

CASE REPORT

Metastatic fibrolamellar hepatocellular carcinoma in the immune checkpoint and multikinase inhibitor era: A case report

Laith Al-Showbaki¹, Aseel Ghanayem^{2*}, Batool Hyari², Ammar M. Bashtawi¹, and Husam Abuawad³

¹Division of Hematology and Medical Oncology, Department of Medicine, Jordan University Hospital and School of Medicine, the University of Jordan, Amman, Jordan

²Department of Medicine, School of Medicine, The University of Jordan, Amman, Jordan

³Department of Pathology, Jordan University Hospital, Amman, Jordan

Abstract

Fibrolamellar carcinoma (FLC) is a rare liver cancer that predominantly affects young adults without liver disease. Its typical symptoms include abdominal pain, palpable mass, and/or generalized signs such as weight loss and fatigue. Although patients with localized FLC frequently experience favorable outcomes after surgical resection, the recurrence rate is high. For patients with metastatic or unresectable FLC, alternative treatments such as chemotherapy and radiation are considered; however, standardized treatment protocols remain scarce. This case report describes a 24-year-old man with de novo metastatic FLC and peritoneal involvement. The patient was administered various therapies, including atezolizumab and bevacizumab combination therapy; lenvatinib, folinic acid, fluorouracil, oxaliplatin; and folinic acid, fluorouracil, irinotecan plus bevacizumab. The response to each regimen varied, ranging from initial response followed by disease progression to no response at all. Although metastatic FLC is an uncommon disease, it presents a substantial challenge to patients and healthcare professionals due to the absence of well-established guidelines. In addition to numerous published cases, this case report may offer clinicians valuable insights into the management of FLC.

*Corresponding author:

Aseel Ghanayem
(asy0192795@ju.edu.jo)

Citation: Al-Showbaki L, Ghanayem A, Hyari B, Bashtawi AM, Abuawad H. Metastatic fibrolamellar hepatocellular carcinoma in the immune checkpoint and multikinase inhibitor era: A case report. *Cancer Plus*. 2025;7(1):122-132. doi: 10.36922/cp.5382

Received: October 21, 2024

1st revised: November 25, 2024

2nd revised: February 15, 2025

Accepted: February 17, 2025

Published online: March 6, 2025

Copyright: © 2025 Author(s).

This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Keywords: Fibrolamellar carcinoma; Hepatocellular carcinoma; Immune checkpoint inhibitors; Folinic acid; Fluorouracil; Oxaliplatin; Folinic acid; Fluorouracil; Irinotecan; Lenvatinib

1. Background

Fibrolamellar carcinoma (FLC), an uncommon primary hepatic malignancy, was first described by Edmondson in 1956.¹ It constitutes approximately 1 – 9% of all primary liver cancer cases, with an age-adjusted incidence rate estimated at 0.02/100,000 individuals.²

FLC is differentiated from hepatocellular carcinoma (HCC) by its distinctive histopathological characteristics and tendency to present in healthy, non-cirrhotic livers. Moreover, alpha-fetoprotein (AFP) levels, correlating with the HCC burden in most cases, are not typically elevated in patients with FLC.^{3,4} FLC is associated with increased

aromatase, B12-binding protein, and neurotensin levels, thereby requiring distinct approaches for diagnosis and treatment.⁵ Due to the absence of specific symptoms or signs, patients with FLC frequently exhibit non-specific manifestations; alternatively, in other cases, cancer is detected as an incidental finding. Typical symptoms include weight loss, abdominal mass, abdominal discomfort, anorexia, fever, and jaundice. Uncommon presentations include biliary obstruction, gynecomastia, Budd Chiari syndrome, severe anemia, and nonbacterial thrombotic endocarditis.⁶⁻⁸

Although surgery is preferred, there are no standardized treatment protocols for treating FLC. Novel therapies, such as immunotherapy (e.g., nivolumab and ipilimumab), demonstrate potential.⁹ HCC research encompasses advancements in combination therapies such as immunotherapy (e.g., atezolizumab and bevacizumab), which improves survival rates in patients with advanced HCC.¹⁰ Locoregional therapeutic modalities, such as transarterial chemoembolization (TACE), are integrated with systemic options to improve outcomes.¹¹ FLC is poorly understood due to its rarity, necessitating additional targeted research and clinical trials to enhance outcomes.

This article presents the case of a 24-year-old man diagnosed with de novo metastatic FLC.

2. Case presentation

A 24-year-old Jordanian man was presented to the emergency unit in October 2022 with progressive right upper quadrant abdominal pain that exacerbated for >2 months. Although the abdominal pain was generalized, it was particularly severe in the right upper quadrant. The pain was exacerbated by coughing and movement and simple analgesia did not induce complete relief. During the same period, the patient experienced intermittent episodes of nausea and vomiting, in addition to a notable weight loss of 22 kg (25% of his original body weight). However, the patient did not experience any change in his bowel habits or bleeding per rectum. His medical history was notable for an episode of provoked deep vein thrombosis earlier in 2022, following an ankle sprain, for which 15 mg of rivaroxaban was administered. The patient has no history of congenital conditions, hepatitis, diabetes mellitus, or other medical conditions. However, the patient's father had succumbed to pancreatic cancer. On physical examination, the vital signs were within the normal range; however, abdominal palpation revealed generalized tenderness.

Laboratory tests revealed normal liver enzyme levels, including alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. The

hemoglobin concentration (14.1 g/dL) and white blood cell counts were also within the normal range.

The Hepatitis B surface antigen and Hepatitis C virus antibody test results were negative. Initial clinical assessment indicated a suspicion of hepatic malignancy with distant metastasis. A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast ([Figure 1](#)) revealed the presence of a large, extensive, enhancing, hypervascular rounded hepatic tumor that occupied the majority of hepatic segments VII and VIII. The tumor measured approximately $14 \times 12 \times 11.5 \text{ cm}^3$ in the anterior-posterior (AP), transverse, and craniocaudal dimensions. The tumor demonstrated an indistinct margin, indicating potential invasion into adjacent tissue. The low-density area within the tumor potentially represented central necrosis with a large central scar. Multiple calcifications of varying sizes were identified in the central region of the tumor, with several metastatic deposits located along both sides of the right hemidiaphragm, especially at the anteromedial aspect. Numerous small dispersed metastatic deposits were noted in the abdominal wall and along the right posterior pararenal space. There were several scattered large, small, and tiny peritoneal and omental deposits, particularly in the right iliac fossa and adjacent part of the pelvis, with the largest lesion measuring 5.5 cm in diameter. A small quantity of ascites was observed in the pelvis. The clinical appearance suggested a large fibrolamellar HCC ([Figure 1](#)).

