We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

4,400 Open access books available
117,000 International authors and editors
130M Downloads

154 Countries delivered to
TOP 1% Our authors are among the most cited scientists
12.2% Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Liver Biopsy After Liver Transplantation

Alpna R. Limaye, Lisa R. Dixon and Roberto J. Firpi

Additional information is available at the end of the chapter
http://dx.doi.org/10.5772/52617

1. Introduction

Histological evaluation of liver allograft biopsies is an integral part of the management of liver transplant patients. From the time of donor hepatectomy onward, the allograft is susceptible to multiple insults, including warm and cold ischemia, complications related to surgical anastomoses, acute cellular rejection, and recurrence of underlying liver disease. It is often quite challenging to distinguish these various entities by their clinical presentation alone. In these situations, evaluation of a liver biopsy is frequently necessary to confirm the diagnosis, to stage recurrent fibrosis, or to monitor response to treatment.

2. Post-transplant liver biopsy techniques

Liver biopsies can be performed with various techniques, including a percutaneous approach (with marking by percussion/palpation, marking by ultrasound (US), or under real-time US or computed tomography (CT) guidance), a transjugular approach, or a surgical/laparoscopic approach. Although percutaneous liver biopsies on non-transplant patients can be done without the use of imaging, it is recommended that patients who have undergone any abdominal surgery (including liver transplantation) undergo biopsies aided by the use of US to avoid vascular or other structures [1]. While US marking followed by biopsy is sufficient in most post-transplant patients, in certain situations (such as split-liver recipients), biopsy under real-time US or CT guidance is preferred to avoid encountering intervening bowel loops. While specimens at least 1.5cm in length and containing at least 6-8 portal tracts are considered adequate for the diagnosis of chronic liver disease [2,3], some advocate a minimum length of 2.0 cm and at least 11 complete portal tracts for accurate grading and staging of liver disease [4].
Percutaneous liver biopsy can be performed rapidly and safely in an outpatient setting with the appropriate monitoring equipment and staff availability [5]. After discharge, patients are typically instructed to avoid strenuous physical activity or driving for 24-48 hours, and are asked to contact the clinical provider in the event of concerning symptoms. In our institution, a review of over 3,000 liver biopsies (including liver transplant patients) demonstrated that the majority of complications were discovered within the first hour after percutaneous liver biopsy, and that shortening the recovery time to 1-2 hours did not impact the frequency of complications [6].

Percutaneous liver biopsy can be performed with suction needles (such as Jamshidi needle or Menghini needle), cutting needles (such as the Tru-Cut needle), or spring-loaded needle “guns”. Specimens adequate for diagnosis, grading, and staging can usually be obtained by all of the biopsy needles used in current practice.

In patients with severe/uncorrectable coagulopathy, thrombocytopenia (typically platelet count < 50,000/mm$^3$), large ascites, morbid obesity, or an inability to cooperate, a transjugular liver biopsy (TJLB) is typically recommended [7]. In addition, TJLB is useful in patients for whom wedged hepatic venous pressure gradient (HVPG) measurement would be clinically useful. Miraglia et al reported on the safety of TJLB in liver transplant patients, with only one complication in 183 biopsies (0.5%) [8].

TJLB is typically performed with the use of automated needle systems, such as the Quick-Core needle and the Flexcore needle. It has been established that these automated needle systems often require multiple passes, and usually collect smaller core samples than those obtained by percutaneous liver biopsy [9]. Despite this fact, specimens obtained via TJLB are adequate for diagnosis, staging, and grading liver disease in greater than 90% of cases [10,11].

Surgical liver biopsies (either open liver biopsy or laparoscopic liver biopsy) are typically performed when patients require a surgical procedure for another indication. In liver transplant patients, this often involves repair of postoperative hernias. Biopsies in this setting can be performed with either automated needle systems or with a wedge resection, and the procedure provides the advantage of direct visualization of the liver and the ability to immediately diagnose and treat any bleeding which occurs.

### 3. Complications of liver biopsy

Although invasive, liver biopsy is a relative safe procedure, whether performed percutaneously or via the transvenous route. In a review of over 60,000 non-transplant patients, death within seven days directly related to liver biopsy occurred in 1 out of every 10,000 procedures, and all-cause mortality within seven days occurred in approximately 0.2% of patients [12]. Serious complications were similarly rare, with pain occurring in 2% of patients, hemoperitoneum occurring in 0.04%, and hemobilia occurring in 0.01% [12]. Similarly, studies of allograft liver biopsies demonstrate a mortality rate of up to 0.2%, and a rate of major com-
Applications between 0.2% and 1.8% [13]. While early studies suggested an increased risk of post-biopsy sepsis in patients with Roux-en-Y choledochojejunostomy, subsequent studies show that the risk is similar to patients with a duct-to-duct anastomosis [14].

