

Fibrolamellar hepatocellular carcinoma: a case report

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Abstract

A 6-year-old Malay boy presented with fever and abdominal pain for 2 months. Computerised tomography showed a nodular mass in the left lobe of the liver. There was also portal vein thrombosis on the left side. Serum alpha-fetoprotein was not elevated and Hepatitis B antigen was negative. Biopsy of the liver mass led to a histological diagnosis of fibrolamellar hepatocellular carcinoma. In view of extensive tumour involvement, he could not be operated on but was treated with chemotherapy. However, the tumour did not respond. While this is expected for fibrolamellar hepatocellular carcinoma, the possibility of the tumour having a component of ordinary hepatocellular carcinoma could not be excluded as the tumour was not resected.

Fibrolamellar hepatocellular carcinoma is a rare histological **subtype** of hepatocellular carcinoma, associated with a better prognosis. It affects the younger age group and has no association with cirrhosis, hepatitis B virus infection or exposure to oral contraceptives, all of which are implicated in ordinary hepatocellular carcinoma. Serum alpha-fetoprotein level is usually within normal limits and other laboratory values are not contributory to the diagnosis. The diagnosis is usually suggested by radiographic studies viz. CT scan of the abdomen, which would show an irregular **non-homogenous** mass in the liver, and confirmed by histological examination. The most characteristic microscopic feature is fibrosis arranged in a lamellar fashion around polygonal and deeply eosinophilic neoplastic hepatocytes.

Key words: Fibrolamellar carcinoma, hepatocellular carcinoma, liver fibrosis.

INTRODUCTION

Fibrolamellar carcinoma (FLC) is a rare histological **subtype** of hepatocellular carcinoma. It was first described by Edmondson in 1956¹ and later popularized by Berman et al² and Craig et al³ in the 1980s. FLC shares a common differentiation with the ordinary hepatocellular carcinoma (**O-HCC**). However, it shows a much greater differentiation than **O-HCC** and has a long-term survival when treated with radical resection.

This case is reported because of the rarity of the tumour and to serve to remind us of this distinct clinical entity that occurs mainly in young patients. It also highlights the poor outcome of patients when tumours were not radically resected. Our patient did not undergo curative surgery and his disease progressed when the tumour did not respond to chemotherapy.

CASE REPORT

A 6-year-old Malay boy was admitted to the hospital for abdominal pain and fever of two

months' duration. There was a firm nodular mass in the epigastrium. His liver function tests were suggestive of hepatitis. His ESR was mildly elevated. The serum **Hbs Ag** was negative and the alpha-fetoprotein level was within normal limits.

The CT scan of the abdomen showed a **non-homogenous** mass that measured 9 x 7 x 6 cm in the left lobe of the liver. The mass had irregular margins. The right lobe of the liver was normal. The left portal vein was thrombosed and the spleen was displaced inferiorly. The ultrasound **imaging** showed similar findings (Fig. 1). The pancreas and both kidneys were normal in appearance. The **paraortic** lymph nodes were not enlarged.

The radiological diagnosis was hepatocellular carcinoma with a differential diagnosis of hepatoblastoma. A liver biopsy was performed.

Pathology

Histological examination of the liver biopsy **showed groups** of **tumour** cells with some **remnant** normal liver parenchyma. These tumour cells

showed minimal atypia. They were large oncocytic polygonal cells with ample eosinophilic cytoplasm. Hyaline globules and pale bodies were seen in the cytoplasm of the tumour cells. The tumour cells appeared well-differentiated. They were segregated by prominent lamellar fibrous tissue of variable thickness (Fig. 2). Focal areas of tumour necrosis were also seen. The non-neoplastic liver tissue was not cirrhotic.

Reticulin stain wrapped the tumour cells individually and in small groups. Bile was not found in the tumour cells. The tumour cells were reactive to monoclonal carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), low molecular weight cytokeratin (CK 8) and fibrinogen by immunoperoxidase staining (Fig. 3). However, the tumour cells did not show any reactivity for alpha-fetoprotein or HBs Ag stain. A histopathological diagnosis of fibrolamellar hepatocellular carcinoma was made.

