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Recurrence of Disease after Liver Transplantation

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Recurrent hepatitis B and C is common following liver transplantation. Autoimmune disease manifests as primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. Metabolic diseases, such as hemochromatosis, Wilson's disease, amyloidosis, and alcoholic liver disease (ALD) also recur. Recurrent malignancy also is reported. Liver transplantation is potentially curative in a subset of patients with hepatocellular carcinoma (HCC) with a small tumor burden. Survival after transplantation is 53%-72% after 1 year and 17%-25% after 5 years. Many cases of cryptogenic cirrhosis are due to clandestine NASH.

Keywords: liver transplantation; cirrhosis; hepatitis

Recurrence of disease following liver transplantation remains a problem for the long-term survivor in several indications and may affect graft function and survival. It does, however, provide useful information about the pathogenesis of the underlying disease process.

Hepatitis C Virus Infection

Incidence and Prevalence:

- Graft infection with hepatitis C virus (HCV) is universal.
- 100% of patients have persistence of HCV RNA after transplantation.
- Serum HCV RNA levels decrease during surgery, both when the recipient native liver is removed and when the donor organ is reperfused. Afterward, the concentrations of circulating HCV RNA increase as early as day 3 posttransplantation and the levels at 1-3 months are greater than pretransplant levels.
- An acute hepatic syndrome occurs in many HCV-infected patients in the first 4 months post-OLT. It may be difficult to distinguish HCV recurrence from acute cellular rejection or a combination of the two.

- Chronic hepatitis is found in 50% of patients at 2 years and 70% at 4 years.
- The prevalence of hepatic cirrhosis in graft recipients at 5 years is at least 10%.
- Up to 10% of HCV-infected recipients develop a cholestatic syndrome associated with ballooning degeneration of hepatocytes, which has been called "fibrosing cholestatic hepatitis." It occurs in the first year and is associated with very high circulating HCV RNA levels. It has a poor prognosis.

Investigation of HCV after Liver Transplantation:

- Biochemical profile
- HCV RNA levels in serum
- Liver biopsy

Many factors have been associated with the severity of recurrent disease (see Table 1).

Treatment of Recurrent HCV

Pretransplant Therapy

- Treatment of the recipient in anticipation of liver transplantation. The difficulty is achieving an adequate viral response on account of

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Table 1 | RISK FACTORS FOR RECURRENT HCV HEPATITIS

Highly probable risk factors:

High levels of immunosuppression. Data implicate use of OKT3 and pulse corticosteroids. Data on choice of calcineurin inhibitor or the effect of MMF are unclear

Age of donor liver

Retransplantation

Putative risk factors for which data are uncertain:

HCV genotype 1

CMV infection

HLA match

Acute cellular rejection

MHC donor/recipient match

Ethnicity

Recipient of a live donor hepatic graft

the intolerance of patients with cirrhosis for combination antiviral therapy.

Posttransplant Therapy

- Interferon and ribavirin

The unwanted effects of therapy have hampered attempts at treatment in the first few weeks after transplant.

Early Therapy (First 6 Months after Transplantation)

- Occasional patients have eradicated the virus with combination therapy using interferon alfa 2b and ribavirin. This should be confined to investigational studies.

Late Therapy (> 6 Months after Transplantation)

- Viral eradication has been recorded in 20% of patients receiving combination interferon alfa 2b and ribavirin. Dose reductions of either agent have been required in many patients.

Prognosis:

- Initial data suggested that graft survival at 5 years was no different than in other indications; however, more complete recent studies suggest that graft and patient survival are reduced.

Hepatitis B Virus Infection

Incidence and Prevalence:

- The early experience of liver transplantation for chronic HBV infection highlighted a significant adverse effect of infection on graft and patient survival. Aggressive reinfection and progression to cirrhosis and subacute graft failure were almost universal; the overall outcome was inferior to other etiologies. HBV infection presenting as FHF had a better prognosis for posttransplant hepatitis on account of the low level of pretransplant HBV DNA.

Investigation of Recurrence:

- Biochemical profile
- HBsAg and Anti-HBs titer
- HBV DNA
- Liver biopsy

Risk Factors for Recurrent HBV Hepatitis:

- Evidence of active viral replication as shown by pretransplant serum HBV DNA levels and/or HBeAg status

The role of vaccination against HBV in this population is controversial.

- Prophylaxis against infection
- All candidates who are actively replicating HBV should receive lamivudine pretransplant.
- Posttransplant: patients should receive hepatitis B immunoglobulin (HBIG). Many centers

PBC

Primary biliary cirrhosis

combine HBIg with lamivudine. The dose, mode of administration, and duration of treatment with HBIg is uncertain. Some centers titrate the dose of HBIg to maintain levels of circulating anti-HBs > 100 IU/ml. The main side effect of i.v. HBIg is severe back and chest pain.

- Posttransplant treatment of recurrent HBV graft hepatitis
 - Lamivudine has allowed effective transplantation of patients who are HBV DNA-positive, although reinfection has occurred in a minority of patients following the emergence of lamivudine resistance (YMDD mutations).
 - Other strategies being evaluated include the use of other antiviral drugs, such as adefovir, tenofovir, and entecavir, and HBV vaccination.