4. Post-transplant liver enzyme abnormalities

Abnormalities in liver enzyme levels are often encountered in liver transplant patients, and can represent hepatocellular injury (reflected by the transaminases), biliary injury (reflected by alkaline phosphatase or gamma-glutamyl transferase (GGT)), or hepatic synthetic dysfunction (reflected by the albumin or by coagulation abnormalities). While the use of serum blood tests (such as viral or autoimmune serologies) and imaging techniques (such as ultrasound with Doppler, angiography, and magnetic resonance cholangiography) can be useful to determine the etiology of abnormal liver enzymes, liver biopsy is often necessary for a definitive diagnosis.

5. Early post-transplant liver enzyme abnormalities

The differential diagnosis of liver enzyme abnormalities varies with the amount of time which has passed since liver transplant. In the normal post-transplant course, liver enzymes typically rise immediately following transplant and become normal or near-normal within 3-5 days. If the enzymes fail to improve or normalize but soon rise again, it is likely that an early complication has occurred (Table 1). In the very early post-transplant period (within the first week), liver enzyme abnormalities can be related to primary graft nonfunction (PNF) or dysfunction, hepatic arterial insufficiency, small for size syndrome (SFSS), or portal venous thrombosis (PVT).

5.1. Primary graft dysfunction

PNF and primary graft dysfunction are associated with prolonged ischemia time [15], and it is likely that preservation and reperfusion injury play a role. PNF is heralded by a precipitous rise in hepatic transaminases in the second or third postoperative day accompanied by signs of hepatic failure (encephalopathy and coagulopathy). Once hepatic artery thrombosis (HAT) has been ruled out by imaging, a liver biopsy confirms the diagnosis. Biopsies in this setting typically show centrilobular hepatocyte dropout due to hepatocellular necrosis, with compensatory zone 2 hepatocyte proliferation and bile ductular proliferation [16].

5.2. Hepatic artery thrombosis

The clinical presentation of HAT is quite similar to that of PNF, with a dramatic increase in hepatic transaminases and bilirubin in the very early post-transplant period. A liver biopsy is typically not required, as the diagnosis can usually be confirmed with angiography.
performed, biopsies of patients with hepatic arterial insufficiency show hepatocyte foamy degeneration or necrosis and features of ischemic cholangitis [17].

| Disease/Complication | Incidence | Time of presentation | Clinical presentation | Risk Factors | Histological Characteristics |
|----------------------|-----------|----------------------|-----------------------|--------------|------------------------------|
| Preservation/Reperfusion Injury | Up to 30% (2-7% severe) | Within 3 days | Elevated transaminases, bilirubin, INR. Encephalopathy in severe injury | Prolonged cold or warm ischemia time, greater than 30% donor steatosis | Centrilobular hepatocyte dropout, zone 2 hepatocyte proliferation, bile duct proliferation |
| Hepatic artery thrombosis | 3-10% in adult transplant (up to 40% in pediatric transplant) | Day 2 to 7 post-transplant | Severe elevation of transaminases, bilirubin, alkaline phosphatase/GGT | Technical/anastomotic complications | Foamy hepatocyte degeneration, features of ischemic cholangitis |
| Acute Cellular Rejection | 24-80% by 6 months post-transplant | Typically 2-3 weeks after transplant, up to 3 months post-transplant | Elevated transaminases, bilirubin, alkaline phosphatase. Possible recent history of inadequate immunosuppression | Younger recipient, older donor, history of autoimmune disorder, ? female recipient | Portal inflammation, biliary inflammation, endothelitis |
| Portal vein thrombosis | Less than 1% | Early: within first week post-transplant Late: within first year post-transplant | Early: acute hepatic failure Late: ascites, variceal bleeding | Hypercoagulable state, prior history of PVT | Often normal, may show features of focal nodular hyperplasia [21, 22] |
| Small for size syndrome | Not well defined, but greatest when graft-to-recipient body weight ratio is less than 0.6 | Sequelae of portal hypertension: 6 to 12 months post-transplant | Ascites, spontaneous bacterial peritonitis, variceal bleeding | Graft-to-recipient body weight ratio less than 0.6 | Centrilobular cholestasis and steatosis, interface bile duct inflammation [20] |

Table 1. Differential diagnosis of early post-transplant liver enzyme abnormalities
5.3. Portal vein thrombosis

Early acute PVT presents clinically as acute hepatic failure and demonstrates histological features of hepatocyte necrosis. Occasionally, PVT presents later, in which case the features of portal hypertension dominate. In this situation, if a biopsy is performed, it can be normal or show features of nodular regenerative hyperplasia [18,19].

5.4. Small for size syndrome

Patients with SFSS present with dominant features of portal hypertension, such as ascites and variceal bleeding. This syndrome is the result of relative portal hyperperfusion compared to hepatic arterial blood flow, and often occurs when the transplanted liver (or liver segment) is less than 0.6-0.8% of the recipient body weight [20,21]. The diagnosis is typically made clinically, with signs of portal hypertension such as ascites and variceal bleeding. If a liver biopsy is performed, the allograft typically shows centrilobular cholestasis, centrilobular steatosis, and interface ductular proliferation [22].

