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Liver Biopsy After Liver Transplantation

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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 triads 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-

plications 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. When

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) [15]	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 [16]
Hepatic artery thrombosis	3-10% in adult transplant (up to 40% in pediatric transplant) [17]	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 [26]	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 [17]	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 [18]	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 [18, 19]	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 endotheliitis (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).
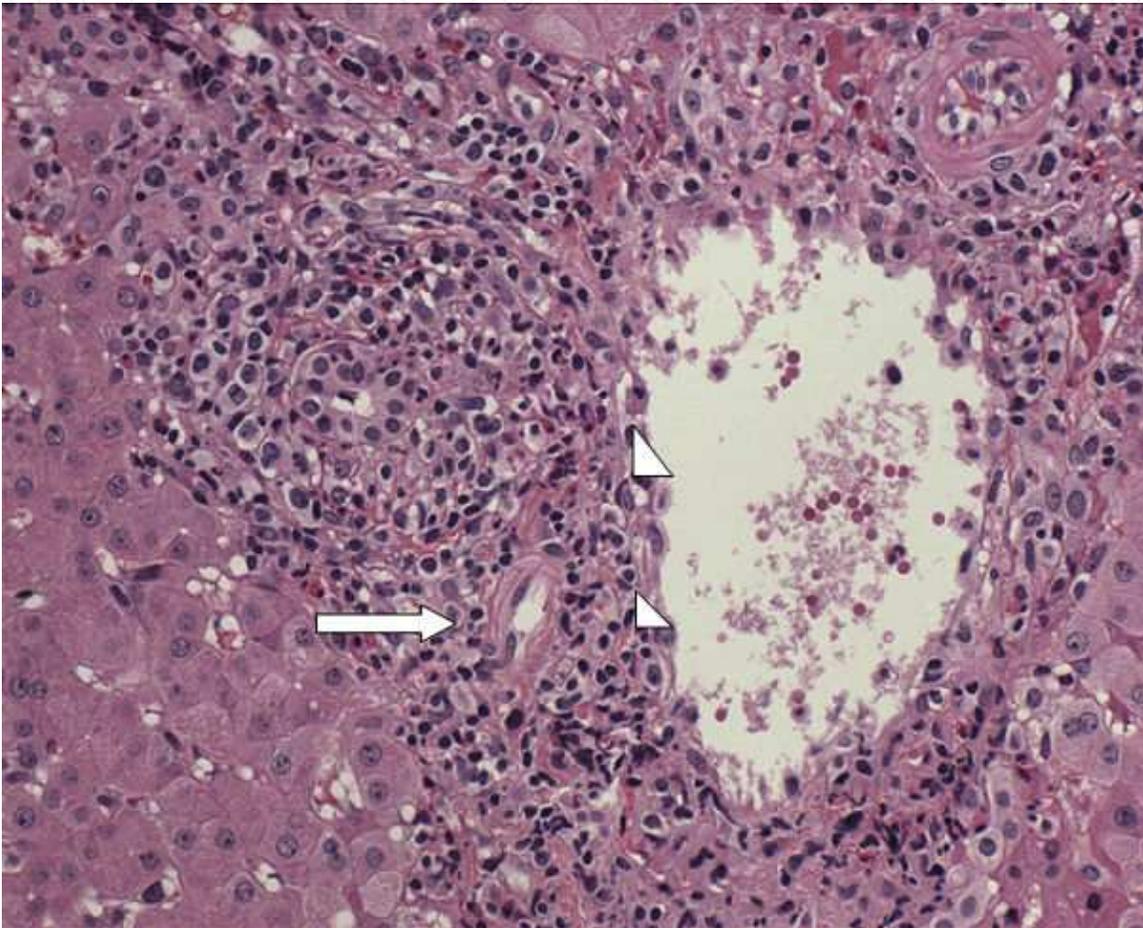
Figure 1. Acute rejection, with endotheliitis (arrowhead), bile duct destruction (arrow), and mixed portal inflammation (40x, H&E)

