Transpl Int (2004) 17: 202–207
DOI 10.1007/s00147-004-0697-4

ORIGINAL ARTICLE

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Hepatic haemangioendothelioma in adults: excellent outcome following liver transplantation

Received: 22 April 2003
Accepted: 15 July 2003
Published online: 28 April 2004

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Abstract Hepatic epithelioid haemangioendotheliomas (HEHEs) are rare, low-grade vascular tumours. Five adults with HEHEs and one adult with a vascular tumour showing combined features of haemangioma and haemangioendothelioma underwent liver transplantation. Two HEHE patients had extrahepatic metastases at the time of transplantation. Median survival time following diagnosis was 10.7 years (range 40 months to 195 months). One patient needed resection of a HEHE in the breast 13 years post-transplantation. All six patients are surviving free from disease 22 to 166 months after transplantation (median 77 months). One HEHE-patient who had been treated for 8 years for vertebral and cerebral localisations is free of disease without immunosuppression 56 months after transplantation. We can conclude that liver transplantation is a valuable treatment for hepatic haemangioendothelioma, even in cases of extrahepatic localisation of the disease.

Keywords Liver vascular tumour · Haemangioendothelioma · Liver transplantation

Introduction

Haemangioendotheliomas of the liver are rare vascular tumours [1]. Because of their rarity and highly variable evolution, the therapeutic value of orthotopic liver transplantation is still under debate [2, 3]. This discussion is important in view of the high frequency of extrahepatic metastases of epithelioid haemangioendothelioma [1, 3]. We present here our experience with six adult liver-transplant patients.

Material and methods

Between 1984 and December 2002, six of 600 (1%) orthotopic liver transplantations (OLTs) performed in adult patients at our institution were for haemangioendothelioma (HE). Hepatic HE was diagnosed in three men and three women at a median age of 26 years (range 23 to 45.3 years). The definition of HE was based on the criteria established by Ishak, Weiss and Dehner [1, 2, 4]. Five patients had hepatic epithelioid haemangioendothelioma (HEHE) (Fig. 1), and one patient had a tumour combining features of haemangioma and hepatic infantile haemangioendothelioma (HIHE).

In five patients, the primary symptom was right upper quadrant pain. Five patients had hepatomegaly, and one patient had signs of portal hypertension. All patients presented with multifocal tumour localisation, and two had extrahepatic lesions. Liver tests showed disturbances in one patient only. They all had normal serum levels of tumour markers and positive immunohistochemistry staining of the HE for factor VIII-related antigen.

A 25-year-old woman (OLT 302) presented with a painful right upper quadrant mass. Hepatomegaly had already been noted 6 months before. Open liver biopsy revealed HEHE. Orthotopic liver transplantation (OLT), with inferior vena cava (IVC) replacement, was uneventful. The weight of the liver was 2,300 g. Thirteen years after liver transplantation (LT) an isolated HEHE located in the breast was resected. The patient is doing well, despite de novo HCV allograft infection, 13 years and 10 months after OLT (and 14 years and 6 months after diagnosis).

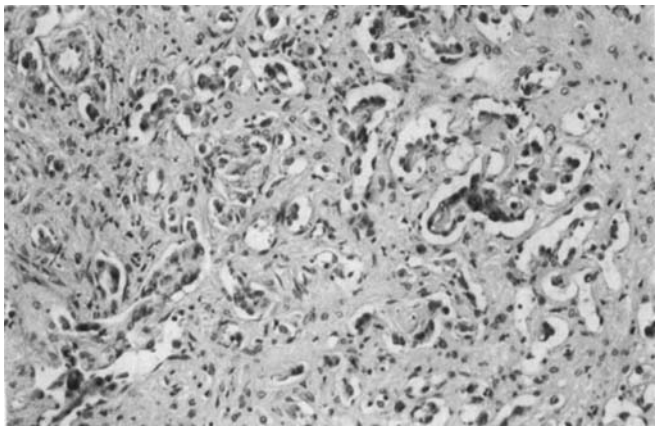

Fig. 1 Histology of HEHE showing epithelioid cells that spread within the sinusoids and small veins. Immunohistological staining was strongly positive for F VIII-related antigen (OLT 1063)