Ultrasound-guided peritoneal core biopsy revealed malignant cells with abundant cytoplasm, hyperchromatic nuclei, prominent nucleoli, irregular nuclear contours, and marked nuclear pleomorphism. [Figure 2](#) shows the histopathological and immunohistochemical analysis for the core biopsy. These cells are separated by dense fibrous bands ([Figure 2A and B](#)). The Hepbar1 immunohistochemical staining revealed diffuse positivity in these cells ([Figure 2C](#)), confirming their identity as hepatocytes. The results of AFP immunohistochemical staining were negative ([Figure 2D](#)). These histopathological

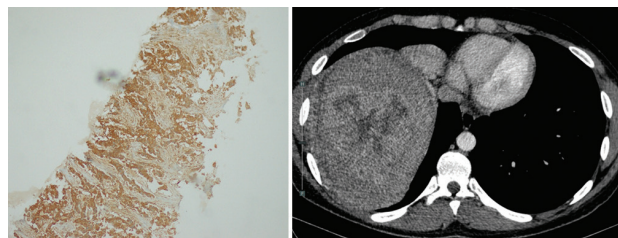


Figure 1. A large, extensive, enhancing, hypervascular, rounded hepatic tumor occupying most of hepatic segments VII and VIII measuring approximately $14 \times 12 \times 11.5 \text{ cm}^3$ was observed in the AP, transverse, and craniocaudal dimensions.

Abbreviation: AP: Anterior-Posterior.

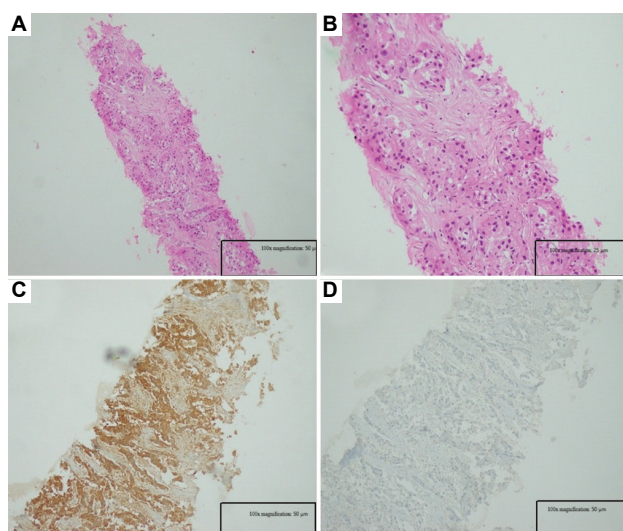


Figure 2. Histopathological and immunohistochemical analysis of the fibrolamellar lesion. (A) H&E, 100 \times : A core biopsy exhibiting the proliferation of malignant cells with thick fibrous bands extending between the cells. (B) H&E, 200 \times : A higher magnification image demonstrating the nuclear and cytoplasmic details of the proliferating cells. (C) Hepbar1 immunohistochemical stain, 100 \times : The cells exhibit diffuse positivity, indicating that these were hepatocytes. (D) AFP immunohistochemical stain, 100 \times : The cells exhibit a lack of immunoreactivity with this stain. Abbreviations: AFP: Alpha-Fetoprotein; H&E: Hematoxylin and eosin stain.

findings indicated a fibrolamellar variant of metastatic HCC. The results of CK7, HepBar1, and CD68 immunohistochemical tests were positive, whereas that for AFP was negative.

The diagnosis of metastatic FLC was confirmed with peritoneal and omental deposits. The hepatobiliary surgery team was consulted regarding the eligibility for surgical resection; however, the extensive peritoneal and omental metastasis of the tumor precluded surgical excision. Hence, systemic therapy as a combination regimen (including atezolizumab [1,200 mg], programmed cell death ligand (PDL-1) antibody, bevacizumab [15 mg/kg], and vascular endothelial growth factor [VEGF] receptor antibody) was administered once every 21 days. Due to the lack of established treatment protocols for FLC, the choice of systemic therapy was extrapolated from the HCC treatment guidelines. The combination of anti-VEGF therapy and immune checkpoint inhibitors holds promise in HCC by addressing the complementary mechanisms of immune evasion. Anti-VEGF therapies induce a more immunogenic tumor microenvironment by decreasing VEGF-mediated immunosuppression and enhancing T-cell infiltration. This boosts the efficacy of death protein 1 (PD-1)/PD-ligand (PD-L1) inhibitors, further restoring T-cell function by inhibiting immune checkpoint pathways.¹²

However, the aforementioned combinations have been implemented in several patients with advanced hepatic FLC, although with varying degrees of success.¹³⁻¹⁵ The treatment was well tolerated, and there were no considerable side effects, including infusion- or immune-related adverse events. A CT scan conducted after three cycles revealed mild disease progression in the peritoneal deposits (Figure 3), whereas a positron emission tomography scan indicated stable disease. Considering that the initial use of anti-PDL-1 inhibitors is associated with pseudoprogression and clinical improvement observed in the patient in terms of abdominal pain, weight loss, vomiting, and the radiological stability of the primary tumor on the CT scan, we continued the atezolizumab and bevacizumab combination therapy for additional 3-month.

Eventually, restaging scans were conducted at the 6-month interval, revealing definitive evidence of disease progression in the primary tumor and the metastatic deposits in the peritoneum and omentum (Figure 4).

