

Fibrolamellar Hepatocellular Carcinoma: Report of a Rare Case with Rapid Progression and Unusual Metastatic Sites

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Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare primary liver cancer that occurs in young adults, and its biology is not well known. We present a 21-year-old woman with metastatic liver cancer 6 months after undergoing embolization procedures for a typical hemangioma. The pathological investigation confirmed metastatic FLHCC. Despite liver mass resection and lung metastasectomy, after 3 months, the tumor recurred. In 18F-FDG PET-CT scan, lung, ovary, colon, and peritoneal invasions were reported. Unfortunately, the patient died a year after diagnosis due to a rapid progression and multiple unusual metastatic sites.

Keywords: Fibrolamellar Hepatocellular Carcinoma, HCC, Metastasis



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INTRODUCTION:

Fibrolamellar hepatocellular carcinoma (FLHCC) is a relatively rare variant of primary liver cancer. It accounts for around 1–9% of all HCC cases in the general population, but it predominantly affects adolescents and young patients (10–35 years of age) without gender predominancy. Unlike HCC, FLHCC is not usually associated with underlying liver diseases, such as viral infections, chronic hepatitis, or cirrhosis (1-4).

In a recent study, Ramaïet et al. found that FLHCC has a slight male predominance, a bimodal age distribution, and does not tend to a specific ethnicity (5). Also, recent studies have found that FLHCC is associated with the presence of DNAJB-PRKACA fusion mutations (6).

Various prognostic factors are associated with FLHCC, including age, stage of the disease, tumor multiplicity, tumor thrombosis, lymphovascular invasion, nodal and distant metastases, and resection completeness (7).

FLHCC was initially described by Edmonson as a rare and distinct form of HCC in 1956. However, Craig et al. and Berman et al. in 1980 established the tumor's clinicopathologic entity, slow-growing pattern, and favorable prognosis (8-10). Common initial symptoms are not specific and include abdominal pain, weight loss, and malaise. Mild elevations in liver transaminases and alkaline phosphatase can be observed. In contrast to formal HCC, it is not usually associated with an increase in α -fetoprotein (AFP) (9).

FLHCC can be often diagnosed through CT and MRI imaging findings. For indeterminate cases, CT-guided core needle biopsy or fine-needle aspiration (FNA) can help differentiate FLHCC from non-FLHCC (11).

Liver resection and liver transplantation are the two potentially curative surgical treatment options (11). The role of chemotherapy in the management of FLHCC is not clear because these tumors do not tend to be chemo-responsive (12).

The common radiological presentation of FLHCC is a single tumoral mass surrounded by a fibrous capsule with or without metastasis to nearby lymph nodes (13). The extrahepatic extension may be diagnosed at the presentation in one-third of patients (14). In a study by Stipa et al., approximately 60% of patients with FLHCC were diagnosed with stage IV disease (metastasis) (15). Survival in fibrolamellar carcinoma is similar to hepatocellular carcinoma arising in a noncirrhotic liver and better than hepatocellular carcinoma arising in a cirrhotic liver. The higher survival rates of fibrolamellar carcinoma may be due to the absence of cirrhosis rather than the tumor's unique clinicopathologic features (16). Uncommon metastatic locations include bone (17) and ovary (18).

In a cohort study including 42 patients carried out by Chakrabarti et al., a 71% recurrence rate was seen in FLHCC patients (stages I to IV) who had surgical resection at presentation (19).

We present a young woman with metastatic FLHCC involving lung, ovary, and colon.

CASE REPORT:

The patient is a 21-year-old Caucasian female born and raised in Tehran with a previous history of hepatic hemangioma in 2016. She had no history of other diseases or drug use, or drug abuse. Also, she had a negative family history of any cancer or liver disease. Ultrasonography and MRI investigations revealed a 7-cm mass in the liver's right lobe with typical hemangioma patterns in 2016. Embolization procedures were performed, and the patient was followed by abdominal sonography every 3-4 months.

