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Structural Integrity and Identification of Causes of Liver Allograft Dysfunction Occurring More Than 5 Years After Transplantation

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Abstract

The clinicopathologic features of liver allograft dysfunction occurring in 51 symptomatic recipients after more than 5 years' survival (mean 7.1 years) with the same hepatic allograft were compared with those of a similar group of 14 asymptomatic patients (mean survival, 9.9 years) who underwent a nonclinically indicated protocol liver biopsy evaluation. Predictably, patients who had clinically indicated biopsies more frequently showed histopathologic alterations (76% versus 36%, $p < 0.002$). After detailed clinicopathologic correlation, the changes in the symptomatic patients were attributed primarily to definite or presumed viral hepatitis in 17 of 51 (33%) patients, 11 of whom had recurrent viral disease; seven of 51 (14%) had nonviral recurrent original disease, three (6%) had obstructive cholangiopathy, and 11 (22%) had acute and/or chronic rejection. In 13 of 51 (25%) of the symptomatic patients, the clinical and pathologic abnormalities were minimal. Long-term liver allograft survival in nine of 14 (64%) of the asymptomatic patients was associated with minimally abnormal histologic alterations. Two of the asymptomatic patients had obstructive cholangiopathy; two others had recurrence of the original disease and one has possible viral hepatitis. Viral hepatitis types B and C, alcoholic liver disease, autoimmune hepatitis, granulomatous hepatitis (not otherwise specified), and probably primary biliary cirrhosis and primary sclerosing cholangitis were shown to recur after hepatic transplantation. The histopathologic changes associated with acute and chronic rejection frequently overlapped with other syndromes causing late dysfunction, such as chronic viral or autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis; more than one insult could be identified in 15 cases, which made the differential diagnosis of causes of late liver allograft dysfunction much more difficult than early after hepatic transplantation. It is important to correlate the biopsy findings with the liver injury tests, the results of viral and autoimmune antibody serologic studies, and review of previous biopsies and to be aware of the original disease, recent changes in immunosuppression, and results of therapeutic intervention(s) to identify correctly the causes of liver allograft dysfunction in this patient population.

Keywords

Liver transplantation; Histopathology; Late dysfunction; Diagnosis; Tolerance; Recurrent disease; Alcoholism; Hepatitis

Orthotopic liver transplantation is now a well-accepted form of therapy for patients with end-stage liver disease (40). Many large centers report patient survival rates that range from 70 to 90% at 1 year, and there is a more gradual attrition or even flattening of allograft and patient survival curves after 2 to 3 years compared with kidney or heart allografts, where progressive deterioration because of rejection is the rule. However, long-term morbidity and allograft dysfunction are not uncommon, so that an increasing number of physicians will be faced with the problem of correctly identifying and then treating liver allograft dysfunction in their patient population, guided by a core needle biopsy and other laboratory or diagnostic tests.

Whereas the clinical and histopathologic features of early (<2 years) causes of liver allograft dysfunction are well described (6,10,12,14,21,23,25,33, 34,38,39,44,46,47), those associated with late dysfunction are more limited in scope (3,5,7,13,17,18, 19,22,27,29,30,31,35,37), and few studies specifically address the problems associated with a clinicopathologic differential diagnosis in long-term survivors (3,5,7,15,17,19,22,27,35). No study has reviewed the material from patients surviving for more than 5 years. Moreover, recognizing baseline changes in long-surviving allografts is important for differential diagnosis and in immunosuppressive drug withdrawal trials (31,36). The following study is designed with two goals in mind: (a) to identify the histopathologic features and causes of late liver allograft dysfunction; and (b) to determine whether long-term, stable allograft livers in patients without clinical signs or symptoms of dysfunction develop any histopathologic changes attributable to prolonged engraftment that would otherwise not be present in age-matched controls.

MATERIALS AND METHODS

Patient Selection

Before December 31, 1988, at the University of Colorado and University of Pittsburgh, 1,833 liver transplant operations were completed in 1,431 patients (686 males and 745 females). The cumulative 5-year patient and allograft survival rates were 65 and 50%, respectively, for females and 58 and 43%, respectively, for males ($p < 0.012$ for patient and $p < 0.0062$ for allograft survival; female versus male: log-rank test). Of the long-term survivors, 51 of 174 who underwent liver biopsy evaluation for hepatic injury or dysfunction occurring more than 5 years after transplantation were randomly chosen from an inhouse computerized data base. Hereafter, these 51 patients who underwent indicated biopsies will be called the “symptomatic” group, which consisted of 32 women and 19 men whose average age was 42.8 years (range, 23–65 years); mean survival was 7.1 years at the time of biopsy (Table 1). The age and distribution of original disease was representative of the total group of long-term survivors. An additional 14 “asymptomatic” patients were randomly selected from a group of 59 patients who were well, who had survived for an average of 9.9 years (range, 5–16 years) with the same liver, and who underwent liver protocol biopsy evaluation to test for hematolymphoid chimerism or drug withdrawal (41). There were 10 women and four men in this group, with an average age of 45.7 years (range, 25–69 years). One patient was initially classified as asymptomatic but later was found to have had signs and symptoms of allograft dysfunction and was switched to the symptomatic group.

Complete information about donor age (average age, 21; range, 11–39 years), sex (27 males, 24 females), ABO blood group, human leukocyte antigen (HLA) type, and crossmatch was available in 56 of the 65 total patients and showed no significant differences between the two groups.

Backtable biopsies obtained from 20 donors who died because of a cerebrovascular accident ($n = 9$), motor vehicle accident ($n = 4$), or other trauma ($n = 7$) served as normal controls.

None had a known history of liver disease, and serologic studies for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) were negative.