Clinical course

A repeat ultrasound imaging was done after the histological diagnosis was made. The portal area was found to be enlarged and suggested lymph node involvement. The patient was referred to the paediatric oncologist in Kuala Lumpur General Hospital where he was given four courses of 2-weekly chemotherapy that included cisplatin alternated with carboplatin and doxorubicin.

After completion of chemotherapy, a repeat CT scan showed that both left and right portal veins were thrombosed. The tumour had not reduced in size. A plan to perform a total hepatectomy with orthotopic liver transplantation was discussed with the parents. However, the parents disagreed and sought traditional medicine instead. The patient was lost to follow-up.

DISCUSSION

Fibrolamellar carcinoma is an uncommon liver neoplasm. It is a true histological variant of the hepatocellular carcinoma and shares a common differentiation with the ordinary hepatoma. This is supported by Berman⁴ and many others who reported cases of "mixed" tumours of FLC with O-HCC. Yamamoto H et al⁵ reported transformation of pure FLC to O-HCC in recurrent lesions and lymph node metastases suggesting the common origin of these two tumours.

Nevertheless, fibrolamellar carcinoma differs from the ordinary hepatocellular carcinoma in many other ways. Fibrolamellar carcinoma commonly occurs in the younger age group, unlike O-HCC. More than 90% occur under 25 years of age⁶. It also has a slight female predominance, unlike O-HCC. The male to female ratio in one series was quoted as 3:4⁷. Serum alpha-fetoprotein (AFP) is usually not raised but the serum carcinoembryonic antigen (CEA) may be elevated.

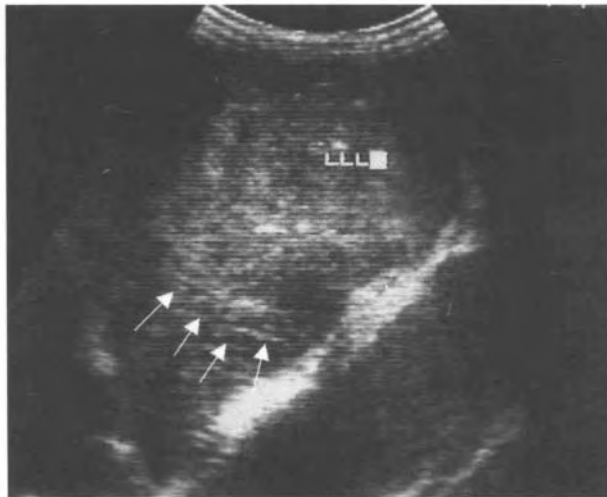


Fig.1: Ultrasound images of the hepatobiliary system. There is a non-homogeneous nodular mass in the left lobe of liver (arrows). The margins of the mass are ill defined. The mass measured 9 x 7 x 6cm. LLL= Left Lobe of Liver.

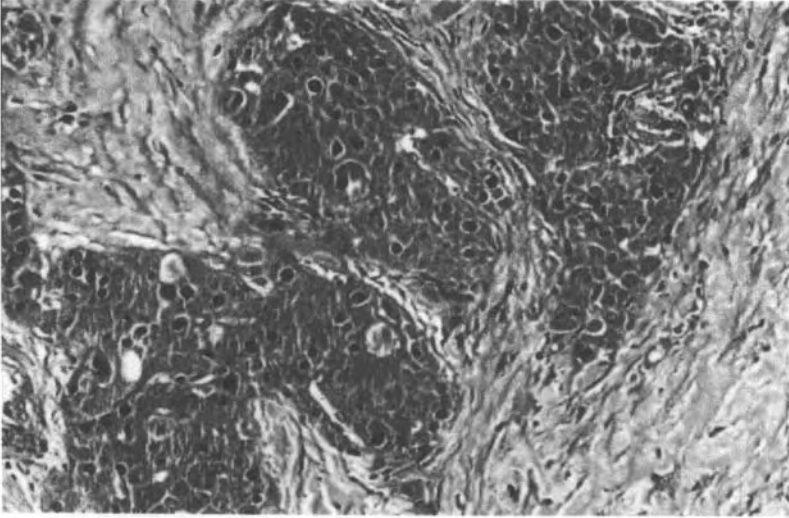


Fig. 2: Large oncocytic cells segregated by lamellar fibrosis. (H&E X 200).



