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ORIGINAL ARTICLE

Orthotopic Liver Transplantation for Benign Hepatic Neoplasms

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Objective: To evaluate the frequency and outcome of liver transplantation for symptomatic, unresectable, benign hepatic neoplasms.

Design: Retrospective study.

Setting: Presbyterian University Hospital, a tertiary care referral center for liver transplantation affiliated with the University of Pittsburgh (Pa).

Patients: All 3239 liver transplant recipients at the University of Pittsburgh from January 1981 until January 1993.

Results: Twelve (0.37%) of 3239 patients required liver transplantation for benign, highly symptomatic hepatic neoplasms that were unresectable. Origins included adenoma (n=6), mesenchymal hamartoma (n=2), massive

hepatic lymphangiomatosis (n=1), hilar fibrous angiodysplasia (n=1), focal nodular hyperplasia (n=1), and hemangioma (n=1). There were three perioperative deaths and two late deaths at 56 and 84 months. The remaining patients are alive, with follow-up ranging from 36 to 145 months. Median survival for the nine patients who survived the perioperative period is 88 months. The early deaths were attributable to hemorrhagic complications (n=2) and necrotizing pancreatitis (n=1). The two late deaths were due to disseminated aspergillosis and hepatitis-associated cirrhosis.

Conclusion: Patients with severe symptoms from benign hepatic neoplasms that are not resectable can be treated by total hepatectomy and orthotopic liver transplantation, with the expectation of good long-term results.

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STANDARD INDICATIONS for orthotopic liver transplantation include chronic end-stage liver disease, fulminant hepatic failure, inborn errors of metabolism, and cholestatic liver disease.¹⁻⁶ Increasingly, patients with primary malignant neoplasms of the liver undergo transplantation after neoadjuvant chemotherapy.⁷⁻⁸ Rarely, benign hepatic lesions require liver transplantation if they cause debilitating or life-threatening manifestations or if they are very symptomatic and too large to be resected.⁹ Isolated case reports of liver transplantation for benign hepatic tumors have been published.¹⁰⁻¹² We report herein our entire experience of liver transplantation for benign liver tumors. Liver transplantation was considered the treatment of choice for benign liver tumors in highly symptomatic patients with potentially life-threatening complications if (1) liver resection was precluded due to the extent or strategic localization of the tumor or (2) hepatic resection had been

performed and was inadequate to control recurrent symptoms.

RESULTS

Five patients were children, aged 4 to 17 years (mean, 8.6 years); one was an infant, aged 4 weeks; and the remaining six were adults, aged 20 to 47 years (mean, 36.3 years). Nine patients were female (75%), and three were male (25%). In six patients, the clinical and histological characteristics of the tumor were typical of hepatic adenoma. In two patients, the liver pathologic specimens revealed mesenchymal hamartoma, and the remaining tumor origins were cavernous hemangioma, massive lymphangiomatosis, hilar fibrous angiodysplasia (inflammatory pseudotumor), and focal nodular hyper-

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PATIENTS AND METHODS

As of January 1993, 12 patients had undergone orthotopic liver transplantation for benign hepatic neoplasms at the University of Pittsburgh (Pa) Medical Center. Data were collected on all patients regarding age, sex, nature of disease, dates of diagnosis, magnitude of the clinical manifestations, previous liver surgery, and posttransplantation course. The histopathologic features of the lesions were confirmed after review of the surgical pathologic specimens (**Table**).

HEPATIC ADENOMAS

Six female patients (five of reproductive age and three with a history of oral contraceptive use) presented with adenomas with recurrent intraparenchymal or intra-abdominal bleeding. The only premenstrual-age female, a 10-year-old girl, had a family history of hepatic adenomatosis. In one of the other patients, the multiple adenomas were related to type I glycogen storage disease, and the clinical course was complicated by liver failure as well as bleeding.

Five of these patients had undergone previous anatomical or minor liver resections, which proved to be inadequate.

MESENCHYMAL HAMARTOMAS

Two patients with mesenchymal hamartomas suffered from intractable abdominal pain and progressive liver failure. Each had undergone prior laparotomy for biopsy and debulking.

