

Fibrolamellar Hepatocellular Carcinoma with Cytokeratin 7 Expression – A Case Report –

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Fibrolamellar carcinoma (FLC) is a rare variant of hepatocellular carcinoma (HCC). A 26-year-old female presented a hepatic mass and mild elevation of liver enzymes. Viral markers were negative, and levels of tumor markers were normal. Radiologically, the mass was well demarcated with central dot-like calcification and hypervascularity. Under the diagnosis of hepatocellular carcinoma, right lobectomy was performed. The tumor was grayish yellow with central fibrosis and focal hemorrhage and invaded a septal bile duct. Non-neoplastic liver was unremarkable. Microscopically, the tumor consisted of large polygonal cells in sheets, cords, and pseudoglands that were interwound by dense collagenous stroma. Tumor cells had abundant deeply eosinophilic cytoplasm and large nuclei with prominent nucleoli. Intracellular bile pigments and pale bodies were present. Tumor cells were diffusely immunostained for cytokeratin 7 (CK7), but not for cytokeratin 20 (CK20). Strong expression of CK7 in the present case suggests dual differentiation of FLC.

Key Words : Carcinoma, Hepatocellular-Keratin

Fibrolamellar carcinoma (FLC) of the liver is a rare variant of hepatocellular carcinoma (HCC) with distinct clinicopathologic features. FLC occurs world-wide with the incidence up to 5% in Western countries.¹⁻³ In Korea, however, the incidence of FLC is much lower and only one case is reported by Kang *et al.*⁴ FLC is different in many aspects from ordinary HCC. Over 90% of FLC occurs under 35 years of age and less than 5% over the age of 50. Both sexes are affected more equally and there is no association with chronic liver diseases including cirrhosis.⁵ Serum alpha fetoprotein (AFP) is seldom raised, while carcinoembryonic antigen (CEA) is rarely elevated.⁶ In contrast to ordinary HCC, surgical resectability rate of FLC is high and even multiple tumors may be curable by hepatectomy and transplantation. The 5-year survival rate has been recorded around 50% and its progress is slow even when the tumor has not been completely eradicated.^{2,3,7} In addition to characteristic pathologic findings showing fibrous lamellae between large polygonal tumor cells, immunohistochemical and electron microscopic findings of FLC

are also different from ordinary type of HCC.^{5,8}

We report a case of pure FLC with lymph node metastasis and bile duct invasion that displayed diffuse and strong immunopositivity for CK7, in which cholangiocarcinoma had to be differentiated.

CASE REPORT

A 26-year-old female was admitted with a hepatic mass that had been found during a work-up of elevated liver enzymes. Her past medical history and family history were unremarkable and there was no history of liver disease or exposure to drugs. Physical examination revealed no signs of chronic liver disease. Serum aspartate transaminase was 48 IU/L and alanine transaminase was 120 IU/L. Serum levels of alkaline phosphatase, total bilirubin, AFP, and CEA were normal. Viral markers were all negative. Computed tomogram demonstrated a large well-demarcated

