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*Case report*

# Fibrolamellar hepatocellular carcinoma complicating ulcerative colitis with primary sclerosing cholangitis

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SUMMARY **This case report describes the previously undocumented association between fibrolamellar hepatocellular carcinoma and ulcerative colitis complicated by primary sclerosing cholangitis.**

The fibrolamellar variant of hepatocellular carcinoma is an uncommon tumour which has distinctive clinical and histological features. No risk factors have yet been identified, and in particular it does not appear to be predisposed to by cirrhosis or infection with the hepatitis B virus.[1,2]

Hepatobiliary carcinoma is a well described complication of ulcerative colitis and primary sclerosing cholangitis.[3,4] In the numerous reported cases, however, the histological diagnosis has almost invariably been cholangiocarcinoma.[3,5] We report the first documented case of fibrolamellar hepatocellular carcinoma developing in a patient with chronic ulcerative colitis complicated by primary sclerosing cholangitis.

## Case report

A 35 year old male Caucasian carpenter presented in 1980 with a four week history of malaise without localising symptoms. His brother had died of Hodgkin's lymphoma, but there were otherwise no diagnostic clues in the history. Examination was unremarkable and in particular there were no stigmata of chronic liver disease. His liver biochemistry was abnormal: aspartate transaminase 107 IU/l (normal range 10–35), alkaline phosphatase 337 IU/l (100–300) and bilirubin 18 μM (3–17) with a normal albumin and INR. Viral serology, HBsAg and autoimmune profile were all negative. He proceeded to liver biopsy which showed a heavy portal tract mononuclear cell infiltrate with piecemeal necrosis consistent with a diagnosis of chronic active hepatitis. Treatment with prednisolone and azathioprine produced a complete symptomatic and biochemical response within three months.

In 1981 he returned with a four week history of bloody diarrhoea. Colonoscopy with biopsies established a diagnosis of total ulcerative colitis, and he settled on treatment with sulphasalazine and a course

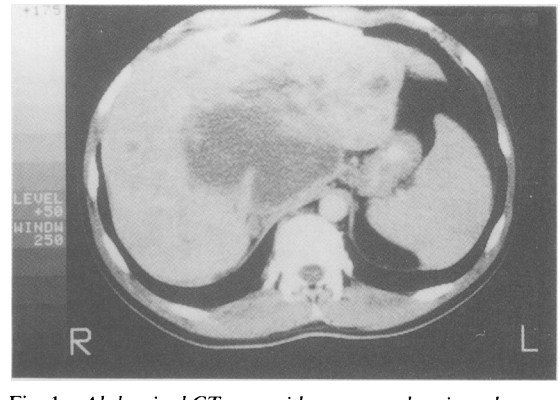


Fig. 1 *Abdominal CT scan with contrast, showing a large, non-enhancing, irregular mass in the region of the porta hepatis, with multiple smaller lesions of similar appearance scattered throughout the liver.*

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of prednisolone. In the light of the development of colitis, his liver disease was reassessed even though his liver biochemistry was at the time normal. Endoscopic retrograde cholangiography revealed characteristic changes of primary sclerosing cholangitis affecting both the intra- and extra-hepatic ducts and repeat liver biopsy was consistent with this diagnosis. Histocompatibility locus antigen typing revealed that he was B8 DR3 positive.

He remained well, with normal or near normal liver biochemistry, until 1985, when he presented with a 10 week history of anorexia, malaise, drenching night sweats, upper abdominal discomfort and weight loss of 10 kg. On examination there was a firm liver edge 3 cm below the costal margin and a palpable spleen tip. He exhibited a swinging pyrexia peaking at 39·5°C. His colitis was clinically and sigmoidoscopically inactive.

Initial investigations revealed abnormal liver biochemistry (aspartate transaminase 51 IU/l and alkaline phosphatase 1019 IU/l: bilirubin, albumin and INR were normal) and a persistent eosinophilia ($0{\cdot}7–1{\cdot}5\times10^9$/l). The serum $B_{12}$ concentration was 770 ng/l (reference range 150–750 ng/l). Serum C-reactive protein was markedly raised at 84 mg/l but serum α-fetoprotein concentration was normal and he remained HBsAg negative. Abdominal computed tomography scan (Fig. 1) showed a large mass at the porta hepatis with a number of smaller lesions throughout the liver. Laparoscopic biopsy of the mass was carried out. His condition continued to deteriorate, however, and he died two weeks later.

