Androgen associated hepatocellular carcinoma with an aggressive course

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Abstract
The hepatocellular carcinomas that develop in patients treated with androgens have previously been associated with a benign clinical outcome. We describe a man who developed a hepatocellular carcinoma after 24 years of androgen treatment, whose tumour initially showed partial regression after withdrawal of androgens but subsequently pursued an aggressive and fatal course.

An association between androgen treatment and the development of hepatocellular carcinoma was first reported in 1965.[1] The initial reports concerned patients treated for Fanconi's anaemia[1-4] but cases were described subsequently in which androgens were given for other anaemias,[5-7] hypogonadism,[8-10] and to enhance athletic performance.[11][12]

Although they have a histological appearance consistent with that of hepatocellular carcinoma, androgen associated liver tumours are usually associated with a benign clinical outcome. In previous reports, tumours have either regressed or have failed to progress after androgens have been withdrawn. We describe a man who developed hepatocellular carcinoma after 24 years of androgen treatment, whose tumour regressed over the 18 months after androgen withdrawal but then pursued an aggressive and fatal course.

Case report

In 1962, a 24 year old electrician was diagnosed as having primary hypogonadism and was begun on methyltestosterone, 25 mg tds. Routine investigations in 1980, when he underwent bladder neck resection, showed a serum alanine transaminase value of 172 U/l (normal value <45). In October 1986, aged 48 years, he presented with upper abdominal pain, weight loss, and a hard 6 cm enlarged liver. He was heterosexual and had never abused alcohol or drugs or had a blood transfusion.

His serum bilirubin concentration was 16 μmol/l (normal <17), alanine transaminase 137 U/l (normal <45), aspartate transaminase 84 U/l (normal <45), alkaline phosphatase 330 U/l (normal <300), albumin 35 g/l (normal 30–50), iron 9 μmol/l (normal range 7–29), total iron binding capacity 96 μmol/l (normal range 45–70), α fetoprotein <10 U/l (normal <10). Serum was negative for antimitochondrial and smooth muscle antibodies and for hepatitis B virus surface antigen and core antibody. Abdominal ultrasound showed multiple echogenic areas throughout the liver. Computed tomography (Fig 1A) showed multiple lesions in both liver lobes with patchy contrast enhance-

ment, an enlarged para-aortic node was also seen.

An ultrasound guided liver biopsy showed hepatic tissue where the cells were two or more cells thick, with a pseudoacinar pattern (Fig 2A). There was a mild degree of nuclear pleomorphism and abundant bile duct production by tumour cells. Immunohistochemical stains were positive for α_1 antitrypsin in a diffuse cytoplasmic pattern but negative for α fetoprotein and hepatitis B surface and core antigens. The appearances were those of a well differentiated hepatocellular carcinoma.

Because the patient also suffered from severe ischaemic heart disease and because of the normally benign course of androgen associated liver tumours, liver transplantation was not performed. The methyltestosterone was stopped and by June 1987 he felt well, had gained weight, his abdominal pain had almost disappeared, and his liver had decreased in size to become just palpable. Serum testosterone was <0·56 nmol/l and he had become impotent. Serum alanine transaminase had fallen to 40 U/l and aspartate transaminase to 32 U/l. Repeat computed tomogram (Fig 1B) showed that several of the liver lesions had decreased by more than 50% in size, some having almost completely resolved, although others remained unchanged and one had increased in diameter. The para-aortic node was no longer enlarged.

In December 1988 he was readmitted to hospital with a six month history of diarrhoea, upper abdominal pain, weight loss, and pruritus. On examination he was wasted and had several spider naevi. The liver was palpable 6 cm below the costal margin and there was bilateral leg oedema and ascites. A fourth heart sound was audible. Serum bilirubin was 53 μmol/l, alkaline phosphatase 676 U/l, aspartate transaminase 109 U/l, albumin 27 g/l, α fetaprotein <10 U/l, prothrombin time 19·4 seconds. Serum was positive for antibodies to hepatitis C virus antigen (C100-3) by ELISA: 2·4 OD units (<0·64).[13] Computed tomogram showed multiple tumour deposits in both liver lobes and the entire liver texture looked abnormal (Fig 1C). He continued to deteriorate and died three weeks after admission.

