

Liver Transplantation for Cardiac Failure in Patients With Hereditary Hemorrhagic Telangiectasia

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Liver involvement in hereditary hemorrhagic telangiectasia may lead to high-output cardiac failure. Few data have been reported on orthotopic liver transplantation (OLT) for these patients. In this paper, we describe two patients treated by OLT as a salvage procedure for cardiac failure, and we review literature on this subject. Our two patients resumed normal cardiac function after OLT. This procedure appears to be a promising therapy with good long-term results despite dissection difficulties encountered due to the collateral arterial network reorganization. (*Liver Transpl* 2005;11:834-838.)

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber disease, is a systemic fibrovascular dysplasia with a dominant inherited autosomal pattern that is caused by the mutation of two genes: ENG and ALK1. The estimated prevalence of HHT varies greatly but is higher in some regions of France (1 per 10,000 individuals).¹ The typical manifestations are mucocutaneous or visceral angiodysplastic lesions (telangiectasias and arteriovenous malformations) including the lungs, gastrointestinal tract, brain, and liver. Hepatic involvement is observed in 8% to 31% of patients,^{2,3} but a high percentage of patients are asymptomatic.^{4,5} The main clinical presentation in patients with liver involvement has been cardiac failure and orthotopic liver transplantation (OLT) appears to be a promising therapy. Few cases of OLT for high-output heart failure have been reported to date.⁶⁻¹² Herein we describe two patients with cardiac failure for

whom OLT was successful but included thrombotic complications in the follow-up.

Case 1

In December 2000, a 59-year-old woman developed anorexia, a 10-kg weight loss over a 2-month period, progressive dyspnea, and encephalopathy. She had a neglected history of nosebleeds, and one of her two sons had iterative epistaxis. Physical examination revealed fever, jaundice, cardiac failure with dilated jugular veins, bilateral pleural effusion, peripheral edema, and telangiectasias on the patient's cheeks, lips, and back. Laboratory data disclosed a neutrophil count of 36,000/mm³, C-reactive protein 66 mg/L and an icteric cholestasis. Echocardiography noted a dilated right ventricular and a small pericardic effusion. An abdominal computed tomography scan showed an 8-cm diameter intrahepatic biloma (Fig. 1A), confirmed by puncture. Visceral angiography showed a bilateral diffusely hypervascular liver parenchyma in the capillary phase with early prominent hepatic venous filling (Fig. 1B); a selective superior mesenteric artery injection indicated shunting of blood away from the mesenteric circuit through the pancreaticoduodenal arcades and into the liver. Gastroscopy revealed two antral telangiectasias but no portal hypertension sign. Right heart catheterization showed cardiac output at 8.4 L/min and cardiac index at 5.09 L/min/m². An elective arterial embolization of the left hepatic artery was performed to decrease the intrahepatic arteriovenous shunting. Although the heart failure improved, hepatobiliary necrosis of segments II and III developed with deterioration of the liver function (factor V level 46%) consecutive to the persistence of the sepsis. The patient underwent OLT in February 2001 as treatment for biliary sepsis and cardiac failure. The dissection was difficult with a spontaneous splenic rupture when the portal vein was clamped, first requiring a temporary portocaval shunt and thereafter an urgent splenectomy. Transfusion of 25 blood units was necessary and the duration of cold ischemia was 8.5 hours. Four months

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; OLT, orthotopic liver transplantation;

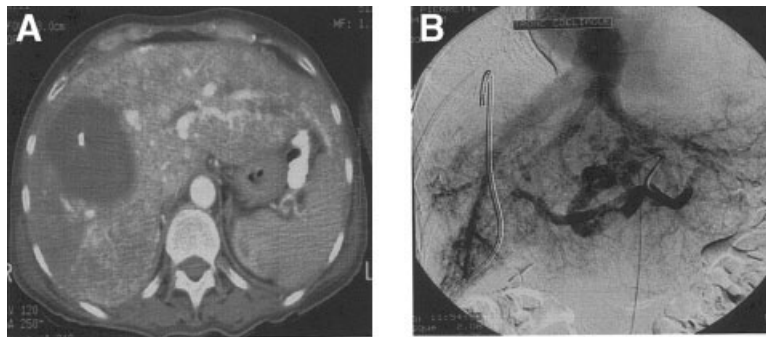
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Figure 1. (A) Abdominal CT scan with IV contrast shows an intrahepatic biloma and diffuse heterogeneous enhancement of liver parenchyma. (B) Hepatic artery angiography shows enlarged hepatic artery and hepatic veins with early opacification of hepatic veins.