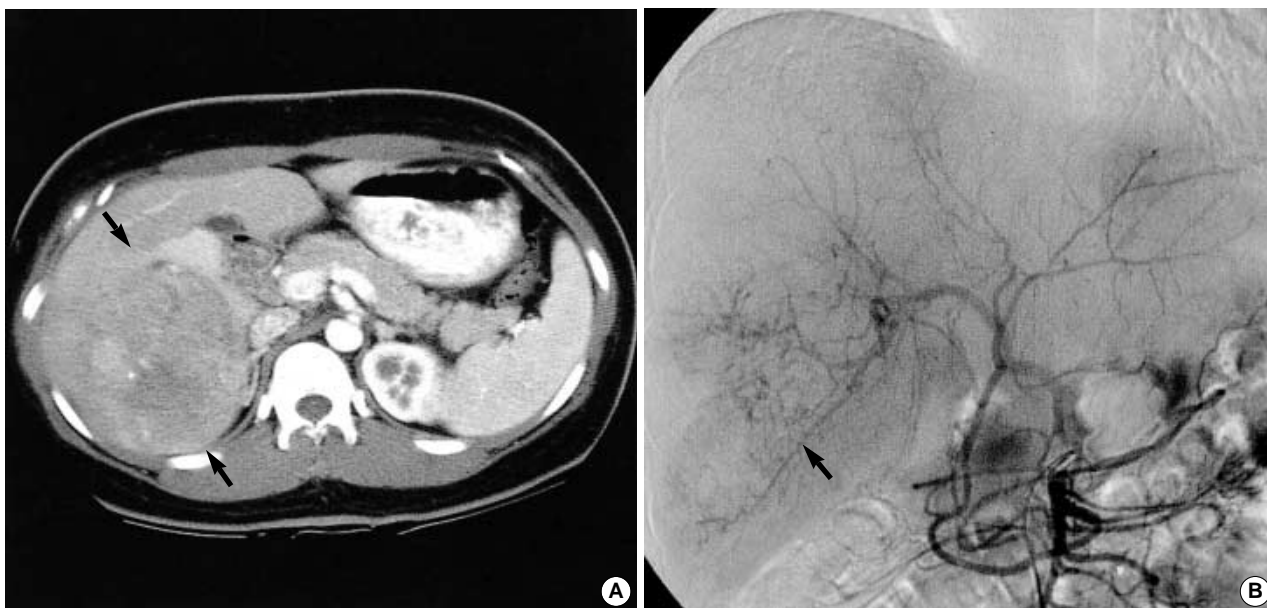


Fig. 1. (A) Hepatic arterial contrast-enhanced computed tomogram demonstrates a large well demarcated mass with central dot-like calcification and heterogeneous hyperattenuation (arrows). (B) Angiography shows a huge tumor staining at the right hepatic artery (arrow).

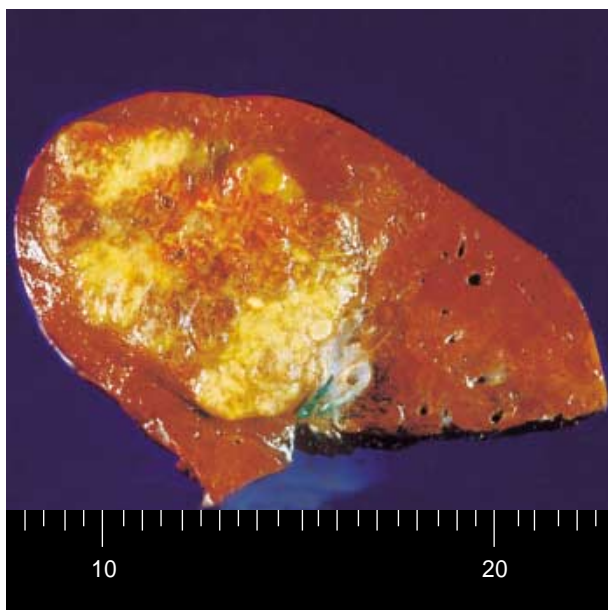


Fig. 2. A well demarcated lobulated firm mass measuring 13 × 10 × 8 cm is present. The cut surface is peripherally grayish yellow, centrally fibrotic, and focally hemorrhagic. The surrounding liver tissue is not cirrhotic.

mass with central dot-like calcification in the posteroinferior segment of the right lobe as well as hilar lymphadenopathy (Fig. 1A). By angiography, a huge tumor staining was present at the posterior segmental branch of the right hepatic artery (Fig. 1B). Right lobectomy was performed. Grossly, the firm tumor was well demarcated and lobulated, measuring 13 × 10 × 8 cm. Cut

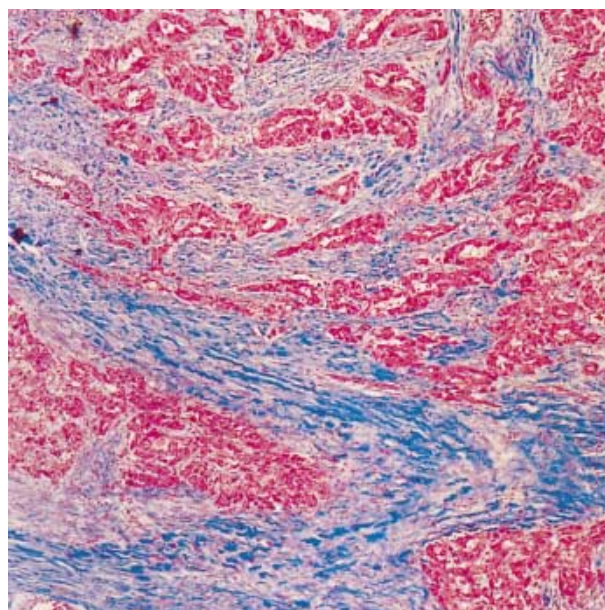


Fig. 3. Microscopically, the trabeculae of tumor cells are separated by fibrous lamellae (Masson-Trichrome stain).

