CASE REPORT

Recurrence of hepatocellular carcinoma as a mixed hepatoblastoma after liver transplantation

J Dumortier, T Bizollon, M Chevallier, C Ducerf, J Baulieux, J Y Scoazec, C Trepo

Abstract

Background—Hepatoblastoma is an exceptional cause of primary malignant liver tumour in the adult.

Patient—The case is reported of an adult patient transplanted for alcoholic cirrhosis complicated by multifocal hepatocellular carcinoma in whom a recurrence in the form of a mixed hepatoblastoma invading the whole transplanted liver developed three months after liver transplantation.

Methods—Complete clinical, histopathological, and immunohistochemical data were reviewed.

Results—The recurrent tumour invaded the whole liver. The major component was a mixed hepatoblastoma, with an epithelial component expressing cytokeratin and a mesenchymal component expressing vimentin. The tumour also contained a minor hepatocarcinomatous component expressing α fetoprotein. The rapid growth of the tumour prevented any attempt at treatment. Although direct evidence is lacking, the most likely hypothesis to explain the observations is a marked phenotypic change in the initial malignant population at recurrence.

Conclusion—This case supports a possible filiation between hepatocellular carcinoma and hepatoblastoma in adults.

(Gut 1999;45:622-625)

Keywords: hepatoblastoma; hepatocellular carcinoma; liver; transplantation

Hepatoblastoma usually occurs in the first three years of life.¹⁻³ It is an exceptional cause of primary malignant liver tumour in the adult; only 35 cases have been reported in the literature since its initial description.⁴⁻⁸ We had the opportunity to observe the case of an adult patient transplanted for alcoholic cirrhosis, complicated by multifocal hepatocellular carcinoma (HCC) detected by examination of the liver explant, who presented three months after orthotopic liver transplantation (OLT) with a tumoral recurrence in the form of a mixed hepatoblastoma, which invaded the whole graft and was rapidly fatal. We report here this exceptional case with its clinical and pathological features, and discuss the possible relations between HCC and hepatoblastoma in adults.

Case report

A 47 year old man with a past history of alcoholism and heavy smoking was first admitted in July 1990 because of variceal bleeding, treated by sclerotherapy. At this time, biological evaluation disclosed hepatocellular deficiency. The diagnosis of alcoholic cirrhosis was confirmed by liver biopsy. Abdominal ultrasonography showed an atrophic but homogeneous liver with no evidence of HCC. Viral serology for hepatitis B and C virus gave negative results. Other causes of chronic liver disease were eliminated. The patient was readmitted to our department because of various complications in December 1990 and May 1991. Serum α fetoprotein (AFP) level was 17 ng/ml (normal level <5 ng/ml) in May 1991. At this time, OLT was considered for this young patient with severely decompensated liver disease, weaned from alcohol for more than six months and without any clinical contraindications.

In March 1992, serum AFP level had increased to 380 ng/ml. A further abdominal ultrasonographic examination showed a heterogeneous liver without focal lesion. Liver computed tomography disclosed a heterogeneous opacification of the liver, with no detectable hypervascular area. The portal vein was permeable. No enlarged lymph node was detected. Hepatic angiography did not show any vascular blush and confirmed the permeability of the portal system.

In May 1992, OLT was performed with venovenous bypass. The graft was obtained from a 19 year old man with normal liver biochemical tests. The histological integrity of the graft was confirmed by a liver biopsy performed at the end of the surgical procedure. At macroscopic examination, the explanted liver weighed 1684 g and displayed typical macronodular cirrhosis. Examination of the whole liver by centimetric sections disclosed three areas suggestive of focal HCC. Histological examination confirmed the diagnosis. One lesion was 2 cm in diameter and was histologically classified as mixed, trabecular, and glandular moderately differentiated HCC. The tumour was not encapsulated and was associated with a large venous extension. The two other lesions were less than 1 cm in diameter

Abbreviations used in this paper: HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; AFP, α fetoprotein.

Unité d'Hépatologie,
Hôtel-Dieu, Lyon,
France

J Dumortier
T Bizollon
C Trepo

Laboratoire
d'Anatomie
Pathologique,
Fondation Marcel
Mérieux, Lyon, France
M Chevallier

Département de
Transplantation
Hépatique, Hôpital de
la Croix-Rousse, Lyon,
France

C Ducerf
J Baulieux

Laboratoire Central
d'Anatomie et
Cytologie
Pathologiques, Hôpital
Edouard Herriot,
Lyon, France
J-Y Scoazec

Correspondence to:
Dr J Dumortier, Hôpital
Edouard Herriot, Fédération
des Spécialités Digestives,
Pavillon O, 5 Place
d'Arsonval, 69437 Lyon
cedex 03, France.