At necropsy, the liver weighed 3130 g and was extensively replaced by multiple nodules of varying size, measuring up to 5 cm in diameter. Histologically, these nodules were composed of well differentiated hepatocellular carcinoma (Fig 2B), again showing diffuse cytoplasmic α_1 antitrypsin positivity and lacking α fetoprotein reactivity, with many nodules showing central necrosis. The non-neoplastic liver exhibited considerable macrovesicular steatosis and mild portal fibrosis but was not cirrhotic and showed no evidence of parenchymal or portal inflamma-

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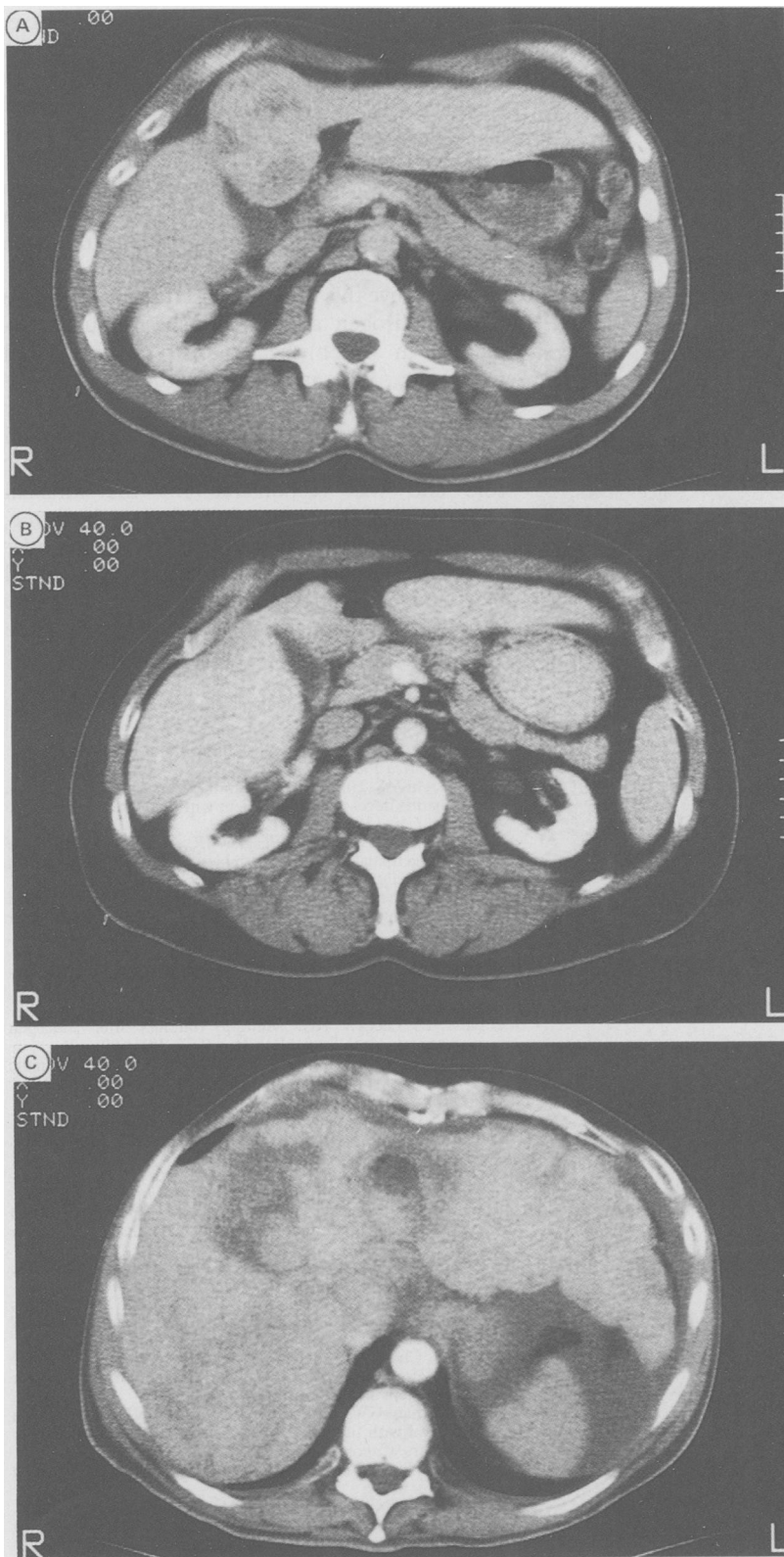
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Figure 1: A. Computed tomogram of the liver showing a mixed attenuation tumour nodule in the right lobe, approximately 5 cm in diameter. B. Computed tomogram at a similar level seven months later shows almost complete resolution of the previously described tumour nodule. C. Computed tomogram performed shortly before death, showing considerable hepatomegaly with diffuse nodularity due to tumour throughout the liver and ascites.