A 42-year-old man (OLT 313) was referred to us with a painful right upper quadrant mass that had been developing for 2.5 years. At clinical examination, huge hepatosplenomegaly was found. The hepatomegaly had caused portal hypertension due to tumour compression, and the patient had grade II oesophageal varices. Diagnosis of HEHE was made on open liver biopsy. OLT with IVC replacement was performed, and part of the right diaphragm that was adhering to the tumour was resected. At histological examination, the diaphragm was free of tumour invasion. The weight of the liver was 2,950 g. The patient is alive, well and free of disease 13 years and 9 months post-LT (and 16 years and 3 months post-diagnosis).

A 45-year-old woman (OLT 787) presented with a painful tumour in the right abdomen. The mass had been present for at least 7 months. At clinical examination, the liver filled the abdominal cavity completely. This huge tumour was responsible for food intolerance due to compression of the gastrointestinal tract, and it also caused supine dyspnoea and lower IVC syndrome. The results from an open liver biopsy, previously done at another centre, were inconclusive. The patient was severely anaemic (Hgb 7.8 g), and cholestatic enzymes were twice the normal level.

The 7.6 kg liver was removed, and OLT with IVC preservation was performed (Fig. 2). Histological examination of the tumour showed features of cavernous haemangioma, mixed with features of HIHE. The tumour was very large and vascular with alternating areas of ectatic vessels and areas of small vessels with papillary projections within fibrous tissue. There were also numerous haemorrhagic and thrombotic foci. Longstanding evolution of this lesion was thought to be responsible for the development of the enormous hepatomegaly. Post-LT follow up was straightforward. The patient is alive and well and disease free, 8 years and 3 months after LT (and 8 years and 10 months after diagnosis).

In a 26-year-old man (OLT 991), a liver tumour was detected during follow up for a resected vertebral chondromyxoid fibroma. In 1990, at the age of 16, he presented with left arm paresis caused by a cervical vertebral chondromyxoid fibroma. A few months later, tumour recurrence at the fourth cervical vertebra was treated with embolisation of the vertebral artery, local radiotherapy and resection of C3–C4–C5 vertebral bodies. From June 1994 to 1996, he had several episodes of headache, nausea and vomiting caused by a right

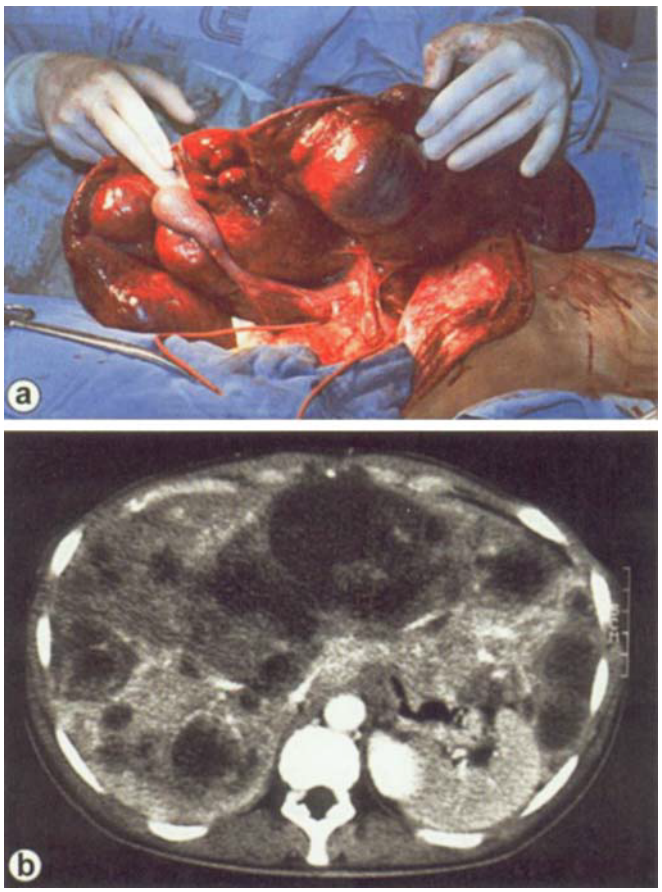

Fig. 2 **a** Intraoperative view of 7.6 kg heavy haemangioendothelioma responsible for IVC syndrome and supine dyspnoea (OLT 787). **b** CT scan showing typical picture of advanced bi-lobar tumorous disease; the right liver contains several concentric zones of that result in different signal intensities

