# Common Problems in Liver Transplant Pathology

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Since 1983 liver transplantation (LT) has been confirmed as an appropriate therapy in selected patients with end-stage liver disease (ESLD) by the National Institutes of Health.[1] Advances in organ preservation, surgical techniques, perioperative care, immunosuppression and graft monitoring have improved the outcome of LT. Excellent clinical outcomes have been consistently reported among many institutions worldwide with patient and graft survival rates at 1 year of 85-87% and 83% and at 5 years of 72-73% and 68%.[2-4] All liver explants must be histologically examined in order to assess the etiology and severity of the primary disease indicated for LT. Also the transplanted graft should be monitored clinically and histologic examination may be occasionally necessary. This review aims to overview pathologic perspectives of LT including indications of LT and complications of LT.

## Indications of liver transplantation

Indications for LT in adults can be divided into three main categories: ESLD, acute liver failure and hepatic neoplasms. A few uncommon diseases are also indicated for LT such as failed liver graft, metabolic diseases, Budd-Chiari syndrome, etc.

End-stage liver disease or cirrhosis is the most common indication for LT in adults accounting for more than 70% of cases.[5] Among these cases, the specific etiology of cirrhosis varies among regions. In the Western country, chronic hepatitis C is the commonest etiology of cirrhosis accounting for approximately 35%,[2] while 25% is alcohol-related which is the second commonest etiology.[6,7] In Spain, the two most common etiologies of cirrhosis are alcohol-related (43%) and HCV-related (39%).[3] In the Nordic countries, primary slcerosing cholangitis (PSC) is the most common followed by hepatitis C and alcoholic cirrhosis.[4] Other etiologies such as primary biliary cirrhosis (PBC), non-alcoholic steatohepatitis (NASH), autoimmune hepatitis (AIH), Wilson disease, alpha-1-antitrypsin deficiency, secondary biliary cirrhosis and hemochromatosis have been also indicated. In pediatric population, the commonest indication is cholestatic liver disease (mainly extrahepatic biliary atresia) accounting for 39%, followed by acute liver failure (13%).[8]

## End-stage liver disease (cirrhosis)

Cirrhosis is a common end result of various chronic liver diseases such as chronic viral hepatitis, alcoholic liver disease, autoimmune liver diseases (AIH, PBC, PSC) and NASH. Most of the time, examination of the explanted cirrhotic livers confirms the previous clinical diagnosis. However uncommonly, the examination of the explant livers provide valuable additional information such as incidental hepatocellular carcinoma (HCC) or a specific etiology in cases of "cryptogenic cirrhosis" have been clinically diagnosed. Examination of the explant livers of cryptogenic cirrhosis can provide the specific diagnosis in up to 85%[9] of cases after the thorough pathologic examination. Incidence of the incidental HCC varies according to the underlying condition and has been reported up to 10%.[10] Most of the incidental HCC is solitary small lesions which are cured by transplantation.[11]

The key pathologic finding of cirrhosis is interconnecting fibrous septa subdividing the parenchyma into nodules throughout the entire liver. The fibrous septa may be delicate bands connecting portal tracts and central veins or broad fibrous bands obliterating adjacent lobules into the fibrous bands. The parenchymal nodules created by fibrous septa are islands of hepatic parenchyma which may vary in size from micronodules (less than 3 mm in diameter) to macronodules (3 mm to several centimeters in diameter). The severity of fibrosis may be very variable in some cases,[12,13] especially diseases associated with bile duct damage, for example PBC, PSC, biliary atresia, secondary biliary cirrhosis. The areas of advanced fibrosis can be seen proximate to areas of preserved normal architecture.

## Acute liver failure

Acute liver failure may be caused by various etiologies such as drug intoxication, AIH and idiopathic which result in different pattern of pathology, but in similar degrees of severity. Drug toxicity is a major cause of liver failure in pediatrics;[14] the most common offending drug is acetaminophen. However after thorough pathologic examination identifiable etiology is still not revealed in almost half of the cases.[14]

Distribution of hepatic necrosis in cases of fulminant hepatic failure can be patchy. The necrotic areas showing panacinar necrosis may be seen next to regenerative areas

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revealing intact parenchyma with pronounced cholestasis. This finding well explains the unreliability of liver biopsy in assessing the severity of liver damage in patients with acute hepatic failure requiring LT.[15] Occasionally submassive hepatic necrosis with prominent regenerative nodules reveal in the cases that had been radiographically diagnosed as cirrhosis.