Immunosuppressive Regimens

All patients originally received a combination of cyclosporin A (Sandoz, Basel, Switzerland) and corticosteroids as baseline immunosuppression; 12 of the patients also received azathioprine (Imuran, Burroughs Wellcome, Research Triangle Park, NC, U.S.A.). Rejection episodes generally were treated with a 1-g bolus of methylprednisolone or a tapering “recycle” of prednisone. Steroid-resistant rejection episodes were treated with 3- to 10-day course of OKT3 (Ortho Pharmaceuticals, Raritan, NJ, U.S.A.). Twenty-five patients in the symptomatic group, but no asymptomatic patients, were switched from a baseline immunosuppression of cyclosporin A (CyA) to FK506 (Fujisawa Pharmaceuticals, Japan) from 2 to 10 years after transplantation for acute or chronic rejection (4) (n = 18), CyA toxicity (n = 5), or viral hepatitis (n = 2). Two of the asymptomatic patients have subsequently been completely weaned from all immunosuppressive drugs for 6 to 8 months without experiencing rejection.

Histopathologic Studies

All patients were followed until June 1, 1993, and any biopsy or failed allograft in these patients after more than 5 years survival with the same liver and before June 1, 1993, was reviewed. Six allograft hepatectomy specimens and 106 needle biopsies were obtained between 5 and 18 years after transplantation. The slides were reviewed together by two of the authors (O.P., A.J.D.) in a systematic fashion without knowledge of the indication for biopsy, liver injury tests, viral serologic data, clinical events, or original disease. The histopathologic features listed in Table 2 were assessed, the results recorded, and a histopathologic diagnosis(es) rendered. When more than one diagnosis was given, they were listed in order of importance, with the one perceived to be the most significant listed first. A chi-squared exact test was used to compare the frequency of histopathologic findings between two different groups: The first comparison was between symptomatic and asymptomatic patients the second between seronegative patients and those who were either hepatitis B surface antigen positive (HBsAg) or anti-HCV-positive using second-generation recombinant immunoblot (RIBA) assays.

Clinicopathologic Determination of Cause of Allograft Dysfunction

The original diagnosis was based only on the observed histopathologic parameters. The final retrospective diagnosis(es) was based on the histopathologic findings and the clinical profile, serologic data, and, if given, response to therapy, including follow-up biopsies. All patients had at least 6 months of follow-up after the index biopsy, and post-transplant serologic studies for HBV and HCV were available in 59 of 65 patients.

RESULTS

Clinicopathologic Events Before 5 Years after Transplantation

At the time of study, the primary liver allograft was in place for more than 5 years in 42 of 51 (82%) of the symptomatic patients and in all of the asymptomatic patients. The second allograft in six of 51 (12%) or the third allograft in three of 51 (6%) had functioned for more than 5 years in the remaining symptomatic patients. The causes of previous allograft failure(s) in the nine symptomatic patients who had nonprimary allografts in place for more than 5 years included acute rejection (n = 4), chronic rejection (n = 2), primary dysfunction (n = 2), and a massive biopsy-induced subcapsular hematoma (n = 1). Three of these patients required a third liver allograft because of chronic rejection (n = 2) and a combination of

ischemic injury and severe cytomegalovirus hepatitis (n = 1). All patients in both groups experienced at least one episode (range, 1–5; mean, 2 ± 1) of histopathologically documented acute rejection in the studied allograft within the first 5 years after transplantation.

The following other significant events were noted during the first 5 years of follow-up in these patients: 18 of the symptomatic and one asymptomatic patient required reconstruction and/or balloon dilatation of the biliary tree for strictures or obstruction; three symptomatic patients developed end-stage kidney disease because of cyclosporine toxicity and underwent renal transplantation; two other symptomatic patients developed an Epstein-Barr virus-related lymphoproliferative disorder, one of which resolved and the other evolved into Hodgkin's disease (28), which was successfully treated with a MOPP regimen of chemotherapy.

Patient and Allograft Survival after 5 Years

All but two of the symptomatic patients are currently alive 5 to 18 years after transplantation. One died from sepsis and multiorgan failure while awaiting hepatic retransplantation, 2,275 days after her first liver allograft had been destroyed by hepatic artery thrombosis and subsequent sepsis. The second patient died of bleeding esophageal varices 6,631 days after his first allograft became cirrhotic because of recurrent chronic HCV infection. All of the asymptomatic patients are alive with their original allograft an average of 9.9 years (range, 5–16 years) after transplantation.

Six failed allografts were removed at the time of hepatic retransplantation from the symptomatic group of patients at 6 to 10 years of survival with the same liver (mean, 7 years). Chronic rejection was the insult solely responsible for allograft failure in three of the patients, two of whom also had superimposed hepatic artery thrombosis. In one other patient, both chronic rejection and hepatitis B contributed to allograft failure. Changes suggestive of recurrent primary sclerosing cholangitis were seen in one (see below), and a combination of chronic HCV hepatitis and portal vein thrombosis destroyed the allograft in the final patient.

Signs and Symptoms of Late Liver Allograft Dysfunction

In most recipients, monitoring of liver allograft function included bimonthly tests for biochemical evidence of liver injury, yearly viral hepatitis serology screens, and yearly physical exams. The most common sign of late liver allograft dysfunction was an elevation of the liver injury test above baseline values for that patient, which included (a) jaundice or total bilirubin higher than 2 mg/dl; (b) increased canalicular enzymes (alkaline phosphatase [ALP] and gamma-glutamyltranspeptidase [γ -GTP]) or transaminases greater than 50% over the lowest value in the preceding month. In total, 19 of 51 (37%) of the patients who had indicated biopsies also had at least one of the following symptoms: fever (5 of 51; 10%); abdominal pain, nausea, vomiting, or loss of appetite (nine of 51; 18%); or jaundice (seven of 51; 14%). In the sicker patients, the presenting symptoms at the time of biopsy included gastrointestinal bleeding (two of 51; 4%) and confusion and lethargy (four of 51; 8%).

