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Review Article

Interpretation of orthotopic liver transplantation biopsy

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ABSTRACT

Liver transplantation is an established treatment for various forms of severe liver disease due to any etiology, as well as selected metabolic and neoplastic conditions. Exposure to liver allograft biopsies among pathology residents is rare, particularly in a hospital where there is no liver transplantation program. Frozen-section evaluation of the liver of extended donor criteria confirms the quality /viability of the donor organ. It excludes features that would either contraindicate transplantation or increase the likelihood of various adverse short and long-term outcomes. Some liver transplant centers perform protocol liver biopsy after transplantation, even in those patients with normal liver function tests. Protocol biopsies are usually ordered at 1-, 3-, and 5-year post-transplantation.

The Banff Working Group on Liver Allograft Pathology periodically updates its guidelines for studying liver allograft biopsies. In this review, we aim to provide a basic approach to interpret orthotopic liver transplant biopsies. This article may be beneficial for surgical pathologists, pathology residents interested in liver pathology, or gastrointestinal and liver pathology fellows in the early stages of their training.

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INTRODUCTION

Liver disease is a major cause of morbidity and mortality worldwide. Liver transplantation is currently the standard treatment for various forms of severe liver disease, including acute liver failure or end-stage disease due to any etiology, as well as selected metabolic and neoplastic conditions. Short-term and long-term outcomes of recipients of liver transplantation are excellent, with published 5-year and 10-year graft survival rates of 81% and 64%, respectively.[1]

According to data from the United Network for Organ Sharing in 2022, alcohol-associated liver disease was the most

common indication for adult liver transplantation, followed by metabolic dysfunction-associated steatohepatitis, hepatocellular carcinoma, cholestatic liver disease, HCV-related cirrhosis, and acute liver failure. The primary disease was unknown in 14.5% of transplant cases.[2] Living donor liver transplantation accounts for approximately 5% of all livers transplanted in North America and Europe, but represents most of the transplants performed in Asia. [3]

Acute cellular rejection is the most common liver allograft rejection. Out of 796 liver transplant biopsies, acute rejection occurred in 278 (34.9%) cases. Out of those acute rejection cases, T-cell–mediated rejection was seen in 254 (91.4%) cases and antibody-mediated rejection in 26 (8.6%) cases.[4]

EVALUATION OF DONOR LIVER BIOPSY

Liver biopsy is an important tool in the evaluation of potential allografts. Frozen-section evaluation of the liver of extended donor criteria (ECD) confirms the quality /viability of the donor organ and excludes features that would either contraindicate transplantation or increase the likelihood of various adverse short and long-term outcomes.

The criteria included in ECDs are advanced donor age (>60 years), large-droplet macrovesicular steatosis (>40%), cold ischemia time (>12 hours), partial liver allografts, donation after cardiac death (DCD), hemodynamic instability, use of vasopressors, hypernatremia, HBV or HCV infection or hepatitis B core antibody (anti-HBc) positivity, history of cancer, or finding of a liver mass, fibrosis, or other focal lesions.[5]

The checklists for deceased or living donors are as below (fig. 1):

- Macrovesicular steatosis, estimated to the nearest 10% (clinical cutoff for donor suitability is <30%)
- Inflammation, portal or lobular, is graded as minimal, mild, moderate, or marked
- Necrosis is estimated to the nearest 10% and indicates zonation and distribution (e.g., focal, diffuse, etc.)
- Fibrosis (pericellular, portal, bridging, cirrhosis)
- Other findings, like granuloma, excessive pigments, and cholestasis

A sample of the donor liver evaluation form (fig. 1) is given below.[6]

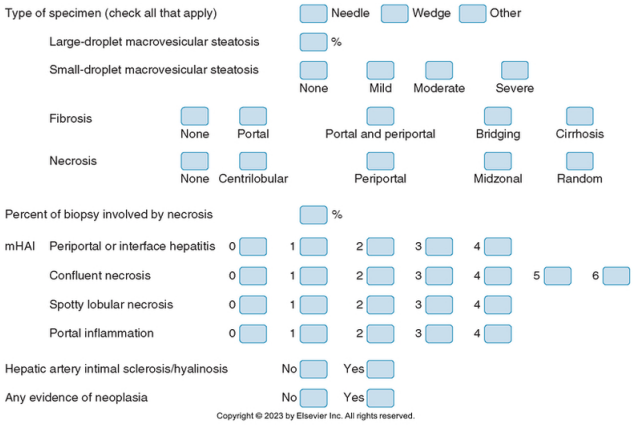

Figure 1: *The percentage of large-droplet macrovesicular steatosis should be estimated and recorded. We record small-droplet macrovesicular steatosis (formerly microvesicular steatosis) semiquantitatively as none, mild, moderate, or severe.*

LIVER ALLOGRAFT BIOPSY

Accurate liver allograft biopsy interpretation requires familiarity with the type of donor and complications during the operation. In Western countries, orthotopic liver transplantation with a whole cadaveric donor liver is the most common procedure. End-to-end anastomoses connect the recipient and donor portal vein, hepatic artery, bile duct (except for those with primary sclerosing cholangitis), and vena cava. Donor and recipient are usually matched for size and ABO blood group, unless the recipient is critically ill or the donor pool is limited by blood type.

Optimal information needed for interpretation of posttransplantation allograft biopsies includes serial laboratory results, immunosuppression drug level, the original disease, ABO compatibility, donor-specific antibody (DSA) status, time after transplantation, and type of donor and transplant operation (e.g., standard whole-organ cadaveric, donation after cardiac death, reduced-size cadaveric, living related).

Allograft biopsies are used to:

- determine the causes of graft dysfunction (preservation injury, graft rejection, drug-induced liver injury, viral infection, bile duct injury, or recurrent disease)
- assess the effect of therapy or progression of disease, and
- document the immunological and architectural tissue status to help guide immunosuppressive therapy.

