

Metastatic Fibrolamellar Hepatocellular Carcinoma in a Young Adult: A Case Report and Narrative Review

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Abstract: Fibrolamellar hepatocellular carcinoma (FLC) is a rare and distinct histologic subtype of hepatocellular carcinoma that typically arises in non-cirrhotic livers of adolescents and young adults without underlying viral hepatitis or chronic liver disease. Accounting for less than 1% of all primary liver cancers, FLC is characterized by unique clinical, radiologic, and molecular features, most notably the highly characteristic *DNAJB1-PRKACA* fusion. Due to its rarity and frequently nonspecific presentation, diagnosis is often delayed or misinterpreted as by benign hepatic lesions such as focal nodular hyperplasia or adenoma. This report presents a rare case of metastatic FLC in a young adult who initially presented with right upper quadrant pain, anemia, and preserved hepatic function. Imaging revealed a large hepatic mass with a central non-enhancing area suggestive of necrosis, and histopathologic evaluation aided in the diagnosis based on characteristic lamellar fibrosis, polygonal eosinophilic cells, and positive CK7 and HepPar-1 staining. Confirmatory molecular testing through *DNAJB1-PRKACA* fusion was not performed. Planned treatment with a combination regimen of nivolumab and neratinib was scheduled; however, the patient deteriorated rapidly, and systemic therapy could not be initiated before death. Through this case and accompanying review, we aim to highlight the diagnostic complexity, molecular underpinnings, and current therapeutic approaches of FLC. This case was notable for advanced peritoneal carcinomatosis at presentation, severe thrombocytosis, and the diagnostic and therapeutic challenges posed by metastatic fibrolamellar carcinoma without molecular confirmation. Taken together, this underscores the importance of early recognition, molecular testing, and coordinated clinical management in optimizing outcomes for this uncommon malignancy.

Keywords: fibrolamellar hepatocellular carcinoma, liver cancer, case report, pathogenesis, diagnosis, treatment, immunotherapy

Literature Background of Fibrolamellar HCC

To contextualize this case, we conducted a narrative review of the literature. We searched PubMed, MEDLINE, and Google Scholar for English-language articles published between January 2000 and December 2025 using the keywords “fibrolamellar hepatocellular carcinoma,” “pathogenesis,” “diagnosis,” and “management.” Case reports, case series, and review articles relevant to clinical presentation, diagnostic strategies, and therapeutic approaches were included. The last search was performed on January 15, 2026. This narrative review was structured according to the SANRA framework to ensure transparency and reproducibility.¹

Introduction to Fibrolamellar Hepatocellular Carcinoma

Fibrolamellar hepatocellular carcinoma (FLC) is a rare liver tumor that accounts for approximately 1% of liver cancers.^{2,3} It typically affects adolescents and young adults, most commonly between the ages of 10 and 35, with a median age at diagnosis around 21 years.^{2,3} The incidence is estimated at 0.02 per 100,000 persons per year

which equates to roughly 200 new cases per year.⁴ Given its rarity and the absence of common hepatocellular carcinoma (HCC) risk factors, it is often underrecognized. Unlike conventional HCC, fibrolamellar HCC is not associated with chronic liver disease, hepatitis B or C infection, or alcohol use.² It is a rare variant of HCC that affects young adults and adolescents without any underlying liver disease or cirrhosis.⁵

Clinical Presentation and Lab Findings

Patients with FLC may exhibit a wide range of clinical symptoms, from asymptomatic incidental findings to significant abdominal discomfort and systemic signs. Typically, patients present with vague symptoms such as abdominal pain, right upper quadrant discomfort, abdominal fullness or distension, weight loss, fatigue, and, in some cases, a palpable mass or ascites.^{2,6–8} In some instances, the tumor may be discovered incidentally due to the preservation of normal liver function and absence of clinical signs or symptoms.^{9,10}

With regards to lab findings in fibrolamellar HCC, they are distinct from conventional HCC due to the lack of liver dysfunction. Alpha-fetoprotein (AFP) levels, which are normally greatly elevated in conventional HCC, are most often normal or only mildly elevated, rarely exceeding 200 ng/mL.^{6,9,11} Liver enzymes, such as AST, ALT, ALP, may be mildly elevated but are often within normal ranges, and bilirubin levels are generally not significantly increased.^{12,13} Other tumor markers, such as CA 19–9 and carcinoembryonic antigen (CEA), are usually within normal limits and lack diagnostic utility.^{6,13} Some patients may seldom show elevations in less conventional markers such as des-gamma-carboxy prothrombin, neurotensin, or elevated vitamin B₁₂ binding protein, though these are neither sensitive nor specific.^{14–17} Overall, the clinical and biochemical profile of FLC is typically unremarkable, which contributes to the somewhat delayed diagnosis and necessitates reliance on imaging and histopathology.

Imaging Characteristics

The techniques often used to evaluate FLC include MRI, CT, and US. Radiologic investigation is essential in detecting less apparent distant disease. On US, FLCs appear as a lobulated mass of varied echotexture and a poorly discernable central scar that is generally seen as an area of enhanced echogenicity.¹⁸ On CT, most of these tumors appear to have well demarcated margins and decreased attenuation on noncirrhotic livers.¹⁹ There also seems to be a calcified central scar in up to 70% of cases.¹⁹

On MRI, FLC's appear to be hyperintense on T2-weighted imaging in up to 54% of cases while they tend to appear hypointense on T1-weighted imaging in 62% of cases.²⁰ In contrast, the fibrous scar in fibrolamellar HCC is typically hypointense on both T1 and T2 modalities.²¹ The above feature can be beneficial in regard to distinguishing fibrolamellar HCC from focal nodular hyperplasia that has a central scar characterized by T2 hyperintensity.¹⁹