Histopathologic Findings

Piecemeal necrosis, bile duct loss, thickened plates, lobular disarray, hepatocyte necrosis, lobular inflammation, Kupffer's cell hypertrophy, and cholestasis (Table 2) were the histopathologic changes present in a higher incidence in biopsies from the symptomatic patients ($p < 0.002$) compared with biopsies from the asymptomatic patients. The changes present in a higher incidence in biopsies from HBV or HCV seropositive patients than in seronegative patients included piecemeal necrosis, bridging fibrosis, bile duct inflammation

or damage and lobular disarray, hepatocyte necrosis, lobular inflammation, and Kupffer's cell hypertrophy (Table 2).

In general, the portal inflammation tended to be slightly more intense in the symptomatic patients but in both groups consisted of lymphocytes, macrophages, and fewer plasma cells. Eosinophils were much less common than early after transplantation, being present in two of 14 (14%) of asymptomatic and six of 51 (12%) of the symptomatic patients.

Clinicopathologic Diagnosis of Late Dysfunction

The final retrospective diagnosis showed that viral hepatitis and recurrence of the original disease accounted for 47% of the episodes of allograft dysfunction occurring more than 5 years after transplantation (Table 3). In another 13 of 51 (25%) symptomatic patients, the clinical and pathologic findings were minimal, and no specific diagnosis was given. Acute cellular or chronic rejection accounted for 22% of late dysfunction syndromes, although another 16% of patients were thought to have acute cellular rejection as a secondary diagnosis. The remaining three (6%) patients had obstructive cholangiopathy. The results of the liver injury tests obtained at the time of biopsy, segregated according to the primary final clinicopathologic diagnosis, are shown in Table 4. The clinical and pathologic features of each of the causes of dysfunction are discussed in greater detail below.

Rejection—Acute rejection was the primary pathologic diagnosis in two of 51 (4%) patients and the secondary diagnosis in eight of 51 (16%) others, all of whom were from the symptomatic group and showed non-selective, concomitant elevations of liver injury tests (Table 4). The histopathologic characteristics were similar to those seen early after transplantation and included a predominantly mononuclear but mixed portal inflammatory infiltrate, with bile duct damage or central vein phlebitis (Fig. 1). Subendothelial inflammation of portal or central veins was not observed, and periportal hepatocellular necrosis, spotty hepatocyte necrosis, and lobular regenerative activity were more prominent than in acute rejection seen early after transplantation (personal observation, Fig. 1). Lobular disarray as a manifestation of acute rejection alone was distinctly unusual. The primary diagnosis in the eight patients with acute rejection as a secondary diagnosis was chronic rejection ($n = 3$; see below), chronic hepatitis ($n = 4$; two HCV, two non-A, non-B, non-C), and minimal change ($n = 1$).

Chronic rejection was the primary histopathologic diagnosis in nine of 51 (18%) patients, all of whom were symptomatic, usually because of a preferential elevation of γ -GTP and alkaline phosphatase (Table 4). One patient also had cholangiographic evidence of intrahepatic biliary tract strictures. Histopathologic changes included mild chronic portal inflammation, hyalinization of the portal tract connective tissue, bile duct loss in more than 25% of the triads, and other biliary epithelial cell alterations, including eosinophilic transformation of the cytoplasm, an increased nuclear:cytoplasmic ratio because of nuclear enlargement, uneven spacing of the nuclei, and change from a dense nuclear chromatin pattern to an open, reticular chromatin profile with the appearance of nucleoli. In the lobules, mild spotty lobular necrosis without significant lobular disarray, mild mixed sinusoidal inflammation, sinusoidal foam cell clusters ($n = 3$). Kupffer's cell hypertrophy ($n = 9$), cholestasis ($n = 4$), and steatosis ($n = 2$) were present.

Follow-up of both patients with a primary diagnosis of acute rejection showed that treatment with increased immunosuppression resulted in improved liver injury tests and decreased liver allograft inflammation on rebiopsy. Of those with a secondary diagnosis of acute rejection ($n = 8$), two required retransplantation because of chronic rejection, one improved clinically and biochemically after a switch to FK506, but a background of chronic rejection persisted, and one improved after treatment with corticosteroids. Two patients with a

primary diagnosis of hepatitis but a secondary diagnosis of acute rejection biochemically responded to increased immunosuppression. One spontaneously improved and another improved after interferon treatment.

Three of the nine patients with chronic rejection showed stable or improved liver injury tests after a switch to FK506. One patient developed intrahepatic bile duct strictures, one has stable elevation of liver injury tests, one required retransplantation because of chronic rejection, one noncompliant patient has shown worsening of liver injury tests, and three remaining patients were accounted for above.

Biliary tract complications—Obstructive cholangiopathy was the primary diagnosis in five patients, three of whom were symptomatic. One of the asymptomatic patients had a long history of biliary tract anastomotic strictures. As expected, the liver injury tests in this group of patients showed a profile similar to chronic rejection, with a preferential concomitant elevation of the “canalicular” enzymes ALP and γ -GTP, which were three times or more than the minimally elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Table 4).

The histopathologic changes in this group of patients was similar or identical to those seen in nonallografted livers with bile duct obstruction or stricturing. The diagnosis was confirmed by cholangiography in all patients, three of whom were successfully treated with operative reconstruction or balloon dilatation of the biliary tree or both.