later, the patient developed celiac artery thrombosis with no evidence of thrombophilia, followed by resumed permeability under fluidione. ALK1 mutation was found 1 year later, and the diagnosis of HHT type 2 with liver involvement was definitively ascertained. Three years later the patient is now in good health with a total recovery of cardiac function.

Case 2

In September 2002, a 62-year-old woman complaining of progressive breathing difficulties was admitted to the cardiology unit of Besançon Hospital. HHT had been diagnosed 30 years previously because of recurrent epistaxis and a family history of nosebleeds. The patient had arterial hypertension, Fernand Vidal syndrome, and had undergone a resection of an aneurysm of the pancreaticoduodenal arcade in 1985. On admission, multiple telangiectasias on the tongue and fingers, and edema of the lower limbs were present. Laboratory data showed anicteric cholestasis (alkaline phosphatase 2.7 N and gammaglutamyl transpeptidase 6 N) with a normal prothrombin time. Color Doppler sonography indicated a high-velocity signal in an enlarged hepatic artery. Gastroscopy showed mucosal telangiectasia in the stomach. An echocardiography revealed severe tricuspid regurgitation, a right dilated cavity with a dilated inferior cava vein. Right heart catheterization showed cardiac output at 10.7 L/min and cardiac index at 6.56 L/min/m². The patient underwent OLT in October 2002 because of high-output heart failure. The mean operation time was 6.5 hours, and 5 blood units were transfused. The result of ALK1 mutation confirmed the diagnosis of HHT type 2. In November 2003 the patient was readmitted because of acute abdominal pain with moderate ascites. Doppler ultrasound detected a mesenteric and splenic vein thrombosis extending to the distal part of the portal trunk without portal cavernoma, suggesting recent portal thrombosis. An investigation was carried out for acquired and inherited

thrombophilia (protein C, protein S, antithrombin III deficiencies, factor V Leiden and factor II mutation, antiphospholipid antibodies, homocysteinemia, paroxysmal nocturnal hemoglobinuria) and for local factors (abdominal computed tomography), but all of these exams were noncontributive. Also, bone marrow examination did not demonstrate overt or latent myeloproliferative disorders. A prompt anticoagulation therapy was started and has been continued. In October 2004 recanalization of portal, mesenteric, and splenic vein was reestablished on color Doppler ultrasound. Likewise, two years after OLT cardiac function and echocardiography returned to normal.

Discussion

HHT remains a clinical diagnosis based on the Curaçao criteria requiring at least two of the following extrahepatic manifestations: epistaxis, cutaneomucosal telangiectasia, and a family history of HHT.¹³ HHT is now more easily confirmed thanks to the recent discovery of two major genes, ENG and ALK-1, which define two disease types with different phenotypic patterns: HHT1 associated with pulmonary arteriovenous malformations,¹⁴ and HHT2 with high incidence of liver involvement.¹⁵

Hepatobiliary manifestations of HHT may be clinically brought to light by the appearance of encephalopathy due to porto-venous shunts, portal hypertension with variceal bleeding, or ascites due to arterio-portal shunts, and recurrent cholangitis or hemobilia.^{16,17} However, the most important symptoms of HHT with liver involvement are related to cardiac failure caused by left-to-right arterio-venous shunts, as in our two cases. Cardiovascular symptoms occur when intrahepatic shunt output is more than 20% of cardiac output.¹⁸ Cardiac output is almost always increased in these patients in up to 21.3 L/min,¹⁹ and the shunt output has been reported as high as 68% of cardiac output.²⁰ Among the 19 patients of the Garcia-Tsao et al. series

