A Rare Form of Hepatocellular Carcinoma in a Patient With Crohn's Disease

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ABSTRACT

Introduction: Fibrolamellar carcinoma (FLC) is a rare variant of hepatocellular carcinoma (HCC) that affects people without underlying cirrhosis. The association between HCC and inflammatory bowel disease has been reported in patients with ulcerative colitis.

Case Presentation: A 23-year-old woman with newly diagnosed Crohn disease was incidentally found to have a large hepatic mass during evaluation of gastrointestinal symptoms. Imaging findings were concerning for HCC. Pathology after surgical resection revealed fibrolamellar variant of HCC. The patient developed recurrent FLC and underwent a portal lymphadenectomy and resection of a portal mass. She was started on lenvatinib and has remained in remission.

Discussion: Reports of HCC in patients with IBD are limited, and previously reported cases of FLC have occurred exclusively in patients with ulcerative colitis. We describe a case of FLC in a patient newly diagnosed with Crohn's disease. Although curative resection is possible, 50% to 100% of patients experience relapse and recurrence.

Conclusions: This case highlights the characteristic clinical, radiographic, histopathologic, and molecular features of FLC and expands the limited literature on the association between FLC and IBD.

INTRODUCTION

Fibrolamellar carcinoma (FLC) is a rare variant of hepatocellular carcinoma (HCC) that typically affects adolescents and young adults without underlying cirrhosis or primary liver disease. In the United States, FLC accounts for less than 1% of primary hepatic tumors. FLC's etiology and pathogenesis are poorly understood. Although FLC most often occurs in younger individuals, a bimodal age distribution has been reported, with peaks at 10 to 30 years and 70 to 79 years.[1] FLC affects males and females equally.

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The clinical presentation of FLC is highly variable and may include nausea, abdominal pain or discomfort, abdominal fullness, weight loss, night sweats, and jaundice. A review of 95 cases of FLC found that 60% of patients had extrahepatic metastases at diagnosis, with regional lymph node involvement being the most common site, followed by the lungs and peritoneum.[2]

Diagnosis of FLC is typically supported by clinical presentation, imaging findings, and normal serum alpha-fetoprotein (AFP) levels. The diagnostic gold standard is characteristic histopathology with confirmation of characteristic gene mutation. Computed tomography (CT) and magnetic resonance imaging (MRI) typically demonstrate a large, heterogeneous, well-defined lesion with lobulated contours, a central scar, calcifications, and areas of necrosis.[3] FLC tumors demonstrate a characteristic DNAJB1-PRKACA fusion; however, this alteration is not specific to FLC and has been identified in other malignancies.[4] Histopathologic findings include large, well-differentiated, polygonal tumor cells with eosinophilic cytoplasm and large central nuclei surrounded by fibrous bands arranged in a lamellar pattern.[5] Immunohistochemical staining is typically positive for CK7, epithelial membrane antigen, CK19 and EpCAM.[3,6] FLC also displays stem cell markers CD133 and CD44.[7]

The most effective treatment for FLC is complete surgical resection with regional lymphadenectomy, which remains the primary curative therapy.[8-11] Liver transplantation may be considered for selected patients with unresectable liver-confined disease.[8,10,11] Locoregional therapies, including radiofrequency ablation, hepatic artery chemoembolization, and external beam

radiotherapy, may provide local disease control or palliation in select patients.[12] Systemic therapy and immunotherapy have been used for advanced, unresectable, recurrent, or metastatic disease, although no standard systemic treatment regimen has been established.[8,13]

The association between HCC, particularly FLC, and inflammatory bowel disease (IBD) has not been clearly established. To our knowledge, only 4 cases of FLC have been reported in patients with IBD—all occurring in patients with ulcerative colitis.[14] Given the rarity of FLC and the limited literature regarding its association with IBD, we present the case of a 23-year-old patient with newly diagnosed Crohn's disease who was found to have FLC.