Viral hepatitis—Definite or presumed chronic viral hepatitis was the primary diagnosis in 17 symptomatic patients and one asymptomatic patient, four of whom also had coexistent acute rejection as a secondary diagnosis. In 11 of these patients, the viral disease in the allograft represented a recurrence of the original disease: two had HBV, seven HCV, and two were presumed to be non-A, non-B, non-C, because the same histopathologic findings were present in the original liver, and HBV, HCV and autoantibody serologic studies were negative. Seven cases represented de novo hepatitis; one patient had HBV, two HCV, and four were presumed to have non-A, non-B, non-C because of the histopathologic findings (see below) and lack of a sustained response to increased immunosuppression therapy.

Liver injury tests in this group of patients showed minimal to marked but nonspecific elevations of both hepatocellular (ALT and AST) and canalicular (ALP and γ -GTP) enzymes. When the patients with coexistent acute rejection were excluded, there was less of an increase in the canalicular enzymes.

Histopathologic changes included chronic portal inflammation, often with formation of lymphoid nodules, damage of only an occasional bile duct, no bile duct loss, minimal to marked piecemeal necrosis, minimal to moderate lobular disarray, inflammation, periportal or midzonal predominant macrovesicular steatosis, hepatocyte necrosis, and lobular regenerative changes (Fig. 2). Significant portal fibrosis was present in 11 of the patients, eight of whom showed focal portal–portal or portal–central bridging.

Seven of the patients with hepatitis were placed on α -interferon (α -IFN), five of whom experienced clinical and biochemical improvement within 6 months of beginning therapy. However, one other patient treated with α -IFN died from variceal hemorrhaging, and the last patient required hepatic retransplantation because of recurrent HBV-induced cirrhosis complicated by chronic rejection. Follow-up in the 11 remaining patients not treated with α -IFN showed that after lowering immunosuppression three patients developed rejection (see above). One other patient developed bile duct strictures requiring balloon dilatation, and one lost his allograft because of recurrent HCV and portal vein thrombosis. Two patients

spontaneously improved without therapeutic intervention, one of whom serologically cleared HBsAg, which had been present for at least 3 years after transplantation. Three other patients showed chronic viral hepatitis with persistent low-grade activity, whereas one progressively deteriorated because of hepatitis. The remaining patient was lost to follow-up.

Minimal chronic changes, not otherwise specified—There were 22 (13 symptomatic, nine asymptomatic) patients in whom the biopsy findings were minimal and could not be classified into a specific histopathologic diagnosis. All but two were seronegative for HBV and HCV infection. Although this group of patients had normal, or only mildly abnormal, liver injury tests, relatively subtle changes in their biopsies could be used to distinguish them from liver biopsies obtained from age-matched normal controls, even when the pathologists were blinded as to the origin of the slides.

A slight increase in mononuclear portal or perivenular inflammation was present in 15 of 22 (68%), and portal arterial and arteriolar mural myocyte hypertrophy/hyperplasia and hyalinization in 12 of 22 (55%) (Fig. 3). Mild and more subtle intralobular regenerative activity was identified in 18 of 22 (82%) patients, characterized mostly by thickening of the plates (Fig. 4). Biliary epithelial cell alterations, similar to, but not as advanced as those described for chronic rejection, were seen in 11 of 22 (50%) patients. In one of 22 patients (5%), more abnormal biliary epithelial alterations and portal inflammation were present, eliciting a secondary diagnosis of acute rejection.

Two biopsies from the clinically well patients with negative viral serologic studies and normal liver injury tests contained focally dense lymphocytic infiltrates without any evidence of bile duct injury or piecemeal necrosis. No specific therapeutic intervention was undertaken in this group of patients, and allograft function remained stable and good for at least 6 months after the biopsy.

Recurrence of Original Disease

Recrudescence of a chronic viral hepatitis was the most common recurrent disease, being responsible for 11 of 18 (61%) cases, all of whom were just described above in detail. Four patients had recurrent alcoholic liver disease, one probable autoimmune chronic active hepatitis, and one granulomatous hepatitis (not otherwise specified). Two patients were suspected of developing reappearance of primary sclerosing cholangitis and one primary biliary cirrhosis. Unfortunately, the design of this study did not afford the opportunity to assess the true incidence of recurrent disease. The histopathology and clinicopathologic correlations for each of these disorders are given in more detail below.

Alcoholic liver disease—Alcoholic relapse was strongly suspected as the primary cause of the liver histopathology in three symptomatic and one asymptomatic patient from the seven total who underwent transplantation for this indication. They all were seronegative for HBV or HCV virus infection, and there was no other apparent explanation for the biopsy findings detailed below. Liver injury tests in this group of patients showed a selective rise in γ -GTP without a concomitant increase in ALP (Table 4). However, the ALT:AST ratio was approximately 1. Two of the four patients denied alcohol abuse, although one had blood alcohol levels of 98 mg/dl at the time of hospitalization. The other patient experienced fluctuating levels of γ -GTP between 150 and 420 IU/L without apparent cause, which spontaneously declined during hospitalization without specific intervention. The remaining two patients admitted to recidivism.

The biopsy histopathology typical of three of four patients is shown in Fig. 5. One patient also showed focal portal-central bridging fibrosis with early regenerative micronodularity, Mallory's hyaline, and megamitochondria.

Primary biliary cirrhosis—Probable recurrent primary biliary cirrhosis was diagnosed in a 60-year-old woman who was one of 16 (6%) patients who underwent transplantation for this indication and shared one HLA B and one HLA DR locus with the female donor. The diagnosis was based largely on hepatic histopathology (Fig. 6), as the liver injury tests were only transiently abnormal. Normal cholangiographic studies, primary biliary cirrhosis in the original liver, and the exclusion of acid-fast bacteria, fungal infection, or drug reactions was then used to further substantiate the diagnosis. Serologic studies for antimitochondrial antibodies were presumed to be positive and were not repeated because of the previously reported near universal reevaluation of this disease marker in PBC patients (7). The mildly abnormal liver injury tests spontaneously returned to normal shortly after biopsy and have remained so for more than 2 years.