Table 1. Main Characteristics of Patients Having Hereditary Hemorrhagic Telangiectasia With Liver Involvement in Which Cardiac Failure Was the Main Clinical Manifestation Requiring Liver Transplantation

Authors	Bauer et al. ¹¹	Neumann et al. ⁷	Boillot et al. ⁶	Le Corre et al. ¹²	Pfizmann et al. ⁹	Azoulay et al. ⁸	Sabba et al. ¹⁰
Age, yrs	33	45	36, 42, 50	40	45, 54, 55, 69	48	33, 49
Sex (n)	F (1)	F (1)	F (3)	F (1)	F (4)	F (1)	F (2)
Portal hypertension	No	EV bleeding	Ascites in 2 patients	No	Ascites in 2 and bleeding of EV in 1	No	ND
History of cholangitis	Yes	Yes, after HA ligation	Yes in 1	No	Yes in 1	No	Yes in 1
History of surgery on hepatic artery	No	HA ligation before OLT	No	No	HA embolization in 1; embolization + banding of HA in 1	No	HA ligation before OLT in 1
Cardiac output (L/min)	Preop: 12	Preop: 8.8	Preop: 9.1, 10.8, 11.3 Postop: 4.1, 4.8, 5.5	Preop: 12.5 Postop: 8	Preop: 8–13.3 Postop: 4.5–6.3	High	High in 2 patients
Echocardiography	ND	ND	Dilatation of RVD + TR in 2; ND in 1	Hypertrophic and dilated left ventricle, preservation of systolic function	RVD preop: 35–58 mm end-diastolic RVD postop: 25–48 mm end-diastolic	ND	ND
Liver histology	No cirrhosis	Enlarged portal tracts with porto-portal SF and PF	Irregular bands of fibrosis containing telangiectasias	No cirrhosis	No cirrhosis but fibrosis in 3	No cirrhosis but irregular bands of fibrosis	ND
Organ involvement	Gastric telangiectasia	Pulmonary lobectomy for AVM at age 15	ND	Pulmonary lobectomy for AVM	Stomach in 1 Bronchial system in 1	Stomach; small bowel	Gastric telangiectasia*; asymptomatic focal vascular dilatation
Follow-up time/dead or living	24 mos/alive with normal CF	ND	29, 53, and 65 mos/alive with normal CF	1 mo/decreased cardiac output	12–65 mos/alive with normal CF	Death at day 11 (bleeding from gastric AVM)	10 yrs and 8 yrs/alive with normal CF

Abbreviations: CF, cardiac function; EV, esophageal varices; HA, hepatic artery; PF, perisinusoidal fibrosis; Postop, postoperatively; Preop, preoperatively; RVD, right ventricular diameter; SF, septal fibrosis; TR, tricuspid regurgitation.

* This malformation was symptomatic 10 years after OLT.

having HHT with liver involvement, only 1 patient had a normal cardiac index.³ Cardiac failure during pregnancy has also been well described, always resulting in premature delivery, due mainly to a 30% to 40% increase in blood volume at the end of gestation combined with the increasing number and size of shunting.^{5,6,17,21,22} The diagnosis can be approached by angiography showing a typically dilated hepatic artery, small vascular lesions scattered in the liver, and early filling of the hepatic vein due to arteriovenous shunting.

Several radiological and surgical therapies attempt to achieve a reduction in cardiovascular symptoms. Embolization, calibration, or ligation of the hepatic artery to reduce the high cardiac output are only successful in the short term because of the development of new arteriovenous hepatic malformations. Furthermore, these invasive procedures performed on the hepatic artery may lead to ischemic cholangitis occurrence because biliary tree vascularization depends mainly on hepatic artery flow.⁷ For all these reasons, OLT is now considered to be a promising treatment for HHT with liver involvement because it restores cardiac function and normalizes arterial and venous hepatic blood flow. To date, only 24 liver transplantations performed for HHT have been reported.^{6-12,23-26} According to the Garcia-Tsao et al. classification, the predominant clinical presentation was cardiac failure in 13 cases (Table 1),⁶⁻¹² biliary disease in 7 cases,^{8,17,23,25} portal hypertension in 3 cases,^{8,24} and not specified in 1 patient receiving a right hemiliver from a living donor.²⁶