5.5. Acute cellular rejection

The most common cause of early allograft dysfunction is acute cellular rejection (ACR). Although most cases of ACR occur in the first three months post-transplant (most often in the second or third post-transplant week), late-onset ACR (occurring up to 10 years post-transplant) has been reported [23]. ACR typically presents as moderate to severe elevations in hepatic transaminases and alkaline phosphatase/GGT, with some degree of bilirubin elevation, often in patients with a recent history of inadequate immunosuppression. The “gold standard” for the diagnosis of ACR remains the liver biopsy, which typically shows variable degrees of mixed portal inflammation (often with increased eosinophils), bile duct inflammation, and endothelitis (typically in the portal vein or central vein branches) (Figure 1). The Banff criteria are the most widely used to describe ACR, and give a score of 1-3 for each component. These scores are added to calculate the Rejection Activity Index (RAI), which ranges from 3-4 (mild ACR) up to greater than 7 (severe ACR) [24]. It should be noted that late-onset ACR often appears quite different histologically, with a greater likelihood of lobular inflammation, less prominent bile duct inflammation, and a tendency towards monotypic portal inflammation [25]. A follow-up liver biopsy after 3-7 days of increased immunosuppression is occasionally used to confirm response to treatment.

5.6. Late post-transplant liver enzyme abnormalities

Beyond three months post-transplant, the differential of liver enzyme abnormalities changes. Broadly, the diagnoses can be categorized as chronic rejection, native disease recurrence, de novo infectious complications, toxic complications, de novo hepatitis, or vascular complications (Table 2).
Figure 1. Acute rejection, with endothelitis (arrowhead), bile duct destruction (arrow), and mixed portal inflammation (40x, H&E)
| Disease/Complication | Incidence | Time of presentation | Clinical presentation | Risk Factors | Histological Characteristics |
|----------------------|-----------|----------------------|------------------------|--------------|-------------------------------|
| Chronic rejection    | 3-5%      | 3-12 months after transplant | Rising alkaline phosphatase/GGT, late elevation in bilirubin | Inadequate immunosuppression, history of multiple episodes of or ongoing acute cellular rejection [17] | Bile duct atrophy/loss, foamy arteriopathy [26] |
| Recurrent HCV        | Near-universal | Re-infection within 72 hours; histological recurrence within 1-2 weeks; clinically significant recurrence within 3 years (within 1 year for FCH) [27] | Elevated transaminases in typical recurrent HCV FCH: jaundice, marked elevation of alkaline phosphatase/GGT, extremely high HCV viral load | FCH: excessive immunosuppression | Portal inflammation, interface hepatitis, lobular activity [28-30] FCH: cholestasis, fibrosis [35] |
| Recurrent HBV        | Less than 10% with adequate prophylaxis [36] | Typical recurrent HBV: 6-12 months post-transplant FCH: within 1 month post-transplant | Elevated transaminases, elevated HBV viral load | Inadequate prophylaxis | Lymphoplasmacytic portal inflammation, Kupffer cell hyper trophy, lobular disarray, ground-glass hepatocytes; positive immunostaining for hepatitis B surface antigen and core antigen [37] |
| Recurrent AIH        | Up to 40% [38] | Variable | Slow progression of transaminase elevation | Inadequate immunosuppression, native type II AIH | Lymphoplasmacytic portal infiltrate, prominent interface activity [29] |
| CMV infection        | 5-8% with prophylaxis | 1-12 months post-transplant | CMV hepatitis: Elevated transaminases Extrahepatic CMV: gastroenteritis, colitis, pneumonitis | Graft from CMV-antibody-positive donor into CMV-antibody-negative recipient | Portal inflammation, hepatocytes with CMV inclusions, focal bile duct damage [29] |
| EBV infection        | Up to 80% of patients who are EBV-antibody-negative at time of transplant | 6-12 or more months post-transplant | EBV hepatitis: usually asymptomatic PTLD: lymphoma-like presentation | Primary infection: EBV-antibody-negative recipient Progression to PTLD: excessive immunosuppression, preceding CMV infection [43] | EBV hepatitis: portal and sinusoidal infiltrates with atypical lymphocytes, +EBER PTLD: immunoblasts, with varying degrees of architectural distortion [45] |

Table 2. Differential diagnosis of late post-transplant liver enzyme abnormalities
5.7. Chronic rejection

Chronic rejection involves immune-mediated injury to the hepatic arterial endothelium and bile duct epithelium. It is most commonly seen in patients who have experienced repeated bouts of significant ACR and/or have a recent history of inadequate immunosuppression. The typical clinical presentation is a slow rise in alkaline phosphatase/GGT, often followed by a rise in bilirubin. Procurement of an adequate biopsy sample (with at least ten complete portal triads) is crucial in the histologic diagnosis of chronic rejection [26]. The minimal criteria for diagnosis of chronic rejection, as defined by the 2000 Banff recommendations, are (1) bile duct atrophy/pyknosis affecting a majority of bile ducts (with or without bile duct loss); (2) foam cell obliterative arteriopathy (Figure 2); or (3) bile duct loss in greater than half of the portal tracts [26].