After one year, she was admitted with severe abdominal pain, nausea, and vomiting. Physical examination revealed moderate hepatomegaly. CT scan investigation showed a 12×10-cm heterogeneously enhancing mass in the liver's right lobe and a 15×6-mm pulmonary lesion suggestive of pulmonary metastases. Neg-

ative viral markers of hepatitis and a normal AFP level were reported (3.1 IU/ml).

An extended hepatectomy, lung metastasectomy, and mediastinal and hepatic hilum dissections were performed in July 2017. Histopathology results indicated a moderately differentiated fibrolamellar hepatocellular carcinoma invading the surrounding fatty tissue and close to parenchymal margins, lung metastasis of FLHCC, and three reactive lymph nodes (pT2N0M1). Another pathologist confirmed the diagnosis.

After recovery from the surgery, Sorafenib (an oral multi-kinase inhibitor) 400 mg per day was started. After 9 days, she experienced a sudden onset of generalized erythematous to purplish rash. Therefore, chemotherapy was withheld. Skin lesions disappeared after one month without any treatment. In October 2017, Sunitinib (a tyrosine kinase inhibitor) was started at a dose of 50 mg per day and discontinued after 3 or 4 days because she was admitted with severe abdominal pain and distension. On physical examination, moderate to severe ascites was detected. Laboratory results showed a serum AFP of 3.1 IU/ml (reference value in females: 0-8.5 IU/ml), and the hepatic viral markers for B and C virus infections were negative. There was a suspicious complex cystic lesion with mild enhancement without a fat component in the right adnexa on the CT scan. Paracentesis of ascites was done, and for further evaluation, an 18F-FDG PET-CT scan was performed. Bilateral pulmonary nodules in favor of metastatic disease, numerous soft tissue lesions in surgical bed, and para-splenic peritoneum, compatible with malignant peritoneal involvement, were shown. An FDG avid lesion within the left liver lobe with central necrosis compatible with metastatic disease, soft tissue mass within the cecum highly suggestive of a neoplastic process, bilateral adnexal masses in favor of metastatic disease, and significant pelvic ascites were reported. After two weeks, she was admitted to the emergency department with severe abdominal pain, nausea, vomiting, diarrhea, and a his-

tory of constipation for two weeks. On physical examination, the abdomen was distended, and severe tense ascites were detected. The multidisciplinary evaluation was performed, and infectious diarrhea was ruled out. Diarrhea was treated with conservative treatment. After paracentesis of bloody ascites, she was referred to the palliative care service and admitted with the probable diagnosis of malignant bowel obstruction. Conservative therapy with analgesics, corticosteroids, antiemetics, and hydration resulted in relief of signs and symptoms, and bowel habits became almost normal. She was discharged after a week with an acceptable general condition. She was admitted to the palliative care unit several times during her disease's terminal phase up to her death.

On one occasion, she came to the outpatient palliative clinic with abdominal pain, nausea, palpitation, and abdominal distention. On physical examination, sinus tachycardia (pulse rate=122/min), abdominal tenderness, and severe ascites were detected. She was admitted to the palliative care unit. In laboratory data, normocytic normochromic anemia (Hb=9.1 g/dl, MCV=86.2 fl, MCH=27.3 pg) was detected. Although all her symptoms were controlled by medical management, her palpitation continued, and despite our best efforts, we were unable to control it. Due to the presence of bloody ascites, 2 units of packed cells were infused. The next day, she was referred to with abdominal pain, severe ascites, palpitation, and hyperalgesia. We checked the level of vitamin B12, which was found to be <83.0 pg/ml (reference range = 201-804 pg/ml). Vitamin B12 was injected intramuscularly, and her palpitation was controlled for a few weeks by the administration of oral propranolol. On the last admission, she was in the terminal phase of her illness. Control of terminal agitation and pain was achieved. The death happened after 10 days of admission despite the appropriate end-of-life care.

CONCLUSION:

There were several challenges, especially regarding the diagnosis of FLHCC in this case, among which the uncommon site of metastases and the rapid disease progression can be mentioned.

