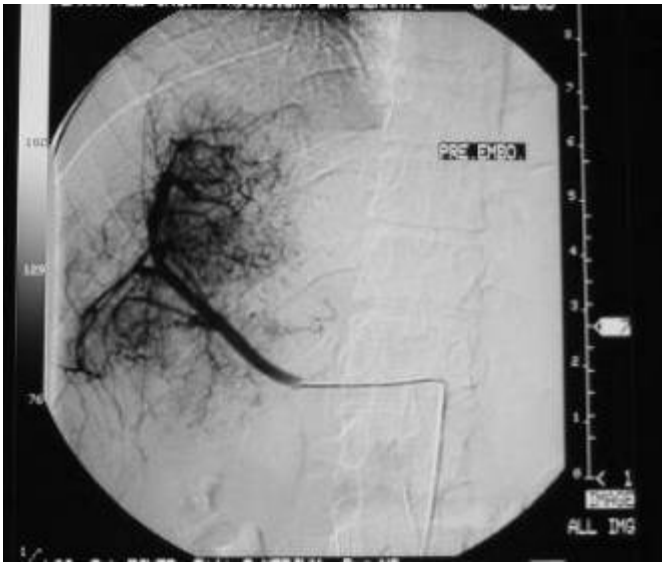

Fig 3a. Angiography before first embolization; super selective catheterization of proper hepatic artery showed hypervascular tumor in right liver lobe.

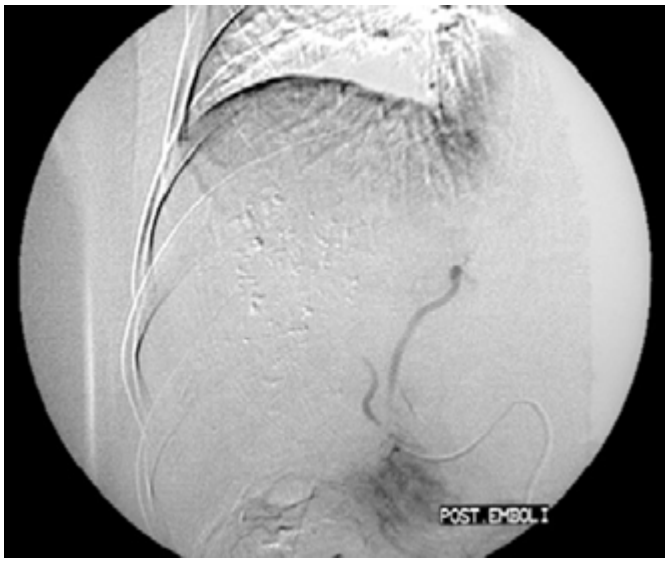

Fig 3b. Angiography after first embolization; angiography with adriablastine lipiodole showed successful Embolization.

bulk (successful embolization criteria) (Figure 1B).

The last CT scan which was taken 3 months ago and after the last episode of embolization, revealed a considerable tumor size reduction.

At the time of this report, after 26 months of the diagnosis, the patient had none of the previous symptoms and his weight loss was reversed. Now, he was a candidate for surgical operation.

Discussion

Fibrolamellar hepatocellular carcinoma (FLHC) arises in non-cirrhotic livers of young individuals and has been considered to be less aggressive than hepatocellular carcinoma.[5] It is believed to be a histological variant of hepatocellular carcinoma (HCC). Radiological evidence of cirrhosis, vascular invasion, or multi-focal disease—findings typical of hepatocellular carcinoma—is uncommon in fibrolamellar carcinoma.[6]

It is a relatively rare condition, accounting for less than 1% of primary liver cancers which is more common in western countries in comparison with Asian and African populations.[2,3] The only reported population-based study of the epidemiology and prognosis of patients with fibrolamellar carcinoma (FLHC) is from USA.[4]

As our case, fibrolamellar carcinoma characteristically manifests as large hepatic mass in adolescents or young adults.[6]

The etiology of FLHC is unclear. It differs from hepatocellular carcinoma in demographics, condition of the affected liver, tumor markers, and prognosis. FLHC strongly resembles focal nodular hyperplasia (FNH), which is a benign liver lesion. Thus, FLHC may originate from FNH, because both occur in the liver with normal parenchyma. In addition, some reports describe areas of FNH adjacent to FLHC tumors; however, this finding likely represents a secondary reaction to local ischemic perfusion caused by the FLHC mass.[2] FLHC is associated with cirrhosis in less than 10% of patients and typically arises in a background of normal liver function and normal histological architecture.[2]

The epidemiological features of FLHC in comparison with HCC are summarized in Table 1.

Our patient manifested with mild abdominal pain with no history of hepatic diseases or prominent physical finding. Patients usually have no symptoms, but if they have, it is abdominal pain and fullness. Symptoms may have existed since 10 days to 40 months.[7]

Patients usually have no sign, but if the tumor is large, a mass will be palpable in physical examination. Because FLHC will appear in a liver with no previous disorder, characteristics of cirrhosis will not be found in physical examination.[2,5]

Other less common manifestations are summarized in the Table 2.