### Hepatocellular carcinoma

In some cases of cirrhosis, hepatocellular carcinoma (HCC) may be incidentally found in the liver explants. The outcome of the patients with small incidental HCC seems to be similar to the cirrhotic patients without HCC. Moreover LT provides similar outcomes in some groups of patients with known HCC selected by Milan criteria[16] to the patients without HCC. Nowadays HCC under certain criteria[16,17] are widely accepted as an indication for LT.

### Complications of liver explants

Complications of liver explants divide into 2 main categories; complications which occurr following LT and recurrences of the primary disease. Common complications following LT include:

1. Liver allograft rejection: acute rejection, chronic rejection
2. Vascular problems: hepatic artery thrombosis
3. Biliary complications: anastomotic complications, non-anastomotic complications

### Liver allograft rejection

Rejection is an immunological response to foreign antigens in the donor organ which is expected to occur in all recipients, but generally is modified by immunosuppressive therapy. In liver transplantation it is important to distinguish between morphologic changes without clinical abnormality (subclinical rejection) and those which are accompanied with clinical graft dysfunction (clinical rejection). This would explain why a protocol biopsy of liver allograft in recipients who have no clinical graft dysfunction has not been recommended in most institutions.

Liver allograft rejection has been divided into three categories based on time of occurrence, pathophysiological mechanisms and clinicopathological features as: hyperacute, acute and chronic rejections.

### Hyperacute (humoral) rejection

Hyperacute or humoral rejection occurs immediately after reperfusion in a recipient harboring performed antidonor antibodies, but clinical presentation in a liver allograft recipient is usually delayed for several hours to a few days. Most cases manifest with severe graft dysfunction including a rapid rise in transaminases, prothrombin time and signs of acute liver failure. The conventional anti T-cell based immunosuppressive therapy usually fails. In severe cases urgent re-transplantation is the only hope.

Pathologic findings show changes of endothelial injury characterized by fibrin deposition in the early phase, then neutrophilic infiltration and coagulative necrosis of hepatocytes or massive hemorrhagic necrosis throughout the liver in severe cases. In clinical practice, liver biopsy is generally contraindicated in most cases due to severe coagulopathy.

### Acute rejection

Acute rejection is the commonest form of liver allograft rejection and occurs early post-transplantation mostly in the first month. Acute rejection is characterized by cellular infiltrates in portal areas damaging bile ducts and vascular structures. As mentioned above histological abnormalities without clinical graft dysfunction or "subclinical" rejection can be seen in most of protocol biopsies up to 80%, while incidence of clinically significant rejection is only approximately 20-40% which is showing a downward trend due to improvement of immunosuppressive therapy.[18,19]

Clinical manifestations include pyrexia, graft enlargement and tenderness and reduce bile flow. Biochemical test reveals a cholestatic pattern of liver test abnormality or a rise of transaminases. Since clinical and biochemical abnormalities are non-specific, the diagnosis must be confirmed histologically by liver biopsy.

Diagnostic triad includes portal inflammation, bile duct damage and venular endothelial inflammation (endotheliitis). At least two features are required for a diagnosis of acute rejection. The degree of inflammation may be considerably varied in different portal areas. Thus biopsies should be serially sectioned to obtain at least five portal tracts for evaluation.

Portal inflammation reveals mixed cellular infiltrates including T-lymphocytes, large activated cells, macrophages, neutrophils and eosinophils. Damage to bile ducts and endothelial cells are mediated by these inflammatory cells. Bile ducts are usually focally infiltrated by mixed inflammatory cells and reveal degenerative epithelial cell injury characterized by vacuolated cytoplasm, loss of nuclear polarity, slightly enlarged hyperchromatic nuclei and focal disruption of the basement membrane. Both portal and hepatic vein branches can be involved by inflammation. In early or mild cases, lymphocytes focally attach to the luminal surface of endothelial cells. Then subendothelial infiltration associated with lifting or disruption of endothelial cells is evidenced in more advanced or severe cases. Venular endothelial inflammation (endotheliitis) is the most specific feature of acute liver allograft rejection (Fig 1).

### Chronic rejection

Chronic rejection is an immune mediated process which usually occurs later than acute rejection and is mostly unresponsive to immunosuppression. Risk factors include donor/recipient factors and post-transplant factors such as severity and number of episodes of acute rejection.[20] Chronic rejection is clinically characterized by progressive jaundice and cholestatic liver biochemistry. Similar to acute rejection, clinical and biochemical abnormalities of chronic rejection are non-specific therefore histological confirmation is required.

