Case reports

Hepatocellular carcinoma in HBsAg-negative chronic active hepatitis

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SUMMARY The occurrence of hepatocellular carcinoma in HBsAg-negative chronic active hepatitis is described in two patients. Signs of the tumour appeared 18 years and nine years after the first clinical signs of chronic active hepatitis, although in one patient analysis of stored sera showed the serum alpha-fetoprotein levels had been rising over the previous 33 months. Female preponderance in HBsAg-negative chronic active hepatitis may partly account for the rarity of this complication, and the occurrence of hepatocellular carcinoma may also be a reflection of the better survival now being obtained in HBsAg-negative chronic active hepatitis.

Hepatocellular carcinoma is a well-recognised complication of long-standing cirrhosis and a particularly high frequency has been reported in cirrhosis consequent on HBsAg-positive CAH.¹ In patients with the HBsAg-negative form of the disease, it has been stated to occur rarely, if ever,² although examination of five large series³⁻⁷ reveals, of the 322 cases included, three apparent instances, all male, in which hepatocellular carcinoma developed. The development of hepatocellular carcinoma in a 60 year old Italian man in whom serum autoantibodies were negative has also been reported from Australia.⁸ In none of these patients, however, had an earlier hepatitis B virus infection been completely excluded by examination of serum for all virus markers, particularly antibody to hepatitis B core antigen, and few details of the patients are given.

In this report, we describe two patients with HBsAg-negative CAH in whom hepatocellular carcinoma developed 18 years and nine years after the first clinical signs of their disease. In one of them, aged only 22 years at death, subsequent analysis of stored sera showed rise in serum alpha-fetoprotein (AFP) levels, which was first detected 33 months before signs of the tumour became evident.

Case 1

A 27 year old English woman was admitted to Guy's Hospital in October 1953 with a six month history of anorexia, recurrent jaundice, and polyarthralgia. Investigations showed a raised erythrocyte sedimentation rate of 110/mm/h, in addition to abnormalities of liver functions (serum bilirubin 62 μ mol/l, alkaline phosphatase 167 IU/l, albumin 21 g/l, and total globulin 67 g/l). Jaundice and joint symptoms quickly resolved with prednisolone, 15 mg daily, which was reduced after a few weeks to 10 mg daily on which she continued until 1966, when she was readmitted with another episode of jaundice. Examination showed palmar erythema, numerous spider naevi, and hepatomegaly (3 cm below right costal margin). The characteristic features of CAH which had progressed to cirrhosis were found on liver biopsy, with evidence of continuing activity including piecemeal necrosis and infiltration of the portal tract with mononuclear cells. She responded quickly to a temporary increase in prednisolone dosage (30 mg daily) and for the next four years was maintained on prednisolone (10-15 mg daily).

In January 1971 she was readmitted to hospital with symptoms of increasing jaundice and right-sided abdominal pain. On examination, the liver was notably tender (palpable 4 cm below the right costal margin) but results of liver function tests showed little change with a serum bilirubin level of 98 μ mol/l,

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Fig. 1 Case 1. Transection of liver, showing tumour replacing the right lobe and a macronodular cirrhosis in uninvolved areas (original scale 1:1.75).

alkaline phosphatase of 180 IU/l, aspartate aminotransferase 130 IU/l, albumin 33 g/l, and globulin 37 g/l. Antibodies to smooth muscle (++) and antinuclear factor (++) were present in serum. Over the next six weeks abdominal pain and distension became increasingly severe and she was transferred to King's College Hospital, but died 48 hours after admission. Serum taken on this admission was negative for AFP, HBsAg, and anti-HBs when tested at a later stage by radioimmunoassay (HBsAg: Ausria II, Anti-HBs: Ausab, Abbott Laboratories, Basingstoke, Hampshire, England).

Necropsy showed an enlarged liver, weighing 4190 g, with a macronodular (0.5–1 cm) cirrhosis. The whole of the right lobe was replaced by tumour tissue (Fig. 1) and on histological examination the appearances were those of a well-differentiated hepatocellular carcinoma.

