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CASE REPORT

Primary yolk sac tumor of the liver: incidental finding in a patient transplanted for hepatocellular carcinoma

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Summary

A 64-year-old man with HBV-related cirrhosis presented with a liver nodule measuring 2.8 cm revealed by a routine ultrasound and concomitant increased alpha-fetoprotein (AFP) up to 400 UI/l. Contrast-enhanced CT was suggestive of hepatocellular carcinoma (HCC) and the patient underwent laser ablation procedure. Five months later, because of raised AFP up to 1600 UI/l, ultrasonography and abdominal CT were repeated, showing an increased diameter of liver nodule, measuring 3.8 cm. The patient underwent down-staged trans-arterial chemoembolization (TACE) and then was entered into the active liver transplant (LT) list. Lamivudine was already started and the patient underwent LT showing HBV-DNA serum levels $<10^3$ log/copies at the time of surgery. Pathological analysis performed on the explanted liver showed, instead of the suspected HCC, hepatic yolk sac tumor with the presence of typical 'Schiller-Duval bodies'. The first 12 months of postoperative follow-up were excellent, with no evidence of tumor recurrence.

Introduction

Yolk sac tumors (YSTs) are rare malignant neoplasms of childhood and adolescence and account for 20% of primitive germ cell tumors [1]. The most common location of these tumors is the testis or ovary, even though in approximately 10–15% of the patients, it arises in extragonadal sites such as the mediastinum, retroperitoneum, sacrococcygeal region and bladder [2]. Less than 20 cases of hepatic YST have been reported worldwide: seven presented in adulthood [3–9], and in only one case, YST was associated with hepatocellular carcinoma [10]. Successful treatment of YST was achieved in most cases by either complete surgical resection or resection with adjuvant chemotherapy. One pediatric case with nonresectable YST was treated with liver transplantation (LT) [11] and the patient was disease-free at 3 years of follow-up. To our knowledge, no cases of YST treated with liver transplantation in adulthood were published yet. We report the case of a 64-year-old cirrhotic man who presented with a large liver nodule suggestive of hepatocellular carcinoma (HCC) and underwent LT with an increased priority on the basis of HCC MELD. Pathological analysis performed on explanted liver showed hepatic yolk sac tumor instead of suspected HCC.

Case report

A 64-year-old man with chronic HBV infection with no history of previous antiviral treatment was admitted to our Liver Unit. Hematologic and biochemical data showed thrombocytopenia at 80 000 cells/mm^3 and transaminases (AST and ALT) $\times$ 3 normal values (normal limit of 38 IU/l), respectively, with no evidence of cholestasis. The patient had 1.8 of international normal ratio (INR) (normal range 0.8–1.15), no history of alcohol intake and negative screening for all autoimmunity assays. Viral hepatitis serology was as follows: HBsAg positive,