Post mortem examination revealed a large liver tumour with metastases in porta hepatis lymph nodes, myocardium and adrenal glands. Histological examination of the tumour revealed the characteristic appearance of fibrolamellar hepatocellular carcinoma, with large polygonal cells lying within a lamellar fibrous stroma (Fig. 2). The cells had eosinophilic cytoplasm, some with pale inclusions, and were shown immunohistochemically to contain alpha-1-antitrypsin but not alpha-fetoprotein. Examination of uninvolved liver showed 'onion-skin' periductal fibrosis characteristic of primary sclerosing cholangitis (Fig. 3), but no evidence of cirrhosis.

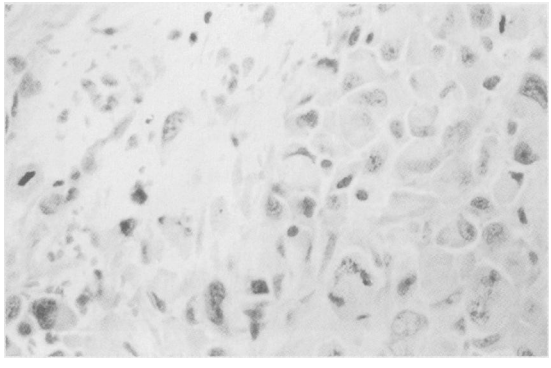

Fig. 2 *Fibrolamellar hepatocellular carinoma (H and E). The tumour cells are polygonal with relatively abundant cytoplasm containing pale inclusions.*

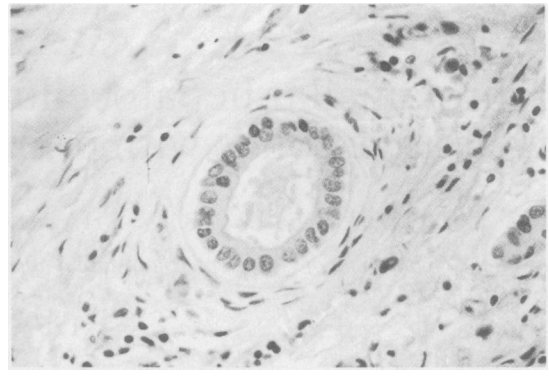

Fig. 3 *Sclerosing cholangitis (H and E). A small septal bile duct showing periductal fibrosis with associated mild chronic inflammation.*

## Discussion

The fibrolamellar variant accounts for 2–10% of cases of hepatocellular carcinoma in Caucasian populations and is therefore a most uncommon tumour.[1,2,6] It has quite distinctive clinical features, which include a predilection for young adults, a relatively good prognosis, normal serum α-fetoprotein and raised serum concentrations of vitamin $B_{12}$ binding capacity[6] and neurotensin.[7] No risk factors for the development of fibrolamellar hepatocellular carcinoma have been identified, and most have been described in non-cirrhotic livers.[1] All of these features are atypical of classical hepatocellular carcinoma in Western countries and most were exhibited by our patient.

The literature concerning hepatobiliary tumours in ulcerative colitis and primary sclerosing cholangitis has focused almost exclusively on cholangiocarcinoma, and over 100 cases have now been described.[5] It has been estimated that the presence of ulcerative colitis confers a relative risk for the development of cholangiocarcinoma of about 30-fold.[5] As the majority of these tumours appear to develop in livers with pre-existing primary sclerosing cholangitis,[4] which is present in less than 5% with ulcerative colitis,[8] primary sclerosing cholangitis must confer a greatly increased risk of cholangiocarcinoma. The mechanism is unknown.

There are a few reports in the literature of hepatocellular carcinoma complicating ulcerative colitis,[3 4 9] but a true association remains to be established. Three such cases were mentioned in a major review of biliary cancers in ulcerative colitis[3] but no details were given. In a detailed pathological study of eight hepatobiliary tumours in ulcerative colitis,[4] one had elements of hepatocellular carcinoma and cholangiocarcinoma whilst the rest were pure cholangiocarcinomas. A consistent feature of all of these cases of classical hepatocellular carcinoma complicating ulcerative colitis is, perhaps not surprisingly, the presence of established cirrhosis.

The fibrolamellar variant of hepatocellular carcinoma has not been previously documented as a complication of ulcerative colitis with primary sclerosing cholangitis. A single case report can never distinguish a causal relationship from coincidence. Nevertheless, the probability of two highly uncommon hepatic/biliary disorders occurring by chance in the same subject is remote and we therefore suggest that ulcerative colitis with primary sclerosing cholangitis may be a risk factor for the development of fibrolamellar hepatocellular carcinoma.

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**Addendum**

Since this report was submitted, another case of (presumed fibrolamellar) hepatocellular carcinoma complicating primary sclerosing cholangitis has been published (*Br Med J* 1988; **296:** 1445).

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