CLINICAL CASE

Liver transplantation for multiple angiomyolipomas complicating tuberous sclerosis complex

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Summary Tuberous sclerosis complex is a genetic multisystem disorder characterised by widespread hamartomas in several organs, including the brain, heart, skin, eyes, kidney, lung, and liver. Hepatic multiple, bilateral angiomyolipomas are a rare and usually asymptomatic complication in patients with tuberous sclerosis. We report here the case of a patient who needed liver transplantation because of debilitating manifestations and mechanical complications of massive liver involvement by multiple angiomyolipomas (severe malnutrition, anorexia and abdominal pain). Seventeen tumors, from 2 to 16 cm in diameter, were identified at examination of the liver explant. No feature suggestive of malignant behaviour was identified at histological examination. In conclusion, this unusual indication of liver transplantation underlines the interest of this therapeutic approach for benign tumors for which the multiplicity of the lesions and their huge volume prevent any attempt at surgical resection.

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Introduction

Tuberous sclerosis complex (TSC) is a genetic, multisystem disease due to alterations in either TSC1 or TSC2 genes, respectively coding for the proteins hamartin and tuberin, which form a heterodimer able to inhibit the activity of mammalian target of rapamycin (mTOR) through the Rheb protein. TSC has an autosomal dominant pattern of inheritance; however, two-thirds of all cases result from de novo mutations. The clinical presentation of the syndrome is highly variable, resulting in various combinations of neurological (epilepsy, learning difficulties, behavioural problems), dermatological (skin lesions), pulmonary (progressive respiratory failure) symptoms. One of the hallmarks of TSC is in its association with tumor-like lesions, usually considered as hamartomas, which may involve a wide range of tissues, especially the central nervous system, the eye, the kidney, the lungs and the skin [1].

One of the most distinctive of TSC-associated tumor lesions belongs to the spectrum of PEComas, a recently defined group of tumors thought to derive from a putative
Liver transplantation for tuberous sclerosis complex

Liver transplantation for tuberous sclerosis complex (TSC) is a rare but life-saving procedure for patients with TSC who have severe complications from their disease. The diagnosis of PEComas relies on their suggestive morphological appearance and their highly distinctive immunophenotype, characterized by the coexpression of smooth muscle cell and melanocytic markers (hence the term “myomelanocytic tumor” used as an alternative to PEComa). The best-known examples of TSC-associated PEComas are renal angiomyolipomas and pulmonary lymphangioleiomyomatosis. Renal angiomyolipomas occur in up to 70—90% of adult patients; they are usually bilateral and multiple; although the vast majority of renal angiomyolipomas behave as benign tumors, some of them may follow a malignant course. Pulmonary lymphangioleiomyomatosis occurs mainly in women and may be found in more than 25% of female patients with TSC [1]; the disease is progressive and may result in severe respiratory failure.

Liver angiomyolipomas in TSC are rare but their actual incidence may be underestimated because of their usually asymptomatic character. Indeed, in two ultrasonographic studies of patients with TSC, the proportion of patients who had hepatic angiomyolipomas was, respectively, 24 and 16% [2,3]. In contrast to renal angiomyolipomas, liver angiomyolipomas are usually unique; multiple lesions are rare and usually seen only in patients with fully expressed TSC [4]. TSC-associated liver angiomyolipomas are more common in adults (23—45%) than in children, and more frequent in women than in men [5]. They grow more slowly than renal angiomyolipomas, with which they are frequently associated, and are usually not life-threatening [6].

We report here the case of a 41 year-old male patient with TSC who required liver transplantation (LT) because of debilitating manifestations of massive liver involvement by multiple angiomyolipomas, in order to illustrate a new indication of LT and to discuss the problems raised by these unusual lesions of uncertain risk of malignancy.

Case report

A 41-year-old man with a clinical and molecular diagnosis of TSC was referred for discussion of LT in July 2008 because of severe malnutrition, anorexia, nausea, and abdominal pain. The clinical diagnosis of TSC was made at the age of 6, in the presence of cutaneous, renal, pulmonary and hepatic lesions. Since the age of 38, the quality of life of the patient progressively worsened. At the age of 40, he was referred to our hospital for clinical evaluation.