anti-HBs negative, HBeAg negative, anti-HBc IgM negative, anti-HBc IgG positive and HBV-DNA 10^4 log copies/ml. Antigen and antibodies for hepatitis delta virus (HDV) were negative. Child-Pugh-Turcotte (CPT) score was B7. The patient had no history of major complications of cirrhosis and his renal function was normal. Lamivudine was started and the patient was followed in our outpatient clinic with hematologic and biochemical tests and radiological procedures. One year later, a routine ultrasound revealed a nodule in the right lobe, on segment 7, measuring 2.8 cm on maximum diameter (Fig. 2a). Alpha-fetoprotein (AFP) was 470 UI/l. After an abdomen CT, confirming the US report and showing an early washout in the venous phase, the patient underwent laser ablation procedure. This procedure was considered the best first approach, considering (i) the size of tumor (<3 cm), (ii) the accessible location, (iii) the similar rates of tumor recurrence, if compared with liver resection, (iv)the risk of major surgery in an elderly patient with Child-Pugh-Turcotte (CPT), score B7. According to current guidelines and recommendations, liver biopsy was not considered mandatory in this case [12]. AFP levels, measured weekly for the first month and then monthly after procedure, significantly decreased and ranged between 50 and 70 UI/l. After 5 months, given that alpha-fetoprotein values had risen up to 1600 UI/l (Fig. 1), once again, ultrasound and abdomen CT were performed showing an increased diameter of liver nodule, measuring 3.8 cm (Fig. 2b). The patient underwent transarterial chemoembolization (TACE) down-staged procedure and then liver transplant assessment was started to get him in to active transplant wait list. After 3 months, the patient underwent liver transplantation. MELD score was 22, on the basis of the presence and size of liver tumor. At the time of transplantation, HBV-DNA was 10^3 copies/mL and the patient received intravenous anti-HBs immune-globulins (HBIG) (10 000 UI/l) intra-operatively and over the four consecutive days after LT before starting the recommended life-long antiviral and immunoprophylactic therapies. Cyclosporine A (CyA) was started during postoperative day 1 at a daily dose of 8 mg/kg, aiming to achieve blood trough levels of 200–300 ng/ml during the first 2 months, and of 100–200 ng/ml thereafter. His postoperative course was uneventful and he was discharged on postoperative day 13. Immediately after LT, the patient became HBsAg-negative and after 3 weeks, he achieved an anti-HBs-protective titer, with no evidence of HBV recurrence. Pathologic analysis performed on explanted liver showed a hepatic yolk sac tumor instead of suspected hepatocellular carcinoma. The explanted liver weighed 1225 g; on the segment 7, there was an encapsulated necrotic-hemorrhagic nodule measuring 4 cm in longitudinal dimension. On cut surface (Fig. 3a) the mass was multiloculated with multiple necrotic areas. Microscopically, the nodule consisted of a mesenchymal and pseudo-papillary proliferation with the presence of 'Schiller-Duval bodies' (Fig. 3b). From the histochemistry study, alpha-fetoprotein, CK 20 and CK 19 resulted positive, whereas hepatocyte (OCH1E5), CD 10, CK 7 and vimentin resulted negative. Twelve months of postoperative follow-up was excellent. All liver function tests, hematologic and biochemical analysis were normal and the tumoral markers as well. HBsAg and HBV-DNA were repeatedly negative with protective anti-HBs titre (>200 UI/l). Liver biopsy showed *grading* 4/18 and *staging* 0–1/6, according to Ishak classification [13]. No tumor recurrence or evidence of extra-hepatic metastasis was revealed by biochemical and radiological assessment after 12 months of follow-up.

Discussion

Primary YST of the liver is rare. After diagnosis, the gold-standard treatment is surgery, usually followed by adjuvant chemotherapy, with a reported mortality rate greater than 50% [2,5,8,14,15]. Otherwise, successful treatment was achieved in several cases using cisplatin-based chemotherapy before surgical resection [3,16,17]. Although the

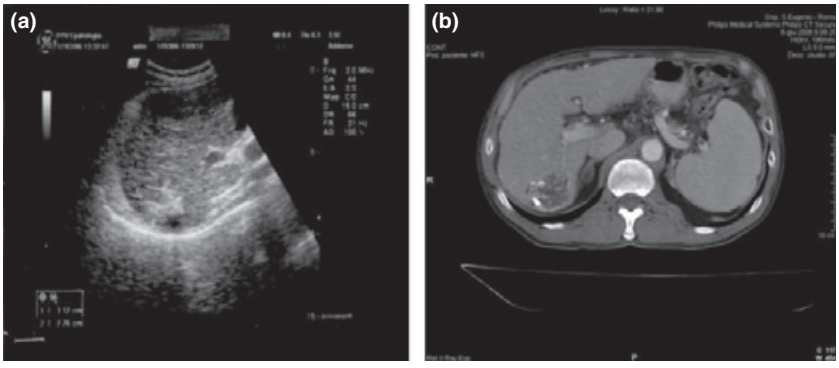

Figure 1 Liver ultrasonography performed before laser ablation procedure, showing LOS in segment 7 (panel b); Abdomen CT arterial phase performed before TACE, showing LOS in segment 7 (panel a).

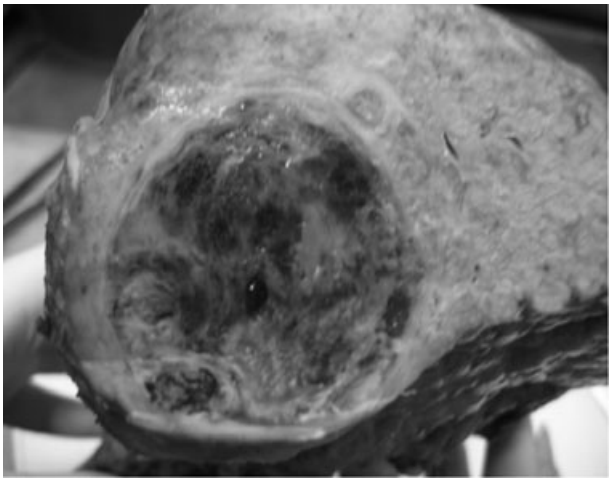

Figure 2 Macroscopic section performed on explanted liver, showing a cirrhotic liver with a necrotic-haemorrhagic nodule which measure 4 cm on maximum diameter.

