Fibrolamellar Carcinoma

A Concise Review

Chun-Chieh Lin, MD, PhD; Hui-Min Yang, MD

• Fibrolamellar carcinoma is a rare primary hepatocellular malignancy arising in noncirrhotic livers of young individuals. Patients commonly present with a large solitary liver mass and nonspecific symptoms. Characteristic histologic features include large polygonal cells with oncocytic cytoplasm and prominent nucleoli separated into trabeculae and cords by dense parallel bands of collagen. Important differential diagnoses include classical hepatocellular carcinoma and intrahepatic cholangiocarcinoma, which may be distinguished by a judicious panel of immunohistochemical studies, including cytokeratin 7, CD68, and hepatocyte paraffin 1 (HepPar-1). In addition, fibrolamellar carcinomas are characterized by activation of protein kinase A. Prognosis of fibrolamellar carcinoma is similar to classical hepatocellular carcinoma occurring in the absence of liver cirrhosis and is strongly correlated with tumor resectability. Other treatment options include liver transplant, chemotherapy, and hepatic artery embolization. In this article, we review the clinical features, gross and microscopic pathology, molecular genetics, differential diagnosis, treatment, and prognosis of this rare and interesting tumor.


Fibrolamellar carcinoma (FLC) is a unique primary hepatocellular malignancy, encompassing patient demographics, risk factors, and tumor markers distinct from those of classical hepatocellular carcinoma (HCC). While the histologic features of FLC were first described by Edmondson in 1956, it was not until the 2010 edition of World Health Organization (WHO) Classification of Tumours that FLC was assigned its own WHO classification code. Unlike classical HCCs, which frequently harbor TP53 and β-catenin (CTNNB1) mutations, FLCs demonstrate activation of protein kinase A, most commonly through a DNAJB1-PRKACA fusion transcript, secondary to somatic intrachromosomal deletion on chromosome 19.

CLINICAL FEATURES

Fibrolamellar carcinoma comprises approximately 1% of HCCs. Fibrolamellar carcinoma shows no sex predilection and typically presents as a large solitary mass (>10 cm in approximately 70% of patients), whereas classical HCC occurs with a male preponderance and presents with smaller tumor sizes (<10 cm in approximately 70% of patients). One of the most distinctive features of FLC is the unimodal age distribution between the teens and sixties. Approximately 80% of FLCs occur in individuals between 10 to 35 years of age. This is in contrast to classical HCC, which typically presents in patients in their fifties and sixties. However, it is worth noting that the most common liver cancer in children and young adults remains classical HCC (60%–80% of hepatic carcinomas in this age group).

Patients with FLC generally present with nonspecific symptoms, such as nausea, vomiting, abdominal discomfort, and weight loss. Major physical examination findings include palpable abdominal mass and/or hepatomegaly; however, a variety of unusual presentations have been reported, such as biliary or caval obstruction, and gynecomastia. Imaging studies typically show a solitary mass in the liver. Lymphadenopathy is detected in 70% of patients at presentation and nearly 50% of patients eventually develop distant metastasis to various sites, including mediastinum, pericardium, and ovaries. Serum levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase can be elevated. Serum α-fetoprotein, frequently elevated in HCC, is normal in most FLCs; only 5% to 10% of the reported FLC cases are associated with α-fetoprotein levels greater than 200 ng/mL.