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Out of 875 protocol biopsies of liver transplantation at Helsinki University Hospital, 20.1% of biopsies showed significant pathological findings.[7]

Therefore, liver transplant centers usually perform protocol liver biopsy after transplantation, even with normal liver function tests. Protocol biopsies are usually ordered at 1-, 3-, and 5-year post-transplant for the following:

- Any recipient of a Hepatitis C NAT-positive graft.
- Any recipient with a donor biopsy showing fibrosis stage 1 and above.

  Any recipient with a donor biopsy showing 40% or more steatosis.

For medical liver diseases, the biopsy core should be at least 3 cm long, with >10 portal tracts to be adequate for evaluation. However, for transplant biopsy, a minimum length of 2 cm, 10 complete portal triads, or 13 partial/complete portal triads should be obtained for exclusion and grading of acute cellular rejection.[8]

The most frequently used special stains, which are ordered only after review of the two H&E-stained slides, include trichrome, PAS-D, iron, and copper to detect chronic cholestasis.

Post-transplant complication

There are many causes of allograft injury in addition to rejection, and these should be considered in the context of the time elapsed since transplantation.

- Preservation/reperfusion injury (first few weeks after Orthotopic Liver Transplantation)
- Allograft rejection
  - Early acute antibody-mediated rejection (AMR)
  - Acute Cellular Rejection (ACR)/T cell-mediated rejection (TCMR)
  - Plasma cell-rich rejection
  - Chronic rejection
- Biliary tract obstruction
- Thrombosis of the hepatic artery or portal vein
- Venous outflow obstruction
- Post-transplant infections (CMV, HSV, human herpes virus 6 and 8, EBV, adenovirus)
- Drug toxicity
- Recurrence of the original disease
- Neoplastic disease
- Posttransplant lymphoproliferative disorder

Different categories of complications are strongly associated with specific post-transplant periods (fig. 2).[9]

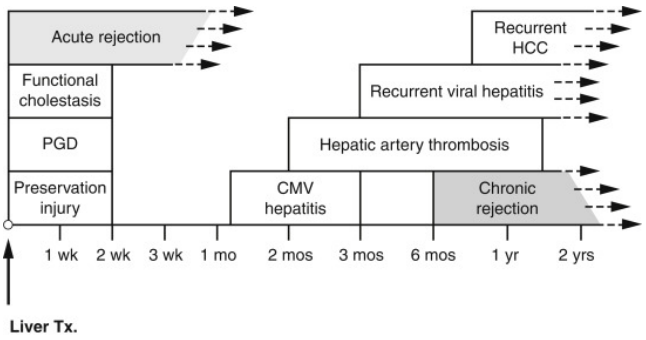

Figure 2: *Common post-transplantation complications, correlated with the approximate time frame in which they develop. Hatched arrows indicate the potential for the condition to develop later. CMV, Cytomegalovirus; HCC, hepatocellular carcinoma; PGD, primary graft dysfunction; Tx, transplantation.*

Preservation/reperfusion injury, vascular thrombosis, and acute rejection are the leading causes of allograft failure within the first several weeks after transplantation. From the second week to 6 months, vascular complications, CMV and other infections, biliary stricture, ACR, and early onset of chronic rejection are common. After 3-6 months to years of transplantation, recurrent viral hepatitis, recurrent autoimmune diseases, de novo diseases, chronic rejection, and posttransplantation lymphoproliferative disorder are common.

PRESERVATION/REPERFUSION INJURY

This refers to a constellation of functional and histological abnormalities related to harvesting, preservation, and reperfusion of allografts. Pathogenesis is primarily related to warm ischemia (hepatocyte injury if >120 minutes), cold ischemia (endothelial cell injury if >12 hours), and reperfusion (both hepatocyte and endothelial cell injury due to reactive oxygen species).

Histological features include prominent zone 3 hepatocyte swelling, hepatocyte necrosis, mild Kupper cell hyperplasia, microvesicular steatosis, lipopeliosis (extrusion of fat from hepatocyte into sinusoids), mild lobular cholestasis, and minimal to mild non-specific portal inflammation (fig. 3).[6] The differential diagnosis includes antibody-mediated rejection (AMR), biliary obstruction, vascular thrombosis, or drug-induced injury.