Primary sclerosing cholangitis—Recurrence of primary sclerosing cholangitis was first suspected 5 to 6 years after transplantation in two of six (33%) patients, both of whom also had a history of ulcerative colitis. One patient had a total colectomy before liver transplantation, and colitis remained active up to the present time in the other patient. Both patients had ABO identical donors, negative lymphocytotoxic crossmatch results, and an “obstructive” liver enzyme profile at presentation. There was no obvious technical or mechanical explanation for the strictures observed on cholangiographic studies, but neither case was felt to be radiographically “classic” for primary sclerosing cholangitis.

The liver biopsies showed changes suggestive of obstructive cholangiopathy, including mild portal expansion because of mild portal fibrosis and acute and chronic pericholangitis. The biliary epithelium showed atrophic changes with eosinophilic transformation of the cytoplasm. One of these patients, who was suspected of being noncompliant, eventually required hepatic retransplantation after 7 years (Fig. 7).

Granulomatous hepatitis—A 44-year-old man with negative viral hepatitis and autoantibody serologic studies was asymptomatic when a liver biopsy obtained 9 years after transplantation showed portal fibrosis and two portal-based and several noncaseating intralobular granulomas without bile duct involvement or loss. The original liver showed mixed micronodular and macronodular cirrhosis with numerous noncaseating granulomas. No microorganisms could be identified with special stains in either the native liver or the hepatic allograft biopsy specimen. Ultimately, no specific cause of the granulomatous hepatitis could be found, and the case was classified as recurrent granulomatous hepatitis, not otherwise specified.

Autoimmune chronic active hepatitis—Late dysfunction was attributed to recurrent autoimmune chronic active hepatitis in a 44-year-old HLA B8 and DR3 positive man who was negative for serologic evidence of HBV but positive for antinuclear antibodies both before and after transplantation. The donor organ was matched for these disease-associated HLA antigens, and a liver biopsy obtained 11 years after transplantation showed chronic portal inflammation with a prominent plasmacytic component and active piecemeal necrosis without significant bile duct damage and no bile duct loss. However, antibodies to the HCV were detected 2 years after the biopsy was obtained. The final diagnosis was recurrent autoimmune and chronic HCV infection.

Prospective Versus Retrospective Diagnosis

In 11 of 65 (17%) cases, the final retrospective diagnosis was different from the original diagnosis. In three cases, an original diagnosis of mild acute rejection was changed to viral hepatitis because of positive serologic studies and lack of a sustained response to additional steroid therapy. In one case, the converse was true; that is, an original diagnosis of hepatitis

was changed to acute rejection. However, even in retrospect, in some cases the distinction between hepatitis and acute or even early chronic rejection was less than certain. In three cases the original descriptive diagnoses were replaced by firm diagnoses of disease recurrence: alcoholic (n = 2) and granulomatous hepatitis, NOS (n = 1). In two cases the possibility of both chronic rejection and biliary strictures was originally raised; later, evidence of chronic rejection could not be substantiated, and the patient had primary sclerosing cirrhosis as an original disease. In one case, it was difficult to determine whether recurrent HCV or recurrent alcohol abuse was primarily responsible for dysfunction. Finally, an original diagnosis of hepatitis was replaced by one of obstructive cholangiopathy.

DISCUSSION

The most common indication for liver allograft biopsy in patients who survive longer than 5 years with the same organ is elevated liver injury tests; 37% of patients present with physical symptoms. The histopathologic changes in this patient population can be attributed to viral hepatitis or recurrent original disease 47% of the time, whereas acute and chronic rejection together account for only 22% of allograft dysfunction episodes, which is much different than early after transplantation. Evolution of the causes of dysfunction over time can be explained by the early manifestation of operative or preservation-related injuries and the dynamic nature of the immunologic interface between the liver allograft and the recipient (8,41).

Our findings are quite similar to those of Nakhleh et al. (27), who studied liver allograft biopsies taken from recipients in the cyclosporine era who had survived an average of 3 to 4 years after transplantation. Porter (33), working with Starzl (42,43), did much of the pioneering work in liver transplant pathology and reported more chronic rejection and less hepatitis in a group of pediatric and adult patients from the precyclosporine era. Hubscher et al. (22) and Eid (13), on the other hand, reported less rejection and more normal or minimally abnormal biopsies in a relatively large series of patients who had survived a median of 18 months and 12 months after transplantation, respectively. Differences in the profile of original diseases in the recipient populations, immunosuppressive regimens, and study designs make it impossible to compare results directly, but more protocol biopsies in both of the latter series and identification of patients with “isolated ductopenia” by Hubscher (22) probably account for these seemingly small disparities.

The syndromes resulting in late liver allograft dysfunction frequently have overlapping histopathologic features; mononuclear or mixed portal inflammation with varying degrees of bile duct damage and piecemeal necrosis can be found in acute and chronic rejection, primary biliary cirrhosis, chronic viral and autoimmune hepatitis. Such changes, when mild, may even be nonspecific, but, in general, when the portal inflammation is mixed and associated with damage of more than an occasional bile duct, and there is mononuclear infiltration in and around the connective tissue sheath of the terminal hepatic venules, a diagnosis of rejection is favored. Conversely, nodular portal lymphoid aggregates or portal inflammation associated with damage of only an occasional bile duct, lymphoplasmacytic portal inflammation directed at periportal hepatocytes (piecemeal necrosis), and lobular disarray and lobular inflammation are features that favor a diagnosis of hepatitis. The usefulness of this paradigm is supported by previous studies (5) and the correlation between the “blind” histopathologic readings and the serologic tests for HBV and HCV infection, but the final diagnosis must take into account all of the clinical and laboratory data.