FLHCC is a rare subtype of hepatocellular carcinoma. There are various reports regarding its prevalence, ranging between 1-9% of all HCC cases (4). The prevalence and characteristics of FLHCC in the Iranian population are almost unknown. Lymph nodes (thoracic and abdominal cavity) are the most frequent site for metastatic spread, with a prevalence ranging between 24-57% of patients (15). Distant metastases to lung, peritoneum, bone, and adrenal occur in approximately 30% of patients (14, 20). There have been reports of cases with unusual extrahepatic metastases, such as to the pancreas (21-24), pericardium (25), brain (26), spleen (21), and ovaries. Only three cases of FLHCC with ovarian invasion have been reported in the literature to date. The first case was reported with bilateral ovarian metastases (27, 28), the second was reported with right ovarian mass (18), and the last was published in 2017 by Silviu Horia Ciurea et al. She was a 23-year-old patient with FLHCC and ovarian (Krukenberg) and peritoneal metastases (29).

To date, our patient is the fourth FLHCC case reported with metastasis to the ovary and the first presentation of large bowel metastases according to the PET scan report.

There are some issues regarding our case. First, the patient complained of migratory hyperalgesia in an advanced cancer stage. It was investigated, but no conclusion was reached regarding the complaint. One of the side effects of the high dose of narcotics (which might be used in end-stage cancer patients to control the symptoms) could be hyperalgesia (30). However, our patient was not on high-dose narcotics. Hyperalgesia may be due to the nature of the disease, which requires

further investigation.

The second point was that she had a very low serum cobalamin level. According to the literature, high serum cobalamin level is a tumor marker in FLHCC (31, 32) and represents a poor prognosis. Only in the very late stages of the disease, in which the patient experiences malnutrition, serum B12 might be low. Yet, our patient had a low level of serum cobalamin from the onset despite having a worse prognosis than the similar cases of FLHCC (33). Another important aspect of this case was the rapid progression of cancer. Existing documents regarding the prognosis of FLHCC are scarce and confined mainly to case series and small cohorts. According to a systematic review conducted in 2012, the 5-year survival of all patients with FLHCC was 44%. Surgical resection was associated with a significantly better outcome, with a 5-year overall survival of about 70% (ranging from 58% to 82%) (34). According to another study published in 2019, FLHCC had the best 5-year overall survival (38.7%) amongst all other variants. Furthermore, FLHCC variants are more likely to require surgery than pure HCC (35).

Hemangioma is the most common benign hepatic tumor. The presence of atypical features in cases of hepatic hemangioma may lead to misdiagnosis and confusion with other lesions (36). Due to the rarity of FLHCC, it is difficult to judge in this case and must be reviewed in future cases.

Chaudhari et al. reported that in patients with FLHCC, nodal metastasis is more common than in patients with conventional HCC. Although it represents stage IV disease, it does not always show equal inoperability (11). Also, it was noted that FLHCC is relatively more resistant to chemotherapy than conventional HCC, and surgery is the mainstay of treatment in FLHCC patients. Imaging studies have a significant role in clinical diagnosis, but pathology is the gold standard in confirming the diagnosis (37). To achieve an accurate and early diagnosis, performing radiological diagnostic procedures

and then confirming it by examining the pathology is warranted.

Although the role of PET-CT scan in the diagnosis of FLHCC has not been well established in previous studies, a paper by Minhas et al. confirmed the role of the method in the diagnosis and management of FLHCC (38).

They explained that in stage-matched non-cirrhotic patients with HCC and FLHCC, FLHCC patients do not necessarily have a favorable prognosis or respond differently to a treatment. The higher survival rate seen in FLHCC compared with conventional HCC is most likely due to younger age at presentation and the absence of cirrhosis (11).

Clinical evidence about treatment and prognosis of patients with FLHCC is infrequent due to the scarcity of this tumor and is confined to case series and small cohorts.

Although FLHCC is uncommon, it is one of the major causes of primary liver tumors in younger patients. Therefore, presenting such cases is helpful for future investigations.

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