surface of the tumor was grayish yellow peripherally and whitish with focal hemorrhage in the center. Necrosis was absent. A septal bile duct was invaded by the tumor. The nonneoplastic liver parenchyma was unremarkable (Fig. 2). Microscopically, the tumor was composed of sheets, cords, and pseudoglands of neoplastic cells separated by irregularly arranged fibrous lamellae (Fig. 3). Tumor cells had large and vesicular nuclei with prominent nucle-

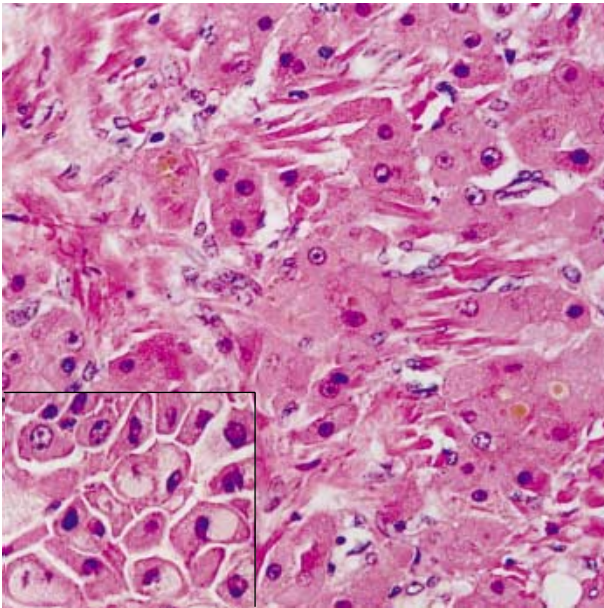


Fig. 4. Large polygonal tumor cells have deeply eosinophilic cytoplasm and prominent nucleoli. Occasional bile pigments are noted within the cytoplasm and bile canaliculi. Sharply defined pale bodies are scattered in the cytoplasm of the tumor cells (inset).

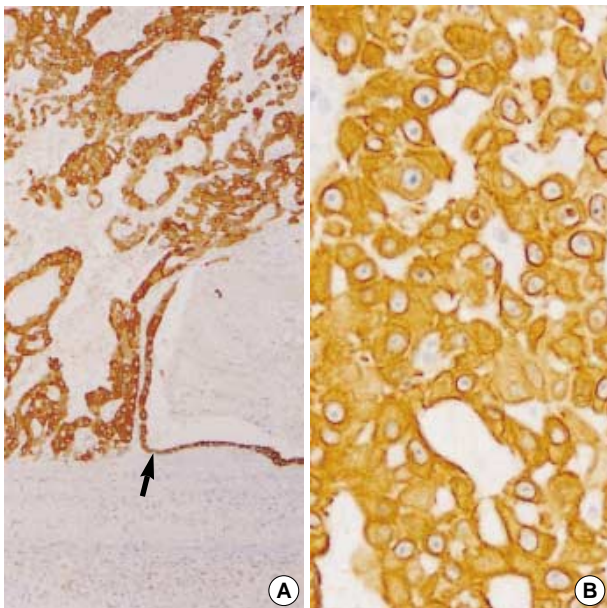


Fig. 5. Immunohistochemical staining for cytokeratin 7 (CK7). A large septal bile duct (arrow) is involved by the tumor (A). Tumor cells show diffuse and strong positivity for CK7 (B).

oli and abundant, deeply eosinophilic cytoplasm with occasional bile pigments or pale bodies (Fig. 4). A large septal bile duct was involved by the tumor (Fig. 5A). Lymph node metastasis was present in a hilar lymph node. By immunohistochemical stain-