The results of OLT are considered to be good despite dissection difficulties due to vascular reorganization.^{6,8,24} In the Paul Brousse hospital experience, OLT required transfusion of 16 to 88 blood units, and the mean operation time varied from 11 to 15 hours for the 6 cases reported.⁸ Of the 24 OLTs currently reported, only 2 patients who underwent transplantation died postoperatively at 7 and 11 days due, respectively, to massive pulmonary and gastric bleeding resulting from the rupture of an arteriovenous malformation. However, a closer screening of the patient with a silent pulmonary arteriovenous malformation should be performed and the malformation detected and treated before the patient receives a right hemiliver from a living donor.²⁶ The hemodynamic parameters and right-heart diameters improved or normalized in all living patients (Table 1). Recently, Sabba et al. highlighted the possibility of reappearance of arteriovenous malformations despite OLTs performed 8 and 10 years earlier in two patients.¹⁰ However, in the second case,

the focal vascular dilatation was asymptomatic and could have been due to peliosis hepatitis, a well-known condition encountered in patients who have undergone transplantation. Close monitoring of these patients, even several years after OLT, should be performed.

Finally, we consider that OLT for HHT with liver involvement is currently the most promising therapy with good long-term results, allowing normalization of the cardiac function. However, liver transplantation for HHT remains a difficult procedure due to the collateral arterial reorganization. Moreover, the occurrence of thrombotic complications in our two cases is intriguing. OLT should probably be considered earlier in the therapeutic strategy before the appearance of a fixed secondary pulmonary hypertension. The various instrumental techniques performed on the hepatic artery should only be recommended as a temporary bridge to bringing the patient to OLT and should be closely monitored, especially in the case of previously altered liver function.

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References

1. Lesca G, Plauchu H, Coulet F, Lefebvre S, Plessis G, Odent S, et al; French Rendu-Osler Network. Molecular screening of ALK1/ACVRL1 and ENG genes in hereditary hemorrhagic telangiectasia in France. *Hum Mutat* 2004;23:289-299.
2. Plauchu H, de Chadarevian JP, Bideau A, Robert JM. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am J Med Genet* 1989;32:291-297.
3. Garcia-Tsao G, Korzenik JR, Young L, Henderson KJ, Jain D, Byrd B, et al. Liver disease in patients with hereditary hemorrhagic telangiectasia. *N Eng J Med* 2000;343:931-936.
4. Ianora AA, Memeo M, Sabba C, Cirulli A, Rorondo A, Angelelli G. Hereditary hemorrhagic telangiectasia: multi-detector row helical CT assessment of hepatic involvement. *Radiology* 2004;230:250-259.
5. Bernard G, Mion F, Henry L, Plauchu H, Paliard P. Hepatic involvement in hereditary hemorrhagic telangiectasia: clinical, radiological, and hemodynamic studies of 11 cases. *Gastroenterology* 1993;105:482-487.
6. Boillot O, Bianco F, Viale JP, Mion F, Mechet I, Gille D, et al. Liver transplantation resolves the hyperdynamic circulation in hereditary hemorrhagic telangiectasia with hepatic involvement. *Gastroenterology* 1999;116:187-192.
7. Neumann UP, Knoop M, Langrehr JM, Keck H, Bechstein WO, Lobeck H, et al. Effective therapy for hepatic M. Osler with systemic hypercirculation by ligation of the hepatic artery and subsequent liver transplantation. *Transpl Int* 1998;11:323-326.
8. Azoulay D, Precetti S, Emile JF, Ichai P, Gillon MC, Duclos-

