Long-Term Outcomes of Liver Transplantation for Hepatic Sarcoidosis: A Single Center Experience

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Aim: **Hepatic sarcoidosis is a rare indication for orthotopic liver transplantation (OLT). Hence, studies evaluating these patients are scarce. We present a single center experience with OLT for hepatic sarcoidosis in a case–control study.** ***Methods:*** **A retrospective chart review was performed on 970 patients with OLT at our center, and 13 patients (1.3%) were identified who underwent 14 OLTs for hepatic sarcoidosis. For each case, two controls matched for etiology of liver disease, recipient age (±5 years), and duration since transplant (within 5 years) were selected.** ***Results:*** **For the 13 patients transplanted for sarcoidosis, the median age was 46 years. The majority were women (62%) and African-American (85%). Cholestatic liver disease was the primary manifestation. Portal hypertensive complications were present in 11 patients (84%). The median MELD score at transplantation was 19. Extra-hepatic manifestations were present in ten patients (77%). All patients received whole deceased 14 donor allografts. Six patients remain alive with a median post-OLT follow-up of 8.4 years. The 1-, 3-, 5-, and 10-year patient survival rates were 84.6%, 76.9%, 61.1%, and 51.3%, respectively for the sarcoidosis group and 82.1%, 78.6%, 78.6%, and 61.9%, respectively for the matched PSC/PBC group (*P* = 0.739). Re-graft free survival for sarcoidosis patients was 84.6%, 76.9%, 61.5%, and 51.3% for 1-, 3-, 5-, and 10-years and for the matched control group re-graft free survival was 78.6% at 1-, 3-, 5-years, and 64.8% at 10-years (*P* = 0.661). Recurrence of hepatic sarcoidosis was found in 4 patients at 11 days, 112 days, 222 days, and 6.6 years.** ***Conclusions:*** **Our study depicts the long-term benefit of liver transplantation in patients with end stage liver disease secondary to sarcoidosis. It shows statistically comparable graft and patient survival for such patients when compared to other cholestatic diseases. Disease recurrence, although possible, has not been shown to cause allograft dysfunction.** **(J Clin Exp Hepatol 2016;6:94–99)**

Sarcoidosis is a multisystem disease characterized by non-caseating granulomas in the affected organs. The most commonly involved organs are lungs, skin, and eyes although any organ can be affected. Liver involvement is seen by biopsy or autopsy in 50–79% of sarcoidosis patients.[1–4] Patients with sarcoidosis are infrequently symptomatic due to liver disease and may present with pruritus, abdominal pain, and fever.[5] Hepatomegaly is found in about 21–50% of the patients.[6–8] Liver involvement may occur without lung involvement in up to 47% of the patients.[9]

Abnormal liver chemistries are noted in only 35% of patients.[9,10] In hepatic sarcoidosis, the histologic abnormalities include non-caseating granulomas, chronic intrahepatic cholestasis, progressive diminution in the number of interlobular bile ducts, peri-portal fibrosis, and micronodular biliary cirrhosis.[11] Jaundice is rare and may be due to intrahepatic cholestasis, hemolysis, hepatocellular dysfunction, or obstruction of the extra-hepatic bile ducts by granulomatous hepatic hilar lymph nodes.[6] Progressive liver disease due to sarcoidosis may lead to the development of portal hypertension.[12,13] Development of cirrhosis is not a pre-requisite for portal hypertension.[14] Severe liver dysfunction and jaundice are uncommon.[12] Other vascular complications include portal vein thrombosis because of stasis from obliteration of small portal veins[12] and Budd-Chiari syndrome because of extrinsic compression of hepatic veins by sarcoid granulomas, causing narrowing of venous vessels, venous stasis, and subsequent thrombosis.[15]

Considering its rarity as an etiology for end stage liver disease, limited information is available on the long-term outcome in recipients with liver transplantation for sarcoidosis. Our aim is to evaluate the long-term outcomes in recipients with orthotopic liver transplantation (OLT) for hepatic sarcoidosis at our center.

METHODS

A retrospective chart review was performed on 970 patients who underwent OLT at our center from October 1993 to

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Abbreviations: OLT: orthotopic liver transplantation; ACE: angiotensin converting enzyme; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; CTP: Child–Turcotte–Pugh; MELD: Model for End Stage Liver Disease; HCV: hepatitis C virus; DM: diabetes mellitus
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February 2016. Thirteen patients (1.3%) were identified who underwent 14 OLTs with hepatic sarcoidosis as the indication. The diagnosis of hepatic sarcoidosis was established by a combination of characteristic clinical findings (lung/skin/eye involvement, high serum ACE levels, etc.), presence of non-caseating granulomas in the pre-transplant liver biopsy specimen (4 patients, biopsies were not done on all patients and on a few records could not be obtained) or the explant (all patients) at the time of transplantation, and the absence of other etiologies.