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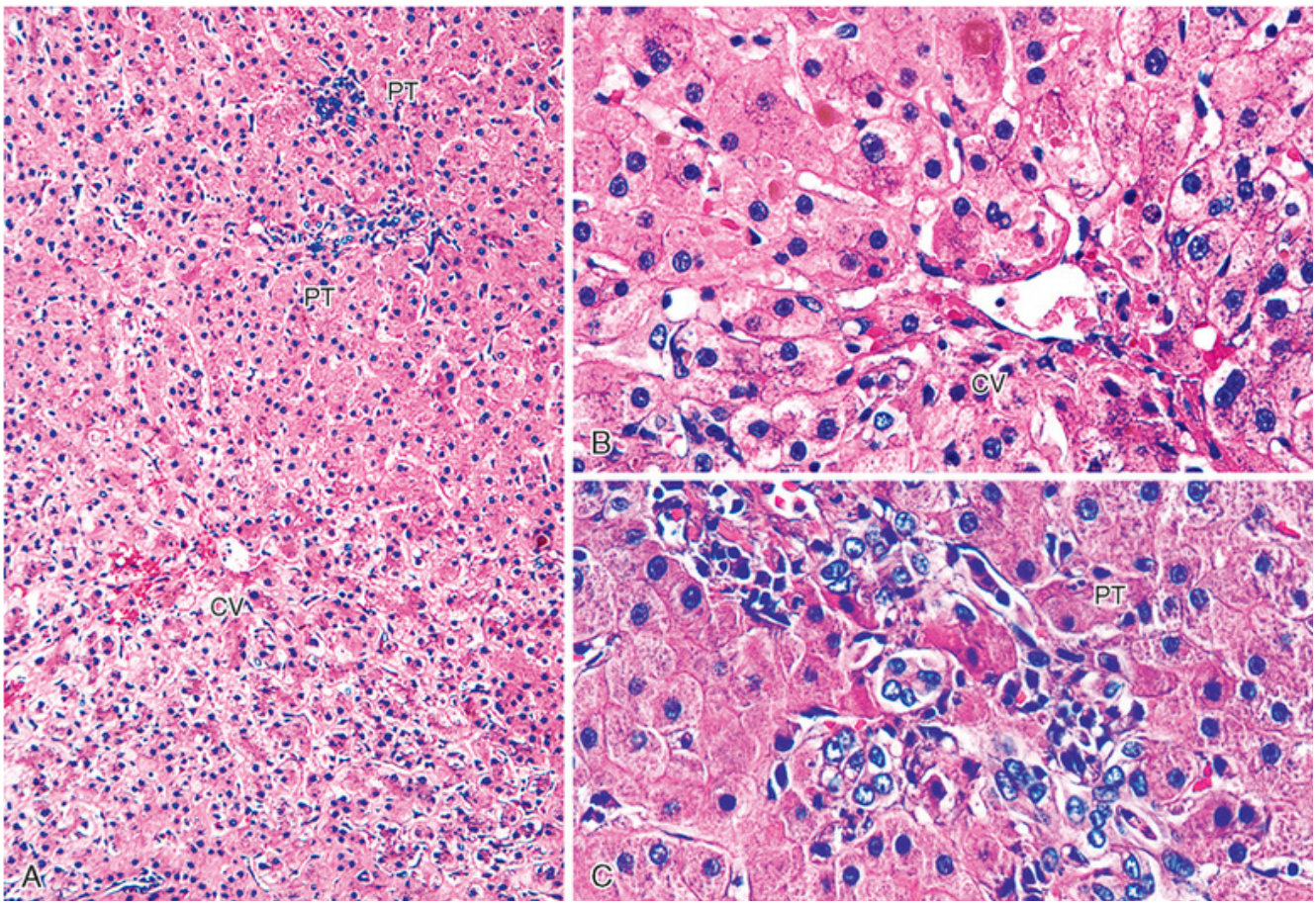

Figure 3: *Mild preservation/reperfusion injury is characterized by centrilobular hepatocyte swelling (A) and mild canalicular cholestasis (B). Note the minimal ductular reaction with no portal edema or inflammation (C). CV, Central vein; PT, portal tract.*

SMALL-FOR-SIZE SYNDROME

Portal hyperperfusion/small for size syndrome occurs most commonly in allograft liver that are less than 30% of the ideal recipient liver volume or less than 0.8% of the recipient body weight.[10]

The histological changes include portal vein dilatation, zone 1 sinusoidal dilatation, and hemorrhage into the portal tract connective tissue. The flow chart showing causes of early graft dysfunction are shown in figure 4. [6]

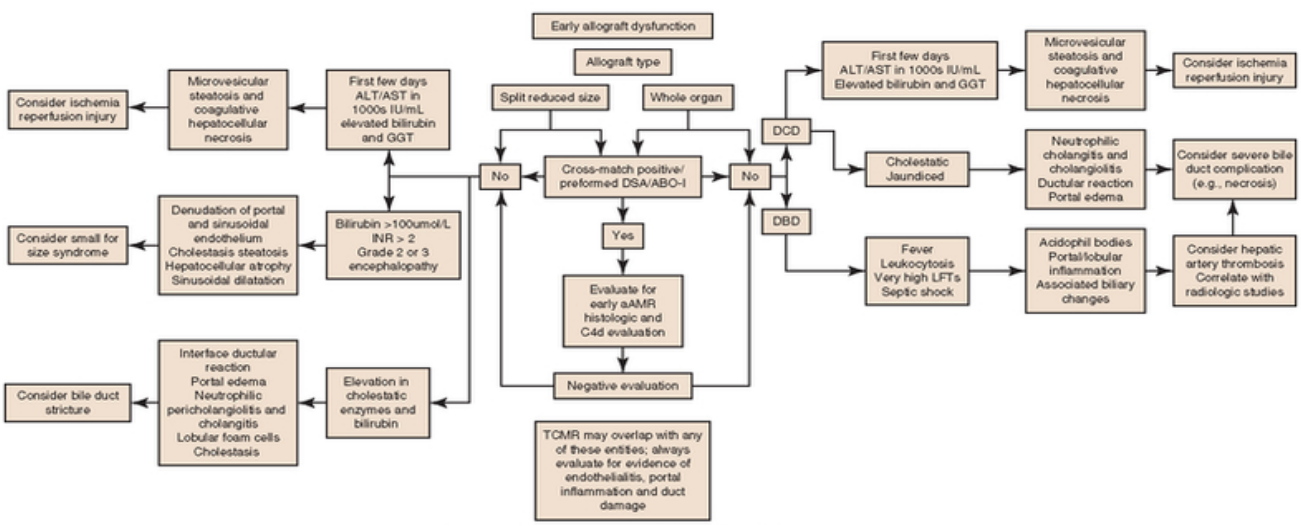

Figure 4: *Flow chart showing causes of early allograft dysfunction. DCD: donation after cardiac death, DBD: donation after brain death*

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ALLOGRAFT REJECTION

The histopathological lesions of liver allograft rejection are broadly classified as AMR, acute cellular rejection/T-cell mediated rejection (ACR/TCMR), plasma cell-rich rejection, and chronic (ductopenic) rejection.

Antibody-Mediated Rejection

Antibody-mediated rejection is rare after liver transplantation and accounts for 8.6% of total acute allograft rejection biopsies.[4] It has been best studied in recipients of ABO-incompatible allografts. AMR results from circulating antibodies that recognize donor antigen in the transplanted liver, leading to graft injury.