Histopathological Features

Fibrolamellar HCC has distinctive histopathological features that are used to confirm the diagnoses. Its defining features typically consist of large polygonal cells of large nucleoli, vesiculated nuclei and abundant eosinophilic cytoplasm - due to mitochondrial proliferation - surrounded by a matrix of dense lamellar fibrosis.²² Fibrolamellar HCCs may present with diverse fibrosis patterns, with the most frequently observed pattern consisting of tumor cells separated by trabeculae.²³ They may also appear as tumors with very limited or even absent intratumoral fibrosis as well as random disorganized collagen deposition.²³ Some of the inclusions that are not specific to fibrolamellar HCC but seen in around 50% of cases include pale bodies as well as the smaller eosinophilic inclusions called hyaline bodies.²⁴ In some cases, fibrolamellar HCC tumors may exhibit pseudoglandular growth with mucin production.⁵ The mucin stains positive with mucicarmine in over half of cases and with alcian blue in all cases.⁵ These gland-like structures are surrounded by neoplastic cells showing typical FLC morphology and expressing biliary-type cytokeratins, suggesting glandular differentiation.⁵

Genetic and Molecular Features

Regarding the genetic and molecular features of FLC, a characteristic alteration is the fusion of PRKACA - the catalytic subunit of PKA - with the 5' region of the heat shock protein DNAJB1 gene resulting from a deletion in chromosome

19.²⁵ FLC type tumors express both the DNAJB1-PRKACA chimera along with the wildtype kinase. The absence of the fusion protein in surrounding normal liver tissue suggests that it is of somatic nature.²⁶ Interestingly, it has been demonstrated that the DNAJB1 moiety is not essential for the development of the FLC phenotype and it is rather the altered localization and the increased activity of the catalytic unit of PKA that is enough to transform cells into FLC.^{27,28}

Certain histochemical features of FLCs have proven to be helpful in the confirmation of the diagnosis. Notably, FLCs express markers of both hepatocellular and biliary origins.²⁹ Hepatocyte Parafin 1 (HepPar-1) is a monoclonal antibody specific to tumors of hepatic origin such as HCC and its rarer counterpart FLC while it is absent in metastatic tumors to the liver.^{30,31} Other hepatocellular markers that tend to be positive in FLC include p-CEA, arginase-1, and glypican-3.³² Two markers of high sensitivity for FLC are CK7 and CD68. For instance, CD68, a transmembrane glycoprotein primarily found on macrophages and other cells of monocyte lineage, has a sensitivity of 96% as well as a specificity of 80% for FLC.³³ Although CK7, a cytokeratin, has a 100% sensitivity for FLC it can also be present in up to 32% of conventional HCC cases.²²

Treatment Strategies and Outcomes

Currently, treatment strategies for fibrolamellar hepatocellular carcinoma remain poorly defined, largely due to its rarity and the absence of large-scale clinical studies. Nevertheless, surgical resection is widely regarded as the cornerstone of fibrolamellar HCC management and remains the most effective curative option, particularly in early stages of the tumor.^{34–36} High level evidence from a recent comprehensive systematic review demonstrated the superiority of surgical resection in the management of FLC, with the 1-year overall survival falling between 67–100%, and the 5-year overall survival being 28–65%.³⁴ These findings are further supported by retrospective cohort studies, which also constitute high-level evidence, and report consistent outcomes.^{34,37,38} Recurrence after surgical resection remains common, particularly in intra-abdominal or intrathoracic lymph nodes, followed by the liver, lungs, and peritoneum.³⁹ However, patients who underwent subsequent surgical resection of recurrent disease demonstrated improved prognoses compared to those who did not based on moderate-level evidence.³⁹

These observed outcomes are notably less favorable in patients with metastatic disease, where recurrence rates are significantly higher and disease progression is markedly more common as shown in observational and registry-based studies that represent moderate-level evidence due to their descriptive design and lack of controlled comparison groups.^{8,37,40,41} Other poor prognostic values, all of which are derived from retrospective analyses and therefore constitute moderate-level evidence, include large primary tumors, elevated AFP levels, macrovascular invasion, lymph node metastasis, unresectable disease, as well as incomplete resection.^{6,8,42} Despite the setbacks of metastatic disease, surgical resection may still confer benefit and is still an important consideration regardless of lymph nodes or metastasis status.⁴³

Systemic therapy, such as chemotherapy, also represents an important component of fibrolamellar HCC management, although its efficacy remains variable and conclusions are often limited by the rarity of the disease and the lack of randomized controlled trials and standardized treatment protocols.^{44–46} Nonetheless, low-level evidence consisting of case reports have described patients with FLC achieving complete responses to chemotherapy regimens such as gemcitabine and oxaliplatin (GEMOX), suggesting that systemic chemotherapy should remain a consideration in select cases.^{47,48}

Recently, interest has grown in exploring novel therapeutic modalities such as immune checkpoint inhibitors, kinase-targeted agents, vaccines, and more. Variable responses are seen with targeted therapies such as immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs). ICI responses have been described in isolated case reports, representing low-level evidence due to their anecdotal nature and inability to establish causality or generalizability. For instance, when using ICIs, a near complete response was seen in a patient with a PD-L1 expressing tumor 2 months after being treated with nivolumab, a PD-1 inhibitor.⁴⁹ Remission was also seen in a patient treated with a combination of nivolumab and ipilimumab despite standard immune checkpoint biomarkers being negative.⁵⁰ Interestingly, a novel treatment modality consisting of triple immunochemotherapy is showing promise as an option to delay disease progression and extend survival in high-risk fibrolamellar HCC patients.^{51,52} A patient with biopsy-proven recurrent FLC with multifocal liver involvement and was treated with the triple therapy regimen of 5-fluorouracil, interferon alfa-2b, and

nivolumab, and achieved complete radiographic and pathologic response prior to orthotopic liver transplantation.⁵² This also represents low-level evidence in view of the previously described methodological limitations inherent to case reports.

