Case report

Hepatocellular carcinoma in primary haemochromatosis in the absence of cirrhosis

I W FELLOWS, M STEWART, W J JEFFCOATE, P G SMITH,
AND P J TOGHILL

From the University Hospital and City Hospital, Nottingham

SUMMARY Two patients with primary haemochromatosis are reported in whom hepatocellular carcinoma supervened despite removal of excess iron after venesection therapy. These are the first patients described in whom hepatocellular carcinoma has complicated primary haemochromatosis in the absence of concomitant cirrhosis.

The prognosis of patients with primary haemochromatosis has improved since the advent of venesection therapy but the survival of haemochromatotic patients with cirrhosis remains shorter than that of the general population.¹ Hepatocellular carcinoma is responsible for part of this increased mortality in patients with primary haemochromatosis and concomitant cirrhosis. Hepatocellular carcinoma has not been reported previously in non-cirrhotic patients with primary haemochromatosis.¹

We describe the development of hepatocellular carcinoma in two patients with primary haemochromatosis in whom venesection had cleared excess iron and in whom there was no evidence of cirrhosis at post mortem examination.

Case reports

PATIENT 1

A 53 year old Caucasian man presented in October 1981 because of an incidental finding of abnormal liver function tests at a pre-employment medical examination. He had suffered from intermittent arthralgia for 13 years. There was no family history of liver disease or diabetes mellitus. His ethanol intake was less than 20 g per day. On examination, he was pigmented but had no stigmata of chronic hepato-

cellular disease. There was minor swelling of the metacarpo-phalangeal joints of the right index and middle fingers.

Liver function tests revealed a mild rise in alanine aminotransferase (ALT) 61 IU/l (normal 2-24 IU/l), gamma glutamyl transpeptidase (GGT) 51 IU/l (normal 4-28 IU/l), but alkaline phosphatase, bilirubin, protein, and albumin were normal. Serum iron concentration was raised at 51 μ mol/l (normal 11-34 μ mol/l), with a serum transferrin concentration of 2.5 g/l (normal 1.7-3.7 g/l). Serum ferritin

Fig. 1 (Case 1). Needle biopsy of liver to show delicate fibrous septa but no cirrhosis.

Address for correspondence: Dr I W Fellows, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH.

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Fig. 2 (Case 1). Necropsy liver showing moderate fibrous septa with normal central vein.

level was over 1000 $\mu\text{g/l}$ (normal 45–200 $\mu\text{g/l}$). Random blood glucose concentration was 5.9 mmol/l. Serum alpha-fetoprotein concentration was less than 20 $\mu\text{g/l}$.

The percutaneous liver biopsy (Fig. 1) showed distortion of lobular architecture with delicate fibrous bands. Extensive deposition of haemosiderin (grade 4)² was present in hepatocytes and bile duct epithelium. Shikata stain was negative. The appearances were consistent with primary haemochromatosis but there was no evidence of cirrhosis.

From December 1981 he was treated by venesection of 540 ml (1 unit) blood, initially twice weekly. Over the next 15 months, 68 units of blood were removed. By March 1983, his haemoglobin concentration had fallen to 9.8 g/dl with serum iron concentration 6 $\mu\text{mol/l}$ and serum transferrin concentration 3.6 g/l. Between March 1983 and November 1985, 23 units of blood were venesected, resulting in a haemoglobin concentration of 8.2 g/dl, serum iron concentration less than 5 $\mu\text{mol/l}$.

He remained well with normal liver function tests until September 1986, when malaise developed. By February 1987, he had lost 9 kg in weight and developed hepatomegaly 6 cm below the right costal margin. Alkaline phosphatase rose to 641 IU/l and GGT to 419 IU/l, but other liver function tests were normal. Alpha-fetoprotein became raised at 544 $\mu\text{g/l}$. Serum iron concentration was 5 $\mu\text{mol/l}$, transferrin 2.4 g/l, and serum ferritin level was 331 $\mu\text{g/l}$.

Percutaneous liver biopsy showed hepatocellular carcinoma. The patient rapidly deteriorated and died. Post mortem examination showed a 4300 g liver almost totally replaced by tumour measuring 20 cm by 17 cm. There was only a small rim of normal hepatic parenchyma, which appeared finely granular. Histology confirmed the presence of hepatocellular

Fig. 3 Needle biopsy of liver to show delicate fibrous septa but no cirrhosis.

carcinoma. The remaining hepatic tissue showed periportal fibrosis, bile duct proliferation and some fibrous bridging between portal tracts but there was no established cirrhosis (Fig. 2). No iron deposition could be detected in the liver or elsewhere. Metastases were present in para-aortic lymph nodes and one adrenal gland. Death was the result of carcinomatosis.

