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Spontaneous regression of hepatocellular carcinoma in a cirrhotic patient: possible vascular hypothesis

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ABSTRACT Spontaneous regression of hepatocellular carcinoma is extremely rare, and the exact pathogenesis leading to this remarkable phenomenon remains unclear. We describe a case of spontaneous regression of an incidentally discovered hepatocellular carcinoma in a 63-year-old man with hepatitis C cirrhosis. The regression followed a series of events, in particular, an upper gastrointestinal haemorrhage. Ischaemic insult may be a major pathway leading to tumour regression. As limited data is available in the literature, knowledge and recognition of this rare event will have implications for patient management and may alter treatment. Further, data may be useful to assess if these patients have an altered prognosis with improved survival.

Keywords: hepatocellular carcinoma, spontaneous tumour regression
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INTRODUCTION

Spontaneous regression of tumours is rare, and the exact pathogenesis leading to this phenomenon remains unclear. Regression of hepatocellular carcinoma (HCC), specifically, is an even rarer event and has been defined as complete or partial involution of tumour without directed therapy.[1] The underlying pathogenesis of HCC regression remains unclear and the possible causes are diverse. Some proposed mechanisms include the induction of an immune response, inflammatory causes and the use of various herbs.[2-4] Alterations of the vascular supply have also been implicated as a cause, including decreased perfusion that could occur in the setting of massive gastrointestinal bleeding.[5,6]

CASE REPORT

A 63-year-old Caucasian man with known hepatitis C and Child's class A cirrhosis presented to the regional public hospital's Emergency Department with mental status changes related to hepatic encephalopathy. Clinical examination was negative for jaundice or icterus but demonstrated asterixis and the presence of ascites. There were no stigmata of chronic liver disease and no organomegaly. Vital signs were normal. Additional history revealed recent fatigue and anorexia. Past medical history was significant for hepatitis C cirrhosis, post-traumatic stress disorder and thrombocytopenia.

The patient's hospital admission was complicated by an upper gastrointestinal bleed. Over a period of 48 hours, he became haemodynamically unstable, with a decline in haematocrit from 37% at admission to 22%, and 400 ml of blood was aspirated from his nasogastric tube. At that time, oesophagogastroduodenoscopy (OGD) showed a small gastric ulcer in the gastric fundus without associated varices. The patient stabilised after copious intravenous (IV) fluids and transfusion of two units of packed red blood cells, which raised haematocrit to 28%. Proton pump inhibitor infusion was also completed and no further evidence of bleeding was found.

The patient was referred for abdominal ultrasonography (US) to evaluate for portal hypertension. US revealed a nodular hepatic contour consistent with cirrhosis, as well as a solid, echogenic mass in the right hepatic lobe (Fig. 1a). Mild ascites and splenomegaly were also present, confirming portal hypertension. Multiphase contrast-enhanced computed tomography (CT) of the abdomen showed a 3.9 cm × 3.8 cm right hepatic lobe mass that demonstrated hypervascularity in the arterial phase and subsequent washout in the portal venous phase (Figs. 1b–d). The patient's serum alpha-fetoprotein (AFP) was 5.5 (normal range < 10.9) ng/mL. No other focal liver lesion was present. His remaining hospital course was uneventful and he was subsequently discharged.

Surgical treatment was deferred due to portal hypertension and comorbidities. Repeat imaging was obtained two months later during workup for possible locoregional treatment. Abdominal US at this time demonstrated that the known mass had decreased in size and was now predominately cystic (Fig. 2a). Repeat multiphase CT of the abdomen showed that the tumour was now uniformly hypodense and cystic on all four phases, without arterial enhancement or portal venous phase washout (Figs. 2b–d). The mass had also slightly decreased in size, measuring 3.3 cm × 3.6 cm, and no new masses had developed. Treatment was deferred at this time and follow-up was recommended by the interventional radiology and hepatology teams. Serum AFP remained normal at 6.7 ng/mL.