Even so, arriving at that final definitive diagnosis in a long-term liver allograft recipient is even more difficult than early after liver transplantation, and in the end the diagnosis may still be left open to subjective judgment. For example, subendothelial inflammation of the

portal or central veins and portal eosinophilia are fairly reliable rejection-related findings in the first several months. In long-term recipients, portal eosinophils are present in many chronic inflammatory liver diseases and, when present with mild ductular proliferation and adequate immunosuppressive levels, obstructive cholangiopathy should be first excluded. Endotheliitis is less often encountered in long-term survivors with acute rejection and is not encountered at all in chronic rejection (6,10,14,18,21,23,25,27,30,34,38,39,44,46). The portal infiltrate associated with late acute rejection also is often not well confined within the limits of the portal tracts as seen early after transplantation, making separation from chronic viral hepatitis more difficult. Moreover, the presence of a virus or autoantibodies does not provide immunity from rejection (9), and more than one process can simultaneously affect the allograft. Finally, reliance on serologic markers alone for detection of HCV infection may underestimate the total number of infected patients and add to the difficulties.

Liver injury test profiles can assist in the differential diagnosis. Preferential elevation of the “canalicular” enzymes (ALP and γ -GTP) was more frequently associated with chronic rejection and biliary tract obstruction. The four patients with alcoholic relapse showed isolated increases of γ -GTP without a concomitant rise of ALP, similar to alcoholics in the general population. Hepatitis, on the other hand, showed elevation of both ALT/AST and ALP/ γ -GTP, but overlapping rejection and “cholestatic” forms of hepatitis likely contribute this nonspecific pattern of enzyme elevation. It is the authors’ opinion that clinicopathologic correlation, awareness of the original disease, review of previous biopsies, and monitoring the effect of therapeutic intervention(s), in addition to a careful review of the index biopsy, is important in arriving at the correct diagnosis (Table 5). Similar conclusions have been drawn by most investigators studying long-term survivors (3,5,7,13,17,18,19,22,27,29,30,31,35,37). In some instances, empiric increases of immunosuppression and follow-up data may be of value in establishing the diagnosis, and, in fact, supported the validity of our final retrospective diagnosis.

Viral hepatitis types B and C, alcohol-related injury, autoimmune and granulomatous hepatitis (not otherwise specified), and primary biliary cirrhosis appear histopathologically similar or identical to the same diseases in native livers and recur after transplantation. Reappearance of primary sclerosing cholangitis was strongly suspected because we could find no other cause of the biliary cirrhosis and large extrahepatic bile duct inflammation in an allograft that failed after 7 years, even when the gross and histopathologic examination was complete. In contrast to the report by Hubscher et al. (22), who showed a recurrence rate of 16%, and in some cases severe allograft liver injury from primary biliary cirrhosis, the pathologic changes in the single patient in this series was minimal. We remain intrigued by this difference in the reported incidence of primary biliary cirrhosis recurrence and disease severity (7,22,32). It is likely related to the addition of azathioprine or to lower baseline cyclosporin levels (7,22,32).

In 24% of symptomatic patients, no identifiable clinical, serologic, or histopathologic cause of the usually mild dysfunction was found. Biopsies from these patients were, for the most part, indistinguishable from those obtained from the long-term asymptomatic recipients. Frequent monitoring of liver injury tests, combined with a lower biopsy threshold, may account for the relatively high frequency of biopsies with minimal pathologic changes.

In contrast, there were two biopsies from asymptomatic HCV- and HBV-negative patients with normal and stable liver injury tests that contained significant chronic portal inflammation but no detectable tissue damage. It is uncertain whether this represents very indolent chronic non-A, non-B, non-C viral hepatitis, undetected HCV infection, rejection, or an immunologic adaptation of the recipient to the allograft similar to that seen in cardiac (1) (Quilty lesions) and renal (20) allografts. The important message illustrated by such

cases is that mononuclear inflammation alone, in the absence of bile duct, vascular, or hepatocyte damage, can be associated with normal and stable liver allograft function and need not be treated with additional immunosuppression. Therefore, a protocol biopsy before attempting to wean immunosuppressive therapy is strongly encouraged (31,36,41).

Many long-term stable liver allografts develop histopathologic changes that are not otherwise present in age-matched controls, although they are minimal deviations from normal. Possible explanations for the mild lymphocytic inflammation were discussed above: the intrahepatic arteriolar changes can be seen as a result of diabetes, hypertension, and perhaps direct drug-related injury from chronic cyclosporine (11) and corticosteroid therapy. The biliary epithelial cell and mild intralobular regenerative changes were far more subtle, the latter being insufficient for the diagnosis of nodular regenerative hyperplasia, a disorder originally described in patients with autoimmune diseases (2), and later found with increased frequency after anabolic steroid and azathioprine administration (16,24,26). In this series, only 12 of 65 of the patients were maintained on azathioprine, and all were on either low-dose or no corticosteroids. Therefore, immunologically mediated perivenular or sinusoidal endothelial cell injury (45) or other immunologic perturbations in the recipient similar to that seen in autoimmune disorders (8) is a possible cause of the regeneration that cannot be dismissed out of hand.

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FIG. 1.

Acute cellular rejection in a patient who initially was asymptomatic, then developed liver dysfunction as a result of immunosuppressive weaning. The portal tract (PT, inset) and pericentral vein (CV) inflammation and liver injury tests worsened after cyclosporin A steroid withdrawal and improved after restarting treatment.