Criteria and categories for the diagnosis of acute AMR have been defined by the Banff Working Group based on a combination of clinical, histopathological, and serological findings.[11]

Definite for acute/ active AMR (all 4 criteria required; fig. 5)[6]

a. Histopathological pattern of injury consistent with acute AMR, portal microvascular endothelial cell hypertrophy, portal capillary and inlet venule dilation, monocytic, eosinophilic, and neutrophilic portal microvasculitis, portal edema ductular reaction, and cholestasis

b. Positive serum DSA (MFI usually >5000)

c. Diffuse microvascular endothelial C4d deposition (C4d score = 3) on formalin-fixed or frozen tissue in ABO-compatible allografts and/or portal stromal C4d in ABO-incompatible allografts.

d. Reasonable exclusion of other insults that may cause a similar pattern of injury

Suspicious (both criteria required)

a. DSA is positive

b. Nonzero h-score with (C4d-score + h-score = 3 or 4)

Indeterminate (requires a + b and c or d)

a. C4d-score + h-score = >2

b. DSA not available, equivocal, or negative

c. C4d staining not available, equivocal, or negative

d. Coexisting insult may be contributing to the injury

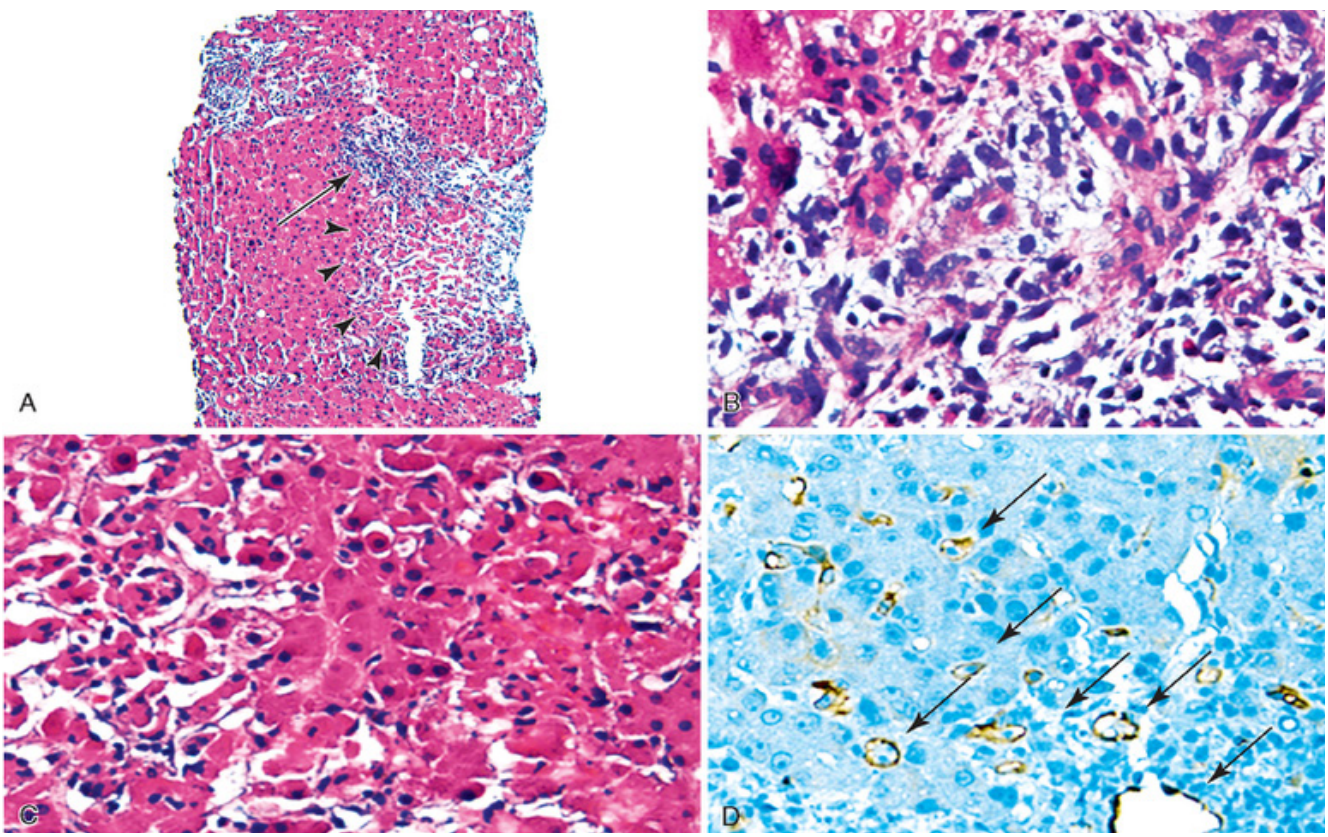

Figure 5: *AMR, 5 days after transplantation of an ABO-incompatible organ. A. Portal tract with neutrophilic cholangiolitis and a small periportal infarct (arrowheads). B. The portal or periportal region indicated by the arrow in A is shown at higher magnification. C. Focal sinusoidal congestion adjacent to a small infarct. D. C4d immunostaining highlights the endothelium of portal veins, capillaries, and sinusoidal cells (arrowhead).*

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Banff working group stresses the importance of these microvascular changes as signature lesions of acute AMR and proposed a histopathology score (h score)[11] as part of the criteria for diagnosing aAMR as below:

1. Portal microvascular endothelial cell enlargement (portal veins, capillaries, and inlet venules) involving a majority of portal tracts with sparse microvasculitis defined as three to four marginated and/or intraluminal monocytes, neutrophils, or eosinophils in the maximally involved capillary with generally mild dilation.
2. Monocytic, eosinophilic, or neutrophilic microvasculitis/capillaritis, defined as at least 5 to 10 leukocytes marginated and/or intraluminal in the maximally involved capillary, prominent portal and/or sinusoidal microvascular endothelial cell enlargement involving a majority of portal tracts or sinusoids, with variable but noticeable portal capillary and inlet venule dilation and variable portal edema.
3. As above, with marked capillary dilation, marked microvascular inflammation (10 or more marginated and/or intraluminal leukocytes in the most severely affected vessels), at least focal microvascular disruption with fibrin deposition, and extravasation of red blood cells into the portal stroma and/or the space of Disse.