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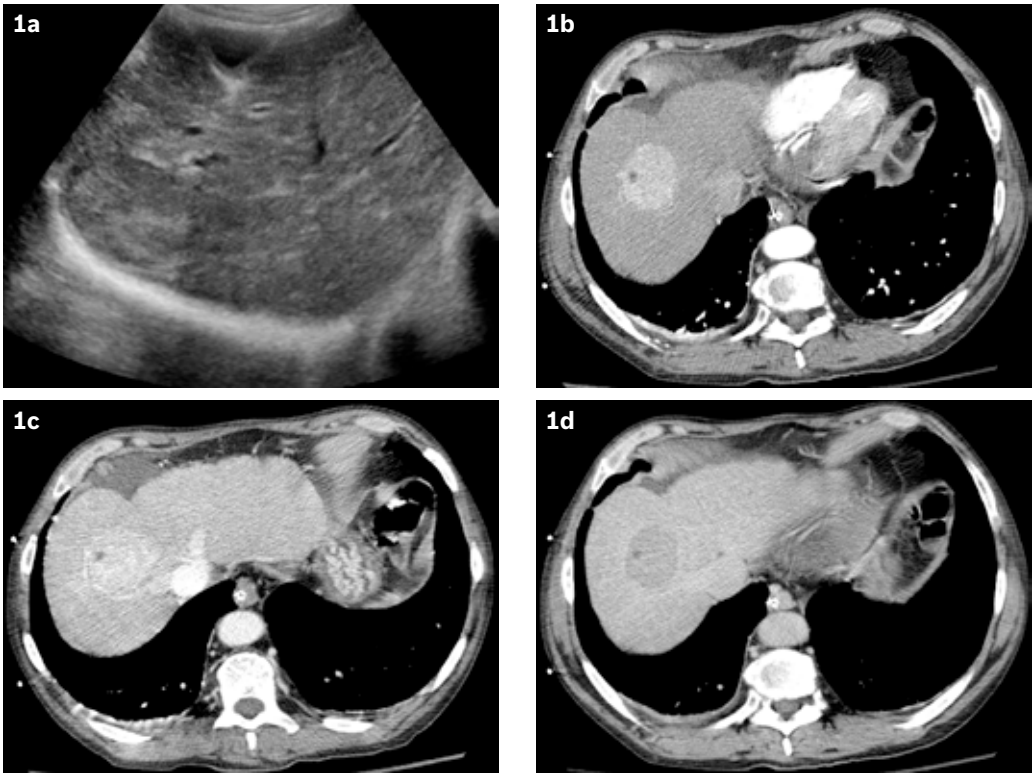

Fig. 1 (a) Abdominal US image shows a solid mass in the right hepatic lobe. (b) Hepatic arterial phase CT image shows a hypervascular mass with a small hypodense area. (c) Portal venous phase CT image shows the tumour remaining hypervascular to the liver. (d) Delayed phase CT image shows tumoural washout of the contrast, relative to adjacent liver parenchyma, compatible with a hepatocellular carcinoma.