Due to disease progression, we offered the patient TACE and transarterial radioembolization, which are viable treatment options and have well-established effectiveness in HCC.¹⁶ However, the patient declined the treatment option and thus was switched to the folinic acid, fluorouracil, oxaliplatin (FOLFOX) regimen (folinic acid 350 mg intravenously over 120 min, oxaliplatin 85 mg/m² intravenously over 120 min, fluorouracil 400 mg/m² intravenous bolus, fluorouracil 2,400 mg/m² intravenous infusion over 46 h) every 2 weeks, along with bevacizumab (7.5 mg/kg) every 2 weeks for 18 cycles (12 cycles of FOLFOX–bevacizumab, followed by six cycles of maintenance capecitabine and bevacizumab). These drugs collectively enhance cytotoxicity, leading to enhanced cancer cell apoptosis, particularly in those in the S-phase (DNA synthesis phase) of the cell cycle.¹⁷ The decision to initiate this regimen was based on the cumulative clinical experience, in which the FOLFOX regimen elicits some response in patients with advanced FLC of the liver.^{5,18,19} The patient maintained stable disease, as the best response, for 9 months, but eventually experienced disease progression at the 1-year interval (Figure 5).

The treatment was subsequently switched to the folinic acid, fluorouracil, irinotecan (FOLFIRI, a chemotherapy regimen combining irinotecan, leucovorin, and 5-fluorouracil) regimen (folinic acid 350 mg intravenously over 120 min, irinotecan 180 mg/m², fluorouracil 400 mg/m² intravenous bolus, fluorouracil 2,400 mg/m² intravenous infusion over 46 h) every 14 days, along with bevacizumab (7.5 mg/kg) every 14 days.

FOLFIRI is predominantly used to treat metastatic colorectal cancer. It works by selectively targeting and

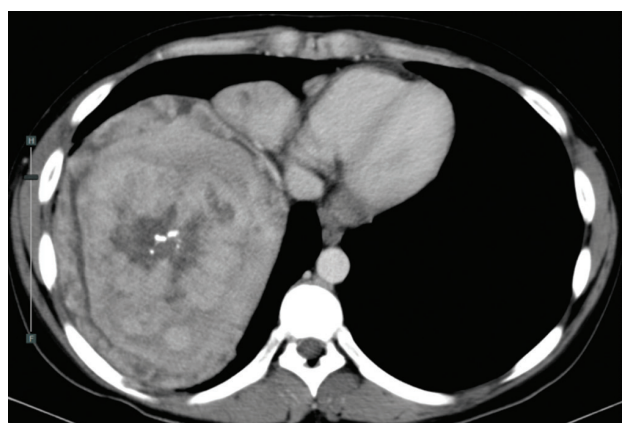


Figure 3. Although the size of the extensive hypervascular hepatic tumor remains stable, substantial metastatic deposits were observed in the right hemidiaphragm, abdominal wall, pararenal space, porta hepatis, and falciform ligament, with newly developed necrotic centers in the abdominal wall, pararenal space, and porta hepatis.



Figure 4. Interval increase in the size of the large hypervascular hepatic tumor, now measuring $13 \times 12 \text{ cm}^2$ (previously $11.7 \times 9.4 \text{ cm}^2$). Considerable growth of multiple metastatic deposits was noted in the right hemidiaphragm, falciform ligament, abdominal wall, pararenal space, and porta hepatis. Interval increases in the size of the numerous scattered peritoneal and omental deposits were observed in the right iliac fossa and pelvis.

disrupting DNA replication in rapidly dividing cancer cells. Irinotecan inhibits topoisomerase I, preventing the DNA unwinding required for replication. Leucovorin enhances the efficacy of 5-fluorouracil, inhibiting thymidylate synthase – an enzyme crucial for DNA synthesis. Altogether, this regimen induces apoptosis in cancer cells and delays tumor progression.²⁰

In HCC, FOLFIRI has been explored as a second-line therapy, often combined with targeted agents such as bevacizumab; however, its efficacy varies with the complexity of HCC and underlying liver dysfunction.

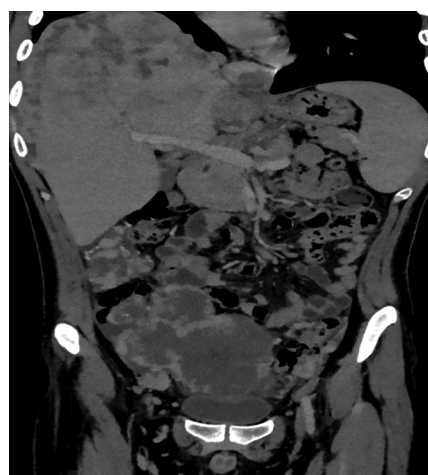


Figure 5. The large hepatic tumor remained grossly stable, measuring approximately $13.3 \times 13.2 \times 12 \text{ cm}^3$. Marked hepatomegaly is noted with a craniocaudal dimension of 28 cm. There is an interval increase in the size of multiple previously documented metastatic deposits, including those in the right anterior pericardial recess, along the fissures of the ligamentum teres and ligamentum venosum, and in the right external iliac region.

Although not a standard FLC treatment, it is sometimes used in clinical trials or off-label settings. Outcomes are currently under investigation because owing to its unique biology, FLC responds differently.

After six cycles, the patient exhibited stable disease, despite substantial toxic effects (comprising fatigue and diarrhea that necessitated dose reduction to 80% and 60% of the optimal dose and the omission of the 5-fluorouracil bolus dose) and treatment delays (Figure 6). He completed nine cycles; however, the patient continued to experience fatigue and Grade 3 diarrhea despite the abovementioned measures. Consequently, pursuant to the patient's request, chemotherapy was discontinued. Two weeks later, the patient's condition improved in terms of exertional capacity and bowel habits.

The decision for administering systemic therapy was reconsidered. The options comprised chemotherapy rechallenge with a modified dose of FOLFIRI plus bevacizumab, and lenvatinib (a multikinase inhibitor approved for first-line treatment of advanced HCC, also used in FLC in several case reports).²¹⁻²³ Conducting next-generation sequencing (NGS) for identifying any actionable genetic mutation was presented, although the test is not funded by public insurance. Finally, the initiation of lenvatinib and deferment of NGS testing until disease progression was decided. Lenvatinib was administered at 12 mg po daily, adhering to the dosing regimen for patients with HCC. Its dosage was subsequently reduced to 8 mg po daily due to extreme fatigue and intolerable dry mouth. The patient has been maintained on that dose to date,



Figure 6. Large hepatic mass with multiple necrotic areas along with satellite lesions and multiple calcified deposits and several enlarged peritoneal deposits.

with stable disease being the best response over the last 4 months. In addition, the patient is currently undergoing multiple radiation therapies at another center as palliative therapy for the recent lymph node enlargement in his neck.