HEMANGIOMA

An infant presented with a giant cavernous hemangioma involving the entire liver, with abdominal distention and the bleeding tendency of the Kasabach-Merritt syndrome

(localized clotting and fibrinolysis within the hemangioma, associated with systemic fibrinolysis).¹³

LYMPHANGIOMATOSIS

One patient had massive diffuse hepatic lymphangiomatosis and presented with liver failure, dyspnea, and debilitating pain. Four years prior to referral, she had undergone splenectomy for hypersplenism related to splenic lymphangiomatosis, and at that time hepatic lymphangiomatosis was noted.

HILAR FIBROUS ANGIODYSPLASIA

Inflammatory pseudotumor is a rare lesion characterized by proliferating fibrovascular tissue mixed with inflammatory cells. It has been described mostly in children and in a wide variety of anatomic locations.¹² Recurrent cholangitis, portal hypertension, and secondary biliary cirrhosis due to the extensive involvement of the liver hilum resulted in the need for liver replacement in an 8-year-old girl.

FOCAL NODULAR HYPERPLASIA

The patient with focal nodular hyperplasia complained of intractable pruritus, fatigue, jaundice, and progressive liver failure due to replacement of the hepatic parenchyma by tumor.

In all cases, liver transplantation was performed according to the standardized surgical technique elucidated by Starzl and Demetris¹ and Iwatsuki et al.³ In spite of the enormous size of the livers in most of these cases (**Figure**), the bilateral subcostal and upper vertical midline incision without a thoracic extension provided adequate exposure when a bilateral subcostal retractor was used. Eleven patients received posttransplantation immunosuppressive therapy based on cyclosporine and steroids, while another was treated with tacrolimus (Prograf).

plasia. There were three postoperative deaths. Two patients received a liver allograft in an emergency setting, and both died. One was the infant suffering from a giant cavernous hemangioma, Kasabach-Merritt syndrome, and associated systemic coagulation disorders. This patient survived the operation, but primary nonfunction of the graft developed, and he died 8 days later of an intraventricular hemorrhage. The other emergency transplantation was in a 43-year-old woman with a large hepatic adenoma causing recurrent intraparenchymal bleeding. After left-sided trisegmentectomy, the remaining healthy parenchyma was inadequate to sustain life. Emergency liver transplantation was performed, and necrotizing pancreatitis resulted in the patient's death. The third fatality occurred in an elective case, that of a 4-year-old boy with a giant mesenchymal hamartoma nearly replacing the liver parenchyma who died during the operation of hemorrhagic shock.

Of the nine patients who survived the early postoperative period, one died 56 months later of disseminated aspergillosis. A second patient died 84 months later of candidal sepsis after her second orthotopic liver trans-

plantation for hepatitis C-associated cirrhosis. The remaining seven patients are alive, with a follow-up period ranging from 36 to 145 months (median, 88 months). Multiple lung lesions developed in one of the patients undergoing transplantation for adenoma 9 years later. Needle biopsy of the lesions revealed hepatocellular carcinoma, and although there was no evidence of malignant neoplasms in the pathologic specimens of the native liver, it is probable that the malignant tumor arose from an undiscovered focus in the original adenoma. She is currently alive with disease.

COMMENT

Benign hepatic neoplasms have been considered a relatively rare entity, but their increased recognition can be attributed to advances in diagnostic imaging technology.¹⁴ Incidental liver lesions can be safely observed as long as benign histological characteristics and clinical behavior are apparent, and the lesion is under radiologic observation.⁹ However, with the exception of hemangiomas and possibly focal nodular hyperplasia, lesions larger