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 hypertrophy, 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].
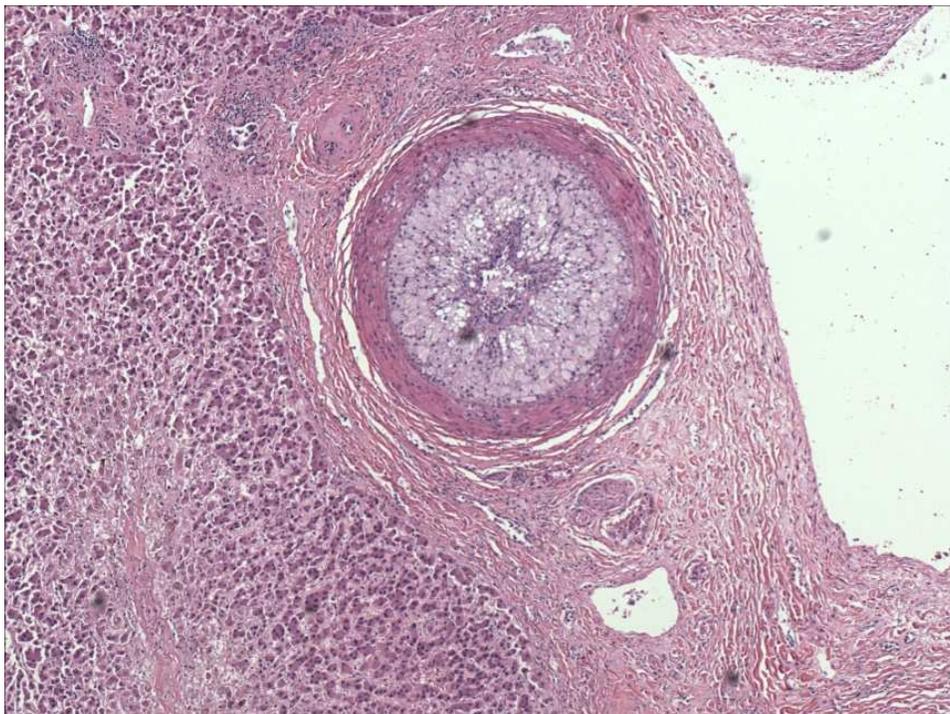

Figure 2. Foamy arteriopathy in the setting of chronic rejection (H&E 10x)

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].
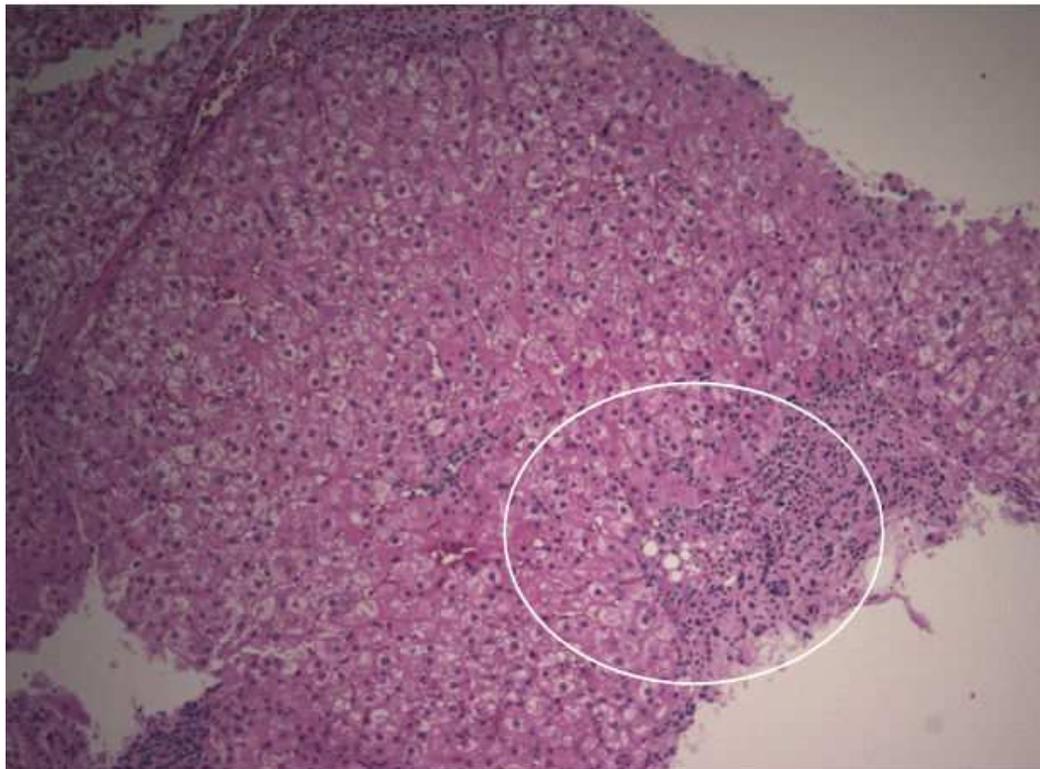