(Table 1) compares between our treatment findings and previously reported cases.

3. Discussion

FLC is a rare and unique primary liver neoplasm. Unlike HCC, which typically develops in older individuals with a history of liver disease, FLC predominantly affects younger patients, often under the age of 40, who are predominantly Caucasian and do not have underlying liver conditions. HCC is frequently caused by factors such as active hepatic inflammation, viral infection, alcohol-related liver damage, non-alcoholic fatty liver disease, cirrhosis, and/or dietary exposure to aflatoxin B1.³⁰

FLC typically presents non-specific clinical features, such as abdominal pain, vomiting, nausea, and early satiety.³ Our patient reported experiencing generalized abdominal pain, nausea, vomiting, and significant weight loss (25% drop in body weight over 2 months). Serum tumor markers play a minimal role in the evaluation and diagnosis of FLC, considering they are elevated only in 10% of cases. However, studies suggest a significant correlation between elevated serum Vitamin B12 levels and the presence of FLC.^{31,32}

The sonographic features of fibrolamellar HCC are usually non-specific, appearing as well-defined masses with variable echogenicity. For further characterization, multiphasic CT employing a hepatic protocol or dynamic contrast-enhanced/magnetic resonance imaging

is usually required. On CT, FLC often manifests as large, heterogeneous lesions with a mean diameter of approximately 13 cm. The mass appears enhanced, and the typical HCC feature of arterial enhancement with portal washout is not visible.^{8,33,34} These tumors are well-defined in 80 – 100% of cases and frequently exhibit a lobulated outline. Calcification is frequently observed in 40 – 68% of tumors, and a central stellate scar is present in 65 – 70% of cases. The presence of calcifications within the central scar is a valuable diagnostic feature. Although intratumoral hemorrhage is rare, tumor necrosis may develop.³⁴ Table 2 demonstrates a comparison between FLC and HCC.

Our patient exhibited normal levels of liver enzymes, negative Hepatitis B surface antigen, and Hepatitis C virus antibody; additionally, the CT scan revealed a large, extensive, enhancing, hypervascular rounded hepatic tumor measuring approximately $14 \times 12 \times 11.5 \text{ cm}^3$ in AP, transverse, and craniocaudal dimensions. This tumor exhibited ill-defined margins with probable invasion of the surrounding hepatic tissue. The low-density area within the tumor potentially represented central necrosis with a large central scar. Multiple variably sized calcifications were observed at the central part of the tumor.

Reports on the genetic and molecular aspects of fibrolamellar HCC report the presence of a 400-kb deletion on chromosome 19 as a notable characteristic, which results in the functional DNAJB1-PRKACA fusion transcript; this fusion is detectable in 100% of patients with FLC and is identified as the primary oncogenic driver of the tumor.^{16,38}

The primary function of the DNAJB1-PRKACA fusion protein is to phosphorylate and inactivate the salt-inducible kinases. This inhibition disrupts the regulation of the CRTC2 transcriptional coactivator and p300 acetyltransferase, leading to transcriptional reprogramming and increased global histone acetylation. These molecular changes facilitate malignant cell proliferation and tumor progression. FLC tumors depend on the continuous expression of DNAJB1-PRKACA for their growth and survival. Depletion of this fusion protein triggers apoptosis, highlighting the tumor dependence on its oncogenic activity. Furthermore, another study revealed an elevated level of tyrosine-phosphorylated β -catenin in patients with FLC. A gene fusion event involving GLIS3, a transcription factor critical for liver, pancreas, and neuroendocrine cell development, and CLPTM1L has also been identified, with oncogenic effects observed in liver cancer cells.³⁹⁻⁴² Cytogenetic studies have shown that FLC is associated with aneuploidy in 50% of cases, whereas the remaining 50% demonstrate tetraploidy.⁶

FLC is predominantly treated through surgical resection, facilitated by the absence of cirrhosis and the typically

Table 1. Comparison of our case findings with previously reported cases of fibrolamellar HCC

