Histopathological Examination of Explanted Liver After Transplantation in Patients With Cryptogenic Cirrhosis

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ABSTRACT

Objectives. Cryptogenic cirrhosis is a common indication for liver transplantation. Diagnosis is made after exclusion of other causes of cirrhosis. In this study, the aim was to evaluate patients with cryptogenic cirrhosis after histopathological examination of explanted liver.

Materials and Methods. A retrospective histopathological chart review of 117 patients with cryptogenic cirrhosis who had liver transplantation between November 2009 and June 2014 was performed. Age, sex, operative features, survival rates, and preoperative and postoperative diagnosis were evaluated.

Results. During the study period, 123 liver transplantations were performed for these 117 patients. Deceased donor liver transplantations were performed in 23 (18.7%) of the cases. Retransplantations were performed in 5 patients. Median age was 48 years, and female-to-male ratio was 41:76. Hepatosteatosis were observed in 29 patients. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis were observed in 20 (12%) and 9 (7.7%) of these patients, respectively. Autoimmune hepatitis was observed in 2 patients. The definitive cause of cirrhosis was unclear in 68 (58%) of the patients. Incidental malignant and premalignant lesions were observed in 15 patients.

Conclusions. Histopathological examination of the explanted liver after liver transplantation in those patients with cryptogenic cirrhosis may significantly help to diagnose the cause of cirrhosis, such as nonalcoholic steatohepatitis or autoimmune hepatitis, with using the scoring system developed by the International Autoimmune Hepatitis Workgroup. In addition, incidental malignant or premalignant lesions may be observed.

CRYPTOGENIC liver cirrhosis is a common indication for liver transplantation and accounts 7% to 14% of all liver transplantations [1]. Viral, metabolic, alcoholic, autoimmune, toxic, and other reasons should be excluded to diagnose a patient with cryptogenic liver cirrhosis [2]. Even with advances in diagnostic evaluations, etiology remains idiopathic in 5% to 30% of liver cirrhosis, and only 5% to 7% of these patients have liver transplantation [3]. True diagnosis of patients with cryptogenic liver cirrhosis is critical for posttransplantation management and immunosuppressive planning. Various studies have confirmed that a detailed diagnostic workup before or after transplantation has potential to document the definitive diagnosis in those patients with cryptogenic liver cirrhosis [2,4–7]. This study aimed to re-evaluate patients with cryptogenic liver cirrhosis after transplantation using pathology results.

MATERIALS AND METHODS

This study consisted of a retrospective analysis of 117 patients with cryptogenic liver cirrhosis who were treated with liver transplantation between November 2009 and June 2014 in our institution. Incomplete histopathological examinations and those patients with fulminant hepatitis with emergent transplantations were excluded from the study. Age, sex, body mass index (BMI), operative features, survival rates, and preoperative and postoperative

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Table 1. Demographic Features of the Patients

Age (median)	48
Female (n, %)	41 (35%)
Male (n, %)	76 (65%)
Body mass index (mean, range)	24.21 (12.40–37.81)
Mean follow-up (mo, range)	28.12 (1–60)
A Rh(+) (n)	43
A Rh(−) (n)	10
B Rh(+) (n)	15
B Rh(−) (n)	2
0 Rh(+) (n)	33
0 Rh(−) (n)	7
AB Rh(+) (n)	7

histopathological findings were extracted from the database of the institution.

RESULTS

During the study period, 123 liver transplantations were performed for 117 patients with cryptogenic liver cirrhosis. In all patients the definitive reason for liver cirrhosis was not clarified even after serological and biochemical laboratory evaluations. Deceased donor liver transplantations were performed in 23 (18.7%) of the patients, and living donor liver transplantations were performed in 100 (81.3%) of the patients. Retransplantations were performed 1 time in 4 and 2 times in 1 of the patients.

The basic demographic and clinical features of the patients, including BMI (mean and range) and blood type distribution, are presented in Table 1. Type 2 diabetes mellitus (DM) was observed in 54 (46.2%; 25 were insulin dependent and 29 were on oral antidiabetics) of these patients. Mean follow-up was 28.1 months, and the 1-year survival rate was 71%. Thirty-six patients were lost during the follow-up period, and 35 of these patients were lost in the first year after transplantation: 14 patients were lost in the first month and 12 patients were lost in the first 3 months. One patient was lost in the first 19 months.

The definitive diagnosis after the histopathological evaluation of the explanted liver is presented Table 2. In 68 (58%) patients, the conclusive diagnosis was not available. In 29 patients, hepatosteatosis was diagnosed. In 9 (7.7%) patients nonalcoholic steatohepatitis (NASH) and in 20 patients (17%) nonalcoholic fatty liver disease (NAFLD) were observed.