FIG. 2.

Chronic viral hepatitis type C often appeared histopathologically similar to that seen in nontransplanted livers, as shown here, with lymphoid nodules in the portal triads, piecemeal necrosis, sinusoidal lymphocytosis, mild steatosis, and spotty lobular necrosis. In other cases of hepatitis C virus, the inflammation was mild and neutrophilic predominant, but marked cholangiolar proliferation, more typical of a “cholestatic hepatitis,” was seen.

FIG. 3.

Hepatic arteriolar thickening and hyalinization with intact bile ducts was seen in patients with minimal other changes and was attributed to hypertension, diabetes, or chronic cyclosporin injury, similar to the lesions seen in the kidney.

FIG. 4.

(a) Mild intralobular regenerative activity characterized by thickening of the plates and even focal nodule formation was a frequent but subtle finding in many of the long-term survivors, even in those without symptoms or other pathologic changes. **(b)** A reticulin stain shows the subtle areas of intralobular regenerative change with thickening of the plates.

FIG. 5.

Recurrent alcohol abuse was most frequently (in three of four cases) associated with centrilobular mixed steatosis with “foamy” degeneration of hepatocytes (inset), lobular neutrophil clusters, perivenular and subsinusoidal fibrosis, and Kupffer’s cell iron deposition. One other patient who admitted to alcoholic relapse showed moderate reticuloendothelial iron deposition, portal and sinusoidal fibrosis, but no steatosis. As always, other causes of steatohepatitis should be excluded.

FIG. 6.

This periductal granuloma with minimal duct damage was seen in a biopsy obtained 6 years after transplantation in one of 16 patients whose original disease was primary biliary cirrhosis and in no other patients, regardless of the original disease.

FIG. 7.

Possible recurrent sclerosing cholangitis (with a component of rejection?) was suspected in this failed allograft (1.100 g) removed 7 years after transplantation. **(a)** There was a well-developed biliary-type cirrhosis with decreased bile ducts and deposition of copper-associated protein at the edge of the regenerative nodules (inset), but no classic “fibro-obliterative” duct lesions. **(b)** Sections through the liver hilum showed chronic inflammation of large bile ducts and mural fibrosis but no obliterative arteriopathy.

TABLE 1

Patients and original disease at the time of transplantation

	Asymptomatic	Symptomatic
Female/male	10/4	32/19
Age at time of transplant (yr)	36.6	36.1
Original disease		
Primary biliary cirrhosis	6	10
Cryptogenic cirrhosis	1	8
Alcoholic cirrhosis	1	6
Metabolic diseases ^a	2	5
Chronic hepatitis C virus	2	5
Primary sclerosing cholangitis	0	6
Autoimmune chronic hepatitis	0	4
Chronic hepatitis B virus	0	4
Other	1	3
Fibrolamellar carcinoma	1	
Total no. of patients	14	51

^aTyrosinemia and porphyria (n = 1), α -1-anti-trypsin deficiency (n = 1), Wilson's disease (n = 4), hemochromatosis (n = 1).

TABLE 2

Histopathologic changes categorized by reason for biopsy

	Symptomatic ^a / Asymptomatic	p Value	Sero ^b _± /Sero _—	p value
Portal tract				
Inflammation				
Mild	27/9 ^c	0.80	8/23	0.39
Moderate	21/4		7/17	
Severe	3/1		0/4	
Eosinophilis	6/2	0.80	2/5	1.0
Piecemeal necrosis	19/2	0.12	8/11	0.01
Bridging fibrosis	10/1	0.43	6/4	0.02
Bile duct loss (>25% of triads)	13/1	0.17	4/9	1.0
Subendothelial inflammation	0/0	1.0	0/0	1.0
Bile duct inflammation/damage	40/9	0.31	16/27	0.006
Ductular/cholangiolar proliferation	14/2	0.49	5/9	0.50
Lobule				
Thickened plates	50/11	0.03	15/40	1.0
Disarray	15/1	0.16	11/4	0.0001
Necrosis	21/2	0.11	9/12	0.07
Inflammation	39/2	0.001	12/25	0.13
Kupffer cell hypertrophy	40/4	0.0009	14/26	0.06
Cholestasis	12/1	0.27	3/7	1.0
Fatty change	14/4	1.0	3/14	0.35
Hepatocytes anisonucleosis	19/4	0.75	3/16	0.22
Sinusoidal dilatation	10/3	1.0	1/11	0.15
Iron deposition	2/1	1.0	0/3	0.56
Vascular				
Arteriolar thickening/hyalinization	20/8	0.36	8/18	0.77
Obliterative arteriopathy	4/0	0.57	0/4	0.33
Central vein phlebitis	13/3	1.00	3/13	0.20
Central vein sclerosis	11/1	0.28	4/8	0.72
Total no. of patients	51/14		16/43	

^a Comparison of the histopathologic findings in symptomatic versus asymptomatic patients.^b Comparison of patients who were either seropositive for hepatitis B surface antigen or anti hepatitis C virus to those seronegative for both viruses.^c Most of the portal inflammation in this group was minimal.

TABLE 3

Final retrospective primary clinicopathologic diagnoses in the symptomatic and asymptomatic patients by primary diagnosis

Clinicopathologic diagnosis	No. of patients (%)	
	Symptomatic ^a	Asymptomatic ^b
Acute rejection	2 (4)	0 (0)
Chronic rejection	9 (18)	0 (0)
Obstructive cholangiopathy	3 (6)	2 (14)
Minimal changes, NOS	13 (25)	9 (64)
Viral hepatitis	17 (35)	1 (7)
Hepatitis C virus	9	
Hepatitis B virus	3	
Non-A, non-B, non-C	5	1
Recurrent original disease	18 (35)	2 (14)
Alcoholic	3	1
Primary sclerosing cholangitis	2	
Primary biliary cirrhosis	1	
Autoimmune hepatitis	1	
Granulomatous hepatitis, NOS	1	
Viral hepatitis (see above)	11	

NOS, not otherwise specified.