Abdominal MRI and CT scan (Fig. 1) showed multiple diffuse angiomyolipomas and cystic formations in both kidneys. No renal biopsy was performed. The liver was grossly enlarged (longitudinal diameter = 32 cm), with the left lobe occupying the mid and left abdomen, causing severe gastric compression. T1-weighted dynamic sequences after gadolinium administration showed multiple, nodular, hypointense and non-homogeneous lesions of different sizes. The largest one (diameter = 12 cm) was located between segment VII and VIII. Upper gastrointestinal endoscopy did not disclose features of portal hypertension.

Figure 1  Liver appearance on CT scan before LT.
Figure 2  Liver explant: typical morphological appearance of one of the liver tumors, made of epithelioid cells admixed with adipocytes and abnormal vessels (hematoxylin-eosin-saffron; original magnification: ×200).

Figure 3  Strong expression of the melanocytic antigen HMB45 by tumor cells (immunoperoxidase; original magnification: ×200).

Patient body weight was 69 kg, his body mass index was 20 and his waist abdominal circumference was 110 cm. All liver function tests (AST, ALT, gamma glutamyl transferase, total bilirubin, albumin, prothrombin time and INR) were normal. During the past 3 years, the patient had progressively lost 14 kg because of anorexia and dysphagia. A guided liver biopsy of one of the hepatic lesions confirmed the diagnosis of PEComa (epithelioid angiomyolipoma), with characteristic morphological and immunohistochemical features. At the time of evaluation, the quality of life of the patient was strongly altered and his Performance Status was 3. The patient was therefore listed for LT in August 2008 and LT was performed in May 2009.

In the operating theater, the surgical dissection was complicated by recurrent hemorrhage from the native tumoral liver. The anhepatic phase lasted 90 min and reperfusion was tolerated without significant incident. The transplantation (with resection of retrohepatic vena cava) lasted 270 min. Total transfusion requirements during surgery were to five units banked red blood cells, and 2400 ml from ‘Cell Saver’ (Hemonetics, Braintree, MA, USA). The resected liver weighed 4.9 kg. The patient was transferred to the intensive care unit. Continued intra-abdominal bleeding caused haemodynamic instability and haemostasis was secured after two repeat laparotomies (day 9 and day 11), with subsequent haemodynamic stability. Initial immunosuppressive regimen included tacrolimus, mycophenolate mofetil and steroids.

At macroscopical examination, the liver explant contained 17 nodular lesions, sometimes coalescent, ranging in diameter from 1 to 16 cm. The cut surface of tumor nodules was usually homogeneous; however, some nodules showed signs of hemorrhage and a few contained calcifications. No cystic lesion was observed. The peritumoral liver was not fibrotic. Extensive sampling of the largest lesions was performed. At histological examination, all tumor nodules presented the typical pattern of angiomyolipomas of the so-called mixed type [4] (Fig. 2). The most important tumor component was made of large, epithelioid cells with ill-defined margins and clear cytoplasm, sometimes containing bright eosinophilic inclusions; nuclei were usually regular. Foci of adipocytes were scattered within the epithelioid component. Numerous vessels of variable size run within the tumor tissue; they were usually irregular and thick-walled. Hematopoietic foci were frequently present. The proportion of the various cell components was variable from one lesion to another.

The immunohistochemical examination confirmed the diagnosis of angiomyolipoma. Most epithelioid cells expressed the melanocytic antigens HMB45 (Fig. 3), Melan-A and PNL2; less than 10% expressed S100 protein; scattered cells expressed alpha-smooth muscle actin and caldesmon. There was no expression of the following cell markers: vimentin, cytokeratins recognized by KL1 and AE1/AE3 antibodies, cytokeratins 7 and 19, CD117, CD31, CD34, chromogranin A, synaptophysin, Hep-Par1.

There was no evidence of vascular invasion. No sign of capsular or extra-hepatic involvement was found. There was no nuclear atypia. Mitoses were exceptionally found. The proliferation index, evaluated with the MIB-1 antibody directed to the Ki67 antigen, was 1%. p53 protein was undetectable.

The non-tumoral liver presented signs of tumor compression, including sinusoidal dilatation and mild portal fibrosis. Steatosis was present in 10% of hepatocytes.

The final pathological diagnosis was therefore: multiple angiomyolipomas of the liver, of mixed type, with low proliferative activity and absence of signs suggestive of local invasion.

Late post-operative course was marked by severe bilateral pneumonia due to multiresistant Pseudomonas aeruginosa, associated with progressive renal failure. The patient died in December 2009, 7 months after LT.