Accepted for publication
18 March 1999

Figure 1 Macroscopic appearance of the tumour that appeared after transplantation. The whole graft is invaded by multiple well limited tumour nodules, presenting areas of necrosis and haemorrhage.

and were classified as trabecular well differentiated HCC. The initial immunosuppressive treatment after OLT consisted of cyclosporin (1 mg/kg/day), methylprednisolone (200 mg/day), and azathioprine (1 mg/kg/day). On day 7 after the operation, the patient developed acute steroid resistant rejection and was treated with OKT3 for 10 days. No adjuvant chemotherapy was used.

In August 1992, three months after OLT, a recurrence of HCC was suspected because of a markedly increased serum AFP level (5500 ng/ml). In September 1992, serum AFP concentration had increased to above 30 000 ng/ml. In October 1992, an abdominal computed tomography scan showed the presence of multiple poorly limited lesions disseminated throughout the whole liver graft. Some of the lesions were calcified. A metastatic nodule was detected in the left adrenal gland. The clinical course was rapidly fatal because of liver failure. No complete post mortem examination was performed. The liver only was excised and referred to our centre. At macroscopic examination, the liver explant weighed 4667 g. It was completely invaded by multiple small to medium sized tumour nodules, which were usually well limited and contained necrotic and haemorrhagic areas (fig 1). At histological examination, the malignant proliferation appeared heterogeneous. Some nodules contain-

Figure 3 Histological appearance of the tumour that appeared after transplantation. This area with a hepatocarcinoma-like appearance presents a trabecular type of architecture and is formed of well differentiated hepatocytes containing steatosis. (Haematoxylin-eosin-saffron stain; original magnification $\times 130$.)

ing a hepatocarcinoma-like proliferation co-existed with most nodules presenting a hepatoblastoma-like appearance (fig 2). In areas resembling hepatocarcinoma, tumour cells were large and polygonal. They presented a distinctive trabecular or glandular architecture. They sometimes contained vacuoles of steatosis (fig 3). Immunohistochemical analysis showed that hepatocarcinoma-like tumour cells were labelled by antibodies against cytokeratin 8 and were negative for cytokeratins 7 and 19. Foci of tumour cells expressed AFP (fig 4). In areas resembling hepatoblastoma, two components, epithelial and mesenchymal, were identified (fig 5). The epithelial component consisted of small to medium sized cells, resembling embryonic or fetal hepatocytes. They were faintly labelled by antibodies against cytokeratin 8 (fig 6), but did not express cytokeratins 7 and 19. They were usually negative for AFP. Malignant epithelial cells formed small nodules scattered throughout abundant mesenchymal tissue, containing numerous spindle cells strongly expressing vimentin and negative for cytokeratins (fig 6). Osteoid foci were sometimes observed within the mesenchymal tissue (fig 7).

Discussion

We report here the first case to our knowledge of an adult patient transplanted for alcoholic cirrhosis complicated by HCC, who, three months after OLT, developed a neoplastic hepatic recurrence with a predominant hepatoblastomatous component. This case provides interesting clues about the possible relation between hepatocarcinoma and hepatoblastoma in adults.

Our patient initially had a multifocal HCC incidentally diagnosed in the liver explant. This situation is not rare: a recent study from our group showed that the prevalence of undetected HCC in adult cirrhotic liver explants is 32%.⁹ In the present case, the lack of detection of tumour lesions by conventional imaging techniques (sonography, computed tomography) underlines the limits of current procedures for the diagnosis of infraclinical lesions and the study of intrahepatic extension. Lipiodol angiography followed by a computed tomography scan three weeks later may have

Figure 2 Histological appearance of the tumour that appeared after transplantation. At low magnification, the coexistence of nodules containing a hepatocarcinoma-like proliferation (arrow) with large nodules presenting a distinctive blastomatous appearance (arrowheads) is evident. (Haematoxylin-eosin-saffron stain; original magnification $\times 80$.)