Fig. 3: Tumour cells of fibrolamellar hepatocellular carcinoma reactive to fibrinogen. (Immunoperoxidase stain X 400).

Fibrolamellar carcinoma lacks specific association with cirrhosis, hepatitis B virus infection and exposure to oral contraceptives or alcohol abuse, all of which are implicated in O-HCC. This lack of association suggests that fibrolamellar carcinoma and O-HCC have different aetiologies. However, the mechanism of **hepatocarcinogenesis** of FLC remains unclear.

Our patient had no intrauterine exposure to oral contraceptives and the liver was not cirrhotic. He was negative for HBs Ag. There were no risk factors or preceding liver disease. He was otherwise well before his present illness. His serum alpha-fetoprotein was within normal limits and the liver function tests were non-specific.

As laboratory values and physical signs may

be minimal, the diagnosis of FLC may not be suspected until radiographic imaging or histopathological examination is done. At times, FLC may be mistaken for focal nodular hyperplasia or hepatocellular adenoma.

Histologically, the tumour cells of fibrolamellar carcinoma resemble hepatocytes with mild atypia and demonstrate infrequent mitotic figures. The tumour cells are large oncocytic cells with intracytoplasmic globules that may be either dark, composed of alpha-1-antitrypsin, or pale and larger when composed of fibrinogen. There is extensive fibrosis surrounding the tumour cells. The abundant fibrous stroma may be responsible for the slow growth of this tumour.

The tumour cells of FLC are usually **non-reactive** to alpha-fetoprotein and **HBs** antigen. In cases of "mixed" tumours of FLC and **O-HCC**, only the tumour cells in the area with **O-HCC** are reactive to alpha-fetoprotein and **HBs antigen**^{4,8}. On the other hand, the tumour cells of FLC are reactive to fibrinogen, alpha-1-antitrypsin and C-reactive protein⁴. These are acute phase reactants and are products of normal hepatocytes. This implies again the better differentiation of FLC cells.

Fibrolamellar carcinoma has a much better prognosis and longer survival rate when compared to **O-HCC**. Craig et al³ reported an average survival of **32** months for patients with fibrolamellar carcinoma. This far exceeded the average survival of **O-HCC**. Their study of **23** patients with **FLC** showed a high operability rate of 48%. The differences in overall survival between fibrolamellar carcinoma and **non-fibrolamellar** hepatoma could be due in part to the rate of resectability of the tumour.

The treatment of choice for **FLC** is radical resection of the tumour. It may involve a partial hepatectomy or total hepatectomy with transplantation.

Fibrolamellar carcinoma is indolent and develops at a slower rate than the **O-HCC**. Its response to chemotherapy is poor. Our patient was given chemotherapy as radioimaging suggested that there was lymph nodal involvement at the portal area. However as predicted, he did not respond to the chemotherapy and his disease progressed. Another possible cause of poor response was that the tumour might have been a 'mixed tumour' with a component of ordinary hepatocellular carcinoma. This may not have been represented in the initial biopsy specimen. As the tumour was not resected, this could not be confirmed histologically.

In their study, Pinna et al⁹ found that patients with positive nodes had a shorter tumour free survival than those with negative nodes. Also, they noted that the prognosis was most adversely affected by the **presence** of vascular invasion. Thus, if the tumour is solitary without lymph node involvement or vascular invasion, the prognosis is better and survival longer.

In conclusion, fibrolamellar hepatocellular carcinoma has to be distinguished from the hepatoma. It has a different presentation from **O-HCC** and has a better prognosis. The tumour is more easily resectable and it is also more indolent. The abundant fibrous stroma that is characteristic of the tumour may be responsible for its slow growth. Because of its lack of

association with liver disease and other tumour markers, it may be mistaken for a benign tumour or disease. Thus, histological confirmation is essential for diagnosis. The treatment of choice is radical resection. It has a poor response to chemotherapy. Survival is prolonged if the tumour is solitary with no lymph node or vascular invasion.

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