Two main diagnostic features include loss of small bile ducts and an obliterative arteriopathy. In the early stages, bile ducts are still present, but show inflammatory infiltration associated with features of epithelial injury which is indistinguishable from acute rejection. When the disease progresses the bile ducts disappear and associated cellular infiltrates are diminished. Typically the affected bile ducts are interlobular (small) bile ducts (Fig 2). Generally a bile duct loss of more than 50% of portal tracts from at least 20 portal tract count[21] is required for a confident diagnosis of chronic rejection.

The characteristic vascular lesions of chronic rejection are aggregates of lipid-laden macrophages mainly in the intimal layer of large and medium-sized arteries leading to obliteration (Fig 3) which may be detected angiographi-
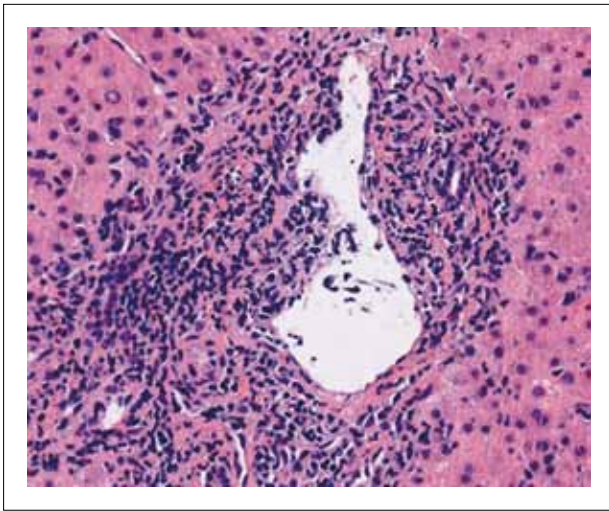
**Fig 1.** Acute rejection. Mixed inflammatory cells present within the portal tracts. The inflammation infiltrates into the bile duct and subendothelial of portal vein leading to disruption of endothelial cells (endotheliitis).
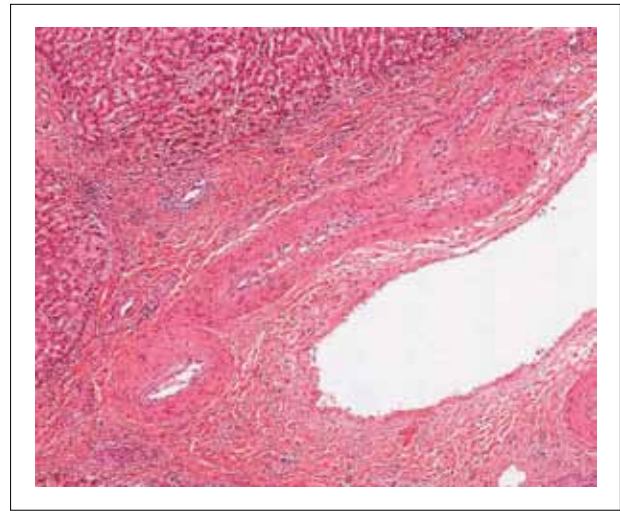
cally.[22] This feature is rarely seen in liver needle biopsy since it rarely affects small vessels.

Other common histologic findings seen in chronic rejection are perivenular cholestasis and perivenular necrosis (Fig 2). Cholestasis is presumably related to bile duct loss or a large bile duct stricture at the hilum which is not uncommonly associated in cases of chronic rejection. Perivenular necrosis is a result of necroinflammatory lesions which occurred during the phase of acute rejection.

### Grading and staging of liver allograft rejection

The grading of liver allograft rejection refers to necroinflammatory activity, mainly seen in acute rejection, whereas staging is more appropriately applied to features indicating progressive liver injury in chronic rejection. The Banff schema is one of the commonly used grading systems for acute liver allograft rejection. This system composes of two components: a global assessment of the overall rejection grade (Table 1) and rejection activity index (RAI), a summation of semiquantitative scores of three main features of acute rejection (Table 2). When the overall diagnosis of rejection is uncertain, grading should not be carried out.