Figure 4 Immunohistochemical characteristics of the tumour that developed after transplantation. A few tumour cells expressing a fetoprotein (arrowheads) are visible along the edge of a tumour nodule. (Visualisation with indirect immunoperoxidase; original magnification $\times 150$.)

provided further diagnostic clues, but was rejected for this patient because of its poor sensitivity and the possible aggravation of the pre-existing portal hypertension.⁹

The most common cause of mortality after OLT in patients transplanted with HCC is tumour recurrence,¹⁰ which is responsible for an overall survival of about 50% at three years. In our patient, several factors of high risk of recurrence were present: a multifocal tumour, a major venous extension, and the absence of a capsule.¹⁰ Tumour recurrence in this case is therefore not surprising. The two unexpected features were the short time before the recurrence (three months) and the histological appearance of the recurrent tumour, which contained large areas with the distinctive appearance of a mixed hepatoblastoma.

Several subtypes of hepatoblastoma have been characterised.^{3–11} The epithelial subtype is composed of epithelial cells resembling embryonal or fetal hepatocytes. The mixed subtype has mesenchymal cells in addition to

Figure 5 Histological appearance of the tumour that developed after transplantation. This area has a distinctive blastomatous appearance. The epithelial component is formed of small embryonal cells, grouped into nodules, scattered in cellular mesenchymal tissue. (Haematoxylin-eosin-saffron stain; original magnification $\times 150$.)

Figure 6 Immunohistochemical characteristics of the tumour that appeared after transplantation. Mesenchymal cells in a blastomatous area (A) readily expressed vimentin and (B) did not express cytokeratin when compared with the epithelial component which is faintly labelled by antibodies against cytokeratin. (Visualisation with indirect immunoperoxidase; original magnification $\times 190$.)

the epithelial components. A third subtype, known as anaplastic hepatoblastoma, is formed by poorly differentiated embryonal epithelial cells. The most common subtype encountered in adults is the mixed one,^{2–4} which corresponds to the tumour discovered in our patient. The presence of areas suggestive of HCC, intermixed within the hepatoblastic population, as

Figure 7 Histological appearance of the tumour that developed after transplantation. An osteoid focus (arrows) is present within the mesenchymal component of a blastomatous nodule. Residual hepatic parenchyma is visible at the periphery of the tumour nodule (short arrow). (Haematoxylin-eosin-saffron stain; original magnification $\times 110$.)

observed in our patient, is not unusual in adults.^{7,12} The particularly fast growth of the tumour in this case prevented any attempt at treatment. This contrasts with most cases of adult hepatoblastoma reported in the literature, in which the tumour usually evolved slowly and was sometimes discovered incidentally at surgery or autopsy.^{4,5,7} In addition, some cases of adult hepatoblastoma have been successfully treated by surgery, leading to complete remission, without any evidence of recurrence after prolonged follow up.⁵ It is likely that the concomitant immunosuppressive treatment administered to our patient was largely responsible for the very rapid evolution of the tumour.

Several hypotheses must be considered when assessing the possible relation between the tumour that developed after transplantation and the initial lesions discovered in the liver explant. Two hypotheses cannot be definitely ruled out but seem very unlikely. The first is that the post-transplant hepatoblastoma represents a *de novo* tumour, bearing no relation to the initial lesions and possibly favoured by immunosuppressive treatments.¹³ The second hypothesis is that there was a pre-existing tumour in the donor liver. This hypothesis is very unlikely because of (a) the rarity of the tumour, (b) the lack of macroscopic abnormalities recorded during graft harvesting and inspection, and (c) the normality of the serum AFP level in the donor (retrospectively measured in stored serum), even though AFP is not a sensitive marker of hepatoblastoma in adults.^{5,7}

The most likely hypothesis to explain our observation is recurrence of the primary HCC with a blastomatous appearance. Definitive evidence of the clonal character of the two sequential lesions cannot be provided because of the lack of material suitable for genetic analysis. However, their relation is strongly suggested by the persistence of areas with a hepatocarcinoma-like appearance within the hepatoblastoma-like proliferation. Our observation underlines the possible close relation between hepatocarcinoma and hepatoblastoma in adults. So far, only incidental reports of association between hepatocarcinoma and hepatoblastoma within the same lesion, as observed in our patient, have raised this possibility.^{5,12} The sequential occurrence of the two lesions, as observed in our patient, provides new evidence supporting this concept. The hypothesis of a close relation between hepatocarcinoma and adult hepatoblastoma is in line with several reports suggesting a different pathogenesis for childhood and adult hepatoblastomas. Hepatoblastomas arising in adult patients differ from childhood hepatoblastomas in the usual absence of AFP synthesis and secretion, a mixed histological appearance contrasting with the usually purely epithelial differentiation of childhood hepatoblastoma, and, possibly, their pattern of cytogenetic alterations.⁸