tory infiltrate or any features of α_1 antitrypsin deficiency. Orcein, copper, and iron stains were negative. The main portal vein was thrombosed and in many of the smaller intrahepatic branches, tumour infiltration by well differentiated hepatocellular carcinoma was noted (Fig 2C). No distant metastases were identified.

Discussion

The hepatocellular carcinomas described in association with androgen treatment tend to be well differentiated. Only one histologically proved case of distant metastases has been reported.[12] The presence of bony metastases in another patient[8] was not confirmed by a follow up report.[14] Indeed, some[15] have disputed the classification of these tumours as carcinomas, especially since hepatic adenomas have also been described in patients treated with androgens.[16][17] Moreover, in contrast with other hepatocellular carcinomas, those associated with androgen treatment run an indolent clinical course. Those patients with Fanconi's anaemia usually die of haemorrhage related to their primary disease, and although four patients[2][4][12] may have died from hepatic malignancy, androgens had been withdrawn only a few months or not at all before death. In patients given androgens for other reasons,[8][10][14] tumours regress or at least show failure of progression after withdrawal of androgen treatment and patients either remain alive up to 14 years later or die of unrelated causes.

It seems likely that long term methyltestosterone treatment was a major factor in the development of hepatocellular carcinoma in our patient. We could confidently exclude most factors commonly predisposing to chronic liver disease and hepatocellular carcinoma – including alcohol abuse, hepatitis B virus infection, haemochromatosis, α_1 antitrypsin deficiency, and autoimmune liver disease. The fact that the patient's serum was positive for hepatitis C antibodies makes it more difficult to exclude a copathogenic role for hepatitis C infection but several features argue against a primary role.

Firstly, although antibodies to hepatitis C have recently been detected in 60–80% of patients with hepatocellular carcinoma,[18-20] we are unaware of any documented case where preexisting cirrhosis has not been present. Our patient's non-neoplastic liver tissue showed no evidence of cirrhosis, nor of chronic active or chronic persistent hepatitis. There was prominent fatty change, which may be explained by the patient's malnourished state. There was also some fibrosis around the portal tracts. Although less easy to explain, this could be a result of cholestasis induced by tumour infiltration or chronic methyltestosterone treatment. The mildly raised serum alanine transaminase activity noted in 1980 might also have been caused by the androgen treatment, since about one third of patients on long term methyltestosterone have raised serum transaminase values.[21] Thus, there was little evidence of underlying liver disease that might predispose to hepatocellular carcinoma. The significance of the positive hepatitis C serology remains unclear, indeed doubts have recently been expressed regarding the specificity of the test.[22]