On the other hand, treatment with ICIs does not always lead to favorable results. For instance, two patients treated with a combination of atezolizumab and bevacizumab did not benefit and there was a lack of any tumor response.⁵³ The same was seen when a 15-year-old girl with suspected fibrolamellar HCC and metastatic disease was treated with atezolizumab and bevacizumab; despite initial surgical resection, she developed progressive disease with new lung and intrahepatic lesions, indicating limited efficacy of the combination in this setting.⁵⁴ Another study similarly reported limited clinical activity of immune checkpoint inhibitors in fibrolamellar HCC, specifically those targeting PD-1/PD-L1 and CTLA-4.⁵⁵ Emerging data, based on moderate-level evidence derived from small observational cohorts and non-randomized studies, suggest that stereotactic body radiotherapy may be an effective and well-tolerated adjunct local therapy in inoperable liver tumors, and its integration with systemic or immunotherapeutic approaches might potentiate local tumor control in FLC.⁴⁴

As with ICIs, there are limited studies on the use of TKIs in patients with fibrolamellar HCC. The most notable study evaluated the use of neratinib, alone or combined with ICIs and/or mTOR inhibitors, in patients with fibrolamellar HCC.⁵⁶ It found that while neratinib was generally well-tolerated, limited clinical benefit was observed when used as a single agent, while combination strategies did show some clinical benefit.⁵⁶ This represents moderate-level evidence from early-phase, non-randomized clinical studies and observational data without randomized comparison.

Several studies have explored novel and unconventional treatment approaches for FLC. For example, in preclinical studies representing exploratory evidence derived from in vitro and animal models, BCL-XL was shown to play a key role in the survival of fibrolamellar HCC cells.⁵⁷ Targeting BCL-XL subsequently induced apoptosis in these cells and demonstrated potential as a therapeutic strategy.⁵⁷ Another preclinical study conducted on patient derived xenograft tumors of fibrolamellar HCC demonstrated the efficacy of Temsirolimus, an mTOR inhibitor, for the treatment of metastatic FLC lesions.⁵⁸ Peptide vaccines derived from the DNAJB1-PRKACA derived protein taken while on PARP inhibitor therapy induced durable, multifunctional Th1-type CD4⁺ T cell responses with high TCR clonality.⁵⁹ Early clinical observations from small cohorts and case reports provided preliminary, low-level evidence on the aforementioned treatment strategy. For example, studies have demonstrated the efficacy of this novel modality in a fibrolamellar HCC patients, with some who suffered from recurrent short interval disease relapses then having over 21 months of relapse-free survival after receiving the vaccine.⁵⁹ More studies are on the way evaluating the efficacy of DNAJB1-PRKACA fusion transcript-based peptide vaccine in fibrolamellar HCC along with other rare tumors carrying the fusion protein.⁶⁰

Case Presentation

A 30 year old male patient presented to the Emergency Department at the American University of Beirut Medical Center, with a history of iron-deficiency anemia diagnosed years prior, with no personal or family history of liver disease, hepatitis infection, or alcohol use. Notably, further investigation revealed that he was a smoker and has smoked an average of 1.5 packs daily for the past 10 years. He presented with a severely distended abdomen that had been progressively worsening over the last month, leading to discomfort and decreased eating. During that same period, he reported experiencing increased fatigue, night sweats, and significant weight loss. The abdominal distension was found to be a result of ascites and fluid buildup in the peritoneum. His liver was found to be enlarged on physical examination, a finding that was subsequently confirmed by imaging. There was no abdominal tenderness.

Initial laboratory evaluation included complete blood count, serum chemistries, and liver enzyme testing, with the abnormal and clinical results displayed in [Table 1](#). Most hematologic and biochemical parameters were within normal limits, including white blood cell count, red blood cell count, monocytes, total protein, globulin, electrolytes (sodium, potassium, chloride), magnesium, calcium, total and direct bilirubin, ferritin, eGFR, BUN, creatinine, lipase, APTT, and INR. Borderline findings included carbon dioxide and phosphate, which were mildly reduced, and gamma-glutamyl transferase (GGT), which was slightly elevated. All results, including normal values, can be found in [Supplementary Table 1](#).

Significant abnormalities were observed in several indices: hemoglobin, hematocrit, MCV, MCH, lymphocytes, iron, transferrin, iron saturation, albumin, and total iron-binding capacity were all decreased, while RDW, neutrophil

Table 1 Summary of Abnormal Laboratory Findings

Hematology			
Test	Reference Range	Result	Interpretation
Hemoglobin (HGB)	13.0–18.0 g/dL	9.4	↓ Low
Hematocrit (HCT)	40–54%	30	↓ Low
MCV	80.0–94.0 fL	66.3	↓ Low
RDW	11.6–14.6%	19.3	↑ High
Neutrophils	40–65%	78	↑ High
Lymphocytes	25–40%	18	↓ Low
Platelets	150,000–400,000 /cu.mm	1,066,000 (Peak)	↑ High
ANC	1,600–7,200 /cu.mm	7,500	↑ High
Liver Function Tests			
Test	Reference Range	Result	Interpretation
Total Bilirubin	0.0–1.2 mg/dL	0.2	Normal
Direct Bilirubin	0.0–0.3 mg/dL	0.1	Normal
Total Protein	60–83 g/L	63	Normal
Albumin	36–53 g/L	30	↓ Low
ALT (SGPT)	0–65 IU/L	88	↑ High
AST (SGOT)	0–50 IU/L	64	↑ High
GGT	≤60 IU/L	61	↑ High
Tumor Markers			
Test	Reference Range	Result	Interpretation
CEA	—	2.3	Normal
AFP	1.0–9.0 U/mL	2.8	Normal
Pancreatic Enzyme			
Lipase	13–60 U/L	18	Normal

percentage, absolute neutrophil count, platelet count, ALT, AST, prothrombin time, and PT ratio were elevated. These findings collectively indicate microcytic hypochromic anemia with iron deficiency features, mild hepatocellular injury, reactive thrombocytosis, and slight prolongation of coagulation parameters.