Discussion

The management of liver angiomyolipomas, and especially of TSC-associated angiomyolipomas, is not standardized,
largely because of their extreme rarity. In our case, three problems were to be addressed simultaneously:

- the multiplicity of the lesions;
- the existence of severe mechanical complications due to the compression of adjacent organs by the tumors;
- the potential risk of malignancy, even low.

Currently, surgery is the only accepted treatment of liver angiomyolipomas. No standardized approach has been defined and surgical resection has been suggested for:

- symptomatic patients;
- masses greater than 5 cm in diameter;
- asymptomatic patients when the rapid progression of the tumour size makes more relevant the risk of haemorrhage and rupture;
- difficult characterization as liver angiomyolipomas after histological evaluation with persisting suspicion of malignancy.

Alternative medical therapeutic strategies have been recently proposed. A beneficial effect of rapamycin, an inhibitor of mTOR pathway, on renal angiomyolipomas has been reported [7,8]: this may be particularly interesting in TSC-associated lesions in which mTOR is constitutively activated because of the loss of function of TSC genes. Other approaches were recently tested. A female patient with TSC and massive multiple liver and renal angiomyolipomas, experienced a remarkable clinical improvement with long-term tamoxifen treatment, associated with tumour size reduction and improved quality of life [9]. In our case however, the importance of mechanical complications secondary to tumor compression and the rapid degradation of the clinical status required a rapid therapeutic effect and prompted us to consider surgery.

Even if liver transplantation has been infrequently proposed in the treatment of benign liver tumors, this procedure appeared as the only possible surgical approach in our case. Indeed, our patient fulfilled all the criteria susceptible to justify the use of liver transplantation in a case of benign liver tumor [10]:

- the multiplicity of the lesions, the huge tumor volume and the low amount of residual liver tissue prevented any attempt at curative surgical resection;
- the lesions were symptomatic and associated with debilitating and/or life-threatening complications;
- they had a malignant potential: indeed, exceptional cases of malignant liver angiomyolipomas have been reported [11—14].

To our knowledge, we report here the first case of liver transplantation for angiomyolipoma. So far, less than 50 cases of liver transplantation for benign tumors have been reported. Etiologies were diverse and included: giant hemangioma (especially when complicated by Kasabach-Merritt syndrome) [15], massive lymphangiomatosis [10,16], adenoma and adenomatosis [17], focal nodular hyperplasia [10], biliary papillomatosis [18], inflammatory pseudotumor [19] and mesenchymal hamartoma [10].

After the early post-operative period, patient survival is usually very good after LT for benign tumor(s). There is no risk of recurrence, except in case of malignant transformation diagnosed only from the explanted liver. Criteria of malignancy are not established for liver angiomyolipomas, because of the rarity of objectively malignant cases. It is however likely that the same criteria than those used in renal angiomyolipomas may be relevant. A very recent report, based on a large series of renal angiomyolipomas, proposed a predictive model based on four atypical features including: (1) ≥ 70% atypical epithelioid cells, (2) greater or equal to two mitotic figures per 10 hpf, (3) atypical mitotic figures, and (4) necrosis; the presence of three or all of the features was predictive of malignant behavior. This model accurately categorized 78% of clinically malignant and 100% of the clinically benign epithelioid angiomyolipomas with atypia [20].

In our case, we found none of the other signs previously associated with a risk of malignancy in the very few cases of malignant liver angiomyolipomas previously reported and in most cases of malignant angiomyolipomas of the kidney. Despite extensive sampling, there was no evidence of cell pleiomorphism or atypia, no necrosis, no high proliferation index, no evidence of local or vascular invasion, no abnormal expression of p53 protein.

Finally, in our case, late post-operative complications were probably favoured by multi-organ lesions related to TSC, leading to death. This suggests that pre-operative evaluation and discussion must be made with caution, and that the possibility of fatal outcome must be kept in mind.

In conclusion, we report here an unusual indication of LT, showing the possible interest of the procedure in the treatment of large, multiple lesions associated with debilitating complications and with a risk of malignancy. Given the shortage of suitable donor worldwide, LT must be proposed only in case of no alternative surgical or medical treatment, in order to preserve the patient from the need of a long-life immunosuppressive therapy. Moreover, the potentially life-threatening risks of the procedure must be kept in mind and balanced with the expected benefits.

**Authorship declaration**

J. Dumortier, J.Y. Scoazec: manuscript writing; J. Dumortier, O. Guillaud, T. Walter, C. Partensky, O. Boillot: medical management of the patient.

**Conflict of interest statement**

Authors disclose no conflict of interest.

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