Figure 2. Foamy arteriopathy in the setting of chronic rejection (H&E 10x)

In the months and early years following liver transplant, recurrence of the underlying disease which led to transplant becomes a common problem. Disease recurrence can be viral (most commonly hepatitis B or C), immunological (such as autoimmune hepatitis, primary sclerosing cholangitis [PSC], or primary biliary cirrhosis [PBC]), metabolic (such as non-alcoholic fatty liver disease [NAFLD]), malignant (hepatocellular carcinoma or cholangiocarcinoma), or idiopathic. The diagnosis of recurrent PSC, PBC, NAFLD, and malignancy is relatively straightforward and is therefore not discussed further. However, the degree of clinical and histological overlap between entities such as rejection, recurrent viral hepatitis, and autoimmune hepatitis can create diagnostic conundrums without close clinicopathological correlation.
5.8. Recurrent hepatitis C

Recurrent hepatitis C (HCV) infection is a universal phenomenon after liver transplantation, and exhibits an accelerated progression to advanced liver disease [27]. Particularly in the early months after transplant, the differential diagnosis of abnormal liver enzymes in HCV patients includes both ACR and recurrent HCV. These entities are usually distinguished histologically. Histologically established recurrent HCV demonstrates portal inflammation, often with lymphoid aggregates, interface hepatitis, and lobular disarray [28-30] (Figure 3). There is often a component of ductular reaction, which is uncommon in HCV in native livers [30]. While endotheliitis was traditionally considered specific to rejection, recent data demonstrate portal branch endothelitis in biopsies of native HCV livers [31,32]. It does appear that moderate to severe central vein branch endotheliitis remains fairly specific for rejection. In a prospective analysis of biopsies from 48 HCV transplant patients, Demetris et al described strict criteria to avoid overdiagnosis of ACR: (1) inflammatory bile duct injury in at least 50% of portal tracts, and/or (2) mononuclear perivenular inflammation with hepatocyte necrosis in at least 50% of terminal hepatic venules [33]. In cases where the differentiation of ACR and recurrent HCV is not clear, the use of an immune function assay can be a useful adjunct [34]. Occasionally, recurrent HCV presents aggressively, in an entity known as fibrosing cholestatic hepatitis (FCH). The risk of FCH increases with aggressive immunosuppression, such as that used to treat ACR. Histologically, FCH is distinguished by a prominent component of cholestasis and fibrosis [35].

Figure 3. Recurrent HCV, with chronic portal inflammation (ellipse), and interface as well as lobular activity (H&E,10x)
5.9. Recurrent hepatitis B

Recurrent hepatitis B (HBV) infection was common in the era before combination prophylaxis with hepatitis B immunoglobulin and oral antiviral agents. The current rate of recurrent HBV (less than 10%) is attributed to a lack of prophylaxis for various reasons [36]. Histologically, recurrent HBV demonstrates lymphoplasmacytic portal inflammation, Kupffer cell hypertrophy, and lobular disarray [37]. Ground glass cells containing HBV surface antigen are often seen. Immunostaining demonstrates HBV surface antigen in hepatocyte cytoplasm and HBV core antigen in hepatocyte nuclei. Recurrent HBV can also cause FCH, characterized by cholestasis, perisinusoidal fibrosis, and swollen hepatocytes with immunoreactivity for HBV core antigen [37]. In patients without demonstrable HBV core antigen staining, other causes of hepatic dysfunction should be sought.

5.10. Recurrent and de novo autoimmune hepatitis

Recurrence of autoimmune hepatitis (AIH) can occur in up to 40% of patients, but the course is typically slowly progressive [38]. The biochemical/serological diagnosis of AIH [39] can be difficult in post-transplant patients, and therefore a liver biopsy is often required for a definitive diagnosis. In the chronic phase, recurrent AIH demonstrates lymphoplasmacytic portal infiltrate with prominent interface activity, perivenular activity and variable degrees of lobular necroinflammatory activity [29] (Figure 4). In patients without a pre-transplant history of AIH, the findings of lymphoplasmacytic infiltrate and perivenular activity, the differential diagnosis includes recurrent HCV, rejection, and de novo AIH. This distinction relies on close clinicopathological correlation which takes into account the timing of onset, the immunosuppressive state, and the degree of perivenular damage [40].

![Figure 4. Portal area with interface hepatitis, numerous plasma cells (arrowhead) and scattered eosinophils (arrow) (H&E, 40x)](image-url)
Liver transplant patients are also at risk of de novo infections due to their immunosuppressed state. While the diagnosis of most of these infections is fairly straightforward, post-transplant cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection can be more difficult.