Case 2

A 13 year old boy was admitted to King's College Hospital in 1970 with a 12 week history of malaise and jaundice, and a previous episode of jaundice lasting two weeks in 1964. Details of his family history, in which there was a high frequency of autoimmune disease and serum autoantibodies, are described elsewhere.⁹ Examination revealed spider naevi and hepatomegaly. Liver function tests showed serum bilirubin 68 μ mol/l, aspartate aminotransferase 1220 IU/l, alkaline phosphatase 366 IU/l, pro-

thrombin time 18 seconds (control 13 seconds), albumin 33 g/l, total globulin 77 g/l, IgG 45.60 g/l. Antinuclear factor was positive in the serum (titre 1:80) as were smooth muscle antibodies (titre 1:80). Liver biopsy showed changes characteristic of chronic active hepatitis at the cirrhotic stage. Lymphocytic portal tract infiltration and piecemeal necrosis were marked. He was started on prednisolone and azathioprine, and over the next four years was reasonably well, although serum AST remained raised (60–160 IU/l).

In August 1975 he became jaundiced again and the serum AST rose to 1035 IU/l and total globulin to 53 g/l. With an increased dose of prednisolone (40 mg daily) some clinical and biochemical improvement occurred.

Finally in June 1979, he was readmitted with a six week history of increasing abdominal pain, fever, and jaundice. Serum bilirubin had risen to 730 μ mol/l and AST to 1090 IU/l. On palpation, the liver was tender and larger than previously. The clinical diagnosis of hepatocellular carcinoma was supported by the finding of a greatly raised AFP (see below); but neither HBsAg, anti-HBs or anti-HBc were detected in radioimmunoassay (anti-HBc: Corab, Abbott Laboratories, Basingstoke, Hampshire, England).

Necropsy revealed an enlarged liver (weighing 21 900 g) with a coarse macronodular cirrhosis. On sectioning, the left lobe was found to be completely replaced by necrotic tumour and tumour nodules were also present in the right lobe, the histological

Fig. 2 Case 2. Serial alpha-fetoprotein (AFP) levels over a nine-year period, showing the first rise in September 1976 and the subsequent exponential increase.

appearance being that of a moderately well-differentiated hepatocellular carcinoma.

SERIAL AFP ESTIMATIONS

Sera were available from the Unit serum bank from 1970 onwards. Using a sensitive radiomunoassay which yields a range of 2–10 ng/ml in healthy subjects,¹⁰ a raised serum AFP was detected for the first time in September 1976, 33 months before tumour became clinically manifest (Fig. 2). From then onwards there was an exponential rise in serum concentration to a level of 100 000 ng/ml at time of final admission.

Discussion

There can be no doubt about the diagnosis of HBsAg-negative CAH in these two patients. The initial presentation in each case was with relapsing jaundice, and laboratory findings of hyperglobulinaemia and anti-smooth muscle antibodies in the serum, as well as the histological appearances, were all characteristic of this condition. Serological investigations were negative for hepatitis B virus infection (including absence of anti-HBc in case 2).

As already referred to, there have, to date, been no well-documented cases of hepatocellular carcinoma in HBsAg-negative CAH in women. The marked female sex predominance in this disease is likely to be one of the reasons why the complication of hepatocellular carcinoma is encountered so rarely. Tumour development is found particularly in those types of cirrhosis which occur predominantly in the male—for instance, alcoholic cirrhosis and HBsAg-positive CAH. Hepatocellular carcinoma is

also very rare in patients with primary biliary cirrhosis, another condition in which females predominate, and, of the four cases reported by us recently, one was male.¹¹ The duration of the cirrhosis is also important and, until the introduction of prednisolone treatment, the overall prognosis for chronic active hepatitis was poor. However, with such therapy life expectancy is considerably prolonged, and in the recently published follow-up study from the Royal Free Hospital¹² patients lived 10 years or longer. Our two patients had histological evidence of cirrhosis five and nine years before clinical signs of the tumour appeared. Studies in alcoholics have suggested that cirrhosis must have been present for five to 10 years for a hepatocellular carcinoma to develop.¹³

The results of the serum AFP estimations in case 2 with the findings of a raised level some 33 months before clinical evidence of tumour is of interest, for it has been reported that the level rises only a short time before the onset of the symptoms.¹⁴ In view of the long-term survival now seen in HBsAg-negative CAH it is suggested that these patients be regularly monitored for changes in serum AFP levels, as cytotoxic drug therapy, particularly Adriamycin, can now give a worthwhile remission in at least 20% of patients with hepatocellular carcinoma.¹⁵

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