A peripheral blood smear demonstrated thrombocytosis with occasional large and giant platelets. Notably, platelet counts continued to increase in the next 5 days until they reached a maximum value of 1,066,000. Specific laboratory tests showed negative hepatitis B and C serologies, as well as negative antinuclear antibody (ANA) and anti-smooth muscle antibody screens. Tumor markers, including AFP, CEA, and carbohydrate antigen 19–9 (CA 19–9), were within normal limits. Interestingly, the C-reactive protein (CRP) level was elevated.

Contrast-enhanced CT of the abdomen and pelvis was performed after intravenous administration of 100 mL of Omnipaque 350, with axial acquisition and coronal and sagittal reformats. It demonstrated hepatomegaly with a large heterogeneous hepatic mass centered in segments VII and VIII and extending into segment IV, measuring 14.5×14 × 12 cm. The lesion contained central hypoattenuating areas, including a dominant irregular central hypodensity with

coarse calcifications, raising the possibility of necrosis or a central scar. The mass caused compression of the intrahepatic inferior vena cava, and the right and middle hepatic veins were poorly visualized, likely due to marked compression. In addition, there were multiple metastatic soft tissue deposits throughout the abdomen and pelvis, including porta hepatis, mesenteric, peritoneal, and omental involvement, with marked omental caking and large-volume ascites. These findings favored an aggressive primary hepatic malignancy, with fibrolamellar hepatocellular carcinoma considered the leading diagnosis radiologically. Representative CT images are shown in Figure 1.

Prior to further radiologic workup with an MRI, his ascitic fluid was drained and appeared serosanguinous in color, with a total of 5L drained in the first 24 hours. Over the following days, a total of 11.3 liters of fluid was drained, including the initial amount. Ascitic fluid studies revealed the presence of malignant cells as well as a SAAG of 0.7 g/dL, indicating that the source of the fluid was likely due to the metastatic peritoneal carcinomatosis. There was no evidence of spontaneous bacterial peritonitis as the absolute neutrophil count was 117 cells/mm³. Metastatic disease was therefore confirmed by both radiologic findings and ascitic-fluid cytology. The cytologic diagnosis was based on morphology alone, for the sake of staging.

MRI of the abdomen was then performed on a 3T scanner before and after intravenous gadolinium administration and included axial and coronal T2-weighted sequences, T1-weighted in- and out-of-phase imaging, diffusion-weighted imaging with ADC maps, and dynamic fat-suppressed 3D T1-weighted post-contrast sequences. It demonstrated

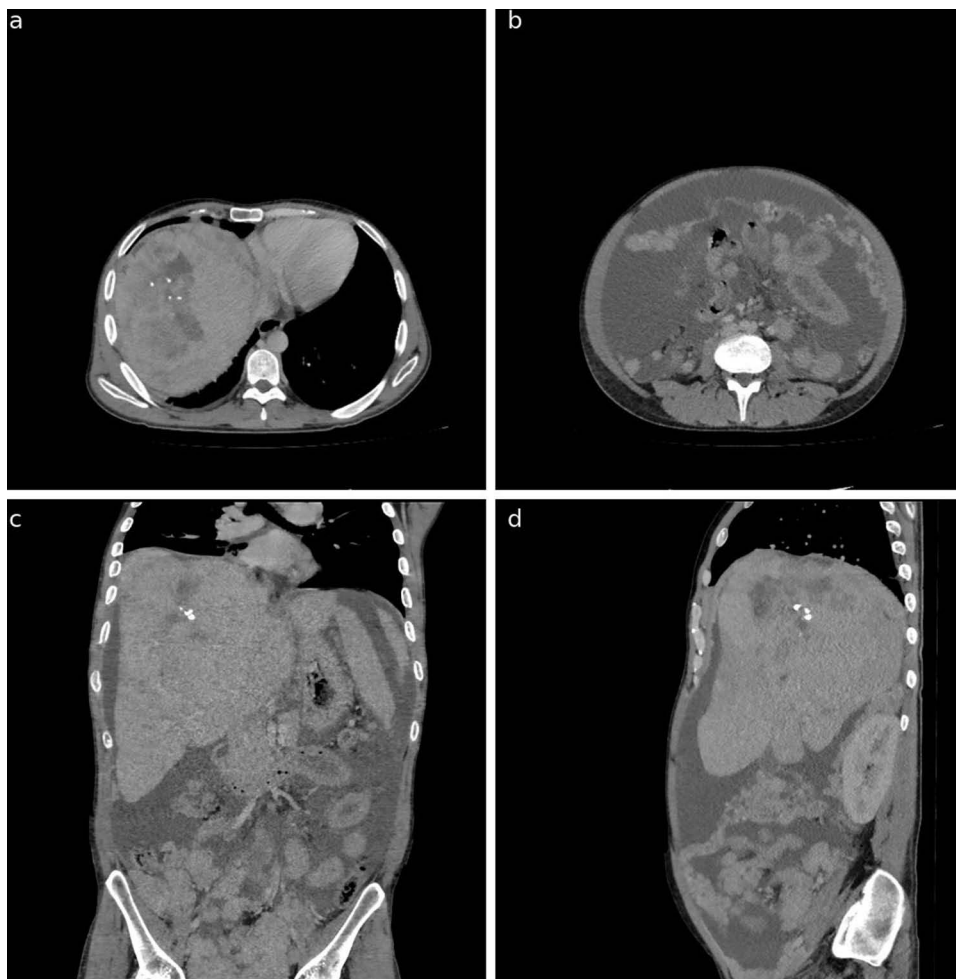


Figure 1 Contrast-enhanced CT of the abdomen and pelvis. (a) Axial contrast-enhanced CT image demonstrating a large heterogeneous right hepatic mass with a central hypodense component and coarse central calcifications. (b) Axial CT image at a lower level showing large-volume ascites and extensive intra-abdominal soft tissue deposits consistent with peritoneal metastatic disease. (c) Coronal reformatted CT image showing the overall extent of the hepatic mass and associated diffuse peritoneal and mesenteric tumor deposits. (d) Sagittal reformatted CT image demonstrating the craniocaudal extent of the hepatic mass with associated ascites and intra-abdominal metastatic disease.