The OLT recipients for sarcoidosis were compared to matched controls that received OLT for an indication of cholestatic liver disease, primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). Two controls were selected in a random fashion after they were matched for recipient age (±5 years) and duration since transplant (within 5 years). Twenty-eight PBC or PSC recipients as controls were matched to the study group.

Retrospective chart review was completed to obtain demographic data, viral serologies, titers of autoantibodies, co-morbid conditions, serum transaminases, alkaline phosphatase, total bilirubin, albumin, INR, prothrombin time, Child–Turcotte–Pugh (CTP) score, Model for End Stage Liver Disease (MELD) score, creatinine, immunosuppression, complications, liver biopsies, and transplant-related outcomes. Liver biopsies were performed at one year post-transplant or for liver dysfunction identified by laboratory studies, and disease recurrence was defined by evidence of non-caseating granulomas in the liver biopsy specimen and absence of other etiologies of hepatic granulomas. Categorical data were compared with Fisher's exact test with Yates correction as appropriate. Continuous variables were compared as medians using Mann–Whitney *U* test. Patient and graft survival rates were estimated using Kaplan–Meier curves with comparison by log-rank test. Statistical significance was set a priori at $P < 0.05$. SPSS 23.0 (IBM Corporation, Armonk, NY) was used for analysis.

RESULTS

Pre-transplant Characteristics

Pre-transplant characteristics are summarized in Table 1. For the 13 patients transplanted for sarcoidosis, the median age was 46 years (range: 30–61 years). The majority were women (62%) and African-American (85%). The indication for OLT in all of our patients was sarcoidosis, but 2 patients had concomitant chronic hepatitis C virus infection. The median duration of disease from diagnosis to OLT was 7.6 years (range: 1–16 years). Five patients (38%) had disease limited to liver only. Extra-hepatic manifestations were present in ten patients (77%): all with pulmonary disease, 2 with hypercalcemia, 1 with cutaneous manifestation, 1 with uveitis, and 1 with arteritis. Three patients had diabetes mellitus preceding OLT (27%). Cholestatic liver disease was the primary manifestation with a median serum total bilirubin of 8.9 mg/dL (range: 0.6–18.0 mg/dL) and median serum alkaline phosphatase of 353 U/dL (range: 85–1100 U/dL). Portal hypertensive complications were present in 11 patients (84%): 7 with ascites, 11 with symptomatic esophageal varices, and 4 with hepatic encephalopathy. The median MELD score at transplantation was 19 (range: 9–29).

Given the long period of the study, post-transplant immunosuppression changed over the course of the study. For patients in either group transplanted prior to 1994 (2 patients), steroids, cyclosporine, and azathioprine were used. From 1994 to early 1998, immunosuppression was steroids, tacrolimus, and azathioprine (2 patients). In early

Table 1 Pre-transplant Characteristics of Cases and Controls.

Characteristics	Cases (*n* = 13, 14 OLTs)	Controls (*n* = 28)	*P*-value
Demographics			
Age at LT (yrs) ± SD (range)	45.5 ± 8.7 (30–61)	46.32 ± 9.32 (25–64)	0.8
Male/female	5/8 (females 62%)	16/12 (females 43%)	0.5
Race (Caucasian/African-American/Other)	2/11 (African-American 85%)	22/5/1 (African-American 18%)	<.0001
Laboratory data			
Serum total bilirubin (mg/dL)	8.9 (0.6–18)	5 (1–33)	.102
Serum alkaline phosphatase (IU/L)	353 (85–1100)	297 (77–1100)	.91
AST (IU/L)	88 (39–209)	154 (33–1600)	.30
ALT (IU/L)	71 (15–172)	96 (13–1200)	.72
Serum albumin (g/dL)	2.6 (1.7–4.2)	3.0 (1.4–4.1)	.44
MELD	19 (9–29)	19 (7–37)	.94
Serum creatinine (mg/dL)	1.1 (0.6–2.6)	1.0 (.6–4.5)	.74
INR	1.4 (1.0–2.4)	1.3 (0.9–2.0)	.83

Data are reported as median (range) except gender and race that are expressed as numbers.