### Vascular problems

Vascular anastomosis in LT includes hepatic artery, portal vein and vena cava which can be compromised due to technical complications (e.g. stricture or kinking) and/or thrombosis resulting in vascular occlusion. This complication leads to graft ischemia and graft failure in the early post-operative period. The characteristic macroscopic finding is irregular geographic infarction surrounded by hemorrhagic borders. In some cases thrombi can be observed in hepatic arteries (Fig 4) and/or portal vein branches, although in many more cases there is no detectable vascular occlusion. Histologic features show coagulative parenchymal necrosis with a variable number of neutrophilic infiltrates corresponding to the area of geographic infarct.

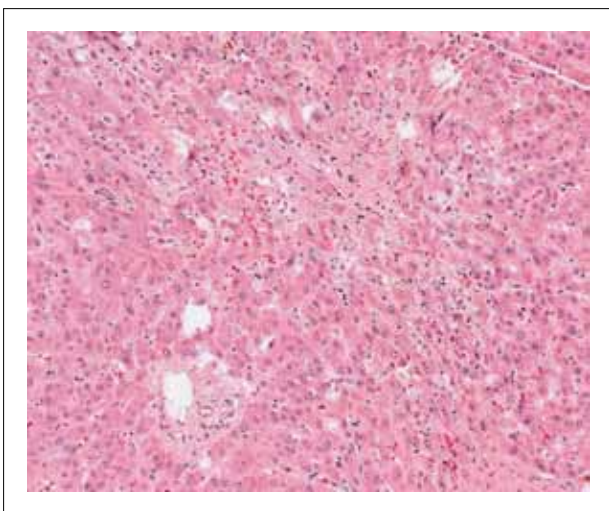Hepatic artery thrombosis occurs in 1-8% of LT patients.[24] In the early post-transplant period, hepatic



**Fig 3.** Chronic rejection. Large and medium-sized arteries show luminal obliteration due to infiltration by lipid-laden macrophages in the intimal layer.



**Fig 2.** Chronic rejection. Interlobular bile ducts have been lossed from the portal tracts. (left lower) Perivenular area demonstrates perivenular hepatocellular necrosis and cholestasis. (right upper)
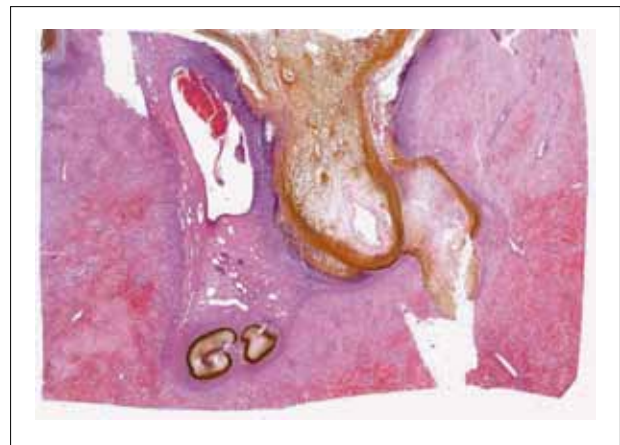


**Fig 4.** Hepatic artery thrombosis. Ischemic necrosis of large bile ducts is evidence adjacent to a thrombotic hepatic artery. Liver parenchyma shows geographic necrosis with hemorrhagic borders.

**TABLE 1.** Banff schema for grading liver allograft rejection – global assessment of overall rejection grade.[23]

| Global assessment* | Criteria |
|---|---|
| Indeterminate | Portal inflammation infiltrate that fails to meet the criteria of the diagnosis of acute rejection |
| Mild | Rejection infiltrate in a minority of the triads, that is generally mild, and confined within the portal spaces |
| Moderate | Rejection infiltrate, expanding most of all of the triads |
| Severe | As above for moderate, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis |

Note: Global assessment of rejection grade made on a review of the biopsy and after the diagnosis of rejection has been established.
*Verbal description of mild, moderate, or severe acute rejection could also be labeled as Grade I, II and III respectively.

artery thrombosis results in ischemic graft necrosis; while leads to ischemic bile duct necrosis typically involving the large intrahepatic bile ducts (Fig 4) which occurs later. The assessment of severity of ischemic damage based on liver biopsy is not recommended due to the unreliability attributed to sampling variation in different areas of the liver. Small peripheral infarctions are commonly present in well functioning liver allografts. On the other hand, livers showing extensive infarction often contain large areas of preserved parenchyma.

## Biliary complications

Anastomotic complications occur at the site of the surgical anastomosis and present as bile leaks in the early post-transplant period or bile duct stricture develops later. Histologic features of acute biliary obstruction include portal edema, bile ductular reaction and neutrophilic infiltration associated with variable cholestasis.