a large lobulated hepatic mass involving the right lobe, predominantly segments IVa, VII, and VIII, measuring 17×16 × 14 cm. The lesion was predominantly isointense to the background liver on both T1- and T2-weighted images, showed heterogeneous arterial phase enhancement with progressive delayed enhancement, and demonstrated diffusion restriction. A central stellate non-enhancing component was present and favored necrosis rather than a fibrous central scar. The mass also obliterated the ascending branch of the right portal vein and the middle hepatic vein. In addition, MRI confirmed extensive peritoneal disease with multiple soft tissue masses along the peritoneal lining and omentum, consistent with widespread peritoneal carcinomatosis. Representative MRI images are shown in Figures 2 and 3.

To aid in the diagnosis of fibrolamellar HCC, a liver biopsy was obtained and evaluated with histopathology and immunohistochemical staining (Figure 4). A core needle biopsy of the right hepatic lobe mass was performed. Histopathologic evaluation of hematoxylin and eosin (H&E) stained slides (Figure 4) revealed a tumor composed of large polygonal cells with abundant, granular eosinophilic cytoplasm and prominent nucleoli. These cells were arranged in nests and trabeculae separated by characteristic dense lamellar collagen bundles. Immunohistochemical (IHC) staining was performed using a polymer-based detection system on automated platforms on 4-μm-thick sections of formalin-fixed paraffin-embedded (FFPE) tissue; appropriate positive controls were utilized for all markers (Table 2). The tumor cells showed diffuse positivity for CK7 and HepPar-1 but were negative for CD68. Markers for potential targeted therapy, including HER2 and PD-L1, were negative. The Ki-67 proliferation labeling index was 1%. DNA mismatch repair (MMR) testing showed retained nuclear expression of MLH1, MSH2, MSH6, and PMS2. Details of the

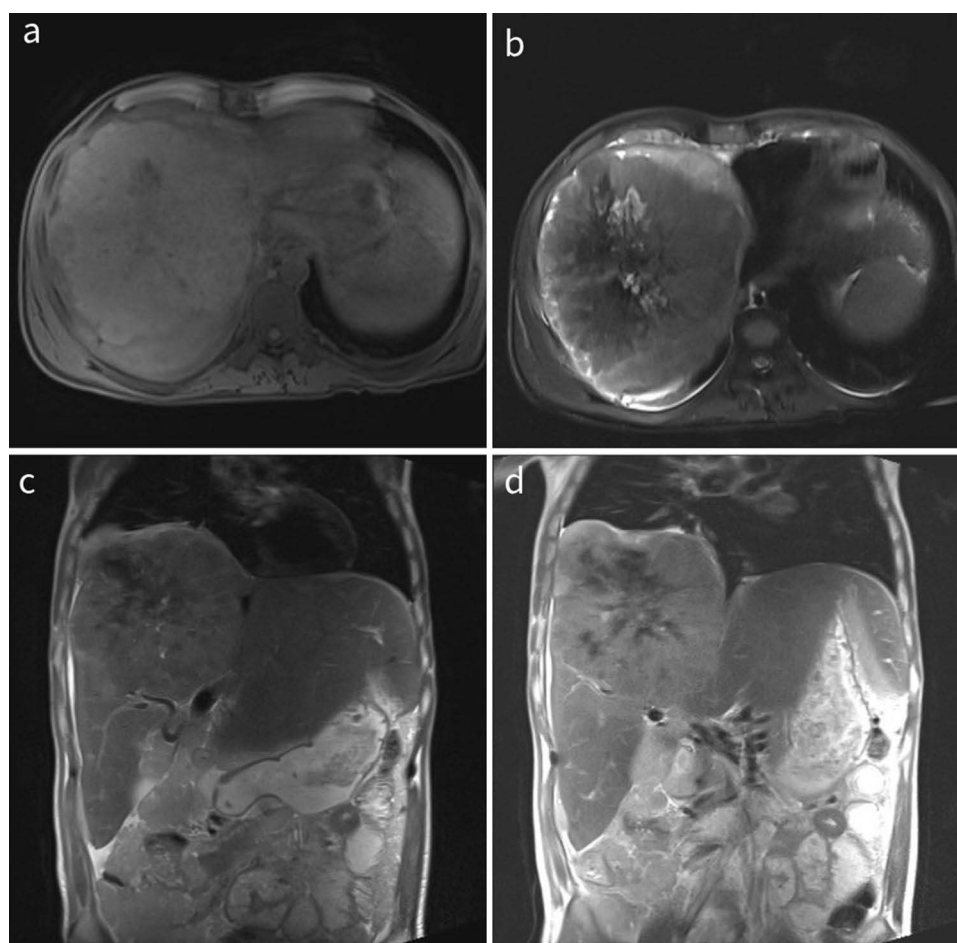


Figure 2 Pre-contrast MRI of the abdomen. (a) Axial pre-contrast T1-weighted image showing a large right hepatic mass that is predominantly isointense to the adjacent liver parenchyma. (b) Axial T2-weighted image demonstrating the lesion with a central stellate hyperintense component corresponding to necrosis. (c) Coronal post-contrast arterial-phase T1-weighted image showing the large lobulated right hepatic mass and its overall extent. (d) Coronal T2-weighted image further demonstrating the heterogeneous internal architecture of the lesion and the central stellate component.

