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(CASE REPORT)

Fibrolamellar hepatocellular carcinoma: Case report of a rare tumor and a brief review of literature

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Abstract

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare primary liver malignancy that typically arises in young adults without underlying cirrhosis or other established hepatic risk factors. We present the case of a 24-year-old male with a four-month history of progressive right upper quadrant abdominal pain, unintentional weight loss, and early satiety. Laboratory evaluation demonstrated mildly elevated liver transaminases and a markedly elevated serum vitamin B12 level of 3,240 pg/mL. Alpha-fetoprotein (AFP) levels were within normal limits.

Cross-sectional imaging revealed a 12 cm hypervascular mass within the left hepatic lobe, with a central fibrotic scar and areas of calcification. Core needle biopsy followed by molecular analysis confirmed the diagnosis of fibrolamellar carcinoma through identification of the pathognomonic DNAJB1–PRKACA gene fusion. The patient underwent an extended left hepatectomy (R0 resection) and achieved a disease-free interval of 20 months. Twenty-six months after the initial diagnosis, routine surveillance imaging detected metastatic recurrence involving the lungs and L3 vertebral body. The patient was managed with a multidisciplinary approach that included pulmonary metastasectomy, platinum-based chemotherapy, and participation in a clinical trial evaluating a PRKACA inhibitor.

This case underscores the importance of vigilant long-term surveillance in patients with FL-HCC and highlights the emerging role of targeted molecular therapies in addressing recurrent diseases.

Keywords: Fibrolamellar hepatocellular carcinoma; Hepatocellular carcinoma; Alpha-fetoprotein; Stereotactic body radiation therapy; Immunohistochemistry; Metastatic recurrence

1. Introduction

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare primary liver neoplasm characterized histologically by large polygonal cells with centrally located nuclei and abundant eosinophilic cytoplasm, arranged in trabeculae separated by dense fibrous bands and a distinctive central lamellated scar. [1] FL-HCC typically occurs in adolescents and young adults, most often during the second and third decades of life, without a clear gender predilection. Notably, it arises in individuals without underlying liver disease or cirrhosis accounting for approximately 1% of all primary hepatic malignancies. [1,2]

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In contrast to conventional hepatocellular carcinoma (HCC), serum alpha-fetoprotein (AFP) levels are generally normal in FL-HCC, whereas beta–human chorionic gonadotropin (β-hCG) and transcobalamin I and II may be elevated. Genetically, the DNAJB1–PRKACA fusion gene, resulting from a 400-kb deletion on chromosome 19, represents a hallmark molecular alteration found in most cases. [3,4]

Clinically, FL-HCC manifests with nonspecific symptoms similar to other hepatobiliary malignancies, including abdominal pain, early satiety, nausea, abdominal fullness, malaise, and unexplained weight loss. Other possible findings are an enlarged liver, jaundice, anemia, low blood sugar, and, more rarely, hepatic encephalopathy. [1] Given this nonspecific presentation, imaging plays a critical role in diagnosis. Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) typically reveal a large, well-circumscribed hepatic mass with a central hypoattenuating region representing fibrosis or necrosis, surrounded by a hyperattenuating rim. [4]

Surgical resection remains the mainstay of management; however, standardized treatment protocols have not been clearly defined due to the rarity of the disease and limited data on long-term outcomes following hepatectomy. [5] Prognosis and etiology remain subjects of ongoing study, though some evidence suggests FL-HCC may carry a more favorable prognosis compared with conventional HCC.

2. Case Presentation

2.1. Clinical Presentation

A 24-year-old male with no significant past medical history presented to his primary care physician with a four-month history of progressive right upper quadrant abdominal pain, unintentional weight loss of approximately 6.8 kg (15 lbs), early satiety, and intermittent low-grade fevers. He initially attributed his symptoms to stress and academic demands. His primary care physician empirically treated him for possible peptic ulcer disease, which yielded no symptomatic improvement over six weeks. A subsequent visit prompted laboratory evaluation and an abdominal ultrasound. The ultrasound revealed a large, heterogeneous hepatic mass, which prompted urgent referral to a specialized hepatobiliary center. The patient denied alcohol use, illicit drug use, viral hepatitis exposure, or a family history of liver disease. He had no prior hepatic conditions, cirrhosis, or metabolic liver disease. Concern for a primary hepatic malignancy was raised, motivating further workup and multidisciplinary evaluation.