Therapeutic approach	Evidence from literature	Current case findings
Surgical resection	Surgical resection is the primary treatment for localized FLC. An SEER database analysis indicates an overall survival rate of 58.2% for patients following resection; however, more than two-third of these patients eventually experience disease recurrence. ^{24,25} In a case report titled “Fibrolamellar hepatocellular carcinoma that was successfully treated with surgical resection: a case report,” a 19-year-old patient diagnosed with fibrolamellar HCC underwent an extended right hemihepatectomy. The patient received follow-up examinations every 3 – 6 months, with no recurrence observed for 3 years and 6 months. ²⁶	Not feasible due to extensive metastatic spread to the peritoneum and omentum
Atezolizumab plus bevacizumab	In HCC, this combination improves survival by targeting VEGF-mediated immunosuppression and restoring T-cell function. 12 Limited data in FLC treatment indicate variable success. ¹³⁻¹⁵ The case report entitled “Fibrolamellar hepatocellular carcinoma treated with atezolizumab and bevacizumab: two case reports,” describes the treatment of two Arabic patients with advanced fibrolamellar HCC with an atezolizumab and bevacizumab combination therapy. Unfortunately, neither patient exhibited clinical benefits from this treatment regimen. Therefore, although this combination has demonstrated benefits in classical HCC, the existing data indicated a lack of benefit and tumor response in FLC. ¹³	Mild progression was noted after three cycles; continued for clinical improvement but was discontinued after 6 months due to disease progression in the primary tumor and the metastatic deposits.
FOLFOX–bevacizumab	These drugs cumulatively enhance cytotoxicity, leading to enhanced apoptosis of cancer cells, particularly those in the S-phase (DNA synthesis phase) of the cell cycle. ¹⁷ In the case report titled “Fibrolamellar Hepatocellular Carcinoma with Multiple Lung Metastases Treated with Multidisciplinary Therapy,” a 20-year-old man was diagnosed with FLC accompanied by multiple lung metastases. The treatment approach was multidisciplinary and included chemotherapy with modified FOLFOX6 regimen [fluorouracil bolus (400 mg/m ²), l-leucovorin (200 mg/m ²), oxaliplatin (85 mg/m ²), and fluorouracil (2,400 mg/m ²)]. Following three cycles of modified FOLFOX6, imaging studies did not indicate any disease progression. Consequently, the patient underwent surgical resection of the liver tumors and received surgical resection and RFA for the lung metastases. Post-treatment evaluations did not reveal any evident residual or recurrent lesions, suggesting that this aggressive multidisciplinary approach was effective in managing the disease. ²⁷	Maintained stable disease for 9 months but eventually progressed at the 1-year interval
FOLFIRI–bevacizumab	The FOLFIRI regimen is typically employed for treating metastatic colorectal cancer. It works by targeting and disrupting DNA replication in rapidly dividing cancer cells. ²⁰ To our knowledge, no clinical trials are specifically investigating the efficacy of the FOLFIRI regimen for treating fibrolamellar HCC. However, recent research has investigated the efficacy of irinotecan when used in combination with other agents for the FLC treatment. The article entitled “Targeting BCL-XL in fibrolamellar hepatocellular carcinoma,” investigated the combination of DT2216, a PROTAC that selectively degrades the antiapoptotic protein BCL-XL with irinotecan, a topoisomerase I inhibitor. This combination was evaluated <i>in vitro</i> and <i>in vivo</i> . The results indicated remarkable synergy between DT2216 and irinotecan, leading to substantial tumor reduction at clinically feasible doses. ²⁸	Stable disease was observed after six cycles; however, after nine cycles, treatment was discontinued due to Grade 3 diarrhea and fatigue.
Lenvatinib	Lenvatinib (a multikinase inhibitor approved as the first-line treatment for advanced HCC, which has also been used in FLC in some case reports). ²¹⁻²³ In the case report titled “A Case of Fibrolamellar Hepatocellular Carcinoma in Which Tumor Control Was Achieved by Re-Administering Atezolizumab and Bevacizumab,” the patient was initially treated with atezolizumab and bevacizumab combination therapy, leading to tumor shrinkage. However, due to adverse events, this treatment was discontinued, causing tumor regrowth. To control progression, the patient was administered lenvatinib at 4 mg/day initiating on August 16, 2023. Despite this intervention, by October 30, 2023, peritoneal dissemination was observed, indicating further disease progression, requiring lenvatinib cessation. Subsequently, the readministration of atezolizumab and bevacizumab successfully re-established tumor control. ²⁹	Achieved a stable disease state over 4 months; however, the dose was reduced due to intolerable fatigue and dry mouth.
Radiation/TACE	Radiation therapy and TACE are viable treatment choices, and their role is well-defined in HCC. ¹⁶	Declined by the patient despite its potential benefits

Abbreviations: FLC: Fibrolamellar carcinoma; FOLFOX: Folinic acid, fluorouracil, oxaliplatin; FOLFIRI: Folinic acid, fluorouracil, irinotecan; HCC: Hepatocellular carcinoma; PROTAC: Proteolysis targeting chimera; RFA: Radiofrequency ablation; SEER: The surveillance, epidemiology, and end results; TACE: Transarterial chemoembolization; VEGF: Vascular endothelial growth factor.

Table 2. Comparison between fibrolamellar HCC and HCC

Characteristic	Fibrolamellar HCC	HCC
Clinical symptoms	<ul style="list-style-type: none"> Occurs in young adults (aged 10 – 40 years) without underlying liver disease Symptoms: Abdominal pain, palpable mass, weight loss, and/or jaundice (rare) Subtle symptoms frequently lead to delayed diagnosis. 	<ul style="list-style-type: none"> Usually in older patients (aged 50 – 70 years), often with chronic liver disease (e.g., cirrhosis and/or hepatitis B/C) Symptoms: Abdominal pain, weight loss, anorexia, fatigue, and jaundice (more common) Associated with alcohol use and metabolic syndrome
Diagnostic markers	<ul style="list-style-type: none"> Elevated serum neurotensin and Vitamin B12 binding protein levels Normal or mildly elevated AFP levels Characteristic marker: DNAJB1-PRKACA fusion gene 	<ul style="list-style-type: none"> Notably elevated AFP levels (in several patients, but not all) Other markers: DCP, glypican-3
Imaging characteristics	<ul style="list-style-type: none"> CT/MRI: Well-circumscribed, large mass with central scar Central scar enhances on delayed imaging Calcifications present in approximately 30% of cases No background liver cirrhosis 	<ul style="list-style-type: none"> CT/MRI: hypervascular mass with arterial enhancement and washout in the venous phase Often develops in a cirrhotic liver Satellite nodules and vascular invasion common
Prognosis	<ul style="list-style-type: none"> Better prognosis than HCC Slow growth, with higher resectability rates Survival can extend for years; however, recurrence is possible Less responsive to systemic therapies 	<ul style="list-style-type: none"> Worse prognosis owing to the aggressive nature and late-stage diagnosis Poorer resectability rates, higher recurrence risk Associated with chronic liver failure and portal hypertension

Notes: Data adapted from Lafaro and Pawlik,³⁵ Abdelhamed and El-Kassas,³⁶ Di Bisceglie.³⁷

Abbreviations: AFP: Alpha-fetoprotein; CT/MRI: Computed tomography/Magnetic resonance imaging; DCP: Des-gamma-carboxy prothrombin; FLC: Fibrolamellar carcinoma; HCC: Hepatocellular carcinoma.

young age at diagnosis, even in the presence of large tumors. Resection rates are high, ranging from 60% to 70%. Unlike classic HCC, lymph node involvement is observed in 30 – 60% of patients with FLC undergoing surgery, making comprehensive periportal lymphadenectomy a critical component of radical resection. According to data from a fibrolamellar research consortium, 42% of patients exhibit vascular invasion, predominantly affecting major vessels such as the hepatic or portal veins.² A SEER database analysis revealed an overall survival rate of 58.2% for patients after resection, although over two-third patients ultimately developed disease recurrence.^{24,25}

Herein, although there was no evidence of cirrhosis, the unfavorable prognosis was indicated by the presence of metastatic disease and consequently by the inability to undergo intensive surgical intervention, such as liver transplantation or tumor resection.