CASE PRESENTATION

A 23-year-old woman with no significant past medical history presented to urgent care with a 6-week history of intermittent bloody diarrhea, fever, polyarthralgia, night sweats, erythema nodosum, oropharyngeal aphthous ulcers, and fatigue.

Initial laboratory values revealed a negative gastrointestinal pathogen panel and negative Clostridioides difficile testing, a white blood cell count of 12.5 K/μL, platelet count of 407 K/μL, erythrocyte sedimentation rate of 48 mm/hour, C-reactive protein level of 14.8 mg/dL, fecal calprotectin level of 309 μg/g, albumin level of 2.6 g/dL, aspartate aminotransferase level of 19 U/L, alanine aminotransferase level of 17 U/L, alkaline phosphatase level of 94 U/L, and total bilirubin level of 0.4 mg/dL.

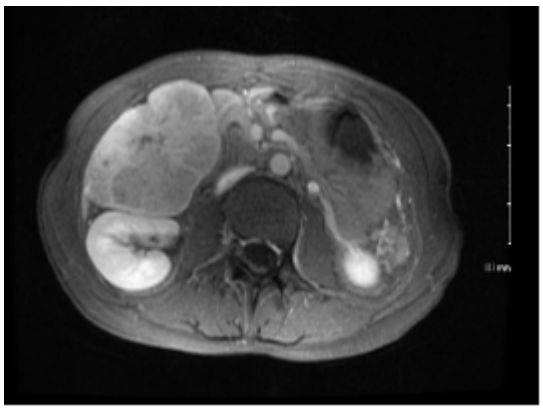
Computed tomography of the abdomen and pelvis demonstrated diffuse sigmoid colonic wall thickening with associated pericolonic fat stranding and incidentally identified a large hepatic lesion. Flexible sigmoidoscopy revealed erythematous mucosal ulcers, and biopsy findings were consistent with Crohn's disease. The patient was started on a prednisone taper and mesalamine.

MRI of the abdomen performed for further evaluation of the hepatic mass (Figure 1) revealed a large lobulated 9-cm hepatic mass arising from segments 4 and 5 with a calcific focus; enhancement characteristics were concerning for HCC.

Additional laboratory testing demonstrated an AFP level of < 2.0 ng/mL and carbohydrate antigen 19-9 (CA 19-9) level of < 2.0 U/mL. Serologic testing for hepatitis A, B, and C and HIV was negative. The tumor was classified as stage IIIB (pT4).

Following diagnosis, the patient underwent resection of segments 4 and 5 with en bloc cholecystectomy, achieving negative surgical margins. Figure 2A shows a well-demarcated multinodular mass with a central scar. Final histopathology confirmed FLC with focal visceral peritoneal involvement and small-vessel vascular invasion. Histologic examination demonstrated large polygonal neoplastic cells with eosinophilic granular cytoplasm and round nuclei with prominent nucleoli arranged in trabeculae separated by bundles of lamellar collagen (Figure 2B and 2C). Tumor cells also showed positive staining for cytokeratin 7 (CK7) and CD68. Additional trichrome staining highlighted abundant lamellar fibrosis. Next-generation sequencing demonstrated the characteristic DNAJB1-PRKACA mutation.

Figure 1. Lobulated Exophytic 9-cm Hepatic Mass Extending Inferiorly Off Segments 4 and 5



Enhancement characteristics concerning for hepatocellular carcinoma.

On surveillance imaging 1 year later, recurrent FLC in the porta hepatis was confirmed by biopsy. At that time, the patient reported night sweats but no other symptoms. She subsequently underwent staging laparotomy, portal lymphadenectomy, and resection of the portal mass. Months later, surveillance CT demonstrated an enlarging portocaval lymph node concerning for recurrent disease. Positron emission tomography-computed tomography revealed a left lower lobe pulmonary nodule suspicious for metastasis but showed no evidence of local abdominal recurrence, including no uptake within the portocaval lymph node. The patients subsequently underwent right portal lymph node dissection, and pathology was negative for malignancy.