2.2. Physical Examination, History, Laboratory, Imaging, and Radiographic Differential

On physical examination, the patient appeared thin and mildly cachectic. Abdominal palpation revealed a firm, non-tender hepatomegaly with a palpable mass in the right upper quadrant extending toward the epigastrium. There was no jaundice, ascites, or spider angiomata. Lymph nodes were not palpable. Family history was non-contributory; no first-degree relatives had hepatic or gastrointestinal malignancies.

Laboratory results demonstrated mildly elevated liver enzymes (ALT 68 U/L, AST 72 U/L) with normal bilirubin and synthetic function. Alpha-fetoprotein (AFP) was normal at 4.2 ng/mL, and Vitamin B12 was markedly elevated at 3,240 pg/mL, attributed to tumor-derived transcobalamin I production. CA 19-9 was mildly elevated. Hepatitis B and C serologies were negative.

Triphasic CT of the abdomen and pelvis revealed a 12 cm heterogeneous, hypervascular mass in the left lobe of the liver with a central fibrous scar and calcifications, classic imaging features of FL-HCC. No evidence of vascular invasion or satellite lesions was observed. MRI with hepatobiliary contrast confirmed an arterially enhancing mass with a hypointense central scar on all sequences. No extrahepatic disease was identified. A chest CT showed no pulmonary metastases. The radiographic differential diagnosis included: (1) FL-HCC, favored diagnosis given patient age, normal AFP, central scar with calcification, and non-cirrhotic liver; (2) Focal nodular hyperplasia (FNH), considered due to central scar but less likely given mass size, calcification, and clinical symptoms; (3) Hepatocellular adenoma, considered in young patient; (4) Conventional HCC, less likely given normal AFP and absence of cirrhosis.

2.3. Multidisciplinary Tumor Board Discussion

The case was presented at the hepatobiliary multidisciplinary tumor board, attended by hepatology, surgical oncology, interventional radiology, medical oncology, pathology, and radiology. The board focused on confirming the suspected diagnosis of FL-HCC in the context of a young, otherwise healthy patient with a resectable hepatic mass and no radiographic evidence of metastatic disease. The resectability of the lesion was assessed, with attention to anticipated liver remnant volume and functional reserve. The tumor board recommended proceeding with percutaneous core needle biopsy for tissue diagnosis prior to definitive surgical planning. Volumetric assessment with CT was advised to

evaluate the future liver remnant. Portal vein embolization was discussed but deferred pending biopsy results and formal surgical assessment.

2.4. Management, Pathology, IHC, Molecular Studies and Final Diagnosis

Following biopsy confirmation of FL-HCC, the patient underwent an extended left hepatectomy with negative surgical margins (R0 resection). Intraoperative findings revealed a well-circumscribed, 12 cm tan-white mass with a firm, fibrous central scar. No lymph node involvement or vascular invasion was identified macroscopically.

Gross pathology demonstrated a lobulated, non-encapsulated hepatic mass with a central stellate scar and areas of hemorrhage. Histological examination showed large, polygonal tumor cells with deeply eosinophilic, granular cytoplasm and prominent nucleoli embedded in dense, parallel lamellar fibrous stroma, the hallmark morphology of FL-HCC. Necrosis was prominent, and hyaline globules were identified. (Figure 1 A, B, C) Pathologic differential diagnosis included: (1) Fibrolamellar hepatocellular carcinoma, confirmed; (2) Conventional HCC with scirrhous features; (3) Intrahepatic cholangiocarcinoma; (4) Combined HCC-cholangiocarcinoma.

Immunohistochemistry (IHC) studies were performed. The tumor was positive for HepPar-1, CK7, CK19, CD68 (focal, pale bodies), and EpCAM. AFP and glypican-3 were negative, consistent with FL-HCC rather than conventional HCC. CD34 highlighted aberrant sinusoidal vascularity. Molecular analysis identified the DNAJB1-PRKACA gene fusion. Next-generation sequencing revealed no additional actionable mutations. The final diagnosis was confirmed as FL-HCC, Stage II (pT2, N0, M0), R0 resection.