PATHOLOGIC FEATURES

Macroscopically, FLC typically presents as a heterogenous and well-circumscribed mass in a noncirrhotic background. The mass is pale tan or yellow and has variable firmness (Figure 1, A). Central scar and calcification are found in approximately 70% of the cases. At the time of resection, the tumor is generally large (9–14 cm in greatest dimension) and vascular invasion is frequently detected (25% for gross vascular invasion and 50% for microscopic vascular invasion).
Microscopically, the tumor is composed of large polygonal cells with prominent nucleoli, well-delineated cell borders, and abundant granular eosinophilic cytoplasm, arranged in nests, cords, and trabeculae surrounded by dense parallel bands of fibrosis, a feature also known as lamellar fibrosis (Figure 1, B and C). The bands of layered collagen often coalesce to form thick septa and scars.\(^9\) Notably, FLCs can show variable patterns of fibrosis, including (1) ribbonlike, which separates tumor cells into trabeculae (most commonly observed); (2) haphazard collagen deposition; and (3) tumors showing areas with little or no intratumoral fibrosis (least commonly observed).\(^5\) The oncocytic appearance to the cytoplasm reflects the abundance of mitochondria at the ultrastructural level.\(^9\) Neuroendocrine markers mostly show negativity in FLCs, although positivity for chromogranin has been reported in rare cases.\(^15\) Bile production is frequently seen, confirming the tumor’s hepatocellular origin. Copper accumulation secondary to the cholestasis is well described.\(^16\) The malignant cells are generally 3 times the size of normal hepatocytes and 1.6 times that of malignant cells in a well-differentiated HCC.\(^6\)

In approximately half of the cases, the tumor cells can contain discrete round to oval, pale, amphophilic cytoplasmic inclusions, so-called pale bodies, which stain positively for fibrinogen.\(^9\) Smaller eosinophilic inclusions, termed hyaline bodies, are also found in approximately half of the cases (Figure 1, D).\(^9\) Despite their distinct histologic appearance, pale bodies and hyaline bodies are not specific for FLC and should not be used as diagnostic criteria.\(^5\) Emphasis is placed on tumor cytology and lamellar fibrosis for the diagnosis of this entity. Occasionally, FLCs can exhibit a prominent pseudoglandular growth pattern with focal mucin production, features not to be mistaken for a cholangiocarcinoma.\(^5\) On imaging studies, approximately 70% of FLCs show calcifications, which may correspond to microscopic calcifications within the central scar, fibrous bands, and/or of individual tumor cells.\(^5,13\)

**IMMUNOPHENOTYPIC FEATURES**

On immunohistochemistry, FLC expresses both hepatocellular and biliary markers.\(^12\) A small panel of immunohistochemical markers including hepatocyte paraffin 1
(HepPar-1), cytokeratin 7 (CK7), and CD68 stains are helpful in confirming the diagnosis of FLC (see Table).

HepPar-1, also known as hepatocyte paraffin 1 or hepatocyte antigen, is a monoclonal antibody that stains positively in hepatoid and hepatocellular neoplasms, and is helpful in distinguishing a hepatocellular neoplasm from metastatic malignancy to the liver. HepPar-1 is expressed in both classical HCC and FLC (Figure 2, A). HepPar-1 positivity is useful in differentiating FLC with pseudoglandular pattern from intrahepatic cholangiocarcinoma and scirrhous HCC, both of which are mostly negative for HepPar-1. Arginase and albumin (labeled via in situ hybridization) are other sensitive and specific markers of hepatocellular differentiation that can be used in conjunction with or as an alternative to HepPar-1.

CK7 staining is strongly and diffusely positive in FLC, scirrhous HCC, and intrahepatic cholangiocarcinoma. While highly sensitive (100%) for FLC (Figure 2, B), CK7 positivity can be seen in up to 32% of classical HCC cases. CD68, a transmembrane protein expressed in lysosomal and endosomal organelles prominent in macrophages, is characteristic expressed in FLCs. CD68 positivity is highly sensitive (96%) and specific (80%) for FLC (Figure 2, C) and is especially helpful for distinguishing scirrhous HCC from FLC. Of note, CK7 staining of biliary ducts and CD68 staining of sinusoidal Kupffer cells in nonneoplastic liver parenchyma can serve as an internal control for these 2 immunohistochemical stains. Given the high sensitivity of these markers, double-negative CK7 and CD68 immunohistochemical staining would likely exclude a diagnosis of FLC.

Overall, it is recommended that potential FLC cases be confirmed with CK7 and CD68 immunostaining.