PATIENT 2

A 65 year old Caucasian man presented in March 1976 because of poorly controlled insulin treated diabetes mellitus, first diagnosed in 1970. There was no family history of diabetes mellitus or liver disease and ethanol intake was less than 10 g per day. There was diffuse pigmentation of the skin and hepatomegaly 4 cm below the right costal margin. Liver function tests were normal apart from a mild rise in ALT (33 IU/l) and bilirubin (24 $\mu\text{mol/l}$). Serum HBsAg was negative. Serum iron concentration was 40 $\mu\text{mol/l}$ with total iron binding capacity (TIBC) of 40 $\mu\text{mol/l}$.

The percutaneous liver biopsy (Fig. 3) showed distortion of lobular architecture by fibrous bands containing bile ducts, giving rise to occasional

Fig. 4 (Case 2). External surface of partial hepatectomy specimen to show apparently nodular parenchyma (with centimetre scale).

irregular 'geographical' islands. Iron deposition (grade 3)² was shown in hepatocytes and bile duct epithelium. The appearances were consistent with haemochromatosis and while suspicious of cirrhosis, there was no complete regeneration nodule to confirm this impression.

Over the next three years, 74 units of blood were venesected resulting in a haemoglobin concentration of 13.5 g/dl, serum iron concentration 24 $\mu\text{mol/l}$, TIBC 45 $\mu\text{mol/l}$ and serum ferritin level of 15 $\mu\text{g/l}$. Liver function tests were normal. Maintenance venesection of 2 to 4 units of blood per year was done keeping serum iron and ferritin concentrations in the normal range. By November 1986, a total of 90 units of blood had been venesected from the time of diagnosis. Although the patient had no symptoms, serum alpha-fetoprotein concentration became raised for the first time at 54 $\mu\text{g/l}$, having previously been less than 5 $\mu\text{g/l}$. By February 1987, alpha-fetoprotein was 2350 $\mu\text{g/l}$. Serum iron concentration was 13 $\mu\text{mol/l}$, TIBC 45 $\mu\text{mol/l}$, and ferritin 49 $\mu\text{g/l}$. Ultrasound and computerised axial tomographic scans showed a 7 cm diameter lesion confined to the right lobe of the liver, consistent with a hepatocellular carcinoma. After coeliac axis angiography,

laparotomy was done with a view to right hemihepatectomy, but the patient died during the operative procedure.

The excised right hemihepatectomy specimen contained a discrete 7.5 cm diameter tumour. Histology confirmed the presence of a hepatocellular carcinoma with a trabecular pattern. The liver elsewhere was finely granular (Fig. 4).

Post mortem examination showed periportal fibrosis and focal fibrous bridging between portal tracts but no evidence of cirrhosis (Fig. 5) and no abnormal storage of iron in the liver or any other organ. No residual tumour was found and death was caused by cardiac failure aggravated by blood loss during the operative procedure.

Discussion

In both patients liver biopsies at presentation confirmed the diagnosis of primary haemochromatosis. In the first patient, there was no evidence of cirrhosis. Although there were occasional islands of parenchyma separated by fibrous bands in the needle biopsy of the second patient, the definitive diagnosis of cirrhosis can be made only when the sample

Fig. 5 (Case 2). Necropsy liver showing delicate portal to central fibrous septum but no cirrhosis.

includes complete regeneration nodules;³ these were not present in this patient. It can be difficult to confirm or refute the presence of cirrhosis, however, on the basis of a needle liver biopsy. Post mortem examination six and 11 years later, respectively, showed normal lobular architecture and loss of excessive iron stores after venesection therapy, but despite this, hepatocellular carcinoma supervened. Hepatocellular carcinoma is a common complication of primary haemochromatosis⁴ but all cases described

previously have arisen in cirrhotic livers, even though venesection may have removed excess iron. Barry *et al*⁵ described one patient who developed hepatocellular carcinoma without cirrhosis, as a complication of iron overload secondary to hereditary spherocytosis. To our knowledge, the two patients described here are the first to develop hepatocellular carcinoma as a complication of primary haemochromatosis in the absence of cirrhosis. This implies that the premalignant potential of haemochromatosis can be independent of the presence of cirrhosis. The precise nature of the oncogenic mechanism remains obscure.

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