The chart depicting the current understanding of AMR is given in figure 6.[6]

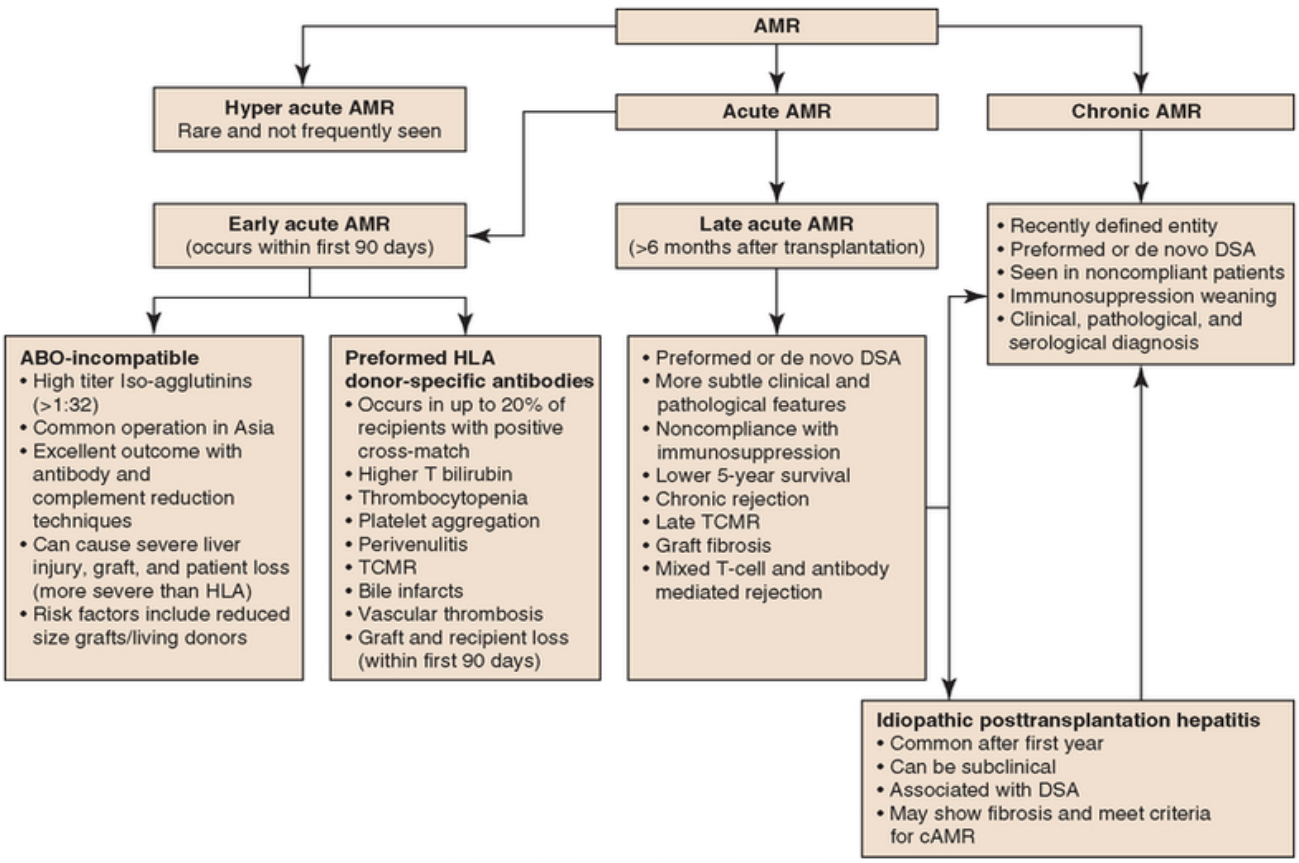

Figure 6: *AMR can be subcategorized into hyperacute (rarely seen), early aAMR, late-onset aAMR, and chronic active AMR (likely the leading cause of pediatric re-transplantation).*

Sinusoidal CD163, Banff H-score, and diffuse C4d are predictors of serum DSA and facilitate recognition of histopathological features associated with serum DSA and tissue-antibody interaction.[12] The differential diagnoses include preservation/reperfusion injury, early biliary obstruction, and hepatic artery thrombosis

Acute Cellular Rejection/T-Cell Mediated Rejection

ACR/ TCMR is the most common form of liver allograft rejection. The rate of acute TCMR after liver transplantation has been reported to be 91.4% of total acute rejection cases.[13] It can occur early (within 6 months), likely secondary to direct alloantigen presentation, or late (>6 months), likely secondary to indirect alloantigen presentation.

Classic early ACR/TCMR (initial 1-3 months): It shows the typical triad of mixed portal inflammation, lymphocytic cholangitis/bile duct injury, and venous endothelial inflammation (endotheliitis). Minimal diagnostic criteria needed to establish a diagnosis of acute TCMR include at least two of the aforementioned pathological findings. (fig. 7)[6]

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- Portal inflammation is composed of activated lymphocytes, scattered eosinophils, neutrophils, plasma cells, and macrophages. Eosinophils are often abundant.
- Bile duct damage with intraepithelial lymphocytes; nuclear overlapping, enlargement, pleomorphism; cytoplasmic vacuolation and eosinophilia
- Endotheliitis with subendothelial lymphocytes, lymphocytes attached to endothelium; endothelium damaged, swollen, detached