In advanced disease, the role of chemotherapy in FLC treatment remains uncertain because these tumors are generally non-responsive to chemotherapy.² Due to the low incidence of FLC, no randomized controlled trials have identified the most effective chemotherapeutic regimen. In addition, to the best of our knowledge, there is no documented evidence of effective neoadjuvant or adjuvant systemic therapies for this disease. Although chemotherapy with agents such as gemcitabine, cisplatin, 5-fluorouracil, interferon, and oxaliplatin has been explored, the response levels have been variable. Continuous 5-FU infusion in conjunction with subcutaneous interferon- α has achieved a response rate of 62% and a median overall

survival of 23 months. Although targeted therapies such as sorafenib have been applied in the FLC treatment, their effectiveness remains limited. Compared with those receiving sorafenib, a recent international, open-label, randomized Phase 3 trial demonstrated that patients with unresectable HCC experienced improved overall and progression-free survivals when treated with atezolizumab and bevacizumab combination therapy.^{12,43,44} However, two case reports have demonstrated treatment failure with atezolizumab and bevacizumab combination therapy in metastatic FLC, indicating disease progression within just 2 months.¹³

Regarding therapies except chemotherapy, radiation therapy has been applied as a treatment for patients with FLC who are ineligible for surgical resection or liver transplantation. Moreover, radiation therapy can be combined with other therapeutic modalities for improved FLC treatment outcomes. Another treatment modality involves the use of immunosuppressive drug regimens. The earliest active immune agent utilized in FLC treatment regimens was rIFN α 2b plus chemotherapy;⁴⁵ however, these drugs exhibit a substantial variability in response between patients with FLC.⁴⁶

Approximately two-thirds of the FLC specimens exhibited membranous PD-L1 expression on tumor cells and PD-L1 expression on TILs and TAMs.⁴⁷ Consequently, a novel drug line of immune checkpoint inhibitors (ICIs) was developed to treat FLC by blocking receptors functioning as natural brakes of the immune system such as programmed cell PD-1⁴⁸ or its PD-L1. Thus, they

have become an integral element of treatment regimens of different malignancies including HCC. However, the effectiveness of ICI therapy in FLC is largely unknown. The limited efficacy of ICI monotherapy can be attributed to intrinsic tumor characteristics of FLC, including low immunogenicity, as evidenced by low TMB and negative PD-L1 expression – two biomarkers that reflect the sensitivity to ICI therapy.¹⁵

Another promising targeted therapy includes the protein kinase inhibitors, particularly those that inhibit cAMP-activated catalytic subunit alpha (PRKACA). In an FLC preclinical model, synthesized DS89002333 – a novel potent PRKACA inhibitor – demonstrated antitumor activity. Moreover, a notable finding in previous studies was the 83% increase in BCL-XL transcripts in FLC when contrasted with the adjacent normal liver tissue. This discovery has reprocessed drug screens and identified a dual inhibition strategy by combining irinotecan (TOPO1 inhibitor) and DT2216 (BCL-XL inhibitor) as potential options to treat FLC.⁴⁵

The 5-year survival rate for patients with FLC is approximately 67%, which is remarkably higher than that of typical HCC and indicates a relatively improved prognosis.⁴⁹ However, for patients with locally advanced or metastatic FLC, the prognosis remains poor. Furthermore, the recurrence rate is considerably high, with up to 60% of cases recurring within the first 5 years.⁵⁰

Herein, the patient received multiple lines of therapies, including atezolizumab and bevacizumab combination therapy, FOLFOX and FOLFIRI, and lenvatinib, with varying responses to each regimen.

4. Conclusion

FLC is a distinctive form of primary hepatic malignancy; its cause remains unknown, and its molecular basis is not entirely understood. Although FLC can be effectively managed with surgical resection and adjuvant chemotherapy in select non-metastatic cases, treatment options for metastatic FLC remain largely undefined. Additional research and modern clinical studies are required to improve characterize the tumor biology and develop targeted therapies aimed at enhancing survival outcomes for all patients, particularly those with advanced disease.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that the research was concluded in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Author contributions

Conceptualization: Laith Al-Showbaki, Aseel Ghanayem, Batool Hyari, Ammar M. Bashtawi

Formal analysis: Laith Al-Showbaki, Aseel Ghanayem, Batool Hyari

Investigation: Aseel Ghanayem, Batool Hyari, Husam Abuawad

Writing – original draft: All authors

Writing – review & editing: Laith Al-Showbaki, Aseel Ghanayem

Ethics approval and consent to participate

Ethical approval is not required at our institution to publish an anonymous case report and written informed consent was obtained from the patient himself.

Consent for publication

Written informed consent was obtained from the patient.

Availability of data

Not applicable.

References

- Edmondson HA. Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. *AMA J Dis Child.* 1956;91(2):168-186.
doi: 10.1001/archpedi.1956.02060020170015
- Chaudhari VA, Khobragade K, Bhandare M, Shrikhande SV. Management of fibrolamellar hepatocellular carcinoma. *Chin Clin Oncol.* 2018;7(5):51.
doi: 10.21037/cco.2018.08.08
- Craig JR, Peters RL, Edmondson HA, Omata M. Fibrolamellar carcinoma of the liver: A tumor of adolescents and young adults with distinctive clinico-pathologic features. *Cancer.* 1980;46(2):372-379.
doi: 10.1002/1097-0142(19800715)46:2<372:aid-cncr2820460227>3.0.co;2-s
- Graham RP, Torbenson MS. Fibrolamellar carcinoma: A histologically unique tumor with unique molecular findings. *Semin Diagn Pathol.* 2017;34:146-152.
doi: 10.1053/j.semdp.2016.12.010
- O'Neill AF, Church AJ, Perez-Atayde AR, Shaikh R, Marcus KJ, Vakili K. Fibrolamellar carcinoma: An entity all