5.11. CMV infection

CMV is the most common clinically significant viral infection after solid organ transplantation, with an incidence of up to 30% prior to the use of routine prophylaxis [41]. The risk of post-transplant CMV infection is greatest in CMV-antibody-negative recipients who receive a graft from a CMV-antibody-positive donor. Clinically, CMV infection can present with fever, myelosuppression, and/or organ involvement (such as gastritis, colitis, hepatitis, or pneumonitis). While detection of CMV in the serum can provide a rapid diagnosis, a liver biopsy is often required to distinguish CMV from allograft rejection or demonstrate that both entities are present [42]. Typically, CMV hepatitis is characterized by mononuclear or mixed portal inflammation, focal bile duct damage, and hepatocytes with CMV inclusions (large eosinophilic nuclear inclusions surrounded by a clear halo [29] (Figure 5). Although some features similar to allograft rejection (portal lymphocytic inflammation, mild endotheliitis) can be seen in CMV hepatitis, immunostaining for CMV antigens and/or the presence of CMV inclusions confirms that CMV is the driving force behind the hepatic dysfunction.

![Figure 5. Hepatocyte with intranuclear CMV inclusion (arrowhead) (H&E, 100x)](http://dx.doi.org/10.5772/52617)
5.12. EBV infection and post-transplant lymphoproliferative disorder

The clinical presentation of EBV infection can vary from asymptomatic hepatitis to post-transplant lymphoproliferative disorder (PTLD). Patients without pre-transplant immunity to EBV are at the greatest risk of infection. Patients with primary post-transplant EBV infection, those with previous symptomatic CMV infection, and those with recent excessive immunosuppression are at the highest risk for progression to PTLD [43]. EBV hepatitis typically demonstrates portal and sinusoidal infiltrates consisting of atypical lymphocytes. Often the lymphocytes are arranged in a single-file pattern within sinusoids [29]. Another histological pattern which can be seen in EBV hepatitis consists of mixed perportal and sinusoidal infiltrates with large atypical mononuclear cells and immunoblasts, mild bile duct damage, and hepatic lobular activity [44]. The finding of EBV-encoded RNAs (EBERs) is confirmatory in most cases.

PTLD is a heterogeneous lymphoproliferative disease divided into three main categories: early lesions, polymorphic PTLD, and monomorphic PTLD [45]. Early lesions demonstrate plasmacytic hyperplasia, and may or may not have prominent immunoblasts [29,45]. Polymorphic PTLD is characterized by mixed infiltrates of monoclonal or polyclonal plasma cells, immunoblasts, and destruction of the underlying lymphoid architecture [45]. In monomorphic PTLD, most cases arise from B cell populations which demonstrate invasion, architectural effacement, and cellular atypia [29]. A fourth category, Hodgkin’s lymphoma-like PTLD, is sometimes described [46], and appears histologically like Hodgkin’s lymphoma which occurs in non-transplant patients. PTLD patients with positive EBER results may represent relatively better histopathological features than patients with EBER-negative PTLD [47].

6. Indication and protocol liver biopsies

The majority of post-transplant liver biopsies are performed in response to changes in liver enzyme levels and/or abnormal imaging findings. Particularly in the early post-transplant period, these so-called “indication” biopsies are usually diagnostic and often result in a change in management. However, as patient and graft survival continues to improve, it has become clear that normal histology is rarely seen in the long-term liver graft [48]. What is not clear, however, is whether the histologic abnormalities seen in most late allograft biopsies correlate to clinically-significant disease, and whether the routine use of so-called “protocol” liver biopsies (performed at regular time points despite normal liver enzyme levels) is clinically justified. In our institution, we no longer perform annual protocol biopsies on patients with alcoholic liver disease, non-alcoholic fatty liver disease, or cryptogenic liver disease. The use of annual or semi-annual protocol biopsies in patients with AIH, PSC, or PBC is left to the discretion of the treating provider and/or the desires of the patient. In all HCV patients, protocol biopsies are performed at four months post-transplant, at one year post-transplant, and annually thereafter for at least the first five years. In contrast, an informal survey of 35 transplant centers found that only 65% of centers perform protocol liver biop-
cies for HCV patients, and only 25% of centers perform protocol biopsies for other post-transplant patients [13].

The rationale for protocol biopsies is the detection of those patients with severe dysfunction in the hopes that early treatment and/or change in immunosuppression might improve graft survival. However, the evidence of the clinical utility of these biopsies is conflicted. In studies of long-term protocol biopsies in non-viral hepatitis transplant patients, it does appear that histological abnormalities in the setting of normal liver enzymes likely are not clinically significant [49,50]. The rationale for the use of protocol liver biopsies in HCV patients is the identification of those with severe HCV recurrence in the hopes that prompt treatment could improve graft survival [51]. This appears to be justified, as several studies have demonstrated the clinical utility of protocol biopsies in HCV patients, even as long as 20 years post-transplant [52-54]. It is notable, however, that the vast majority of patients with recurrent HCV (and all patients with severe recurrent HCV) had abnormal liver enzymes at the pre-determined time of protocol biopsy.