morphologic and cytomorphologic features of hepatic YST have been extensively described in the literature [18], this rare neoplasm frequently poses significant diagnostic problems. The serum AFP is uniformly elevated when HCC, hepatoblastoma or YST malignancy occurred and preoperative differential diagnosis, on the basis of serum markers, is usually difficult. Moreover, reported imaging findings of YST range from solid to predominantly cystic mass [19,20], displaying heterogeneous appearances and exhibiting prominent enhancement on contrast or post-contrast CT phases, like a large nodule of HCC. Several clinical differences between YST and HCC were exhaustively shown by Wong *et al.*, who analyzed the first seven reported cases of YST of the liver. The female gender, age less than 30 years, very high levels of serum AFP and the presence of a predominantly cystic mass within a non-cirrhotic liver were considered suggestive of YST. Radiological features, however, on the basis of CT or NRM differences between the two tumors, have never been extensively described.

Otherwise, distinguishing preoperatively between HCC and primary YST of the liver has important therapeutic implications, in terms of chemotherapy and surgical options. The diagnosis of primary hepatic YST should be considered easier in patients with a noncirrhotic liver, when an increased AFP and appearance of liver mass occurred, even though a US- or CT-guided biopsy has to be always considered in this setting. In our case, the patient had HBV-related cirrhosis and the appearance of liver nodule during follow-up, the concomitant increase of AFP and the typical enhancement on CT images strongly suggested an HCC. Moreover, our patient was an adult when the liver mass appeared first, whereas the YST mostly occurred in childhood or adolescence.

Our patient underwent LT with an increased priority on the basis of conviction of the presence of HCC and the diagnosis of YST was possible and performed by pathological analysis only on explanted liver. Therefore, to our knowledge, this patient represents the first adult case transplanted in the presence of primary YST of the liver. Extrahepatic sources of neoplasm had never been found after surgery and serum tumoral markers were repeatedly negative. The current 1 year of follow-up was uneventful and the patient has till now an excellent quality of life. Similar outcomes were reported in a 2-year-old boy presented with a nonresectable YST and was successfully treated with LT [11]. In the last decade, the use of split-liver grafting and living-related liver transplants in childhood has led to improving organ's shortage [21] and LT is more routinely used to treat nonresectable primary liver tumors in this setting. Improved survival after LT and increased availability of grafts using living-related donors should increase the use of transplant as a treatment of nonresectable and rare neoplasms, such YST, also in adulthood.

In conclusion, our report evidences as: (i) the diagnostic performance of current guidelines for cirrhotic patients with liver nodule, may be lacking in the presence of rare malignancies; (ii) LT appears to be an alternative therapeutic chance, not yet recognized in adult, and with

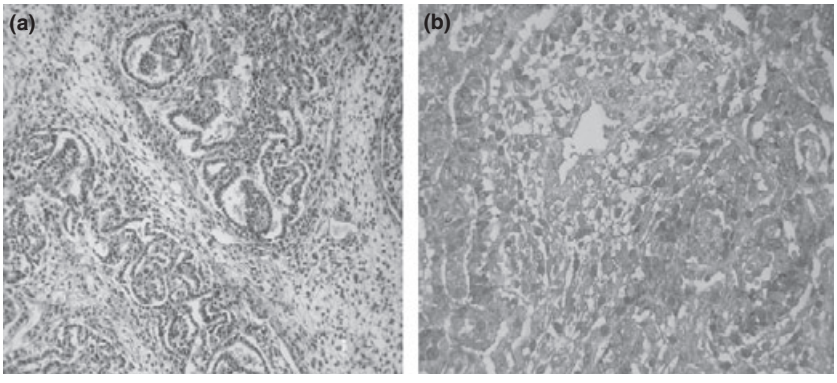

Figure 3 Microscopic section performed on explanted liver, showing a mesenchymal and pseudo-papillary proliferation with the presence of 'Schiller-Duval bodies' (Hematoxylin–eosin, 400 × magnification) (panel a); Microscopic section showing the positivity for alpha-fetoprotein immunostaining (panel b).

a good early survival although the uniformly reported poor prognosis.

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