### DIFFERENTIAL DIAGNOSIS

The main histologic differential diagnosis for FLC includes HCC (in particular, the scirrhous variant) and intrahepatic cholangiocarcinoma, which are all primary hepatic tumors that may show significant intratumoral fibrous stroma. A significant number of HCCs may show focal areas with features of FLC. In addition, the scirrhous variant of HCC shows abundant fibrosis admixed with malignant hepatocytes. Immunohistochemical and in situ hybridization studies may be helpful in differentiating FLC from classical HCC in these scenarios (see above). Importantly, any FLC with poorly differentiated histology should prompt careful reexamination, as most FLCs are well to moderately differentiated. In young female patients with a history of estrogen-progesterone use, focal nodular hyperplasia (FNH) should be considered because a central stellate scar could exist in both FLC and FNH. However, FNH exhibits prominent ductular reaction at the interface between fibrous septa and normal parenchyma, which is not observed in FLC. In children with suspected FLC, hepatoblastoma and mesenchymal hamartoma should be considered in the differential diagnosis.

### MOLECULAR GENETICS

Fibrolamellar carcinomas demonstrate activation of protein kinase A, most commonly as a result of the DNAJB1-PRKACA fusion transcript. In 2014, Honeyman et al described a recurrent DNAJB1-PRKACA fusion transcript in fibrolamellar carcinoma that occurred as a result of a microdeletion on chromosome 19, leading to a fusion between the DNAJB1 gene promoter and the PRKACA gene, which encodes a catalytic subunit of protein kinase A. The promoter of DNAJB1 is constitutively active and thus the fusion product results in overexpression/activation of protein kinase A. More recently, PRKARIA loss was implicated in a subset of FLCs occurring in patients with the Carney complex, who carry PRKARIA germline mutations. As PRKARIA is the regulatory unit of protein kinase A that inhibits PRKACA activity, inactivating mutations in PRKARIA provide an alternative pathway for activation of protein kinase A, which may lead to the development of FLCs. Given that most FLCs demonstrate the DNAJB1-PRKACA fusion transcript and that this fusion transcript is 100% specific for FLC in the setting of primary hepatocellular neoplasms, in situ hybridization and/or reverse transcription–polymerase chain reaction studies detecting this fusion transcript are highly useful confirmatory studies.

### TREATMENT AND PROGNOSIS

The key to successful management of FLC is early diagnosis followed by complete surgical resection, which may include extended lymph node dissection. Furthermore, resection of metastatic disease may be beneficial. When partial hepatectomy is not feasible owing to extent of invasion and adhesion, total hepatectomy followed by orthotopic liver transplant may be considered.

Chemotherapy may be advantageous in cases of inoperable FLC. Commonly used chemotherapy agents include cisplatinum, epirubicin, 5-fluorouracil, and recombinant interferon α-2b; however, FLC does not respond to chemotherapy as well as classical HCC. For patients who are not candidates for surgical resection/transplant and whose condition is nonresponsive to chemotherapy, hepatic embolization could be an alternative treatment option.

While sex, tumor size, atypia, and cellular proliferation do not appear to correlate with survival, liver cirrhosis is a well-recognized adverse prognostic factor. In the absence of cirrhosis, the 5-year and overall survival is not significantly different in patients with FLC (45% and 40%) and patients with HCC (56% and 56%). However, patients with HCC occurring in the setting of cirrhosis exhibit poorer 5-year and overall survival (27% and 23%). Metastasis status is

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Abbreviations: CK7, cytokeratin 7; HepPar-1, hepatocyte paraffin 1; NA, not applicable; +, positive; −, negative.

a Please refer to the immunophenotypic features section for detailed discussion.
also an important adverse prognostic factor. Five-year survival rates for patients with and without metastasis at presentation are 39% and 86%, respectively. When no metastatic disease is noted at presentation, 5-year survival is 1144 Arch Pathol Lab Med—Vol 142, September 2018

CONCLUSIONS

Fibrolamellar carcinoma is a rare but distinct malignant hepatocellular neoplasm that should be considered in the differential diagnosis of malignant hepatic neoplasms especially in young individuals without background liver cirrhosis. While the clinical symptoms are generally nonspecific, the tumor demonstrates characteristic histologic, immunophenotypic, and molecular features enabling its proper diagnosis. An early diagnosis that allows for appropriate therapy and surgical resectability remains one of the most important prognostic factors.

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References