A separate but equally important factor in long-term patient survival is the avoidance of extrahepatic complications of chronic immunosuppression, including renal insufficiency, the development of diabetes mellitus, and infectious complications. In this regard, another utility of protocol liver biopsy is the identification of those patients in whom immunosuppression can be safely lowered. A retrospective study of patients with various liver diseases found that protocol biopsy results led to a change in immunosuppression in almost on third of patients [55]. Recently, an international working group developed recommendations for protocol biopsy monitoring in patients in whom minimizing or weaning immunosuppression is being considered [56].

7. Summary

The liver allograft is susceptible to a broad range of insult and injury from the time that it is removed from the donor. While some complications are easily diagnosed by the clinical presentation and advanced imaging, the majority of conditions display overlapping clinical features. As the treatment of these various conditions can be radically different, a definitive diagnosis is crucial. To that end, post-transplant liver biopsy continues to play a key role in the evaluation of liver transplant patients with hepatic dysfunction. While the role of protocol biopsies in patients with no biochemical evidence of hepatic dysfunction has begun to fall out of favor (especially in non-HCV patients), the use of biopsy in immunosuppression-weaning protocols could promote a renewed interest in this methodology. The current data support the use of protocol biopsies in HCV patients (particularly in the first few years post-transplant). Areas for future investigation include non-invasive alternatives to liver biopsy such as immune assays and advanced imaging, and the use of routine protocol biopsies in weaning of immunosuppression.
Author details

Alpna R. Limaye¹, Lisa R. Dixon² and Roberto J. Firpi³

*Address all correspondence to: roberto.firpi@medicine.ufl.edu

1 Section of Hepatobiliary Diseases, Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Florida, Gainesville, FL, USA

2 Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL, USA

References

[1] Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. Hepatology. 2009 Mar;49(3): 1017-44.

[2] Chan J, Alwahab Y, Tilley C, Carr N. Percutaneous medical liver core biopsies: correlation between tissue length and the number of portal tracts. J Clin Pathol. 2010 Jul; 63(7):655-6.

[3] Bravo AA, Sheth SG, Chopra S. Liver Biopsy. N Engl J Med. 2001 Feb 15;344(7): 495-500.

[4] Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. J Hepatol. 2003 Aug;39(2):239-44.

[5] Jacobs WH, Goldberg SB. Statement on outpatient percutaneous liver biopsy. Dig Dis Sci. 1989 Mar;34(3):322-3.

[6] Firpi RJ, Soldevila-Pico C, Abdelmalak MF, Morelli G, Judah J, Nelson DR. Short recovery time after percutaneous liver biopsy: should we change our current practices? Clin Gastroenterol HEPATOL. 2005 Sep;3(9):926-9.

[7] Van Ha TG. Liver biopsy in liver transplant recipients. Semin Intervent Radiol. 2004 Dec;21(4):271-4.

[8] Miraglia R, Maruzzelli L, Minervini MI, Volpes R, Vissini G, Gruttadauria S, Caruso S, Luca A, Gridelli B. Transjugular liver biopsy in liver transplant patients using an 18-gauge automated core biopsy needle. Eur J Radiol. 2011 Dec;80(3):e269-72.

[9] De Hoyos A, Loredo ML, Martinez-Rios MA, Gil MR, Kuri J, Cardenas M. Transjugular liver biopsy in 52 patients with an automated Trucut-type needle. Dis Dis Sci 1999;44:177-80.
[10] Cholongitas E, Quaglia A, Samonakis D, Senzolo M, Triantos C, Patch D, Leandro G, Dhillon AP, Burroughs AK. Transjugular liver biopsy: how good is it for accurate histological interpretation? Gut. 2006 Dec;55(12):1789-94.

[11] Cholongitas E, Senzolo M, Standish R, Marelli L, Quaglia A, Patch D, Dhillon AP, Burroughs AK. A systematic review of the quality of liver biopsy specimens. Am J Clin Pathol. 2006 May;125(5):710-21.

[12] West J, Card TR. Reduced mortality rates following elective percutaneous liver biopsies. Gastroenterology. 2010 Oct;139(4):1230-7.

[13] Mells G, Neuberger J. Protocol liver allograft biopsies. Transplantation. 2008 Jun 27;85(12):1686-92.

[14] Ben-Ari Z, Neville L, Rolles K, Davidson B, Burroughs AK. Liver biopsy in liver transplantation: no additional risk of infections in patients with choledochojejunostomy. J Hepatol. 1996 Mar;24(3):324-7.

[15] Sirivatanauksorn Y, Taweerutchan V, Limsrichamrern S, Kositamongkol P, Mahawithitwong P, Asavakarn S, Tovikkai C, Sanphasitvong V. Analysis of donor risk factors associated with graft outcomes in orthotopic liver transplantation. Transplant Proc. 2012 Mar;44(2):320-3.

[16] Kakizoe S, Yanaga K, Starzl TE, Demetris AJ. Evaluation of protocol before transplantation and after reperfusion biopsies from human orthotopic liver allografts: considerations of preservation and early immunological injury. Hepatology. 1990 Jun;11(6):932-41.