2.5. Outcome, Follow-Up, Complications, and Surveillance

Postoperative bile leak was managed with percutaneous drainage and resolved in three weeks. The patient recovered well and was discharged on postoperative day ten. No adjuvant systemic therapy was administered, given the R0 resection and absence of Lymphovascular invasion. A structured surveillance protocol was implemented, consisting of triphasic CT of the abdomen/pelvis and chest CT every 3 months for the first 2 years, along with serum AFP, vitamin B12, and CA 19-9 measurements at each visit.

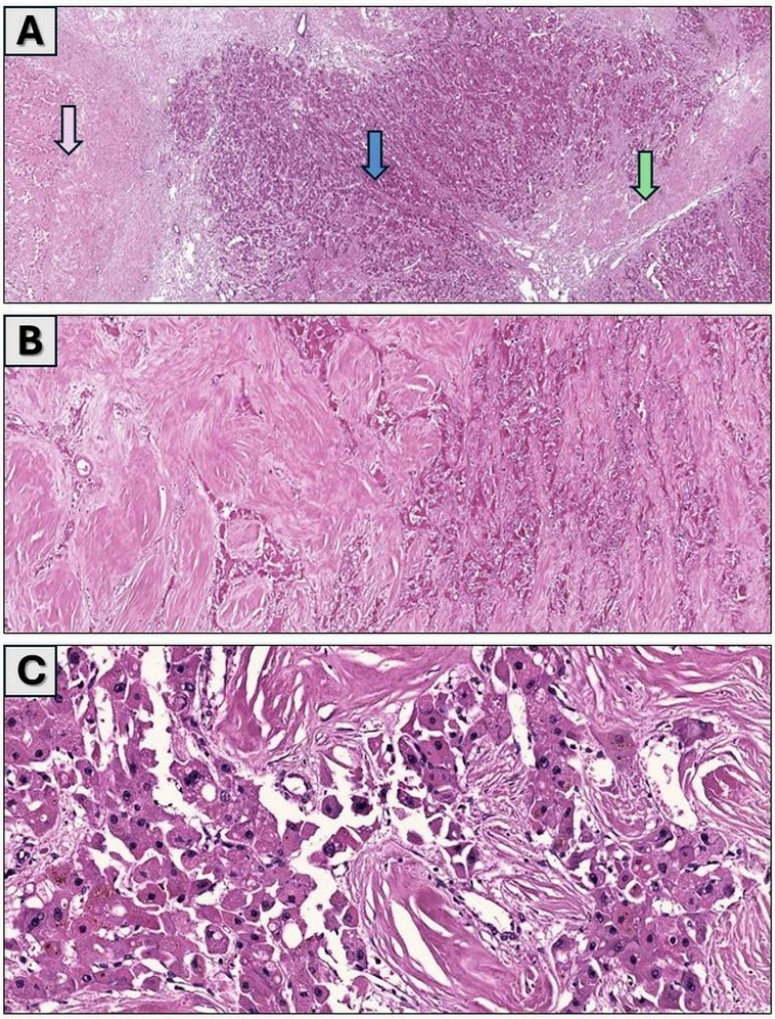
At the two-year follow-up, the patient reported an excellent performance status with full return to normal activities and weight restoration. Serial imaging for the first eighteen months showed no evidence of local recurrence or distant metastasis. The patient remained disease-free and asymptomatic through month twenty. Liver function tests had normalized completely. Oncology, hepatology, and surgery continued joint surveillance.

2.6. Metastatic Recurrence, Tumor Board Discussion, Treatment and Outcome

At the 26-month surveillance visit, the patient reported new-onset right-sided chest discomfort and lower back pain. Chest CT revealed two new pulmonary nodules in the right lower lobe (largest 1.8 cm), and a bone scan with confirmatory MRI identified a lytic lesion in the L3 vertebral body suspicious for osseous metastasis. PET-CT demonstrated FDG-avid activity at both sites with no additional disease. CT-guided biopsy of the pulmonary nodule confirmed metastatic FL-HCC, with the characteristic DNAJB1-PRKACA fusion identified on molecular testing.