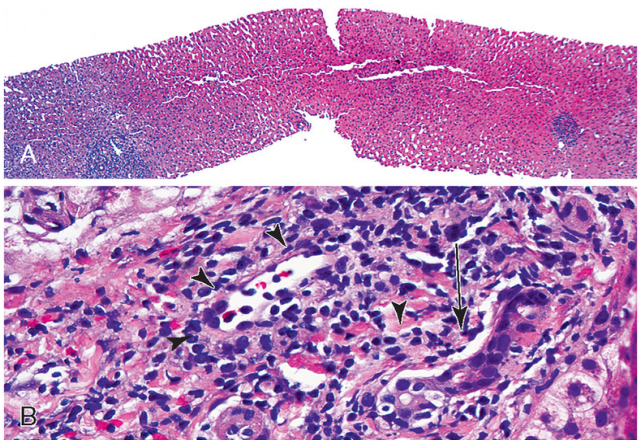

Figure 7: *A. Low power view of ACR with mild portal inflammation. B. The three typical features of classic ACR can be seen at higher magnification [H&E].*

The infiltrate contains blast-like and smaller lymphocytes, eosinophils, and occasional neutrophils and macrophages. Inflammatory bile duct damage (arrow) and subendothelial infiltration of the portal vein branches (arrowheads) are evident.

Shi Y et al suggested that sinusoidal endotheliitis scoring could be a reliable parameter to the existing Banff schema for diagnosing acute liver allograft rejection.[14]

The qualitative assessment of ACR/TCMR has been updated by Banff working Groupfor liver allograft rejection (Table 1).[11]The Working Group also developed a method for *quantitative* assessment of allograft rejection (Table 2)[11], called the rejection activity index (RAI) wherein each of the triad of histologic findings for ACR (portal inflammation, bile duct inflammation, and venous endothelial inflammation) are each graded on a 3-point scale, resulting in scoring scheme ranging from 3 to 9, with 9 being most severe.

Table 1: Banff grading criteria for ACR/TCMR (Global assessment)

Grade	Criteria
Indeterminate	Portal inflammatory infiltrate that fails to meet the criteria for 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 or all portal tracts.
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 is made on a review of the biopsy and after the diagnosis of rejection has been established.

Table 2: Banff grading criteria for ACR/TCMR (Rejection activity index, RAI)*

Category	Criteria	Score
Portal inflammation	Mostly lymphocytic 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 nucleus-to-cytoplasm ratio of the epithelial cells	1
	Most or all of the ducts are infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, 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 most of the portal and/or hepatic venules	1
	Subendothelial infiltration involves most or all 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

*The Rejection Activity Index (RAI) is the sum of the scores for each of the three components of acute rejection. RAI ≥ 4 (mild), RAI ≥ 6 (moderate or severe).

Histological variants of late ACR/TCMR

- Isolated central perivenulitis: no typical portal features
- Plasma cell-rich rejection: Portal &/or perivenular inflammation with > 30% plasma cells, original disease other than autoimmune hepatitis
- Hepatic rejection: lobular necroinflammation not restricted to interface or perivenular areas
- Idiopathic post-transplant hepatitis: chronic hepatitis with no identifiable cause, variable interface or lobular activity, no ductopenia, bile duct damage, endotheliitis

Differential diagnosis

For a typical case of early ACR/TCMR, preservation injury and drug reactions are mimickers. Drug reaction can be associated with bile duct inflammation and increased eosinophils. Cholestasis that is out of proportion to the degree of bile duct injury, therefore, represents a useful feature to favor the drug effect. Biliary obstruction is associated with neutrophilic cholangitis.

In the late post-transplant period (3 months or later), de novo or recurrent autoimmune hepatitis or recurrent hepatitis C are close mimickers.

CHRONIC REJECTION

Chronic rejection (vanishing bile-duct syndrome) is characterized by bile duct loss (ductopenia) and/or obliterative arteriopathy of medium and large-sized vessels. Degenerative bile duct epithelial changes like nuclear pleomorphism and hyperchromasia often precede frank ductopenia. Ductopenia is typically defined as the absence of bile ducts in >50% of portal tracts. In needle core biopsy, a useful method of assessing bile duct loss is to identify branches of the hepatic artery. These small arteries run side by side with smaller bile ducts, and both structures should normally be identified in proximity on histologic sections (bile duct-hepatic artery parallelism). Cytokeratin 7 or 19 immunostains are useful for evaluating bile duct loss. Histologic findings of early and late chronic rejection are given below.[15]

Early chronic rejection (fig. 8)[6]

Small bile ducts (<60 μm): a)Senescence-related changes involving most ducts: eosinophilic transformation of the cytoplasm; nuclear hyperchromasia; uneven nuclear spacing; ducts only partially lined by biliary epithelial cells; b) Bile duct loss in <50% of portal tracts

Terminal hepatic venules and zone 3 hepatocytes: Intimal inflammation, lytic zone 3 hepatocyte necrosis and inflammation, mild perivenular fibrosis.

Portal tract hepatic arterioles: Occasional loss involving <25% of the portal tract, transition hepatitis with spotty necrosis of hepatocytes

Others: So-called 'transition' hepatitis with spotty necrosis of hepatocytes

Large perihilar hepatic artery branches: Intimal inflammation, focal foam cell deposition without lumenal compromise.