[17] Gao Z. Seeking beyond rejection: an update on the differential diagnosis and a practical approach to liver allograft biopsy interpretation. Adv Anat Pathol. 2009;16:97-117.

[18] Wang JT, Zhao HY, Liu YL. Portal vein thrombosis. Hepatobiliary Pancreat Dis Int. 2005 Nov;4(4):515-8.

[19] Shimamatsu K, Wanless IR. Role of ischemia in causing apoptosis, atrophy, and nodular hyperplasia in human liver. Hepatology. 1997 Aug;26(2):343-50.

[20] Selzner M, Kashfi A, Cattral MS, Selzner N, Greig PD, Lilly L, McGilvray ID, Tерапондос G, Adcock LE, Ghanekar A, Levy GA, Renner EL, Grant DR. A graft to body weight ratio less than 0.8 does not exclude adult-to-adult right-lobe living donor liver transplantation. Liver Transpl. 2009 Dec;15(12):1776-82.

[21] Alves RC, Fonseca EA, Mattos CA, Abdalla S, Goncalves JE, Waisberg J. Predictive factors of early graft loss in living donor liver transplantation. Arg Gastroenterol. 2012 Jun;49(2):157-61.

[22] Demetris AJ, Kelly DM, Eghtesad B, Fontes P, Wallis Marsh J, Tom K, Tan HP, Shaw-Stiffler T, Boig L, Novelli P, Planinsic R, Fung JJ, Marcos A. Pathophysiologic observations and histopathologic recognition of the portal hyperperfusion or small-for-size syndrome. Am J Surg Pathol. 2006 Aug;30(8):986-93.
[23] Nakanishi C, Kawagishi N, Sekiguchi S, Akamatsu Y, Sato K, Miyagi S, Takeda I, Hukushima K, Aiso T, Sato A, Fujimori K, Satomi S. Steroid-resistant late acute rejection after a living donor liver transplantation: case report and review of the literature. Tohuku J Exp Med. 2007 Feb;211(2):195-200.

[24] No authors listed. Banff schema for grading liver allograft rejection: an international consensus document. Hepatology. 1997 Mar;25(3):658-63.

[25] Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, Czaja A, Daskal I, El-Monayeri MS, Fontes P, Fung J, et al; Banff Working Group. Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology. 2006;44:489-501.

[26] Demetris AJ, Adams D, Bellamy C, Blakolmer K, Clouston A, Dhillon AP, Fung J, Gouw A, Gustafsson B, Haga H, Harrison D, Hart J, et al. Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. An International Panel. Hepatology. 2000 Mar;31(3):792-9.

[27] Limaye AR, Firpi RJ. Management of recurrent hepatitis C infection after liver transplantation. Clin Liver Dis. 2011 Nov;15(4):845-58.

[28] Gane EJ. The natural history of recurrent hepatitis C and what influences this. Liver Transpl. 2008;14(Suppl 2):S36-S44.

[29] Adeyi O, Fischer SE, Guindi M. Liver allograft pathology: approach to interpretation of needle biopsies with clinicopathological correlation. J Clin Pathol. 2010;63:47-74.

[30] Moreira RK. Recurrent hepatitis C and acute allograft rejection: clinicopathologic features with emphasis on the differential diagnosis between these entities. Adv Anat Pathol. 2011 Sep;18(5):393-405.

[31] Souza P, Prihoda TJ, Hoyumpa AM, Sharkey FE. Morphologic features resembling transplant rejection in core biopsies of native livers from patients with Hepatitis C. Hum Pathol. 2009 Jan;40(1):92-7.

[32] Yeh MM, Larson AM, Tung BY, Swanson PE, Upton MP. Endotheliitis in chronic viral hepatitis: a comparison with acute cellular rejection and non-alcoholic steatohepatitis. Am J Surg Pathol. 2006 Jun;30(6):727-33.

[33] Demetris AJ, Eghtesad B, Marcos A, Ruppert K, Nalesnik MA, Randhawa P, Wu T, Krasinskas A, Fontes P, Cacciarelli T, Shakil AO, Murase N, Fung JJ, Starzl TE. Recurrent hepatitis C in liver allografts: prospective assessment of diagnostic accuracy, identification of pitfalls, and observations about pathogenesis. Am J Surg Pathol. 2004 May;28(5):658-69.

[34] Cabrera R, Ararat M, Soldevila-Pico C, Dixon L, Pan JJ, Firpi R, Machicaco V, Levy C, Nelson DR, Morelli G. Using an immune functional assay to differentiate acute cellular rejection from recurrent hepatitis C in liver transplant patients. Liver Transpl. 2009 Feb;15(2):216-22.
[35] Dixon LR, Crawford JM. Early histologic changes in fibrosing cholestatic hepatitis C. Liver Transpl. 2007 Feb;13(2):219-26.