The case was represented at the multidisciplinary tumor board. Given oligometastatic disease in a young patient with good performance status, the board recommended a combination approach: stereotactic body radiotherapy (SBRT) for the L3 osseous lesion to reduce pain and prevent neurological compromise, surgical resection of the pulmonary metastases, and initiation of systemic therapy with a platinum-based regimen (gemcitabine and cisplatin), given limited evidence-based options for FL-HCC. Enrollment in a clinical trial targeting PRKACA kinase inhibition was strongly encouraged.

Following pulmonary metastasectomy and SBRT, the patient tolerated chemotherapy with manageable toxicity (grade 2 fatigue and nausea). Restaging imaging at 6 months post-treatment showed no new metastatic lesions, and the prior sites remained free of evidence of active disease. The patient was enrolled in a PRKACA inhibitor clinical trial and continued quarterly surveillance. His performance status remained favorable; he was ambulatory and maintained employment at the last follow-up.



1A: Low power view showing the infiltrating tumor (Blue arrow), Tumor necrosis (Pink arrow), and lamellar sclerosis (Green arrow) (H&E Stain X20).; 1B: Intermediate power view showing prominent tumor necrosis (Right side) and lamellar tumor sclerosis (Left side) (H&E Stain X40).; 1C: High power view showing large, polygonal tumor cells with deeply eosinophilic, granular cytoplasm and prominent nucleoli embedded in dense, parallel lamellar fibrous stroma (H&E Stain X60)

Figure 1 Microscopic examination of fibrolamellar hepatocellular carcinoma (FL-HCC)

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

Fibrolamellar hepatocellular carcinoma (FL-HCC) was first characterized as a distinct clinical and pathological entity by Edmondson in 1956, who described a unique "eosinophilic hepatoma with lamellar fibrosis" in a young patient. [6,7] It is a rare primary liver malignancy, accounting for less than 1% of all hepatocellular carcinomas, with a reported incidence of approximately 0.2 per million person-years. [8] Epidemiologically, FL-HCC is distinguished from conventional HCC by its predilection for adolescents and young adults, with a median age at diagnosis of around 25 years and no significant gender disparity. [8]

A defining characteristic of FL-HCC is the absence of typical risk factors associated with most liver cancers. Most cases arise in individuals with no underlying cirrhosis or chronic liver disease, such as viral hepatitis or alcohol-related liver injury. [4] The cause and development of this condition in healthy young people remain under active investigation. The 5th Edition of the World Health Organization (WHO) Classification of Digestive System Tumors (2019) solidified its status as a distinct tumor entity, moving beyond morphology to define it at a molecular level. [9] It is now formally recognized as a specific subtype of hepatocellular carcinoma characterized by the presence of the DNAJB1-PRKACA gene fusion, which is absent in conventional HCC and serves as its pathognomonic molecular signature. [9,10]
[4] The fact that this condition appears in other healthy young people makes its causes and development the focus of much research.

3.2. Pathogenesis, Pathophysiology

FL-HCC is a distinct molecular entity, fundamentally different from conventional HCC. Its pathogenesis is not associated with chronic liver disease or cirrhosis but is instead driven by a unique somatic mutation. [1] In over 80% of cases, a 400-kb deletion on chromosome 19 results in the fusion of the DNAJB1 gene, which encodes a heat shock protein, and the PRKACA gene, which encodes the catalytic subunit of protein kinase A (PKA). [2,3] This DNAJB1-PRKACA fusion gene produces a chimeric protein, DNAJ-PKAc, that leads to constitutive, cAMP-independent activation of PKA signaling pathways. [4]

The aberrant PKA activity is the central oncogenic driver, promoting tumorigenesis through several mechanisms. Recent studies have shown that the DNAJ-PKAc fusion protein impairs the function of Salt-Inducible Kinases (SIKs), leading to the activation of the transcriptional co-activator CRTC2. This, in turn, mediates a broad transcriptional reprogramming that drives tumor growth. [5] The fusion protein also interacts with other cellular components, such as β-catenin, and rewires signaling networks, including the mobilization of local ERK signaling, to promote cell proliferation and survival. [6,7] This distinct molecular cascade explains the unique clinical and pathological features of FL-HCC, setting it apart from other liver malignancies.