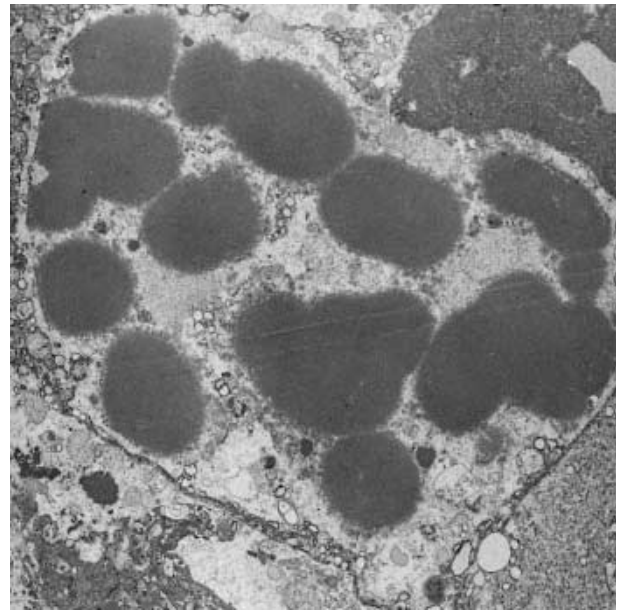


Fig. 6. Ultrastructurally, the tumor cell cytoplasm shows globular electron-dense structures ($\times 2,500$).

ings, tumor cells were diffusely and strongly stained for CK7 (Fig. 5B) but not for CK20. Ultrastructurally, tumor cells were filled with abundant back-to-back mitochondria and electron dense pale body (Fig. 6).

DISCUSSION

The present case has a hilar lymph node metastasis which is rare in ordinary HCCs. FLC is known to be more frequently associated with nodal metastasis than ordinary HCC. The frequency of nodal metastasis in FLC was reported 33% (3/9), while 1.6% in ordinary HCCs.⁹ Even after surgical resection, FLC can recur in lymph nodes of various sites.⁹⁻¹¹ The presence of nodal metastasis in HCC is one of the most important prognostic factors in addition to tumor size, multiplicity, capsular invasion, and vascular invasion. Hepatic resection or transplantation offers the only chance of cure for FLC, thus, right lobectomy was performed even in the presence of lymph node metastasis in the present case. By El-Gazzaz *et al.*¹², overall survival of FLC at 1, 3, 5 years was 89.5%, 75%, and 50%, respectively and all prognostic factors did not show a significant difference. However, there was tendency that tumor stage was the most significant for prognosis. The present tumor is in stage IIIB, thus close follow-up is obligatory, although the patient has been free of tumor for 5 months.

Hyperbilirubinemia is present in about one third of ordinary

HCCs, but rare in FLC. The mechanisms of jaundice are liver failure due to cirrhosis, massive tumor involvement of liver parenchyma and obstruction of common hepatic or common bile ducts. Gross extension of HCC into large bile ducts is uncommon, occurring in 1.4 to 2.1% of autopsy cases, while it was observed in 7.3% of combined autopsy and surgical cases by Kojiro *et al.*¹³ who showed quite frequent microscopic intrahepatic bile duct involvement by HCC. In this case, lack of jaundice was attributable to the absence of large bile duct obstruction by the tumor, although a polypoid tumor growth was present in an intrahepatic bile duct.

Immunohistochemical staining for various types of CK is used for differential diagnosis between bile duct carcinoma from HCC or metastatic adenocarcinoma. The present case shows strong as well as diffuse immunopositivity for one of biliary cytokeratins, CK7. Ordinary HCC expresses generally CK8 and CK18, but not CK7 and CK19. FLC, however, has been known to express both hepatic type CKs and biliary type CKs. Unusually high expression of CK7 was demonstrated in 2 cases of FLC by immunohistochemical staining and two-dimensional gel electrophoresis with Western blotting in which tumor cells of both primary lesions and metastasis expressed CK7 as well as CK8 and 18.¹⁴ Huang *et al.*¹⁵ reported that 9 cases of 11 FLCs (82%) expressed CK7, while 2 cases of 12 ordinary HCCs (17%) were positive for CK7. Although the strong expression of CK7 and the intraductal tumor growth of the present case suggested bile duct carcinoma, cholangiocarcinoma could be excluded on the basis of characteristic features of tumor cells with bile production. The differential diagnosis also includes sclerosing hepatocellular carcinoma (SHCC), which was found in middle-aged people, male predominant, and often positive for HBsAg and AFP, or cirrhosis. Also, the histologic findings were different to that of FLC and cancer cells of the SHCC showed less eosinophilic small cytoplasm and inconspicuous cytoplasm.¹⁶

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