Large perihilar bile ducts: Inflammatory damage and focal foam cell deposition

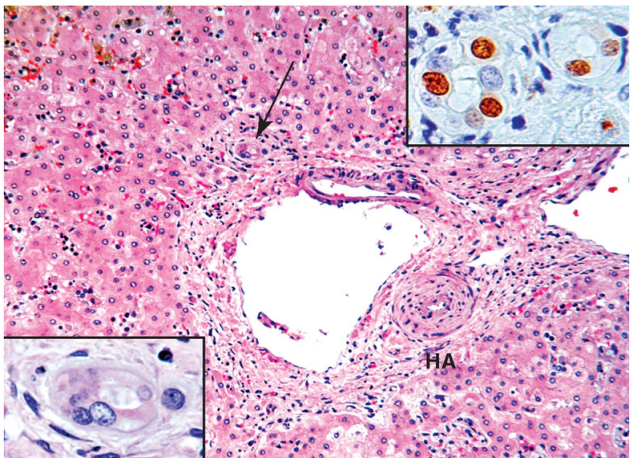

Figure 8: *Early chronic rejection is characterized by senescence changes of the biliary epithelium (arrow and bottom inset), such as cytoplasmic eosinophilia, syncytial formation, ducts partially lined by epithelial cells, and expression of CDKN1A (top inset) without simultaneous expression of Ki67. Note the fibrointimal hyperplasia and luminal narrowing of a branch of the hepatic artery (HA).*

Late Chronic rejection (fig. 9)[6]

Small bile ducts (<60 μm): a) Degenerative changes in remaining bile ducts; b) Bile duct loss in equal or more than 50% of portal tracts

Terminal hepatic venules and zone 3 hepatocytes: Focal obliteration, variable inflammation, severe (bridging) fibrosis.

Portal tract hepatic arterioles: Loss involving >25% of the portal tract, other findings include sinusoidal foam cell accumulation and marked cholestasis.

Other: Sinusoidal foam cell accumulation, marked cholestasis

Large perihilar hepatic artery branches: Luminal narrowing by subintimal foam cells, fibrointimal proliferation.

Large perihilar bile ducts: Mural fibrosis

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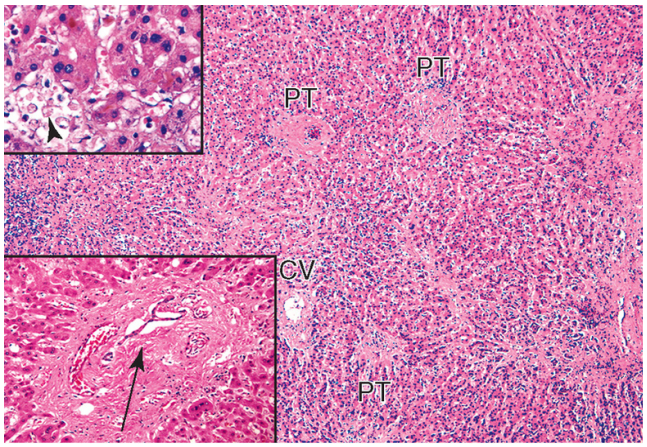

Figure 9: *Severe perivenular fibrosis and at least focal central-to-central bridging fibrosis. It is almost invariably accompanied by centrilobular hepatocanalicular cholestasis and intrasinusoidal foam cell clusters (top inset, arrowhead). In the portal tracts, the late stage of chronic rejection is characterized by loss of small hepatic artery branches and small bile ducts, although an occasional biliary epithelial cell can be detected in portal tracts (bottom inset, arrow). CV, Central vein; PT, portal tract.*

The obliterative arteriopathy (fig. 10) [6] involve large and medium sized arteries near the hepatic hilum (commonly recognized in failed allografts). It is characterized by infiltration of foamy macrophages in subintimal space and, less commonly, within deeper layer of vascular wall.

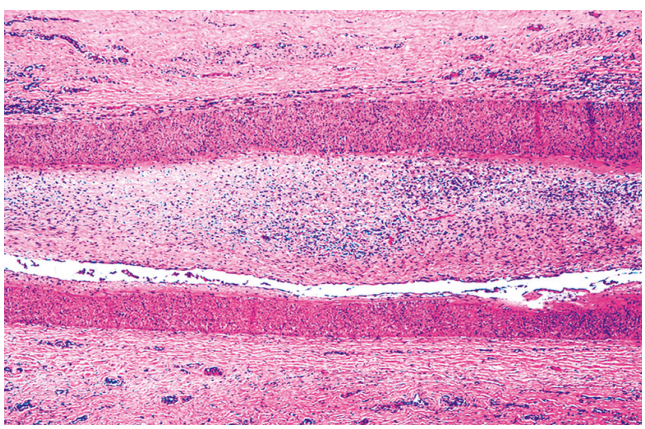

Figure 10: *The obliterative arteriopathy is characterized by intimal thickening and narrowing of the lumen. Intimal thickening is related to the deposition of foamy macrophages and proliferation of myofibroblasts, which are intermixed with lymphocytes and foamy macrophages.*

Differential diagnosis of chronic rejection includes primary sclerosing cholangitis, chronic biliary obstruction, which histologically exhibits biliary obstruction associated with portal edema early in its course, followed by significant ductular reaction, and Drug-Induced Vanishing Bile Duct Syndrome.

LATE LIVER ALLOGRAFT DYSFUNCTION (>1 YEAR)

In adults, recurrence of the patient's original disease (Autoimmune hepatitis, alcohol induced liver disease, Primary biliary cirrhosis, primary sclerosing cholangitis, or bile duct stricture or chronic viral hepatitis B and C) is quite common and a significant cause of late liver allograft injury, whereas TCMR is most common in pediatric recipients.[16]

Rejection (TCMR and chronic AMR) is playing an increasingly common role in late graft injury along with recurrent hepatocellular and cholangiocarcinomas, and metabolic conditions (e.g., alcohol abuse, adverse drug reactions, metabolic syndrome). Criteria used to diagnose the various causes of late liver allograft dysfunction should be supported by positive serological, molecular, immunological, or radiographic evidence.

VASCULAR COMPLICATIONS

Most vascular complications are related to anastomotic imperfections (e.g., narrowing, flaps, dramatic caliber reductions), preexisting donor atherosclerotic disease, vascular tree trauma, creation of kinks or abnormal tortuosity, metabolic or physiological abnormalities that predispose to thrombosis, or a combination of these factors.