- Vallee JC, et al. Liver transplantation for intrahepatic Rendu-Osler-Weber's disease: the Paul Brousse hospital experience. *Gastroenterol Clin Biol* 2002;26:828-834.
9. Pftzmann R, Heise M, Langrehr JM, Jonas S, Steinmuller T, Podrabsky P, et al. Liver transplantation for treatment of intrahepatic Osler's disease: first experiences. *Transplantation*. 2001; 72:237-241.
 10. Sabba C, Gallitelli M, Longo A, Cariati M, Angelelli G. Orthotopic liver transplantation and hereditary hemorrhagic telangiectasia: do hepatic vascular malformations relapse? A long term follow up study on two patients. *J Hepatol* 2004;41:687-688.
 11. Bauer T, Britton P, Lomas D, Wight DG, Friend PJ, Alexander GJ. Liver transplantation for hepatic arteriovenous malformation in hereditary haemorrhagic telangiectasia. *J Hepatol* 1995; 22:586-590.
 12. Le Corre F, Golkar B, Tessier C, Kavafyan J, Marty J. Liver transplantation for hepatic arteriovenous malformation with high-output cardiac failure in hereditary hemorrhagic telangiectasia: hemodynamic study. *J Clin Anesth* 2000;12:339-342.
 13. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000;91:65-67.
 14. Berg J, Porteous M, Reinhardt D, Gallione C, Holloway S, Umasunthar T, et al. Hereditary haemorrhagic telangiectasia: a questionnaire based study to delineate the different phenotypes caused by endoglin and ALK1 mutations. *J Med Genet* 2003;40: 585-590.
 15. Abdalla SA, Geisthoff UW, Bonneau D, Plauchu H, McDonald J, Kennedy S, et al. Visceral manifestations in hereditary haemorrhagic telangiectasia type 2. *J Med Genet* 2003;40:494-502.
 16. Martini GA. The liver in hereditary haemorrhagic telangiectasia: an inborn error of vascular structure with multiple manifestations: a reappraisal. *Gut* 1978;19:531-537.
 17. Hillert C, Broering DC, Gundlach M, Knoefel WT, Izbicki JR, Rogiers X. Hepatic involvement in hereditary hemorrhagic telangiectasia: an unusual indication for liver transplantation. *Liver Transpl* 2001;7:266-268.
 18. Spurny OM, Pierce JA. Cardiac output in systemic arteriovenous fistula complicated by heart failure. *Am Heart J* 1961;61:21-24.
 19. Razi B, Beller RM, Ghidoni J, Linhart JW, Talley RC, Urban E. Hyperdynamic circulatory state due to intrahepatic fistula in Osler-Weber-Rendu disease. *Am J Med* 1971;50:809-815.
 20. Radtke WE, Smith HC, Fulton RE, Adson MA. Misdiagnosis of atrial septal defect in patients with hereditary telangiectasia (Osler-Weber-Rendu disease) and hepatic arteriovenous fistulas. *Am Heart J* 1978;95:235-242.
 21. Gong B, Baken LA, Julian TM, Kubo SH. High-output heart failure due to hepatic arteriovenous fistula during pregnancy: a case report. *Obstet Gynecol* 1988;72(Pt 2):440-442.
 22. Livneh A, Langevitz P, Morag B, Catania A, Pras M. Functionally reversible hepatic arteriovenous fistulas during pregnancy in patients with hereditary hemorrhagic telangiectasia. *South Med J* 1988;81:1047-1049.
 23. Odorico JS, Hakim MN, Becker YT, Van der Werf W, Musat A, Knechtel SJ, et al. Liver transplantation as definitive therapy for complications after arterial embolization for hepatic manifestations of hereditary hemorrhagic telangiectasia. *Liver Transpl Surg* 1998;4:483-490.
 24. Saxena R, Hytioglou P, Atilasoy EO, Cakaloglu Y, Emre S, Thung SN. Coexistence of hereditary hemorrhagic telangiectasia and fibropolycystic liver disease. *Am J Surg Pathol* 1998;22:368-372.
 25. McInroy B, Zajko AB, Pinna AD. Biliary necrosis due to hepatic involvement with hereditary hemorrhagic telangiectasia. *Am J Roentgenol* 1998;170:413-415.
 26. Giacomoni A, De Carlis L, Sammartino C, Lauterio A, Osio C, Slim A, et al. Right hemiliver transplants from living donors: report of 10 cases. *Transplant Proc* 2004;36:516-517.