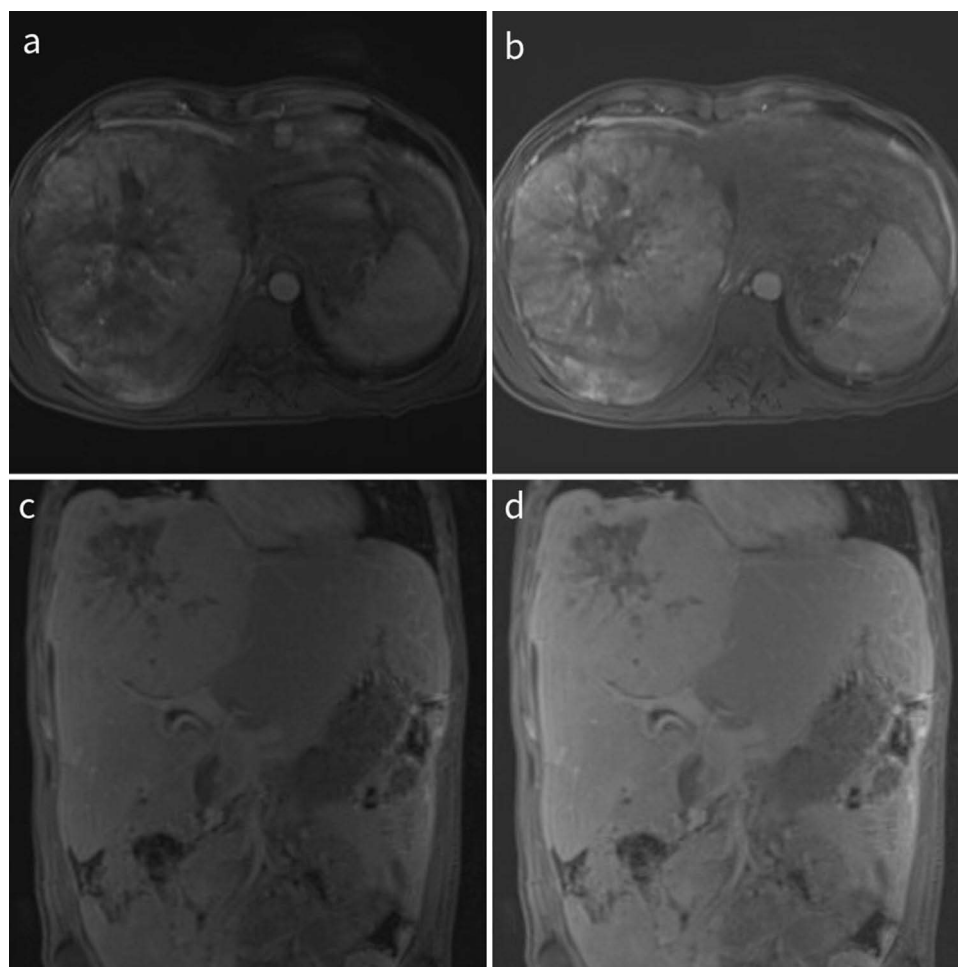


Figure 3 Post-contrast MRI of the abdomen. (a) Axial post-contrast T1-weighted fat-suppressed image demonstrating heterogeneous enhancement of the hepatic mass with relative nonenhancement of the central stellate component. (b) Axial post-contrast image showing persistent central nonenhancement, favoring necrosis rather than a fibrous central scar. (c) Coronal arterial-phase post-contrast T1-weighted image demonstrating the enhancing right hepatic mass and its relationship to the surrounding liver parenchyma. (d) Coronal T2-weighted image showing the lesion's heterogeneous internal signal and central stellate component.

immunohistochemical markers used in this case are summarized in Table 2. Molecular confirmation to check for the DNAJB1–PRKACA fusion protein was not performed due to financial constraints.

The histopathologic and immunohistochemical impression of FLC was based on classic morphology and diffuse CK7 expression. Although CD68 often highlights “pale bodies” in FLC,³³ its absence in our case does not preclude the diagnosis when the characteristic histopathologic triad is present.²² While the DNAJB1–PRKACA fusion remains the diagnostic gold standard,²⁵ the combination of characteristic morphology and immunophenotype in a non-cirrhotic liver allows for a reliable distinction from mimics such as scirrhous HCC.²³

The final diagnosis of metastatic fibrolamellar hepatocellular carcinoma was made through a multidisciplinary assessment integrating clinical presentation, radiologic features, histopathologic findings, and immunohistochemical profile. Clinically, the patient's age, absence of underlying liver disease, and nonspecific systemic symptoms were consistent with reported FLC profiles. Imaging studies demonstrated a large hepatic mass with features typical of FLC, along with evidence of intra-abdominal metastatic spread. Histopathologic examination of the liver biopsy revealed the characteristic lamellar fibrosis and large polygonal tumor cells with abundant eosinophilic cytoplasm, further supported by immunohistochemical positivity. These findings supported a clinicopathologic diagnosis of metastatic fibrolamellar HCC, representing the first reported case at AUBMC, although molecular confirmation was not performed.