parieto-temporal "haematoma". A complete check-up revealed a multifocal liver tumour. Stereotactic cerebral biopsy demonstrated a metastasised HEHE. Because of his previous medical history, the liver lesions were treated with a combination of radiotherapy and seven sessions of intra-arterial chemoembolisation. In August 1996, the cerebral metastasis was completely resected. Histology showed the lesion to be almost entirely necrotic. For the next 2 years the patient was asymptomatic, and the liver lesions remained stable. It was finally decided to perform OLT in August 1998. Resection of the IVC was necessary, due to its adhesion to the atrophic right liver. The atrophy had been caused by the previous chemoembolisations.

The hepatectomy specimen weighted 1,420 g; the liver still contained five "active" bi-lobar lesions of HEHE. The patient's post-LT course was straightforward. One year after LT, he had haematuria caused by a bladder urothelioma, which was not related to one of the previous tumoral lesions. This tumour was treated with endoscopic resection and irrigation-chemotherapy. Immunosuppression was completely stopped 42 months post-LT. He is now doing very well, and is free of disease 4 years and 8 months after LT (and 12 years and 4 months after diagnosis).

A 26-year-old man (OLT 1063) presented with a 1-year history of ongoing right upper quadrant pain. Clinical examination revealed hepatomegaly, and on his chest X-ray he was found to have pulmonary micronodules. The nature of these lesions remains unknown as they were not biopsied; however, they did not change during the whole pre-transplant and post-transplant follow up. Open liver biopsy confirmed diagnosis of HEHE. OLT, with IVC preservation, was performed. Histological examination of the 1,900 g liver revealed tumour involvement of one hilar lymph node. The patient is doing very well and is free of disease 41 months after LT and (4 years and 5 months after diagnosis).

A 24-year-old woman (OLT 1162) presented with an 18-month history of recurrent right upper quadrant pain. Pre-transplant examination showed typical multifocal bi-lobar lesions. OLT with IVC preservation was uneventful. The patient is doing well 22 months post-LT (and 3 years and 4 months post-diagnosis). OLTs 302 and 313 were carried out, immunosuppression was based on cyclosporine A, and tacrolimus was administered to the remaining four patients. Five patients are actually under sub-therapeutic monotherapy immunosuppression; immunosuppression was successfully withdrawn in OLT patient 991; in two patients (OLT 1063 and 1162) immunosuppression has been almost completely withdrawn. All patients are enjoying excellent quality of life, as demonstrated by a Karnofsky index of 100% for all of them (Table 1).

Discussion

Hepatic epithelioid and infantile haemangioendotheliomas are low-grade malignancies, derived from endothelial cells, which have a highly variable evolution [1, 2, 3, 5, 6, 7, 8]. Epithelioid haemangioendothelioma (EHE) was first described in soft tissues [4]. Weiss and Enzinger recognised the similarity between these EHEs and the intravascular bronchoalveolar tumour described in 1975 by Dail and Liebow [9]. Similar lesions were later described in the head and neck region [10] and in many other organs, such as the spleen and the heart [3]. Liver involvement occurs as a metastasis or, most often, as a primary tumour [1, 11, 12]. The first report of the features of primary HEHE was by Ishak in 1984 in a series of 32 patients [1].