^a Patients had clinical symptoms or elevated liver injury tests as an indication for biopsy: n = 15.

^b Patients were asymptomatic and had normal or minimally abnormal liver injury tests; biopsies were done by protocol; n = 14.

TABLE 4

Liver injury test listed according to the primary clinicopathologic diagnosis

Diagnosis	TBILI (mg/dl) (nl = 0.3–1.5)	AST (IU/L) (nl ≤ 40)	ALT (IU/L) (nl ≤ 40)	ALP (IU/L) (nl = 40–125)	γ-GTP (IU/L) (nl ≤ 65)
Minimal changes	0.6 ± 0.3 (0.2–1.0)	68 ± 62 (13–264)	100 ± 84 (22–323)	173 ± 114 (74–573)	246 ± 167 (39–947)
Obstructive cholangiopathy	2.4 ± 2.1 (0.8–7.3)	72 ± 25 (43–119)	73 ± 24 (46–292)	331 ± 187 (145–647)	320 ± 167 (119–635)
Chronic hepatitis	1.3 ± 1.4 (0.2–6.8)	204 ± 214 (35–895)	193 ± 242 (30–961)	133 ± 76 (21–239)	237 ± 235 (45–944)
Alcohol injury	0.9 ± 0.2 (0.7–1.2)	99 ± 60 (42–198)	108 ± 62 (56–226)	89 ± 49 (44–156)	375 ± 245 (178–705)
Acute rejection ^a	1.1 ± 0.9 (0.4–3.5)	116 ± 97 (11–314)	90 ± 61 (14–204)	194 ± 263 (39–780)	231 ± 205 (77–628)
Chronic rejection	2.4 ± 2.2 (0.5–9.5)	113 ± 64 (45–229)	184 ± 174 (67–362)	496 ± 360 (178–1192)	736 ± 286 (30–2270)

^a Includes patients with both a primary and secondary diagnosis of acute rejection.

Values represent the mean ± standard deviation.

TABLE 5

Paradigm used for clinicopathologic evaluation of liver biopsies from long-term survivors

	Portal tract findings	Lobular findings	Vascular findings	Liver injury tests	Clinical history
Acute rejection	Mixed inflammation, more than an occasional damaged bile duct, "moth-eaten" limiting plate	Kupfer cell hypertrophy, mild sinusoidal lymphocytosis, minimal to no lobular disarray ± cholestasis	Perivascular inflammation, central subendothelial inflammation	↑ ALT/AST ↑ γGTP/ALP ↑ → TB	Inadequate immunosuppression
Chronic rejection	Minimal/mild inflammation, chronic bile duct changes (see text), bile duct loss, "hyalinization" of connective tissue	Spot necrosis, cholestasis, foam cell clusters; central hepatocyte ballooning/dropout	Foam cell obliterative arteriopathy ^a , perivascular sclerosis, sinusoidal foam cell clusters	↑ γGTP/ALP ↑ AST/ALT ↑ → TB (early) ↑ → TB (late)	Inadequate immunosuppression, chronic rejection in previous graft, acute rejection unresponsive to treatment, positive crossmatch
Obstructive cholangiopathy	Intraepithelial neutrophilic/eosinophilic inflammation, periductal edema, duct/cholangiolar proliferation ± fibrosis	Sinusoidal neutrophil clusters ± cholestasis	None	↑ γGTP/ALP → ↑ AST/ALT ↑ → TB	"Difficult" biliary anastomosis, hepatic artery stenosis/thrombosis original disease; PSC
Viral hepatitis	Mononuclear/mixed inflammation piecemeal necrosis, cholangiolar proliferation, nodular lymphoid aggregates, only occasional damaged bile duct	Spot necrosis, disarray, swelling; steatosis (periportal/midzonal); mononuclear inflammation/Kupfer's cell hypertrophy	None	↑ ALT/AST → γGTP/ALP ↑ γGTP/ALP in cholestatic form	Original disease; HCV, HBV, cryptogenic, autoimmune cirrhosis; positive HCV, HBV serologic/PCR tests; biochemical response to α-interferon therapy
Alcohol abuse ^b	± Mononuclear/mixed inflammation	Mixed steatosis (central predominant), "acute foamy degeneration" of hepatocytes, + Kupfer's cells iron deposition	Perivascular sclerosis, sinusoidal fibrosis	↑ γGTP, → ALP ↑ → AST/ALT ↑ → TB	Original disease: alcohol abuse; improved liver injury test on hospitalization w/o intervention: positive blood alcohol test; R/O other causes of steatohepatitis
Primary biliary cirrhosis (15,22,29)	Mononuclear inflammation, noncaseating granulomas, bile duct damage/loss, cholangiolar proliferation	Kupfer's cell hypertrophy/granuloma, mild inflammation, periportal copper deposition (late)	+/- Focal arterial thickening	↑ γGTP/ALP ↑ → ALT/AST → TB	Original disease; PBC R/O other causes of granulomas

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; γ-GTP, gamma glutamyl transpeptidase; TB, total bilirubin; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; HCV, hepatitis C virus; HBV, hepatitis B virus; PCR, polymerase chain reaction; R/O, rule out.

^aUncommonly detected in needle biopsies.

^bOther causes of nonalcoholic steatohepatitis, if present, should be excluded.