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Fibrolamellar carcinoma: A histologically unique tumor with unique molecular findings

Rondell P. Graham, Michael S. Torbenson *

Division of Anatomic Pathology, Mayo Clinic, 200 First Street SW, Rochester, MN, United States

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ABSTRACT

Fibrolamellar carcinoma is a unique type of hepatocellular carcinoma with a distinctive predilection for young patients without underlying liver disease, characteristic large neoplastic cells with intervening, dense fibrosis, co-expression of keratin 7 and CD68 and activation of protein kinase A (most often by formation of DNAJB1-PRKACA). Fibrolamellar carcinoma has a similar prognosis to conventional hepatocellular carcinomas arising in non-cirrhotic livers. The current American Joint Cancer Committee staging system does not provide optimal stratification of patients with fibrolamellar carcinoma and an alternate systems should be considered in the future. The only effective treatment for fibrolamellar carcinoma is complete resection. Novel therapies may be on the horizon as investigation into the molecular biology of fibrolamellar carcinoma continues.

Fibrolamellar carcinoma is a unique variant of hepatocellular carcinoma characterized by a predilection for youth, distinctive morphology, and a distinctive immunophenotype. A unique somatic intrachromosomal *DNAJB1-PRKACA* fusion gene is found in almost all fibrolamellar carcinomas,[1] a seminal finding that has reinvigorated research in this field and led to new discoveries with patient care and basic science implications.

Case history

A 21-year-old young man presented to his family physician with early satiety and unexpected 15-pound weight loss. His personal medical and family histories were unremarkable. Serum laboratory values included normal alpha-fetoprotein levels, negative viral hepatitis B and C studies, and normal transaminases. Abdominal magnetic resonance imaging revealed an 11 cm mass occupying the right lobe of the liver, associated with a central T2 signal scar and multiple adjacent satellite nodules. The porta hepatis lymph nodes were enlarged and concerning for metastasis. The patient was treated with a right lobectomy and lymphadenectomy.

Pathologic and molecular findings

The tumor was grossly well circumscribed, with a yellow tan color and irregular central area of scarring (Fig. 1A). A small amount of background liver parenchyma was present and grossly looked unremarkable. Histologic sections showed a tumor composed of large cells with abundant eosinophilic cytoplasm, centrally located nuclei with vesiculated chromatin, and very prominent macronucleoli (Fig. 1B). The neoplasm also showed dense bands of lamellar fibrosis that separated the tumor cells into linear trabecula (Fig. 1B). These fibrous bands coalesced centrally to form a scar. The lymph nodes showed metastatic disease. Focal psuedoglands were present (Fig. 1C) These histologic features are characteristic of fibrolamellar carcinoma.

The tumor cells were positive for HepPar1 and co-expressed keratin 7 and CD68 (Fig. 1D, E). In addition, the tumor cells were positive for *PRKACA* rearrangements when tested using break-apart fluorescence in situ hybridization for *PRKACA* (Fig. 1F).

Diagnosis: *Fibrolamellar carcinoma*

Discussion

Edmondson first described fibrolamellar carcinoma as a distinct histologic entity.[2] At that time, he recognized that this was a histologically unique tumor based on the monotonous large cells with abundant, granular, eosinophilic cytoplasm, conspicuous

* Corresponding author.