[36] Laryea MA, Watt KD. Immunoprophylaxis against and prevention of recurrent viral hepatitis after liver transplantation. Liver Transpl. 2012 May;18(5):514-23.

[37] Thung SN. Histologic findings in recurrent HBV. Liver Transpl. 2006 Nov;12(11 Suppl 2):S50-53.

[38] Ayata G, Gordon FD, Lewis WD, Pomfret E, Pomposelli JJ, Jenkins RL, Khettry U. Liver transplantation for autoimmune hepatitis: a long-term pathologic study. Hepatology. 2000 Aug;32(2):185-92.

[39] Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, et al; International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008 Jul;48(1):169-76.

[40] Demetris AJ, Sebagh M. Plasma cell hepatitis in liver allografts: Variant of rejection or autoimmune hepatitis? Liver Transpl. 2008 Jun;14(6):750-5.

[41] Lee SO, Razonable RR. Current concepts on cytomegalovirus infection after liver transplantation. World J Hepatol. 2010 Sep 27;2(9):325-36.

[42] Razonable RR. Cytomegalovirus infection after liver transplantation: current concepts and challenges. World J Gastroenterol. 2008 Aug 21;14(31):4849-60.

[43] Knight JS, Tsodikov A, Cibrik DM, Ross CW, Kaminski MS, Blayney DW. Lymphoma after solid organ transplantation: risk, response to therapy, and survival at a transplantation center. J Clin Oncol. 2009 Jul 10;27(20):3354-62.

[44] Randhawa P, Blakolmer K, Kashyap R, Raikow R, Nalesnik M, Demetris AJ, Jain A. Allograft liver biopsy in patients with Epstein-Barr virus-associated posttransplant lymphoproliferative disease. Am J Surg Pathol. 2001 Mar;25(3):324-30.

[45] Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. The World Health Organization classification of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November, 1997. Hematol J. 2000;1(1):53-66.

[46] Jagadeesh D, Woda BA, Draper J, Evens AM. Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. Curr Treat Options Oncol. 2012 Mar;13(1):122-36.

[47] Izadi M, Taheri S. Significance of in situ hybridization results for EBV-encoded RNA in post-transplantation lymphoproliferative disorder setting: report from the PTLD.Int Survey. Ann Transplant. 2010 Oct-Dec;15(4):102-9.

[48] Ekong UD. The long-term liver graft and protocol biopsy: do we want to look? What will we find? Curr Opin Organ Transplant. 2011 Oct;16(5):505-8.
[59] Maor-Kendler Y, Battis KP, Burgart LJ, Wiesner RH, Krom RA, Rosen CB, Charlton MR. Comparative allograft histology after liver transplantation for cryptogenic cirrhosis, alcohol, hepatitis C, and cholestatic liver diseases. Transplantation. 2000 Jul 27;70(2):292-7.

[50] El-Masry M, Gilbert CP, Saab S. Recurrence of non-viral liver disease after orthotopic liver transplantation. Liver Int. 2011 Mar;31(3):291-302.

[51] Firpi RJ, Clark V, Soldevila-Pico C, Morelli G, Cabrera R, Levy C, Machicao VI, Chaoru C, Nelson DR. The natural history of hepatitis C cirrhosis after liver transplantation. Liver Transpl. 2009 Sep;15(9):1063-71.

[52] Berenguer M, Rayon JM, Prieto M, Aguilera V, Nicolas D, Ortiz V, Carrasco D, Lopez-Andujar R, Mir J, Berenguer J. Are posttransplantation protocol liver biopsies useful in the long term? Liver Transpl. 2001 Sep;7(9):790-6.

[53] Firpi RJ, Abdelmalek MF, Soldevila-Pico C, Cabrera R, Shuster JJ, Theriaque D, Reed AI, Hemming AW, Liu C, Crawford JM, Nelson DR. One-year protocol liver biopsy can stratify fibrosis progression in liver transplant recipients with recurrent hepatitis C infection. Liver Transpl. 2004 Oct;10(10):1240-7.

[54] Sebagh M, Samuel D, Antonini TM, Coilly A, Degli Esposti D, Roche B, Karam V, Dos Santos A, Duclos-Vallee JC, Roque-Afonso AM, Ballott E, Guettier C, Blandin F, Saliba F, Azoulay D. Twenty-year protocol liver biopsies: invasive but useful for the management of liver recipients. J Hepatol. 2012 Apr;56(4):840-7.

[55] Mells G, Mann C, Hubscher S, Neuberger J. Late protocol liver biopsies in the liver allograft: a neglected investigation? Liver Transpl. 2009 Aug;15(8):931-8.

[56] Adeyi O, Alexander G, Baiocchi L, Balasubramanian M, Batal I, OC BC, Bhan A, Bridges N, Bucuvalas J, Charlotte F, et al; The Banff Working Group on Liver Allograft Pathology. Importance of liver biopsy findings in immunosuppression management: Biopsy monitoring and working criteria for patients with operational tolerance (OT). Liver Transpl. 2012 May 29. [Epub ahead of print].