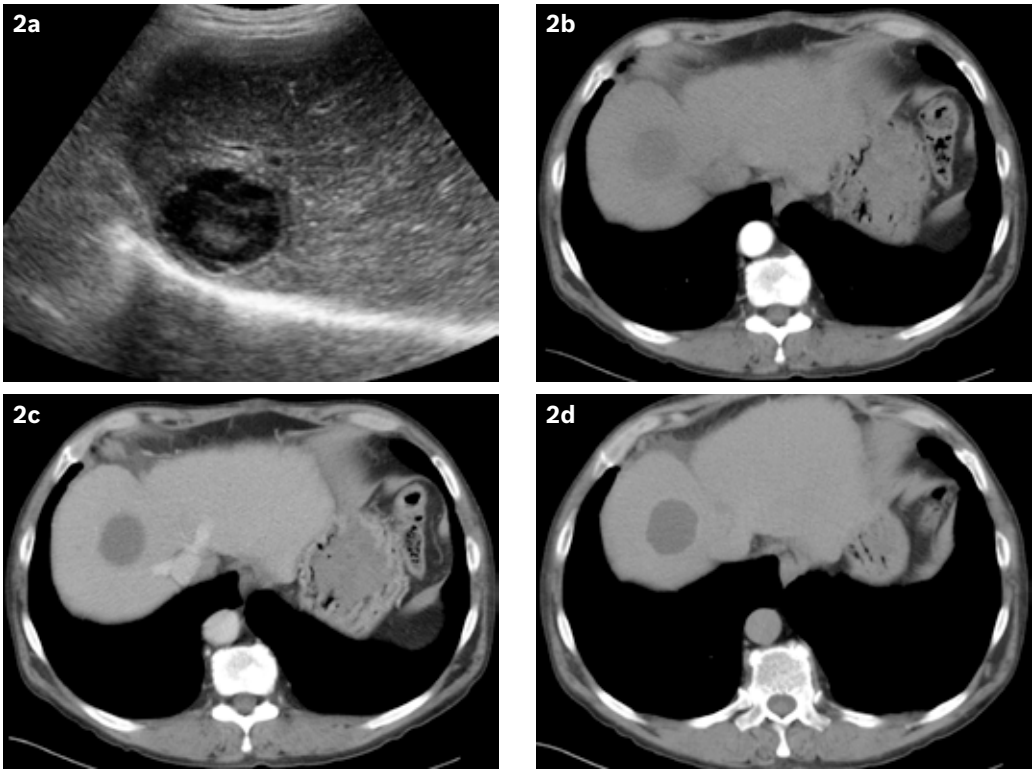

Fig. 2 Images obtained two months after the initial presentation show cystic degeneration and mild reduction in size of the known hepatocellular carcinoma. (a) US image shows that the previously solid hepatic mass is now predominately cystic. (b) Hepatic arterial; (c) portal venous; and (d) delayed multiphase CT images performed on the same day confirm that the mass is cystic and has reduced in size. No residual areas of enhancement are seen.

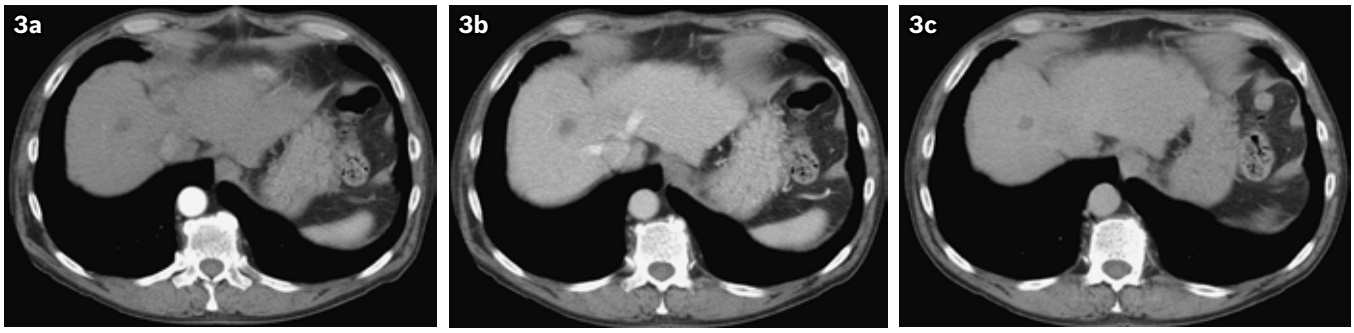

Fig. 3 (a) Hepatic arterial; (b) portal venous; and (c) delayed phase CT images ten months after the initial presentation show continued tumour regression with reduction in size of the known hepatocellular carcinoma and a small residual cystic area, which is likely necrosis. No residual areas of enhancement are seen with the mass.