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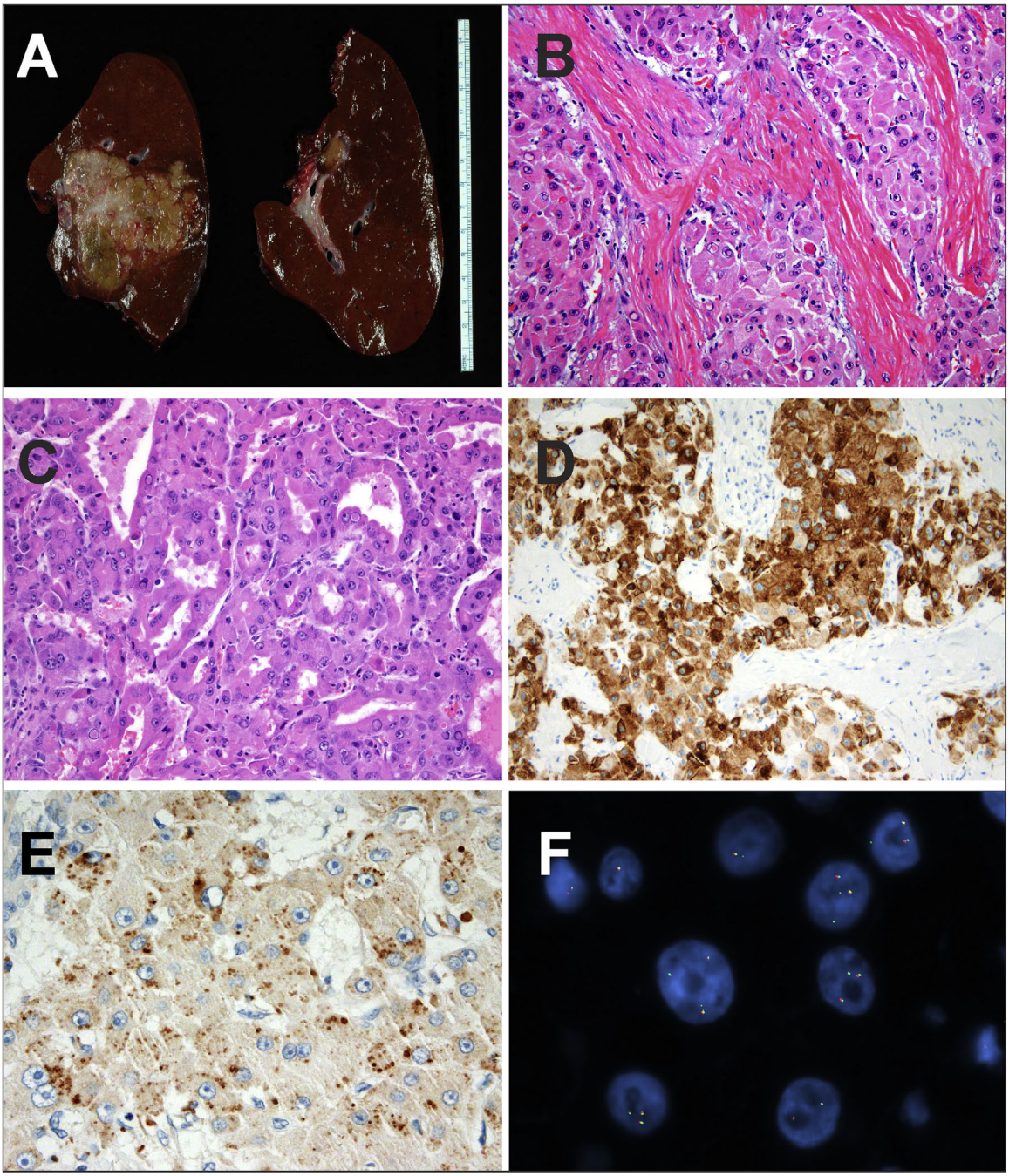

Fig. 1. A) Fibrolamellar carcinoma with a central scar and multinodular cut surface. Note the macroscopic large vessel invasion shown in the cut section on the right. This is seen in about 25% of resected cases of fibrolamellar carcinoma. B) Typical histologic findings of fibrolamellar carcinoma are shown. Nodules and trabecula of tumor cells with abundant eosinophilic cytoplasm and conspicuous macronucleoli are separated by lamellar bands of fibrosis. C) Pseudoglandular growth may be seen in fibrolamellar carcinoma and can be confused with a cholangiocarcinoma if not reviewed carefully. D) Keratin 7 is characteristically positive as shown in this example of fibrolamellar carcinoma. E) CD68 is similarly positive. F) Interphase FISH using *PRKACA* break apart probe reveals a separate green and intact yellow signals indicative of *PRKACA* rearrangement which confirms the diagnosis of fibrolamellar carcinoma.

macronucleoli, and dense/lamellar intratumoral fibrosis. Craig et al. [3] subsequently gave the tumor the name "fibrolamellar carcinoma" and detailed the distinctive clinicopathologic features.

Fibrolamellar carcinoma represents 1% of hepatocellular carcinoma based on data from several large series.[4–8] Clinically, fibrolamellar carcinoma affects patient without underlying chronic liver disease and most often arises during the 2nd to 4th decades, with a median age of presentation of 22 years (range 4–65 years of age).[9]

While the association of fibrolamellar carcinoma with both a normal background liver and a predilection for young age individuals is well recognized, it is important to note that conventional hepatocellular carcinoma is still the most common hepatocellular malignancy in individuals less than 40 years of age. Rare reports of *bona fide* fibrolamellar carcinoma in children under 10 years of age [10,11] and adults over 55 years of age [12,13] have been described. However, these cases should be carefully examined histologically and confirmed with additional testing.

Clinical presentation

Most cases of fibrolamellar carcinoma present with a mass