In this case, liver enzymes and bilirubin were nor-

Table 1. Epidemiological features of fibrolamellar hepatocellular carcinoma versus hepatocellular carcinoma[2]

Characteristic	HCC	FLHC
Associated with	Active inflammation, hepatitis B and C, alcohol related cirrhosis and aflatoxin	Unclear; Association with cirrhosis is less than 10%
Prevalence	The most common liver malignancy	Relatively rare
Frequency	Most common in Asia and Africa where prevalence of HCV and HBV is high	Most common in United States and Europe
Gender	Male > female	Male = female
Age	Fifth and sixth decades	Young adults (20-40 years) with no prior liver disease

mal. Serum transaminases and alkaline phosphatase are mildly elevated; rarely bilirubin is elevated.[8]

Also, other laboratory tests, consisting of AFP and CEA, were normal. AFP levels are normal in the majority of patients with fibrolamellar carcinoma, a variant of HCC. In fact, less than 10% of patients with FLHC have an elevation of AFP higher than 200 ng/mL. Serum carcinoembryonic antigen can occasionally be elevated. Other tumor markers such as CEA, binding capacity of serum vitamin B12, and plasma neurotensin can be elevated; but they are not useful as screening tests; for example, neither binding capacity of B12 nor plasma neurotensin can differentiate HCC from FLHC.[2]

Fibrolamellar carcinoma characteristically appears on radiological images as a lobulated heterogeneous mass with a central scar in an otherwise normal liver.[4]

As represented in our case, ultrasonography shows this tumor as a solitary well-defined mass with variable echogenicity texture. The central scar, if present, is visualized as a central area of hyperechogenicity. It occurs in only 30–60% of patients when compared to CT scan results and pathologic analysis.[2,6]

In this case also a huge hypervascular solitary mass was seen. The mass was heterogeneous including hypodense patches suggesting necrosis; that is compatible with the FLHC characteristics. FLHC usually appears as a hypo-attenuated, well-defined, solitary mass on a non-enhanced CT scan. Mass is seen in a liver with a normal parenchyma. Other findings in favor of malignant tumor (e.g., calcification, pseudoencapsulation, retraction of the adjacent capsule) can occur in FLHC and thus can be used to differentiate it from a benign position like FNH. The central scar, if present, can be viewed on non-enhanced and arterial phase scans; however, it is best viewed on delayed images.[6,9]

Table 2. Less common features of fibrolamellar hepatocellular carcinoma[2]

Symptoms	Signs
Weight loss	Migratory thrombophlebitis
Fatigue	Hemobilia
Malaise	Obstructive jaundice
Fever	Gynecomastia
Chills	
Abdominal distension	
Amenorrhea	

On radiography, we have to differentiate FLHC from focal nodular hyperplasia, hepatocellular adenoma, hepatocellular carcinoma, intrahepatic cholangiocarcinoma, giant hemangioma and, hypervascular metastases.[2,6,9]

In some patients, fine-needle aspiration biopsy (FNAB) can allow a histopathologic diagnosis to be made prior the operative intervention. But FNA is useful just when the diagnosis is unclear.[2]

Microscopically, features include large polygonal tumor cells arranged in a trabecular formation with eosinophilic and granular cytoplasm. These cells are surrounded by a prominent, hypocellular, stromal fibrosis composed mainly of collagen. Infiltrating collagen deposition and lamella formation result in compartmentalization and the central fibrous scar. An important characteristic of FLHC is the presence of a central satellite scar similarly presenting in the benign liver lesion of FNH. A central scar is reported in 20–60% of patients with FLHC, and similar scars are found in metastatic lymph nodes of FLHC.[5] Biopsy report of our case was compatible with FLHC.

The treatment of choice in hepatic lesions is complete resection. Unlike typical HCC, FLHC rarely is associated with cirrhosis. For this reason, the resectability rate is high.[6,7] Positive factors for surgical resection are small tumor size (<5 cm), favorable tumor location, a well-differentiated histological grade (the

most important factor), presence of a tumor capsule, and a lack of vascular invasion. In inoperable cases of fibrolamellar carcinoma, the patient may benefit from adjuvant chemotherapy (either systemic or intraarterial).[2]

In this case the mass was not resectable, so intraarterial chemotherapy was performed.

A study revealed that age, gender and tumor size did not correlate with survival.[5] Another study demonstrated that FLHC patients diagnosed before 23 years of age have worse prognosis than those diagnosed after age 23. Other factors associated with worse prognosis in this study are: lack of surgical treatment, presence of positive surgical margins, vascular invasion, and altered hepatic enzymes.[10] Overall 5-year survival rate differs from 25 to 63% for both resectable and non-resectable tumors. Better survival rate exists for FLHC compared to typical HCC; this is largely due to the increased resectability rate and the lack of associated cirrhosis. Median patient survival is 50 months for patients with resectable FLHC versus 7 months for patients with non-cirrhotic resectable HCC.[2,5]

At present, about 2.5 years have passed from the first presentation, and the patient is a candidate for surgery.

Fibrolamellar hepatocellular carcinoma should be kept in mind in young patients with hypervascular liver masses and no history of hepatic diseases.

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