The decision was made to initiate lenvatinib, a tyrosine kinase inhibitor, to reduce the risk of further recurrence. Subsequent imaging demonstrated spontaneous resolution of the pulmonary nodule. After completing 1 year of lenvatinib therapy, serial imaging of the chest, abdomen, and pelvis obtained every 3 months showed no evidence of residual or recurrent disease. As a result, lenvatinib was discontinued, and the patient has remained in remission.

DISCUSSION

FLC is a rare primary hepatocellular carcinoma variant, accounting for about 1% to 9% of all hepatocellular carcinomas, according to the Surveillance, Epidemiology, and End Results (SEER) Program database, and most commonly arises in noncirrhotic livers.[15,16] FLC tumors present with unique radiologic and histopathologic findings. While there is no specific data or recommendations regarding posttreatment surveillance, most clinicians

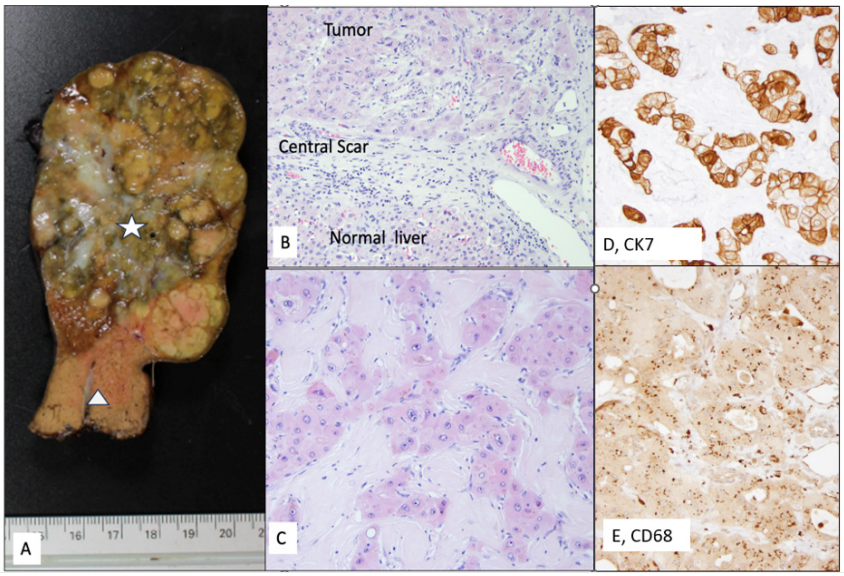
perform surveillance imaging at 3-month or 6-month intervals for the first few years after resection.[17]

Surgical resection with regional lymphadenectomy remains the cornerstone of curative therapy for FLC.[8-11] Reported 5-year survival rates after complete resection approach 70% to 76%; however, recurrence remains common, occurring in 50% to 100% of patients in published series.[17-21] Our patient's disease course reflects this pattern, with biopsy-confirmed recurrence in the porta hepatis 1 year after initial resection despite negative surgical margins. For patients with unresectable liver-confined disease, liver transplantation may be considered in carefully selected cases, although long-term outcomes are generally less favorable than those reported following complete resection.[8,10,11]

Management of recurrent, unresectable, or metastatic FLC remains challenging because no standard systemic therapy has been established.[8,13] Locoregional therapies, including radiofrequency ablation, transarterial chemoembolization, and radiotherapy, may provide local disease control or palliation in selected patients.[12] Systemic therapies, including cytotoxic chemotherapy, targeted therapies, and immune checkpoint inhibitors, have been used with variable success.[13,22,23] In the present case, lenvatinib was initiated following recurrence and concern for metastatic disease. Although the contribution of lenvatinib to the patient's favorable outcome cannot be determined, she has remained disease-free following treatment, highlighting the individualized nature of therapeutic decision-making in FLC.