Hepatitis D Virus Infection

HDV is a rare cause of liver failure leading to transplantation. Treatment strategies are the same as for HBV.

Hepatitis A Virus Infection

Anecdotal reports of patients transplanted for fulminant HAV show infection of the graft may occur, but it is of little clinical significance.

Autoimmune Disease

Primary Biliary Cirrhosis

Incidence and Prevalence:

- Following transplantation, antimitochondrial antibodies remain positive in 72%-100% of cases; however, the persistence of these antibodies does not indicate recurrent disease.
- Diagnosis of recurrent PBC is made on histological appearances.
- Follow-up studies suggest that PBC may affect up to 20%-40% of recipients at 10 years after transplantation.
- Recurrence of PBC does not appear to affect allograft or patient survival.

PSC

Primary sclerosing cholangitis

Investigation of Recurrence:

- Biochemical markers, such as serum alkaline phosphatase, have a low sensitivity and specificity.
- Serum IgM levels fall immediately after transplantation; they rise again in some patients with recurrence.
- Histologically, there is overlap between PBC recurrence, chronic rejection, and chronic HCV infection in the graft.
- Granulomatous destruction of bile ducts is considered pathognomonic.

Risk Factors

There are suggestions that the type of immunosuppression may influence the incidence of disease prevalence. In particular, there may be an increased susceptibility to recurrence with tacrolimus immunosuppression.

Treatment of Recurrent PBC

The same principles may apply as pretransplantation; ursodeoxycholic acid is usually prescribed, albeit without definitive data on its effect.

Prognosis:

- Long-term follow-up data are awaited.
- There seems to be little adverse effect on graft function, and the majority of patients are asymptomatic.

Primary Sclerosing Cholangitis

Most patients transplanted for PSC have a cholecystojejunostomy with a Roux loop. Differentiation of recurrent PSC from secondary sclerosing cholangitis may be difficult in the transplant setting.

Incidence and Prevalence:

- Possibly 20% of graft recipients

Investigation of Recurrence:

- Differentiation between primary sclerosing cholangitis and the onset of secondary sclerosing cholangitis may be difficult.
- Imaging of biliary tree (MRCP or PTC).

Table 2 | METABOLIC DISEASES CURED BY LIVER TRANSPLANTATION

Associated with Liver Damage:

Wilson's disease

 α 1-anti-trypsin disease

tyrosinemia

Crigler-Najjar syndrome

Byler's disease

Not associated with liver damage:

primary oxaluria

amyloidosis

primary hypercholesterolemia

- Liver biopsy may show characteristic “onion skin” fibrosis around interlobular bile ducts.

Prognosis:

- Long-term follow-up data are awaited.

Autoimmune Hepatitis (AIH)

The distinction between graft hepatitis and recurrent AIH is difficult; there are no unequivocal criteria for the diagnosis of recurrent AIH. Therefore, the literature on this topic is confusing.

Incidence and Prevalence:

- There is graft recurrence of AIH in between 10% and 60% of recipients.
- De novo graft AIH also occurs in a small proportion of patients.
- Acute rejection in patients transplanted for AIH occurs in upwards of 80% of individuals, but its prognostic significance is uncertain.

Risk Factors:

- Low-maintenance immunosuppressive regimes
- Absence of azathioprine
- The role of HLA matching is conflicting

Treatment of Recurrent AIH:

- Many programs maintain long-term corticosteroid therapy in low doses (< 10 mg per day).
- Prevention of recurrent AIH is possible if patients are maintained on a small dose of prednisolone after transplantation (5-10 mg), although immunosuppression should be tapered

to the minimum tolerated regimen for each patient. This requires close supervision and regular liver biopsies.

Prognosis:

- Long-term follow-up data are awaited.

Metabolic Diseases

Recurrence of the original disease, both hepatic and extrahepatic, depends on both the location of the primary metabolic defect and its target organs. Transplantation “cures” the patient for those metabolic diseases in which the primary defect resides in the hepatocyte itself. These include metabolic disorders in which the liver is damaged, and those disorders in which liver function remains intact but which are associated with severe damage to other organs (see Table 2). In the latter group, the recipient “explanted” liver may be perfectly healthy except for the single metabolic defect. Occasionally these explants have then been used to provide a liver graft to another recipient in whom the metabolic defect is not of immediate concern. This has been called “the domino procedure.”

Other metabolic diseases are associated with a more generalized metabolic defect and the original disease may recur. Examples include hemochromatosis, Niemann-Pick disease, Gaucher's disease, cystic fibrosis, and protoporphyria.

Hemochromatosis

- Defect in hemochromatosis is dysregulation of iron absorption in the enterocyte.
- Hepatic iron reaccumulation occurs after transplant, but long-term follow-up is needed

AIH

Autoimmune hepatitis

to establish the rate and risk for hepatic iron reaccumulation in allograft.