Hepatic Artery Thrombosis

- Zone 3 hemorrhage and hepatocyte dropout in the early posttransplant period
- Ischemic bile duct injury: a) Denuded, necrotic bile duct epithelium sloughs into the lumen, forming eosinophilic bile casts; b) Bile leakage into the periductal connective tissue; c) In time, chronic ischemia can lead to biliary strictures, fibrosis, and duct loss
- Hepatic infarction: Necrosis of hepatocytes and portal connective tissue

Portal vein thrombosis and venous outflow obstruction

Portal vein complications are less common than hepatic artery complications. The histological findings depend on the severity of portal vein flow compromise, time after transplantation, and the structural integrity of the allograft. Complete portal vein obstruction after transplantation in a noncirrhotic allograft often causes massive coagulative necrosis with sinusoidal dilatation, along with areas of centrilobular congestion and hemorrhage.

Miscellaneous findings in liver allograft biopsy are: Mild non-specific portal and lobular inflammation; b) Wall thickening and hyalinization of hepatic artery branches, portal venopathy; c) Von Meyenburg complex; d)Nodular regenerative hyperplasia; e) Sinusoidal fibrosis; f)Pseudo groundglass inclusion in hepatocytes mimicking Hepatitis B-related ground glass cells.

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Pseudo–ground-glass cells are probably related to abnormal glycogen accumulation within the cytoplasm of hepatocytes and typically occur in the setting of multimedication therapy. Similar deposits can be seen in Lafora disease, type IV glycogenosis, adult-onset polyglucosan disease, fibrinogen storage disease, and inclusions associated with cyanamide therapy.

CONCLUSIONS

Evaluation of orthotopic liver transplant biopsy needs extensive clinicopathological correlation, including the type of donor, time for cold and warm ischemia, and the specific post-transplantation period of biopsy taken. The Banff Working Group on Liver Allograft periodically updates a set of consensus criteria for the evaluation of liver allograft biopsy. Common differential diagnoses of allograft rejection and vascular complications are also briefly discussed. By emphasizing key histological features of allograft rejection of orthotopic liver transplant biopsy along with differential diagnoses, the review may be beneficial for surgical pathologists, pathology residents interested in liver pathology, or gastrointestinal and liver pathology fellows in the early stages of their training.

REFERENCES

1. Kwong AJ, Ebel NH, Kim WR, et al. OPTN/SRTR 2021 Annual Data Report: Liver. Am J Transplant. 2023;23(2 Suppl 1):S178-263. doi: 10.1016/j.ajt.2023.02.006.
2. Kwong AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2022 Annual Data Report: Liver. Am J Transplant. 2024;24(2S1):S176-265. doi: 10.1016/j.ajt.2024.01.014
3. Tanaka K, Kiuchi T. Living-donor liver transplantation in the new decade: perspective from the twentieth to the twenty-first century. J HepatobiliaryPancreat Surg. 2002;9(2):218-22. doi: 10.1007/s005340200022.
4. Tang LCY, Chetwood JD, Lai MSM, et al. Incidence, epidemiology, and outcomes of acute allograft rejection following liver transplantation in Australia. Liver Transpl. 2024;30(10):1039-49. doi: 10.1097/LVT.0000000000000375.
5. Vodkin I, Kuo A. Extended Criteria Donors in Liver Transplantation. Clin Liver Dis. 2017;21(2):289-301. doi: 10.1016/j.cld.2016.12.004.
6. Robert D. Odze, John R. Goldblum. Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas. pp1628-90.
7. Liukkonen VH, Nordin AJ, Färkkilä MA, Mirtti TK, Arola JT, Åberg FO. Protocol liver biopsy predicts graft survival after liver transplantation. Clin Transplant. 2024;38(3):e15286. doi: 10.1111/ctr.15286.
8. Agarwal AN, Nania J, Qiu L, Lewis B, Mais DD. Impact of Liver Biopsy Size on Histopathologic Evaluation of Liver Allograft Rejection. Arch Pathol Lab Med. 2022;146(12):1530-4. doi: 10.5858/arpa.2021-0257-OA.
9. Jay H. Lefkowitch . Scheuer's Liver Biopsy Interpretation. pp: 380-409.
10. Demetris AJ, Kelly DM, Eghtesad B, t al. Pathophysiologic observations and histopathologic recognition of the portal hyperperfusion or small-for-size syndrome. Am J SurgPathol. 2006;30(8):986-93. doi: 10.1097/00000478-200608000-00009.
11. Demetris AJ, Bellamy C, Hübscher SG, e al. 2016 Comprehensive Update of the Banff Working Group on Liver Allograft Pathology: Introduction of Antibody-Mediated Rejection. Am J Transplant. 2016;16(10):2816-35. doi: 10.1111/ajt.13909.
12. El Hag MI, Kaneku H, Jorgensen D, et al. Morphologic and immunophenotypic evaluation of liver allograft biopsies with contemporaneous serum DSA measurements. Clin Transplant. 2023;37(8):e14997. doi: 10.1111/ctr.14997.
13. Tang LCY, Chetwood JD, Lai MSM, et al. Incidence, epidemiology, and outcomes of acute allograft rejection following liver transplantation in Australia. Liver Transpl. 2024;30(10):1039-49. doi: 10.1097/LVT.0000000000000375.
14. Shi Y, Dong K, Zhang YG, et al. Sinusoidal endotheliitis as a histological parameter for diagnosing acute liver allograft rejection. World J Gastroenterol. 2017;23(5):792-9. doi: 10.3748/wjg.v23.i5.792.
15. Demetris A, Adams D, Bellamy C, 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;31(3):792-9. doi: 10.1002/hep.510310337.
16. Feng S, Bucuvalas JC, Demetris AJ, et al. Evidence of Chronic Allograft Injury in Liver Biopsies from Long-term Pediatric Recipients of Liver Transplants. Gastroenterology. 2018 Dec;155(6):1838-51.e7. doi: 10.1053/j.gastro.2018.08.023.