Figure 3. Recurrent HCV, with chronic portal inflammation (ellipse), and interface as well as lobular activity (H&E,10x)

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].
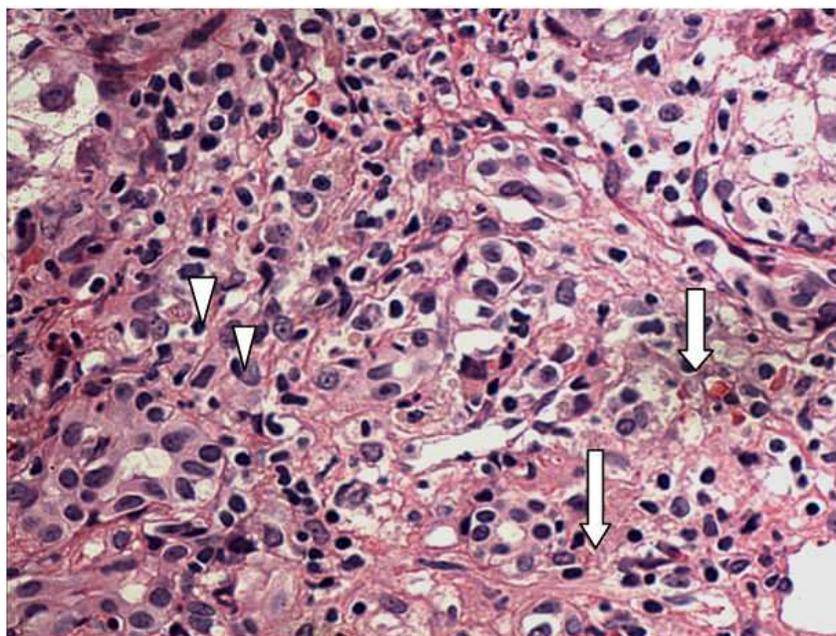

Figure 4. Portal area with interface hepatitis, numerous plasma cells (arrowhead) and scattered eosinophils (arrow) (H&E, 40x)

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, posttransplant 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.
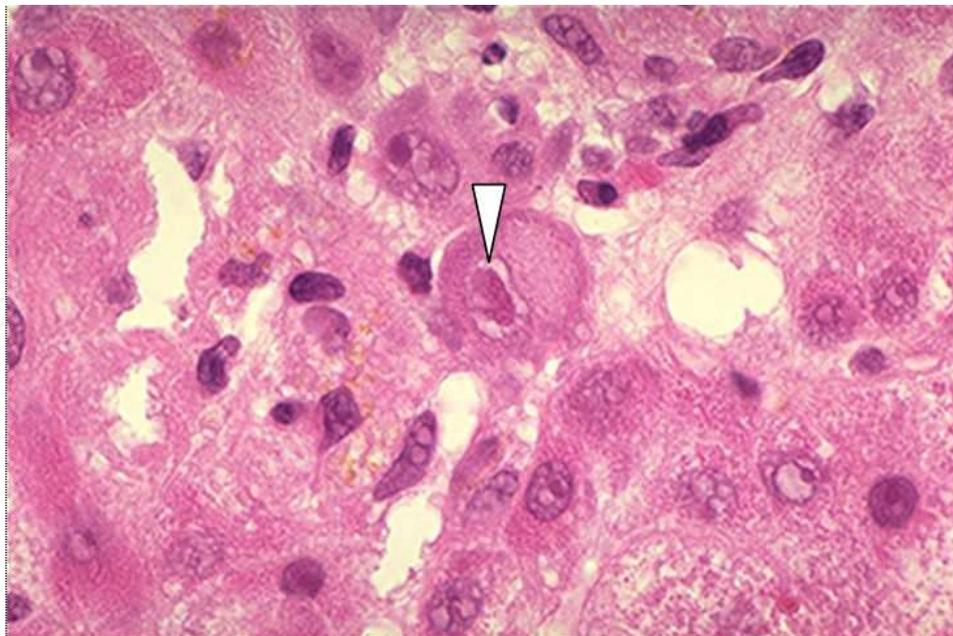

Figure 5. Hepatocyte with intranuclear CMV inclusion (arrowhead) (H&E, 100x)

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 periportal 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-

sies 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.

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