The patient's performance status at presentation was borderline (ECOG 2), with severe ascites, cachexia, and rapid clinical decline. Formal staging was performed according to the AJCC 8th edition for hepatocellular carcinoma, which

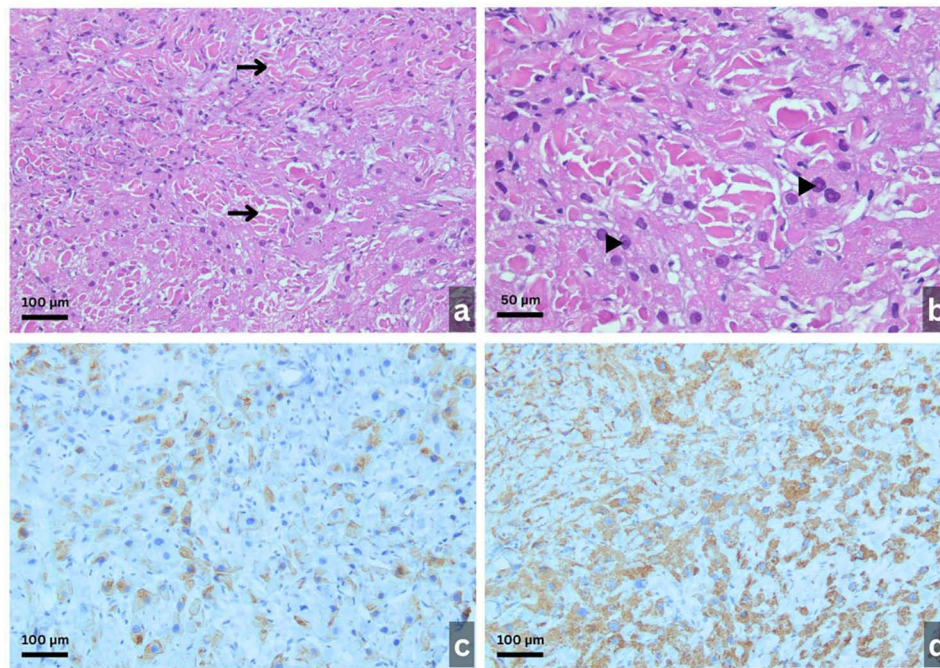


Figure 4 Histopathologic and immunophenotypic features of fibrolamellar hepatocellular carcinoma. (a) Hematoxylin and eosin (H&E) stain (20x) showing large polygonal tumor cells separated by parallel (lamellar) bundles of dense collagen (arrows). (b) High-power view (H&E, 40x) highlighting cells with abundant granular eosinophilic cytoplasm and characteristic prominent nucleoli (arrowheads). (c) Immunohistochemistry for CK7 (20x) demonstrating diffuse cytoplasmic and membranous positivity. (d) Immunohistochemistry for HepPar-I (20x) showing granular cytoplasmic staining.

classified the disease as stage IVB due to peritoneal metastases. Given the extensive metastatic burden, vascular involvement, and poor functional status, surgery and liver-directed therapies were not considered feasible.

Following expert consultation and multiple multidisciplinary tumor board discussions, it was decided to initiate a combination therapy of neratinib (Nerlynx) and nivolumab. This approach was further supported by a very recent report which evaluated neratinib monotherapy versus neratinib in combination with immune checkpoint inhibitors with or

Table 2 Immunohistochemical Markers Used in This Case, Including Antibody Clone, Vendor, Staining Platform, and Positivity Criteria for Interpretation

Marker	Clone	Vendor	Platform	Positivity Criteria
CK7	RN7	Leica	Leica BOND-MAX	Cytoplasmic/membranous staining
HepPar-I	OCHIE5	Invitrogen	Leica BOND-MAX	Granular cytoplasmic staining
CD68	514H12	Leica	Leica BOND-MAX	Granular cytoplasmic staining
MLH1	ES05	Dako	Leica BOND-MAX	Nuclear expression (Retained/Lost)
MSH2	FE11	Dako	Leica BOND-MAX	Nuclear expression (Retained/Lost)
MSH6	EP49	Dako	Leica BOND-MAX	Nuclear expression (Retained/Lost)
PMS2	EP51	Dako	Leica BOND-MAX	Nuclear expression (Retained/Lost)
HER2	4B5	Roche	Ventana	Membranous staining (per ASCO/CAP)
PD-L1	22C3	Dako	Ventana	Membranous staining (CPS/TPS)
Ki-67	MIB-1	Dako	Leica BOND-MAX	Nuclear staining (Labeling Index %)

Table 3 Clinical Timeline of Presentation, Diagnostic Workup, Treatment Planning, and Outcome

Time Point	Clinical Event
Years prior	History of iron-deficiency anemia; no known liver disease, hepatitis infection, or alcohol use.
1 month before presentation	Progressive abdominal distension with discomfort, decreased oral intake, fatigue, night sweats, and weight loss.
Presentation	Exam showed marked ascites and hepatomegaly without abdominal tenderness.
Initial laboratory evaluation	Iron-deficiency microcytic anemia, rising thrombocytosis, mild transaminitis, elevated CRP, and normal AFP, CEA, and CA 19–9.
Initial imaging	CT showed a large heterogeneous mass in hepatic segments VII/VIII with central hypodensity/calcifications, IVC compression, and extensive peritoneal metastatic disease.
Ascitic fluid evaluation	Serosanguinous ascites was drained; cytology showed malignant cells, with low SAAG and no evidence of spontaneous bacterial peritonitis.
Further imaging	MRI confirmed imaging features favoring fibrolamellar HCC, with vascular involvement and extensive peritoneal carcinomatosis.
Pathologic evaluation	Liver biopsy with histology and immunohistochemistry supported fibrolamellar hepatocellular carcinoma; molecular confirmation was not performed.
Staging and treatment planning	Multidisciplinary evaluation confirmed metastatic disease (AJCC 8th edition stage IVB). Surgery and liver-directed therapies were not feasible; neratinib plus nivolumab was planned.
Clinical outcome	The patient deteriorated rapidly before systemic treatment could be initiated and subsequently died.

without mTOR inhibitors in patients with FLC.⁵⁶ As previously mentioned, neratinib monotherapy demonstrated limited clinical efficacy compared to the combination regimens, which showed improved outcomes in a subset of patients.⁵⁶

Therefore, the proposed regimen involved a stepwise escalation of neratinib dosage: 120 mg/day on days 1–7, 160 mg/day on days 8–14, and 240 mg/day thereafter, in combination with nivolumab 240 mg administered every 2 weeks (or 480 mg every 4 weeks, per FDA-approved schedules). Additionally, next-generation sequencing via Tempus was planned to further guide treatment selection through the identification of actionable mutations or dysregulated signaling pathways.