HEHE seems to be more frequent in women. The tumour can occur at any age, but is an exception in children under 15 years of age [1, 3, 10, 13]. Although various aetiological factors were suspected in several

Table 1 Clinical data of six patients who underwent transplantation for HEHE (*F* female, *M* male, *RUQ* right upper quadrant, *CsA*. cyclosporine, *TAC* tacrolimus, *CC-LT* cavo-caval LT with preservation of the recipient IVC, *IS* immunosuppression

OLT no.	Age (years)	Gender	Symptoms and signs	Delay diagnosis–LT (months	Liver weight (g)	Particularity at OLT	Post-OLT outcome		Actual immunosuppression	Particularities	
302	25	F	RUQ pain Hepatomegaly	8	2,300		Alive without disease	13 years 10 months	Sub-therapeutic CsA	HCV-graft de novo infection	
313	42	M	RUQ pain Hepatomegaly Portal hypertension	30	2,950		Partial resection diaphragm	Alive without disease	13 years 9 months	Sub-therapeutic CsA	Breast EHE Resected 13 years post-LT
787	45	F	RUQ pain Lower IVC syndrome Supine dyspnea GI intolerance Hepatomegaly Anaemia	>7	7,600	CC-LT	Alive without disease	8 years 3 months	Sub-therapeutic TAC		
991	26	M	None Two resections of vertebral chondromyxoid fibroma (92 months pre-LT) Resection cerebral metastasis (24 months pre-LT)	92	1,420	Difficult hepatectomy due to previous hepatic chemoembolisation	Alive without disease	4 years 8 months	Stop immunosuppression at 42 months	Endoscopic resection bladder urothelioma 1 year post-LT	
1063	26	M	RUQ pain Hepatomegaly Pulmonary micronodules	12	1,900	CC-LT Involvement hilar lymph node (pos F-VIII staining)	Alive without disease	3 years 5 months	Sub-therapeutic TAC IS withdrawal		
1162	24	F	RUQ pain	18	1,048	CC-LT	Alive without disease	1 year 10 months	Sub-therapeutic TAC IS withdrawal		

All patients remained disease-free after additional follow-up of 1 year

cases, and previous use of oral contraceptives had been reported in approximately one third of cases [12, 14, 15], there is no clear aetiological factor that can be considered to be responsible for HEHE [1, 3 11]. HEHE of the liver is a vascular tumour that is intermediate between a haemangioma and an angiosarcoma [1]. Nowadays, the definition of HEHE, as a unique form of vascular lesion originating from endothelial cells, is based on immunohistochemical staining for factor VIII-related antigen in the tumour [1, 12, 15, 13].

The clinical manifestations of HEHE are non-specific and variable, ranging from complete absence of symptoms to hepatic failure. This malignancy has a protracted clinical course. The most commonly reported symptoms are non-specific right upper quadrant or epigastric discomfort or pain, weight loss (25%) and impaired general condition (10%). Serum alkaline phosphatase level is frequently raised (70%), and levels of serum tumour markers are almost always normal [1, 3, 11].

Findings visualised with ultrasonography, CT or MRI include hepatosplenomegaly and signs of portal hypertension. Tumoral compression or infiltration of the liver veins may cause the latter. Two different patterns of haemangioendotheliomas can be recognised. The nodular type, usually bi-lobar, presents as an early manifestation of the disease. These multiple lesions are mostly spread along the margins of the liver ("peripheral lesions") and contain several concentric zones that result in different signal intensities. During the later stage of the disease, these tumours form confluent lesions (diffuse pattern) with eventual invasion of greater vessels and nodular transformation of the uninvolved liver. Focal calcifications are found in 20% of tumours [16, 3, 17]. The internal architecture of the tumours is best depicted on T2-weighted MRI [17]. Angiography reveals only moderate vascularisation, with displacement of marginal vessels [3, 17].

Due to the non-specific evolution and the rarity of this tumour, diagnosis may be difficult. The association of radiological features with a specific set of clinical findings can be of great help for the diagnosis. Attention must be paid to the following clinical features: occurrence in young adults; the contrast between the presence of numerous intrahepatic tumours and good condition; the slow course of the disease suggested by a long-standing clinical history, and, possibly, the presence of intratumoral calcification [1, 11, 12, 16, 18]. The final diagnosis can be reached only by immunohistochemical and ultrastructural examination of appropriate material obtained from (surgical) biopsy specimens [1, 11, 12, 13 15].