- its own. *Curr Probl Cancer*. 2021;45(4):100770.
doi: 10.1016/j.currproblcancer.2021.100770
6. Alshareefy Y, Shen CY, Prekash RJ. Exploring the molecular pathogenesis, diagnosis and treatment of fibrolamellar hepatocellular carcinoma: A state of art review of the current literature. *Pathol Res Pract*. 2023;248:154655.
doi: 10.1016/j.prp.2023.154655
 7. Alsadery HA, Almainan H, Alibrah R, *et al*. Case report of fibrolamellar hepatocellular carcinoma in A 15-year-old male. *Med Arch*. 2022;76(5):387-390.
doi: 10.5455/medarh.2022.76.387-390
 8. Bacinschi X, Zgura AF, Mercan-Stanciu A, *et al*. Management of diagnosis and treatment in a case of fibrolamellar carcinoma. *Cancer Diagn Progn*. 2021;1(1):23-28.
doi: 10.21873/cdp.10004
 9. Berger R, Dinstag G, Tirosh O, *et al*. Fibrolamellar carcinoma transcriptomic-based treatment prediction: Complete response after nivolumab and ipilimumab. *J Immunother Cancer*. 2022;10(12):e005620.
doi: 10.1136/jitc-2022-005620
 10. Wu J, Liu W, Qiu X, *et al*. A Noninvasive approach to evaluate tumor immune microenvironment and predict outcomes in hepatocellular carcinoma. *Phenomics*. 2023;3(6):549-564.
doi: 10.1007/s43657-023-00136-8
 11. Tan J, Fan W, Liu T, *et al*. TREM2⁺ macrophages suppress CD8⁺ T-cell infiltration after transarterial chemoembolisation in hepatocellular carcinoma. *J Hepatol*. 2023;79(1):126-140.
doi: 10.1016/j.jhep.2023.02.032
 12. Finn RS, Qin S, Ikeda M, *et al*. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *New Engl J Med*. 2020;382(20):1894-1905.
doi: 10.1056/nejmoa1915745
 13. Al Zahrani A, Alfakeeh A. Fibrolamellar hepatocellular carcinoma treated with atezolizumab and bevacizumab: Two case reports. *J Med Case Rep*. 2021;15(1):132.
doi: 10.1186/s13256-021-02695-8
 14. Matsuki R, Okano N, Hasui N, *et al*. Atezolizumab and bevacizumab combination therapy and sequential conversion hepatectomy for advanced fibrolamellar hepatocellular carcinoma presenting pseudoprogression. *Liver Cancer*. 2023;12(2):180-183.
doi: 10.1159/000527250
 15. Chen KY, Popovic A, Hsiehchen D, *et al*. Clinical outcomes in fibrolamellar hepatocellular carcinoma treated with immune checkpoint inhibitors. *Cancers (Basel)*. 2022;14(21):5347.
doi: 10.3390/cancers14215347
 16. Bernon MM, Gandhi K, Allam H, Singh S, Kloppers J, Jonas E. Trans-arterial therapy for fibrolamellar carcinoma: A case report and literature review. *Int J Surg Case Rep*. 2022;94:106980.
doi: 10.1016/j.ijscr.2022.106980
 17. Zhang N, Yin Y, Xu SJ, Chen WS. 5-Fluorouracil: Mechanisms of resistance and reversal strategies. *Molecules*. 2008;13(8):1551-1569.
doi: 10.3390/molecules13081551
 18. Hundal J, Nagaraj A, Luke A, Vredenburg J. A rare case of metastatic ectopic fibrolamellar hepatocellular carcinoma in a young healthy patient: A case report. *Curr Probl Cancer Case Rep*. 2021;4:100099.
doi: 10.1016/j.cpccr.2021.100099
 19. Thakral N, Simonetto DA. Hyperammonemic encephalopathy: An unusual presentation of fibrolamellar hepatocellular carcinoma. *Clin Mol Hepatol*. 2020;26(1):74-77.
doi: 10.3350/cmh.2018.0042
 20. Chai Y, Liu JL, Zhang S, *et al*. The effective combination therapies with irinotecan for colorectal cancer. *Front Pharmacol*. 2024;15:1356708.
doi: 10.3389/fphar.2024.1356708
 21. Kent P, Stockwell T, Tasse JC, *et al*. Lenvatinib, gemcitabine, and oxaliplatin for 67 patients with fibrolamellar carcinoma. *J Clin Oncol*. 2024;42:e16151.
doi: 10.1200/JCO.2024.42.16_suppl.e16151
 22. Kent P, Tasse JC, Schadde E, *et al*. Early experience with nivolumab, gemcitabine, and lenvatinib for fibrolamellar hepatocellular carcinoma. *J Clin Oncol*. 2023;41:4076.
doi: 10.1200/JCO.2023.41.16_suppl.4076
 23. Gottlieb S, Gliksberg A, Schadde E, Kent P. *Novel Systemic Therapies in the Treatment of Fibrolamellar Carcinoma*. United States: Wolters Kluwer Health; 2021.
 24. Chakrabarti S, Tella SH, Kommalapati A, *et al*. Clinicopathological features and outcomes of fibrolamellar hepatocellular carcinoma. *J Gastrointest Oncol*. 2019;10(3):554-561.
doi: 10.21037/jgo.2019.01.35
 25. Smith M, Tomboc PJ, Markovich B. Fibrolamellar hepatocellular carcinoma. *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2024.
 26. Na SK. Fibrolamellar hepatocellular carcinoma that was successfully treated with surgical resection: A case report. *J Liver Cancer*. 2022;22(2):178-182.
doi: 10.17998/jlc.2022.06.10
 27. Tanaka H, Hijioka S, Iwaya H, *et al*. Fibrolamellar hepatocellular carcinoma with multiple lung metastases