3.3. Comparative analysis of our case with the existing literature. (Clinical, radiology, pathology, Lab, diagnosis, management, and outcome)

This case exemplifies the classic presentation of FL-HCC and aligns closely with the established literature. The patient, a young male (24 years old) without underlying liver disease or cirrhosis, fits the typical demographic profile of adolescents and young adults predominantly affected by this malignancy. [4,8] His clinical presentation with nonspecific abdominal pain, weight loss, and a palpable mass, coupled with a normal serum alpha-fetoprotein (AFP) level, is characteristic of FL-HCC and contrasts with conventional HCC, where AFP is often elevated. [11] Furthermore, the markedly elevated Vitamin B12, a result of tumor-derived transcobalamin I, served as a crucial biochemical clue, a finding reported in a subset of FL-HCC patients. [13]

The radiographic findings of a large, solitary hepatic mass with a central scar and calcifications are hallmark features of FL-HCC, observed in up to 70% of cases. [11] The final diagnosis was solidified by the histological demonstration of large, eosinophilic tumor cells within a lamellar fibrous stroma and, critically, the molecular identification of the pathognomonic DNAJB1-PRKACA gene fusion. [12] The clinical course, involving an initial R0 resection followed by metastatic recurrence after a disease-free interval of over two years, aligns with the natural history of the disease. Despite successful initial surgery, recurrence rates are high, often exceeding 50%. [5] Recurrence in the lungs and bone represents a characteristic pattern, and multidisciplinary management of this oligometastatic condition, including SBRT, metastasectomy, and systemic chemotherapy, exemplifies current treatment approaches for patients with limited extrahepatic disease. [4,14]

4. What Have We Learned from This Case?

This case provides several practical clinical insights. First, it underscores the importance of maintaining a high index of suspicion for FL-HCC in any young, otherwise healthy individual presenting with persistent, nonspecific upper abdominal symptoms and weight loss, particularly when a palpable mass is present. The absence of cirrhosis and a normal AFP level should not deter investigation but rather increase suspicion for this rare tumor. An elevated Vitamin B12 level can serve as a valuable, albeit non-universal, diagnostic red flag.

Second, this case powerfully illustrates the natural history of FL-HCC, reinforcing that even after a complete (R0) surgical resection and a significant disease-free period, the risk of recurrence remains substantial. This challenges the concept of a definitive "cure" and highlights the critical need for long-term, structured surveillance. Current guidelines for HCC surveillance are often debated for FL-HCC, but this case, along with recent reports of very late recurrences, argues for extending surveillance indefinitely. [15]

Finally, the management of the patient's recurrence demonstrates the value of an aggressive, multidisciplinary approach in the setting of oligometastatic disease. The combination of localized treatments like SBRT and surgical metastasectomy with systemic therapy was crucial in controlling the disease and maintaining the patient's performance status, reinforcing that a nihilistic approach is not warranted in these young, fit patients. [4,14] This case reinforces the need for enrollment in clinical trials targeting the underlying molecular drivers, such as PRKACA inhibitors, to improve long-term outcomes. [16]

Abbreviations

- Fibrolamellar hepatocellular carcinoma (FL-HCC);
- Hepatocellular carcinoma (HCC),
- Alpha-fetoprotein (AFP);
- Stereotactic body radiation therapy (SBRT);
- Immunohistochemistry (IHC)

5. Conclusion

This case of fibrolamellar hepatocellular carcinoma highlights the classic yet challenging trajectory of a rare liver malignancy. It illustrates the typical presentation in a young adult without underlying liver disease, the characteristic diagnostic features, including the pathognomonic DNAJB1-PRKACA fusion, and the aggressive surgical management that remains the cornerstone of treatment. The key contribution of this report is its clear depiction of the entire disease continuum, from initial diagnosis and successful R0 resection to the eventual development of oligometastatic recurrence more than two years later. It underscores the high risk of late recurrence, reinforcing the absolute necessity of vigilant, long-term surveillance beyond conventional timelines. Furthermore, it showcases a modern, multidisciplinary strategy for managing recurrent disease, providing a valuable real-world example of combining surgery, radiotherapy, and systemic therapy. This case serves as a crucial reminder to clinicians to maintain a high index of suspicion for FL-HCC and to pursue aggressive, multimodal treatment strategies throughout the patient's journey.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

This study was conducted as a retrospective review of archival pathology material collected during routine clinical care. All data were fully de-identified prior to analysis. No patient contact or intervention was involved, and informed consent was not required in accordance with institutional policies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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