Table 2. Histopathological Diagnosis of Explanted Livers

	N = 117
Idiopathic	68
Nonalcoholic fatty liver disease	20
Nonalcoholic steatohepatitis	9
Hemochromatosis	4
Secondary biliary cirrhosis	4
Hepatitis B virus	3
Sclerosing cholangitis	2
Autoimmune hepatitis	2
Wilson disease	2
Alpha-1 antitrypsin deficiency	1
Echinococcus alveolaris	1
Hemophagocytic syndrome	1

Table 3. Incidental Malignant and Premalignant Lesions

	N
Hepatocellular carcinoma	8
Cholangiocarcinoma	1
Epithelioid hemangioendothelioma	1
Biliary intraepithelial neoplasia type 1	1
Dysplasia	4

Incidental findings after histopathological evaluation of the explanted liver are presented in Table 3. In 15 patients, incidental malignant or premalignant lesions were reported. Hepatocellular carcinoma (HCC) was reported in 8 patients (with a size ranging from millimeters to 2.5 cm).

DISCUSSION

Cirrhosis is generally accepted as cryptogenic with exclusion of common etiologies after an extensive evaluation. Various descriptions have been advocated for its development, such as secret alcoholism, unknown viruses (non-B or non-C), silent autoimmune hepatitis, α-1 antitrypsin phenotype abnormalities, or progression of NASH [5]. Diagnosis of cryptogenic cirrhosis merits the completion of tests for viral hepatitis (A, B, and C), autoantibodies for autoimmune hepatitis (anti-smooth muscle antibody [ASMA], anti-nuclear antibody [ANA], anti-mitochondrial antibody [AMA], etc.), iron and ceruloplasmin levels, α-1 antitrypsin phenotype, and histopathological analysis of liver biopsy. In addition, overt alcoholism and hepatotoxic drug intake should be excluded [8].

Age, sex, blood group, and BMI of the patients with cryptogenic cirrhosis in our series were similar to those with known etiologies for cirrhosis. Observation of type 2 DM in 46% of the patients with cryptogenic cirrhosis was significant. This ratio was almost twice that of the normal population. DM may develop because of immunosuppressive therapy, but this ratio is still higher than previously reported for those patients with known etiologies for cirrhosis [9,10]. DM and obesity have been reported as risk factors for cryptogenic cirrhosis, and initial series have reported a coexistence rate of 73% [11,12]. Yalamanchili et al. have reported DM in 21% of 239 patients with cryptogenic cirrhosis, and this ratio was not different from other groups with cirrhosis [13]. Marmur et al. have reported DM in 26% of the patients with cryptogenic cirrhosis and in 11% of the patients with a known etiology for cirrhosis, and this difference was found to be significant [3]. Our mean follow-up period was 28 months and mean survival rate was 71%, which is similar that found in the literature [8,9,13].

NAFLD defines a nonalcohol-dependent spectrum that varies from fatty liver to cirrhosis. NASH is an entity in this spectrum that constitutes one third of all NAFLD cases [14]. Ludwig et al. were the first to define this entity [15]. The pathogenesis is not known, but it is considered to be a hepatic

manifestation of metabolic syndrome due its relationship with obesity and type 2 DM [16]. In recent years, NASH has been considered as a cause of cryptogenic cirrhosis in most cases. Cirrhosis develops in more than 20% of NASH patients. NASH is expected to be a primary indication for liver transplantation [16,17]. NAFLD was observed in 25% of the patients in our series, and one third of these patients were found to have NASH. Previous reports have documented a higher ratio in the United States [5,11,18]. However, our ratio is similar with reports from Europe [2,7,9].

Autoimmune hepatitis (AIH) is a common cause of cirrhosis. However, a pathognomonic marker is not available for this disease and diagnosis requires the exclusion of other causes of cirrhosis. Definitive or possible AIH diagnosis may be completed with the scoring system developed by the International Autoimmune Hepatitis Workgroup [19]. In recent years, NASH and AIH are defined as the leading causes of cryptogenic cirrhosis (in some series in 54% of the cases) [2,5]. In our series, only 2 patients were considered to have AIH. This may be attributable to a lack of data in this retrospective study, which limits AIH scoring.

Hepatitis B virus (HBV) was diagnosed in 3 of the patients who were previously considered to have cryptogenic cirrhosis. These patients were considered as seronegative occult HBV because preoperative and postoperative hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B e antigen, hepatitis B core antibody, and HBV DNA test results were negative [20].

Incidental malignant or premalignant lesions were observed in 15 patients. HCC was observed in 8 of these patients. In 3 cases, preoperative diagnosis of HCC was available. However, in the other 5 cases, millimetric HCC was diagnosed incidentally. HCC development is observed less in cryptogenic cirrhosis patients than those patients with viral cirrhosis. However, cryptogenic cirrhosis should be considered as a risk factor for HCC [9,13,21].

In this study, the etiology of the cirrhosis was not defined, even by histopathological examination in 58% of the cases. This rate is lower in previous reports in the literature [3,5,12]. In consideration of the lower rates of AIH in our series, it may be that some of these patients might have undiagnosed AIH [22,23].

CONCLUSIONS

The results of this study have documented that histopathological examination of the explanted livers after liver transplantation in patients with cryptogenic cirrhosis may significantly help to diagnose the definitive cause of cirrhosis, such as NASH and AIH, using the scoring system. In addition, incidental malignant or premalignant lesions may be observed.

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