- treated with multidisciplinary therapy. *Intern Med.* 2018;57(24):3537-3543.
doi: 10.2169/internalmedicine.1243-18
28. Shebl B, Ng D, Lalazar G, *et al.* Targeting BCL-XL in fibrolamellar hepatocellular carcinoma. *JCI Insight.* 2022;7(17):e161820.
doi: 10.1172/jci.insight.161820
 29. Hagiwara S, Oda I, Ueshima K, *et al.* A case of fibrolamellar hepatocellular carcinoma in which tumor control was achieved by re-administering atezolizumab and bevacizumab. *Cancer Rep (Hoboken).* 2024;7(12):e70090.
doi: 10.1002/cnr.2.70090
 30. Torbenson M. Review of the clinicopathologic features of fibrolamellar carcinoma. *Adv Anat Pathol.* 2007;14(3):217-223.
doi: 10.1097/PAP.0b013e3180504913
 31. Assi HA, Mukherjee S, Machiorlatti M, Vesely S, Pareek V, Hatoum H. Predictors of outcome in patients with fibrolamellar carcinoma: Analysis of the national cancer database. *Anticancer Res.* 2020;40(2):847-855.
doi: 10.21873/anticancer.14017
 32. Wahab MA, El Hanafy E, El Nakeeb A, Ali MA. Clinicopathological features and surgical outcome of patients with fibrolamellar hepatocellular carcinoma (experience with 22 patients over a 15-year period). *World J Gastrointest Surg.* 2017;9(2):61-67.
doi: 10.4240/wjgs.v9.i2.61
 33. Friedman AC, Lichtenstein JE, Goodman Z, Fishman EK, Siegelman SS, Dachman AH. Fibrolamellar hepatocellular carcinoma. *Radiology.* 1985;157(3):583-587.
doi: 10.1148/radiology.157.3.2997835
 34. Ganeshan D, Szklaruk J, Kundra V, Kaseb A, Rashid A, Elsayes KM. Imaging features of fibrolamellar hepatocellular carcinoma. *AJR Am J Roentgenol.* 2014;202(3):544-552.
doi: 10.2214/AJR.13.11117
 35. Lafaro KJ, Pawlik TM. Fibrolamellar hepatocellular carcinoma: Current clinical perspectives. *J Hepatocell Carcinoma.* 2015;2:151-157.
doi: 10.2147/jhc.S75153
 36. Abdelhamed W, El-Kassas M. Fibrolamellar hepatocellular carcinoma: A rare but unpleasant event. *World J Gastrointest Oncol.* 2022;14(6):1103-1114.
doi: 10.4251/wjgo.v14.i6.1103
 37. Di Bisceglie AM. Epidemiology and clinical presentation of hepatocellular carcinoma. *J Vasc Interv Radiol.* 2002;13(9 Pt 2):S169-S171.
doi: 10.1016/s1051-0443(07)61783-7
 38. Bauer J, Köhler N, Maringer Y, *et al.* The oncogenic fusion protein DNAJB1-PRKACA can be specifically targeted by peptide-based immunotherapy in fibrolamellar hepatocellular carcinoma. *Nat Commun.* 2022;13(1):6401.
doi: 10.1038/s41467-022-33746-3
 39. Xu L, Hazard FK, Zmoos AF, *et al.* Genomic analysis of fibrolamellar hepatocellular carcinoma. *Hum Mol Genet.* 2015;24(1):50-63.
doi: 10.1093/hmg/ddu418
 40. Cieply B, Zeng G, Proverbs-Singh T, Geller DA, Monga SP. Unique phenotype of hepatocellular cancers with exon-3 mutations in beta-catenin gene. *Hepatology.* 2009;49(3):821-831.
doi: 10.1002/hep.22695
 41. Neumayer C, Ng D, Jiang CS, *et al.* Oncogenic addiction of fibrolamellar hepatocellular carcinoma to the fusion kinase DNAJB1-PRKACA. *Clin Cancer Res.* 2023;29(1):271-278.
doi: 10.1158/1078-0432.Ccr-22-1851
 42. Gritti I, Wan J, Weersekara V, *et al.* DNAJB1-PRKACA fusion drives fibrolamellar liver cancer through impaired SIK signaling and CRTC2/p300-mediated transcriptional reprogramming. *Cancer Discov.* 2025;15(2):382-400.
doi: 10.1158/2159-8290.Cd-24-0634
 43. Patt YZ, Hassan MM, Lozano RD, *et al.* Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon Alfa-2b for treatment of hepatocellular carcinoma. *J Clin Oncol.* 2003;21(3):421-427.
doi: 10.1200/JCO.2003.10.103
 44. Ang CS, Kelley RK, Choti MA, *et al.* Clinicopathologic characteristics and survival outcomes of patients with fibrolamellar carcinoma: Data from the fibrolamellar carcinoma consortium. *Gastrointest Cancer Res.* 2013;6(1):3-9.
 45. Gummadi J, Wang X, Xie C. Current advances in the treatment of fibrolamellar carcinoma of liver. *J Hepatocell Carcinoma.* 2023;10:745-752.
doi: 10.2147/jhc.S406902
 46. Kang E, Martinez M, Moisander-Joyce H, *et al.* Stable liver graft post anti-PD1 therapy as a bridge to transplantation in an adolescent with hepatocellular carcinoma. *Pediatr Transplant.* 2022;26(3):e14209.
doi: 10.1111/petr.14209
 47. El Dika I, Bowman AS, Berger MF, *et al.* Molecular profiling and analysis of genetic aberrations aimed at identifying potential therapeutic targets in fibrolamellar carcinoma of the liver. *Cancer.* 2020;126(18):4126-4135.
doi: 10.1002/cncr.32960

-
48. Kang S, Magliocca J, Sellers M, *et al.* Successful liver transplantation of recurrent fibrolamellar carcinoma following clinical and pathologic complete response to triple immunochemotherapy: A case report. *Oncol Res Treat.* 2022;45(7-8):430-437.
doi: 10.1159/000524872
49. Kunz G Jr., Chung J, Ali SZ. Hepatocellular carcinoma-fibrolamellar variant: Cytopathology of an unusual case. *Diagn Cytopathol.* 2002;26(4):257-261.
doi: 10.1002/dc.10088
50. Bawashkhah AS, Sindi GA, Almatrafi SB, Obaid EF, Bakhsh RI. Fibrolamellar hepatocellular carcinoma in the absence of risk factors: A case report. *Cureus.* 2022;14:e32483.
doi: 10.7759/cureus.32483