- There have been no reports of graft failure attributed to iron overload.
- Patient survival after transplant in patients with hemochromatosis is less than for other forms of cirrhosis. This phenomenon appears to be related to cardiac and infectious complications and may also be related to lack of pre-transplant diagnosis and treatment. Several reports have suggested that iron depletion prior to transplant can improve postoperative survival.

Clinical Approach:

- Monitor serum ferritin and iron saturation in these patients on an annual basis.
- Consider venesection if there is evidence of excessive iron overload.

There have been several reports of patients who inadvertently received livers from donors with hemochromatosis. In the short term, these recipients have shown a progressive and rapid reduction in hepatic iron concentration over time.

Wilson's Disease (WD)

- Liver transplantation does not always completely reverse the nervous system complications associated with WD but significant improvements are often seen.
- Liver transplantation does not fully correct copper kinetic measurements to normal, although it does result in normalization of serum copper and ceruloplasmin.
- Transplantation converts the response to one similar to that found in a heterozygote for WD.
- Despite incomplete metabolic normalization, transplantation effectively cures the patient as the heterozygote state is not associated with clinical disease.

Amyloidosis

- Transthyretin amyloidosis is a group of hereditary, often fatal, systemic disorders caused by mutant TTR.

- Familial amyloidotic polyneuropathy is the commonest hereditary form and is a systemic disease that most seriously affects the heart, kidneys, and eyes.
- Although hepatic amyloidosis is common, clinically significant liver failure is rare.
- Liver transplantation replaces mutated with donor wild-type TTR and halts amyloid production and further systemic amyloid deposition. After transplant, improvement in extra-hepatic symptoms may occur, especially in gastrointestinal disturbances. Liver transplant may prevent further decline and the onset of new complications.
- Survival after transplantation is determined by disease duration, hereditary and geographic factors, nutritional status, gastrointestinal and cardiac involvement. Five-year survival of 75% has been reported.

Alcoholic Liver Disease (ALD)

Survival rates after liver transplantation are similar among alcoholics and nonalcoholics, at least in the short and intermediate term. Long-term follow-up data are needed.

Incidence:

- Up to 30% adult recipients are affected by alcohol addiction.
- A return to alcohol use within 5 years of transplantation is seen in up to 50% of those grafted for ALD.
- A return to alcohol consumption is usually seen in the first year.
- Drinking to excess is reported in up to 10% of alcoholic liver transplant recipients within 5 years.
- Graft injury, due to alcohol excess, is rare.
- Other medical problems, such as infection, pancreatitis, and alcohol withdrawal occur in these recipients who relapse to abusive drinking.

Risk Factors:

- It is difficult to identify those patients who are at risk of relapse.

ALD

Alcoholic liver disease

- The period of abstinence prior to transplant is an insensitive prognostic indicator for alcoholic relapse.

Therapy:

- The efficacy of alcoholism therapy in post-transplant patients is unproven, but all such patients should be offered support and therapy.

Malignancy

Hepatocellular Carcinoma (HCC)

Liver transplantation is potentially curative in a subset of patients with HCC with a small tumor burden

Incidence:

- Initial series described a very high tumor recurrence rate, but the majority included patients with advanced HCC. Recurrence is negligible if the criteria outlined in the article by Michael R. Lucey, "Assessment for Liver Transplantation" (see this issue), are met, and survival is excellent with a 4-year survival rate of 75%, and rate of recurrence-free survival of 83%.
- Tumor recurrence is usually observed in the liver and less frequently in the lungs. Recurrence has been observed at the site of prior liver biopsy suggesting seeding of tumor along biopsy site tract.
- Therapy of HCC after liver transplantation is ineffective, and the prognosis is poor.

Cholangiocarcinoma

The majority of studies have reported poor survival after transplantation with 1, 2, and 5-year survival ranging from 53% to 72%, 32% to 48%, and 17% to 25%, respectively. The main explanation for poor survival is a high incidence of tumor recurrence. Tumor recurrence occurs early; 85% of recurrences occur within 2 years of transplant. Recurrence is most common in the allograft, followed by lung.

Metastatic Neuroendocrine Tumors

There has been little experience with liver transplantation in secondary hepatic tumors. In contrast

to many other carcinomas, neuroendocrine tumors generally behave less aggressively and have a slower growth rate, and patients with such tumors are more likely to benefit from liver transplantation. Reports have been confined to small numbers of patients and short follow-up.

Despite overall good medium-term survival, tumor recurrence is common (most commonly in liver, followed by bone) and recurrence-free 5-year survival does not exceed 24%. Despite this, transplantation offers relief of symptoms from the neuroendocrine tumors.

Cryptogenic Cirrhosis

- It is clear that many cases of cryptogenic cirrhosis are due to clandestine nonalcoholic steatohepatitis (NASH).
- Recurrence of NASH has been recorded among patients transplanted for NASH.
- No data are available about the long-term consequences of NAFLD or NASH in liver allografts, nor are there data on strategies to prevent fat accumulation.

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HCC

Hepatocellular carcinoma

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