There are limited reports of hepatocellular carcinoma in patients with inflammatory bowel disease, and all previously reported cases of FLC have occurred in patients with ulcerative colitis. Herein, we describe a case of FLC in a patient with newly diagnosed Crohn disease. The diagnosis was supported by characteristic clinical, radiographic, histopathologic, immunohistochemical, and molecular findings. The patient was a young adult without underlying liver disease who was incidentally found to have a large, well-demarcated hepatic mass with a calcified central scar and a normal AFP level. Histopathologic examination demonstrated large polygonal neoplastic cells arranged in trabeculae separated by lamellar fibrous stroma, with positive CK7 and CD68 staining. Molecular analysis identified the characteristic DNAJB1-PRKACA fusion. Collectively, these findings are highly characteristic of FLC and help distinguish it from conventional HCC.[3-7]

Figure 2.



A. Resection specimen of segments 4 and 5, a well-demarcated variegated multinodular mass with a central scar (white star), normal tan liver in the lower portion (white triangle).

B. Interface of tumor with normal liver at central scar. Note small size of hepatocytes compared to large tumor cells.

C. Large polygonal cells with abundant bright pink granular cytoplasm and round nuclei with prominent nucleoli, arranged in trabeculae, characteristically interspersed with bundles of lamellar collagen, pathognomonic of fibrolamellar carcinoma.

D and E. Tumor cells show characteristic positive staining with cytokeratin 7 (CK7) and CD68, in addition to hepatocellular markers, HSA and arginase. On molecular analysis, via next generation sequencing, tumor cells displayed characteristic DNAJB1-PRKACA mutation.

CONCLUSIONS

Fibrolamellar carcinoma is a rare primary hepatic malignancy that typically occurs in young adults without underlying liver disease and may be discovered incidentally during evaluation of unrelated gastrointestinal symptoms. This case highlights the importance of recognizing the characteristic clinical, radiographic, histopathologic, and molecular features of FLC to facilitate timely diagnosis and treatment. To our knowledge, this represents the first reported case of FLC in a patient with Crohn disease, expanding the limited literature describing a possible association between FLC and inflammatory bowel disease. Continued reporting of similar cases may help clarify whether this association is coincidental or reflects a shared pathogenic mechanism.

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REFERENCES

1. Eggert T, McGlynn KA, Duffy A, Manns MP, Greten TF, Altekruse SF. Epidemiology of fibrolamellar hepatocellular carcinoma in the USA, 2000-10. *Gut*. 2013;62(11):1667-1668. doi:10.1136/gutjnl-2013-305164

2. 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.

3. Ichikawa T, Federle MP, Grazioli L, Madariaga J, Nalesnik M, Marsh W. Fibrolamellar hepatocellular carcinoma: imaging and pathologic findings in 31 recent cases. *Radiology*. 1999;213(2):352-361. doi:10.1148/radiology.213.2.r99nv31352

4. Vyas M, Hechtman JF, Zhang Y, et al. DNAJB1-PRKACA fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for fibrolamellar hepatocellular carcinoma. *Mod Pathol.* 2020;33(4):648-656. doi:10.1038/s41379-019-0398-2

5. Chagas AL, Kikuchi L, Herman P, et al. Clinical and pathological evaluation of fibrolamellar hepatocellular carcinoma: a single center study of 21 cases. *Clinics (Sao Paulo)*. 2015;70(3):207-213. doi:10.6061/clinics/2015(03)10

6. Ward SC, Waxman S. Fibrolamellar carcinoma: a review with focus on genetics and comparison to other malignant primary liver tumors. *Semin Liver Dis*. 2011;31(1):61-70. doi:10.1055/s-0031-1272835

7. Zenali MJ, Tan D, Li W, Dhingra S, Brown RE. Stemness characteristics of fibrolamellar hepatocellular carcinoma: immunohistochemical analysis with comparisons to conventional hepatocellular carcinoma. *Ann Clin Lab Sci.* 2010;40(2):126-134.