Non-anastomotic complications occur in the large intrahepatic bile duct which are attributable to an ischemic process.[25] Hepatic artery thrombosis and obliterative vasculopathy of chronic rejection are examples among several recognized risk factors.[26] Patients mostly present with either strictures or dilatations of the large intraheaptic bile ducts between 1 to 6 moths post-transplant.[27] Liver biopsy shows typical features of biliary obstruction which are frequent patchy in distribution.

## Pathology of the recurrent diseases

Most of the common diseases indicated for LT can recur which result in varied consequences from mild or sub-clinical to high mortality. Histologic features of the recurrent diseases are greatly overlapped with other complications of LT. Examples of the common diseases with diagnostic difficulty include histologic similarities between: hepatitis C vs. acute rejection, PBC vs. chronic rejection, and PSC vs. ischemic cholangiopathy. Immunosuppressive therapy may contribute a preventive effect for immune-mediated diseases (e.g. AIH or PBC), although it may conversely aggravate an aggressive behavior of viral infections.

## Recurrent hepatitis B

Active viral replication is the most important risk factor for recurrent infection. Pre-transplant antiviral therapy and post-transplant prophylaxis by a combination of lamivudine and anti-HBs immunoglobulin have successfully reduced the incidence and severity of recurrent hepatitis B.[28] The risk of developing recurrent hepatitis B is now reduced to less than 10%, compared with 50% at 3 years post-transplantation in the earlier period during the 1980s and early 1990s before the introduction of antiviral therapy.[29]

Histologic features during early re-infection (usually 1-6 months post-transplant) show mild lobular hepatitis with

**TABLE 2.** Banff schema for grading liver allograft rejection: rejection activity index (RAI).[23]

| Category | Criteria | Score |
|---|---|---|
| Portal inflammation | Mostly lymphocyte inflammation involving, but not noticeably expanding, a minority of the triads | 1 |
| | Expansion of most or all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils and eosinophils | 2 |
| | Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma | 3 |
| Bile duct inflammation/ damage | A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear:cytoplasmic ratio of the epithelial cells | 1 |
| | Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomophism, disordered polarity and cytoplasmic vacuolization of the epithelium | 2 |
| | As above for 2, with most or all of the ducts showing degenerative changes or focal luminal disruption | 3 |
| Venous endothelial inflammation | Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules | 1 |
| | Subendothelial infiltration involving most or all of the portal and/or hepatic venules | 2 |
| | As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis | 3 |

Note: Total score = sum of components

varying degrees of portal inflammation. Typical "chronic hepatitis" features including portal and periportal inflammatory changes are more prominent in the later stage (more than 6 months post-transplant) similar to those seen in chronic hepatitis B in non-transplanted livers.

### Recurrent hepatitis C

More than 90% of patients transplanted for chronic hepatitis C have virological markers of recurrent infection post-transplant[30] and the majority of them will eventually develop histologic features of hepatitis. Early recurrent infection occurs 2-4 months post-transplant and is characterized by typical features of acute hepatitis including lobular inflammatory infiltration, lobular disarray, hepatocellular ballooning, acidophil bodies and Kupffer cell hyperplasia. At a later stage (more than 6 months post-transplant) reveals features of chronic hepatitis similar to those seen in chronic hepatitis C in non-transplanted livers. The problematic difficulty usually encountered in the assessment of post-transplant biopsy is the distinction between recurrent hepatitis C and acute rejection. Since both conditions have overlapped features including predominant portal-based inflammation with involvement of bile ducts and portal veins. In most cases the distinction can be established based on the timing of events and typical histologic features of both conditions. Typically recurrent hepatitis C reveals portal inflammation by mononuclear cells with variable interface activity and a mild degree of bile duct inflammation; parenchymal changes including spotty necrosis with lobular disarray and acidophil bodies. Typical features of acute rejection include portal inflammation by mixed inflammatory infiltrate, prominent bile duct inflammation and venous endothelial inflammation. Parenchymal changes usually occur in severe cases including perivenular inflammation accompanied with hepatic vein endotheliitis and cholestasis.

## CONCLUSION

The pathology of liver transplantation has been increasingly encountered in clinical practices. Clinicians and pathologists should be aware and recognize the emerging diseases or complication from the ongoing emerging treatment modalities. This review briefly introduces some of the common problems of liver transplant pathology. The ultimate goal of this review is to stimulate awareness and recognition of these existing problems from all physicians taking care of liver transplant patients.

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