In our patient, the predominant blastomatous appearance of the post-transplant tumour may be explained by either expansion of a pre-

existing component or phenotypic transformation of the malignant population at recurrence. The occurrence of blastomatous lesions associated with otherwise typical hepatocarcinoma has been previously described.⁵ In the present case, this possibility has been excluded by careful examination of the resected liver. It is therefore more likely that the malignant population experienced a marked phenotypic change at the time of recurrence. The acquisition of a blastomatous appearance suggests an early differentiation blockade, which may be related to changes in growth factor expression¹⁴ or abnormal expression of specific transcription factors.¹⁵

In conclusion, the most likely hypothesis to explain our observation is recurrence of the initial HCC with the appearance of a mixed hepatoblastoma containing residual areas of hepatocarcinoma. The tumour that developed after transplantation was characterised by dramatically fast growth, which was responsible for the precocity of the recurrence and the rapidly fatal evolution. The appearance of a predominant blastomatous component in a recurrent primary liver tumour after OLT points to a possible filiation between HCC and hepatoblastoma in adults.

Jean-Dominique Boyer, MD, and Anne Boulant, MD (Centre Hospitalier de Vienne) referred the patient to our centre. Monique Fabre, MD (Laboratoire Central d'Anatomie Pathologique, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France) is gratefully acknowledged for her expert advice. The authors thank David Mutimer, MD (Queen Elizabeth Hospital, Birmingham) for his review of the manuscript and Marie-France Jacquier (INSERM U45, Hôpital Edouard Herriot, Lyon) for her help in preparing the microphotographs.

- Weinberg AG, Finegold MJ. Primary hepatic tumours of childhood. *Hum Pathol* 1983;14:512-37.
- Lack EE, Neave C, Vawter GF. Hepatoblastoma: a clinical and pathological study of 54 cases. *Am J Surg Pathol* 1982;6:693-705.
- Stocker JT, Ishak KG. Hepatoblastoma. In: Okuda K, Ishak KG, eds. *Neoplasms of the liver*. New York: Springer Verlag, 1987:127-36.
- Harada T, Matsuo K, Kodama S, et al. Adult hepatoblastoma: case report and review of the literature. *Aust N Z J Surg* 1995;65:686-8.
- Altmann HW. Epithelial and mixed hepatoblastoma in the adult. *Pathol Res Pract* 1992;188:16-26.
- Pollice L, Zito FA, Troia M. Hepatoblastoma: a clinico-pathologic review. *Pathologica* 1992;84:25-32.
- Green LK, Silva EG. Hepatoblastoma in an adult with metastasis to the ovaries. *Am J Clin Pathol* 1989;92:110-15.
- Parada LA, Bardi G, Hallén M, et al. Cytogenetic abnormalities and clonal evolution in an adult hepatoblastoma. *Am J Surg Pathol* 1997;21:1381-6.
- Bizollon T, Rode A, Bancel B, et al. Diagnostic value and tolerance of lipiodol computed tomography for the detection of small hepatocellular carcinoma: correlation with pathologic examination of explanted livers. *J Hepatol* 1998;28:491-6.
- Bismuth H, Chiche L, Adam R, et al. Liver resection versus transplantation for HCC in cirrhotic patients. *Ann Surg* 1993;218:145-51.
- Gonzales-Crussi F, Upton MP, Maurer HS. Hepatoblastoma. Attempt at characterization of histologic subtypes. *Am J Surg Pathol* 1982;6:599-612.
- Carter R. Hepatoblastoma in the adult. *Cancer* 1969;23:191-7.
- Penn I. Cancers complicating organ transplantation. *N Engl J Med* 1990;323:1767-9.
- Block GD, Locker J, Bowen WC, et al. Population expansion, clonal growth, and specific differentiation patterns in primary cultures of hepatocytes induced by HGF/SF, EGF and TGF α in a chemically defined (HGM) medium. *J Cell Biol* 1996;132:1133-49.
- Ninomiya T, Hayashi Y, Saijoh K, et al. Expression ratio of hepatocyte nuclear factor-1 to variant hepatocyte nuclear factor-1 in differentiation of hepatocellular carcinoma and hepatoblastoma. *J Hepatol* 1996;25:445-53.