Contrast-enhanced, multiphase CT of the abdomen approximately ten months after the patient's initial presentation showed continued reduction in size of the known hepatic mass. CT showed that it now measured 1.3 cm × 1.1 cm, was non-enhancing and remained cystic in nature (Fig. 3). Again, no additional hepatic mass had developed in the interim. The patient continued to be well without signs of recurrence at the time of this writing.

DISCUSSION

HCC is a frequent complication of liver cirrhosis and has a poor prognosis with a rapidly fatal course if untreated. Without treatment, the five-year survival rate is less than 5%.[7] A minority of patients can be treated curatively with surgical resection, liver transplantation or percutaneous ablation.

Spontaneous tumour regression is a rare event that has been estimated to occur in one per 60,000–100,000 cases, and various underlying mechanisms have been suggested.[1] Ischaemia is one of the several proposed mechanisms based on the high metabolic requirement of the malignant tissue. Ischaemic insult to a HCC may be due to hepatic artery thrombosis, altered vasculature due to underlying cirrhosis, and may occur during rapid tumour growth or due to haemorrhagic shock related to bleeding.[4,8] The latter is of particular interest, as our patient experienced upper gastrointestinal haemorrhage during his hospital course. Local ischaemia may have contributed to cystic degeneration of the tumour. Tocci et al reported complete HCC regression following massive haematemesis and prolonged shock due to a bleeding gastric ulcer. The tumour completely disappeared within three years of presentation, with small residual microcalcifications.[4] A similar case reported by Gaffey et al describes complete regression of a 10 cm × 10 cm HCC following multiple episodes of upper gastrointestinal haemorrhage related to an active duodenal bulb ulcer and ulcerated oesophageal varices.[5] Tumour regression was confirmed on autopsy, which showed that the area of tumour was replaced by green-yellow necrosis and areas of fibrosis. Histopathological confirmation in our case was not performed, as the enhancement characteristics at the initial presentation were classical for HCC and follow-up imaging had demonstrated progressive reduction in tumour size, internal necrosis and resolution of enhancing soft tissue components.[9]

While the exact cause of our patient's tumour regression is unknown, we suspected a vascular aetiology related to haemorrhage-induced ischaemia. It is possible that our patient's acute onset of haemodynamic instability had altered the tumoral blood supply, resulting in tumour infarction and necrosis. While aetiologies of tumour regression are multifactorial, alterations in vascular supply, particularly ischaemia, have been reported in the literature. A systemic review of HCC regression performed by Oquiñena et al noted ischaemia as a cause in 44% of patients, from ischaemia-related to haemorrhagic shock, hepatic artery thrombosis and/or rapid tumour growth.[6] Another often suggested pathway is inflammatory or immune-mediated, and related to cytokine production.[3] Interestingly, regression of benign liver masses has also been reported in adults as well as children, such as haemangioendothelioma and hepatic adenoma.[10]

In addition to the above mechanisms, the specific biological behaviour of the tumour itself may also predispose regression. HCC carcinogenesis is complex, indicated by variable clinical phenotypes, tumour grade differentiation, metastatic potential, growth rate, sensitivity to treatment agents and potential for venous invasion, among other characteristics. Current genomic and proteomic investigations at the DNA and RNA level will help facilitate identification of tumour behavioural factors that may lead to spontaneous regression. Future research related to the specific molecular signature of regressed HCCs is needed to help further understand the biology of tumour regression and guide therapy.[7]

In conclusion, spontaneous regression of HCC is an extremely rare event and a definite cause of regression has not been determined. Knowledge of the possible mechanisms related to tumour regression and recognition of HCC regression as a possibility has implications for future therapies and patient management. The known survival spectrum for patients with nonresectable HCC may be extended. In our case, ischaemia may have been a contributing factor; however, it is difficult to explain based solely on ischaemia as other systemic and local effects are likely involved. More cases of HCC regression are needed for further understanding of this rare phenomenon. Aggressive treatment may not be warranted and further data may be useful to assess if these patients have a better prognosis with improved survival.

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