Despite these efforts, the patient’s clinical condition deteriorated rapidly, and treatment initiation could not be undertaken prior to his death. A concise timeline of the patient’s presentation, diagnostic evaluation, management planning, and outcome is shown in Table 3, in keeping with CARE case-reporting recommendations.^{61,62}

Discussion

This case highlights the diagnostic and therapeutic complexity of fibrolamellar hepatocellular carcinoma, particularly in young adults without underlying liver disease. Our patient presented with an aggressive metastatic pattern, characterized by a large hepatic mass, extensive intra-abdominal spread including peritoneal carcinomatosis, and rapid clinical deterioration before systemic therapy could be initiated. The diagnosis was supported by the clinical presentation, imaging, and characteristic histopathologic and immunophenotypic findings, although molecular confirmation was not performed. In this context, distinguishing fibrolamellar carcinoma from conventional hepatocellular carcinoma is particularly important, as the two entities differ in their clinical setting, pathology, diagnostic framework, and management considerations. Despite expanding molecular insights and emerging targeted or immunotherapeutic strategies, effective systemic options remain limited. Continued efforts toward early recognition, molecular characterization, and enrollment in clinical trials are essential to improving outcomes in this rare malignancy.

Fibrolamellar carcinoma differs from conventional hepatocellular carcinoma in its epidemiology, pathologic features, and clinical setting. Unlike conventional HCC, which usually develops in the setting of cirrhosis or chronic liver disease,

FLC typically arises in non-cirrhotic livers and in younger patients. Its diagnosis relies on integration of clinical context, imaging, morphology, and immunophenotype, with DNAJB1–PRKACA fusion testing serving as an important molecular confirmatory tool when available.²⁵ A comparison between FLC and other liver lesions is provided in [Table 4](#).^{63–65}

The value of the present case lies not primarily in scientific novelty, but in its diagnostic and practical implications. Notable features included advanced peritoneal carcinomatosis at presentation, severe thrombocytosis, and the challenge of establishing the diagnosis without molecular confirmation. Despite ongoing advances in systemic and supportive therapies, surgical resection remains the cornerstone and only potentially curative treatment for fibrolamellar carcinoma. However, in our patient, this option was precluded by the extent of metastatic disease at presentation. Therefore, the case also underscores the difficulty of therapeutic decision-making in a rapidly deteriorating patient, in whom potential treatment-relevant markers were evaluated but systemic therapy could not be initiated before death. In this context, the report offers regional educational value as the first reported case at AUBMC and highlights the complexity of managing advanced FLC in real-world practice.

Nevertheless, this report has several important limitations. Confirmatory molecular testing for the DNAJB1–PRKACA fusion was not performed; therefore, the diagnosis was established on clinicopathologic, immunophenotypic,

Table 4 Comparison of the Key Clinicopathologic, Radiologic, Immunohistochemical, and Prognostic Features of Various Liver Lesions

Features	Fibrolamellar HCC (FLC)	Conventional HCC	Focal Nodular Hyperplasia	Hepatic Hemangioma
Epidemiology	Adolescents–young adults	Older adults (>50–60 yrs)	Young women	Any age, most common benign liver tumor
Underlying liver	Non-cirrhotic	Usually cirrhosis	Normal liver	Normal liver
Risk factors	None known	HBV, HCV, alcohol, NAFLD	Vascular malformation	Congenital vascular malformation
Clinical presentation	Abdominal pain, mass	Variable; screening in cirrhosis	Usually incidental	Usually incidental
AFP levels	Normal	Often elevated	Normal	Normal
Gross pathology	Large solitary mass with central scar	Variable nodules	Well-circumscribed lesion with central scar	Blood-filled vascular lesion, spongy appearance
Histology	Large polygonal eosinophilic cells and lamellar fibrosis	Trabecular or pseudoglandular or solid	Normal hepatocytes with fibrous scar and bile duct proliferation	Dilated blood-filled vascular channels lined by flat endothelium
Fibrosis pattern	Lamellar fibrosis	None	Central fibrous scar	None
Imaging (CT/MRI)	Heterogeneous mass and possible scar/calcification	Arterial enhancement with venous washout	Arterial enhancement with central scar and delayed enhancement	Peripheral nodular discontinuous enhancement with centripetal fill-in
Immunohistochemistry	CK7+, CD68+, HepPar-I variable	HepPar-I+, Arginase-I+	Glutamine synthetase “map-like” pattern	CD31+, CD34+
Molecular marker	DNAJB1–PRKACA fusion	TERT, TP53, CTNNB1	β-catenin activation in subset	Nonspecific
Prognosis	Intermediate; recurrence common	Variable, often poor if cirrhotic	Benign	Benign
Treatment	Surgical resection	Resection, transplant, systemic therapy	Observation	None unless symptomatic

and radiologic grounds without molecular confirmation. In addition, no systemic therapy was delivered before the patient's death, precluding assessment of treatment response and limiting conclusions regarding the clinical utility of the proposed therapeutic options. Finally, as a single-case report accompanied by a non-systematic literature review, this report has limited generalizability and should be interpreted accordingly.

Ethics Statement

Institutional Review Board approval was not required for this de-identified single-patient case report, in accordance with institutional policies. Written informed consent for publication of this case report was obtained from the patient's next of kin (brother) in accordance with applicable ethical standards as the patient is deceased.

Disclosure

The authors report no conflicts of interest in this work.

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