The therapeutic algorithm for HEHE is difficult. Its unpredictable behaviour and prognosis raises controversy about the role of liver transplantation, especially in view of (a) the spontaneous, long-term survival [6, 1, 3]; (b) the 28% to 45% incidence of extrahepatic, mostly pulmonary, osseous, peritoneal and/or lymph node disease [1, 3, 4]; (c) the reported recurrent allograft disease [16, 19, 20, 21, 22, 23, 24].

A review of the literature, comprising 127 HEHE-patients, indicates that the treatment of choice is radical hepatic resection [3]. Partial resection is not a good method of treatment because these tumours often multiple, and they also tend to behave aggressively after partial liver resection because liver regeneration depends on angiogenesis [5, 24]. Radiotherapy, systemic or locoregional chemotherapy and arterial chemoembolisation are of limited value [3, 11]. There are no clinical or histological criteria by which the evolution of the disease can be predicted [1, 4, 15, 22], and, moreover, it is impossible for one to compare results from the literature between untreated and medically treated patients and transplant patients [11, 3]. Lauffer's review, including all tumour treatments, mentions a 5-year survival rate of 55.5% [3]. The results of the largest reported transplant series in the literature [21], and the results of several case reports [10, 11, 15, 16, 19], indicate that LT offers the best survival, even if extrahepatic disease is present at the time of transplantation. Prolonged disease-free survival after LT for patients with extrahepatic disease has been documented [11, 19, 21, 22]. The 5-year actual survival rate in 16 Pittsburgh patients was 71.3%; the disease-free 5-year survival rate was 60.2% [21]. Penn's transplant cancer registry, comprising 21 patients, indicates a 5-year patient survival rate of 67% and a 5-year disease-free survival rate of 43%. The latter series is not conclusive, due to its heterogeneity and the lack of detailed data analysis [24]. Invasion of lymph nodes and presence of extrahepatic metastases are not definite contraindications to LT; infiltration of the transected vessels of the hepatectomy specimen, however, negatively influences outcome [15, 19]. The mitotic index and presence of necrotic and fibrotic cellular areas have been suggested to be histological prognostic criteria [1, 3], but this has not been confirmed [3, 12].

The histological differentiation between HEHE and HIHE is important because of their different behaviour [1, 6, 7, 9]. HIHE, the most common tumour of the liver in the infant age group (< 3 years), can be diagnosed in older children and adolescents. If so, these tumours may harbour foci of angiosarcoma. In the exceptional case of manifestation of HIHE in an adult (as shown in one of our patients), treatment should, therefore, be aimed at radical resection, e.g. OLT, on the condition that angiosarcoma has been formally excluded [2, 25]. HIHE does not metastasise; similar tumours may, however, be present simultaneously in the spleen, lungs and bone [7]. The role of re-transplantation in the treatment of recurrent allograft disease remains open, as only one case (without beneficial result) has been published so far [16].

Life expectancy for patients with HEHE is potentially long, so limited extrahepatic disease should not be

considered as an absolute contraindication to LT. The real value of LT can be measured only by analysis of disease-free survival rates beyond 5 years. Indeed, spontaneous survival, after diagnosis, of up to 28 years, has been reported, and survival times of more than 5 years have repeatedly been reported after surgical (partial or total) resection, even in the presence of metastases [1, 11, 19, 21].

A more aggressive attitude towards HEHE of the liver, by the proposal of early total hepatectomy, seems to be warranted, especially in view of the more recent development of minimising immunosuppressive protocols [26]. In order for the role of LT, in the treatment of this disease, to be defined, especially when the disease is presenting (limited) extrahepatic localisation, detailed (prospective, as well as retrospective) multicentric studies with long-term follow up need to be performed. We are, at present, reviewing, under the auspices of the European Liver Transplant Association (ELTA), the experience of 68 transplant cases collected in the audited database of the European Liver Transplant Registry (ELTR), in order to further clarify the role of LT in this rare liver disease.

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