8. Frenette C, Mendiratta-Lala M, Salgia R, Wong RJ, Sauer BG, Pillai A. ACG clinical guideline: focal liver lesions. *Am J Gastroenterol.* 2024;119(7):1235-1271. doi:10.14309/ajg.0000000000002857

9. Aziz H, Brown ZJ, Panid Madani S, Kamel IR, Pawlik TM. Fibrolamellar hepatocellular carcinoma: comprehensive review of diagnosis, imaging, and management. *J Am Coll Surg*. 2023;236(2):399-410. doi:10.1097/XCS.0000000000000476

10. Polychronidis G, Murtha-Lemekhova A, Fuchs J, Karathanasi E, Hoffmann K. A multidisciplinary approach to the management of fibrolamellar carcinoma: current perspectives and future prospects. *Onco Targets Ther.* 2022;15:1095-1103. doi:10.2147/OTT.S296127

11. Glavas D, Bao QR, Scarpa M, et al. Treatment and prognosis of fibrolamellar hepatocellular carcinoma: a systematic review of the recent literature and meta-analysis. *J Gastrointest Surg.* 2023;27(4):705-715. doi:10.1007/s11605-023-05621-z

12. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary cancers, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2021;19(5):541-565. doi:10.6004/jnccn.2021.0022

13. Gottlieb S, Gliksberg A, Schadde E, Kent P. Novel systemic therapies in the treatment of fibrolamellar carcinoma. *J Clin Oncol.* 2021;39(suppl 15):e16161. doi:10.1200/JCO.2021.39.15_suppl.e16161

14. Snook JA, Kelly P, Chapman RW, Jewell DP. Fibrolamellar hepatocellular carcinoma complicating ulcerative colitis with primary sclerosing cholangitis. *Gut*. 1989;30(2):243-245. doi:10.1136/gut.30.2.243

15. Lafaro KJ, Pawlik TM. Fibrolamellar hepatocellular carcinoma: current clinical perspectives. *J Hepatocell Carcinoma.* 2015;2:151-157. doi:10.2147/JHC.S75153

16. National Cancer Institute, Surveillance Epidemiology, and End Results Program. SEER*Explorer: 2015. Accessed September 24, 2024. https://seer.cancer.gov/statistics-network/explorer/.

17. Maniaci V, Davidson BR, Rolles K, et al. Fibrolamellar hepatocellular carcinoma: prolonged survival with multimodality therapy. *Eur J Surg Oncol.* 2009;35(6):617-621. doi:10.1016/j.ejso.2008.12.009

18. Stipa F, Yoon SS, Liau KH, et al. Outcome of patients with fibrolamellar hepatocellular carcinoma. *Cancer*. 2006;106(6):1331-1338. doi:10.1002/cncr.21703

19. Mavros MN, Mayo SC, Hyder O, Pawlik TM. A systematic review: treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma. *J Am Coll Surg.* 2012;215(6):820-830. doi:10.1016/j.jamcollsurg.2012.08.001

20. Herman P, Chagas AL, Perini MV, et al. Surgical treatment of fibrolamellar hepatocellular carcinoma: an underestimated malignant tumor? *Hepatobiliary Pancreat Dis Int.* 2014;13(6):618-621. doi:10.1016/s1499-3872(14)60294-0

21. Stevens WR, Johnson CD, Stephens DH, Nagorney DM. Fibrolamellar hepatocellular carcinoma: stage at presentation and results of aggressive surgical management. *AJR Am J Roentgenol.* 1995;164(5):1153-1158. doi:10.2214/ajr.164.5.7717223

22. Lamarca A, Frizziero M, Fulton A, et al. Fibrolamellar carcinoma: challenging the challenge. *Eur J Cancer.* 2020;137:144-147. doi:10.1016/j.ejca.2020.06.035

23. Kent P, Stockwell T, Tasse J, et al. Lenvatinib, gemcitabine, and oxaliplatin for 67 patients with fibrolamellar carcinoma. *J Clin Oncol.* 2024;42(Suppl 16):e16151. doi:10.1200/JCO.2024.42.16_suppl.e16151

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