Patients With Benign Hepatic Tumors Treated by Orthotopic Liver Transplantation

Age/Sex	Histological Characteristics	Clinical Manifestations	Interval From Diagnosis to Transplantation	Previous Liver Surgery	Posttransplantation Survival	Status
Patients With Hepatic Adenomas						
10 y/F	3 y	Exploratory laparotomy (×2)	65 mo	Alive
17 y/F	Adenomas	Intraparenchymal and/or intraperitoneal hemorrhage	2 y	Portacaval shunt	145 mo	Alive
20 y/F			5 y	Left lateral segmentectomy	101 mo	Alive
31 y/F	2 y	Right trisegmentectomy	130 mo	Alive
35 y/F	15 y	Exploratory laparotomy (×2)	36 mo	Alive
43 y/F	6 mo	Left trisegmentectomy	10 d	Died of necrotizing pancreatitis
Patients With Miscellaneous Tumors						
4 y/M	Mesenchymal hamartoma	Pain, respiratory distress, liver failure	2 y	Biopsy and attempted resection	58 mo	Alive
4 y/M	Mesenchymal hamartoma	Pain, liver failure, portal hypertension	2 y	Debulking (×2)	...	Intraoperative death
4 wk/M	Cavernous hemangioma	Kasabach-Merritt syndrome	4 wk	...	8 d	Died of coagulopathic cerebral hemorrhage
47 y/F	Massive hepatic lymphangiomas	Pain, respiratory distress, liver failure	4 y	Splenectomy	88 mo	Alive
8 y/F	Hilar fibrous angiodysplasia (inflammatory pseudotumor)	Recurrent cholangitis, portal hypertension	3 mo	Exploratory laparotomy	56 mo	Died of disseminated aspergillosis
42 y/F	Diffuse focal nodular hyperplasia	Pain, pruritus, jaundice	5 y	Exploratory laparotomy	55 mo	Alive

than 3 cm should be excised, especially when the histological characteristics of the tumor are ambiguous, or there is a considerable risk for complications. In extreme cases, a curative excision of the tumor cannot be accomplished due to the extension of the lesion in the liver parenchyma and its bilobar location. In such cases, a variety of palliative therapeutic strategies have been proposed, including radiotherapy and hepatic artery ligation or embolization, but good long-term results are rare.^{9,15} Liver transplantation has been used successfully in sporadically reported cases of benign hepatic neoplasms complicated by life-threatening manifestations, as well as for treatment of the diffuse benign cystic lesions of polycystic liver disease in patients with poor quality of life due to liver size (J.R.M., Giorgio Zetti, MD, Ignazio Marino, MD, Satoru Todo, MD, Andreas G. Tzakis, MD, Guiseppa Carneri, MD, S.I., T.E.S., John J. Fung, MD, PhD, unpublished data, 1993).^{9-12,16-18}

In the cases we report herein, total hepatectomy was indicated because of failure of alternative therapies to control the disease and relieve its symptoms. Eleven of 12 patients had already undergone at least one laparotomy to treat the disease, with eventual failure. Five of the six patients in the adenoma group underwent urgent operation because of intraparenchymal and/or intraperitoneal hemorrhage. Three of the six underwent anatomical liver resection to eradicate



Massive hepatic lymphangiomas and stigmata of portal hypertension.

the disease, with eventual recurrences. The obvious risk for a life-threatening hemorrhage necessitated total hepatectomy and liver replacement in these patients. The median interval between the primary diagnosis of adenoma and transplantation was 36 months. During this time period, sustained growth and recurrent hemorrhage was the rule, and death was imminent for all of these patients without transplantation. For this reason, unresectable hepatic adenomas that are associated with hemorrhage and/or continued growth should be an indication for liver replacement. Often, the course of these aggressive lesions can be anticipated at the outset of symptoms, and the patients undergo elective transplantation before extreme circumstances exist.

The remaining six patients presented uniformly with abdominal pain, malaise, fatigue, and other manifestations related to liver size and the extensive replacement of hepatic parenchyma by the neoplasm. All six patients had a very poor quality of life and had suffered potentially lethal complications. Liver transplantation can be considered the treatment of choice for symptomatic benign hepatic neoplasms that are extensively replacing the liver parenchyma.

CONCLUSION

Excellent long-term outcome after elective liver transplantation for large, life-threatening, benign hepatic lesions should prompt consideration of this therapeutic option in difficult cases.

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Surgical Anatomy

Structures entering the adductor canal are the (1) femoral artery and vein, (2) profunda artery and vein, (3) nerve to the vastus medialis, and (4) saphenous nerve, artery, and vein.

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