Secondly, serum α fetoprotein remained within normal limits in our patient, as is the case with virtually all androgen associated liver tumours. In contrast, most hepatitis C antibody positive patients with hepatocellular carcinoma (90% in one series[20]) have some increase in α fetoprotein. A third argument favouring a pre-
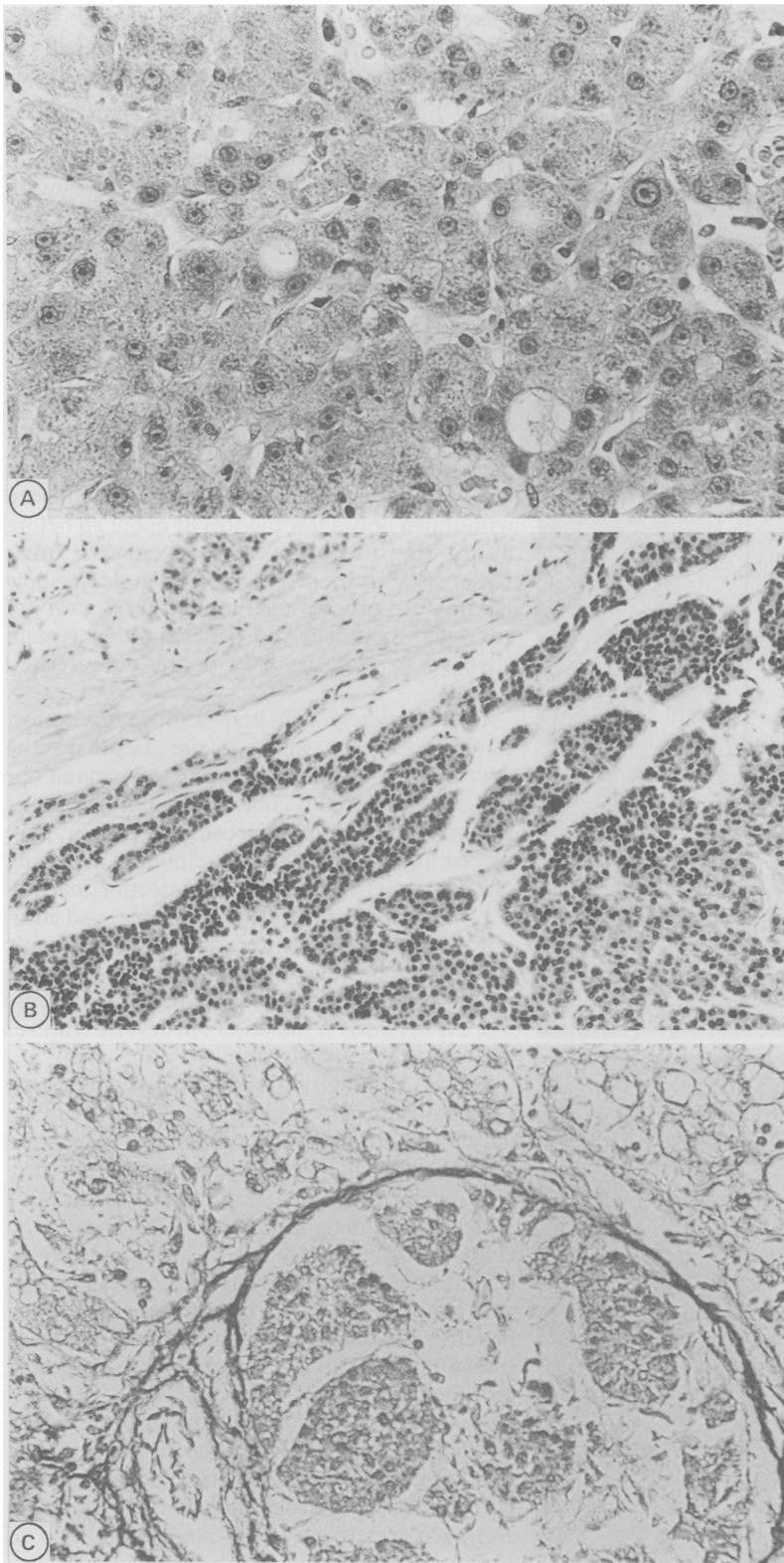
Figure 2: A. Original needle biopsy specimen showing expansion of liver cell plates, pseudoacinus formation, mild nuclear pleomorphism and prominant nucleoli. The appearances are those of a well differentiated hepatocellular carcinoma (haematoxylin and eosin, original magnification ×400). B. Necropsy liver showing trabeculae and nodules of similar tumour (haematoxylin and eosin, original magnification ×160). C. Portal vein branch invaded by tumour (elastic Van Giesen stain, original magnification ×400).

dominant pathogenic role for androgens is the clinical, biochemical, and radiological evidence of tumour regression over the 18 months after withdrawal of the methyltestosterone.

The unusual feature about this patient was that after the initial period of regression, the tumour then pursued an aggressive and fatal course. Rapid tumour growth was evident clinically, biochemically, and radiologically during the last months of life. At necropsy, the tumour occupied most of the liver, probably explaining the hepatocellular decompensation before death, and was invading the portal vein. Thus, although no distant metastases were present, this lesion clearly exhibited the biological behaviour of a malignant tumour.

We believe this to be the first documented case of an androgen associated hepatocellular carcinoma in which the tumour, despite initial regression on androgen withdrawal, subsequently pursued a fatal course. We can only speculate about the extent to which coincidental hepatitis C infection played a co-carcinogenic role and was responsible for the unusual behaviour of the tumour. The case, however, illustrates that not all androgen associated liver tumours are benign in terms of 'biological behaviour' as suggested by others.[14] These patients require long term follow up and, in some cases, resection or liver transplantation.

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