SPECIAL ARTICLE

Liver Biopsy Interpretation for Causes of Late Liver Allograft Dysfunction

Banff Working Group[1]

Evaluation of needle biopsies and extensive clinicopathological correlation play an important role in the determination of liver allograft dysfunction occurring more than 1 year after transplantation. Interpretation of these biopsies can be quite difficult because of the high incidence of recurrent diseases that show histopathological, clinical, and serological features that overlap with each other and with rejection. Also, more than one insult can contribute to allograft injury. In an attempt to enable centers to compare and pool results, improve therapy, and better understand pathophysiological disease mechanisms, the Banff Working Group on Liver Allograft Pathology herein proposes a set of consensus criteria for the most common and problematic causes of late liver allograft dysfunction, including late-onset acute and chronic rejection, recurrent and new-onset viral and autoimmune hepatitis, biliary strictures, and recurrent primary biliary cirrhosis and primary sclerosing cholangitis. A discussion of differential diagnosis is also presented. (HEPATOLOGY 2006;44:489-501.)

Distinguishing among potential causes of late liver allograft dysfunction can be difficult because of overlapping clinical, serological, and histopathological features. Most problematic biopsies are obtained more than 1 year after transplantation. Currently, diagnoses are made using center-specific criteria, but a standardized set of criteria has not been generally agreed upon. Availability of standardized criteria[1,2] would enable centers to compare and pool results, improve therapy, and better understand pathophysiological disease mechanisms.

Native disease recurrence is a significant problem and can be categorized as follows: (1) infectious (viral hepatitis A, B, C, D.), (2) dysregulated immunity (autoimmune hepatitis [AIH], primary biliary cirrhosis [PBC], primary sclerosing cholangitis [PSC], and sarcoidosis),[3] (3) malignancies, (4) toxic (*e.g.*, alcohol, adverse drug reactions.), (5) metabolic disorders, including nonalcoholic steatohepatitis, and (6) other diseases, such as idiopathic granulomatous hepatitis,[4] postinfantile giant cell hepatitis,[5] and Budd-Chiari syndrome,[6] that are of uncertain etiology or multifactorial in origin. Recurrent infectious and dysregulated immunity diseases pose the most difficult diagnostic challenges and are addressed herein. Some diseases in the remaining categories can also recur, but because they do not usually present diagnostic challenges they are not discussed further.

Immunological Considerations

Immune recognition of differences in major histocompatibility complex antigens triggers a characteristically robust inflammatory response in the first few months after transplantation referred to as early acute rejection.[2] Like all other immune responses, acute and especially chronic rejection reactions[7,8] evolve over time and diversify via "epitope spreading."[9] Tissue damage during the initial phase releases cryptic antigens that activate endogenous danger signals. Recipient dendritic cell antigen uptake and self-reactive T and/or B lymphocyte priming[10] triggers "autoantibody" production and immunity directed against non–major histocompatibility complex determinants. Some non–major histocompatibility complex cytoplasmic, nuclear, and matrix protein antigens[11-14] (reviewed in Graft[15-18]) are shared by the donor and recipient, whereas others may be donor-specific.

Long-Term Protocol Biopsies

Most programs obtain biopsies when changes in liver tests represent a significant deviation from baseline values. Obtaining protocol allograft biopsies in asymptomatic

Abbreviations: AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HCV, hepatitis C virus; LAR, late-onset acute rejection.

[1]*See end of article text for complete list of authors and affiliations.*

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Address reprint requests to: A. J. Demetris, M.D., E741 UPMC Montefiore, 200 Lothrop Street, Pittsburgh, PA 15213. E-mail: demetrisaj@upmc.edu; fax: 412-647-2084.

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long-term survivors with normal or near-normal liver tests is controversial. Considerations such as potential morbidity and mortality, cost, inconvenience, use of resources, and potential impact of unexplained histopathological findings should be weighed against potential individual and/or societal benefits.[4,19-24] These include (1) early detection of clinically inapparent disease,[19,24] (2) recognition of nonalcoholic steatohepatitis as a significant cause of cryptogenic cirrhosis in the United States[25] but not in England,[26] (3) identification of recipients that might be successfully weaned from immunosuppression,[27] (4) recognition of late-onset rapid hepatitis C virus (HCV) progression,[21] and (5) impact of alcohol use.[20]

Approximately 75% of biopsies from long-surviving recipients with abnormal liver tests or symptoms show significant histopathological abnormalities.[4,19-23] These abnormalities are usually attributable to recurrent disease or biliary tract strictures, some of which occur as a late complication of preservation injury.[4,19-23] The incidence and significance of histopathological abnormalities in long-surviving recipients without abnormal liver tests or symptoms is dependent on the original disease: up to 25% show significant abnormalities when obtained from recipients with original diseases that commonly recur (*e.g.*, HCV, PBC, AIH).[4,19-23]

Even in the absence of recurrent disease, minor histopathological abnormalities appear in approximately two thirds of biopsies obtained from long-surviving asymptomatic recipients with normal liver tests.[4,19-23] These include nodular regenerative hyperplasia changes and thickening/hyalinization of small hepatic artery branches[4,28] (probably side effects of immunosuppression) and "nonspecific" portal and lobular inflammation.[4,22-24] The pathogenesis, significance, and long-term consequences of nonspecific inflammation (*e.g.*, idiopathic posttransplantation hepatitis), portal venopathy, and nodular regenerative hyperplasia are in need of further study.

Recurrent HCV disease progression is significantly more rapid than HCV in native livers. Disease progression rates for recurrent hepatitis B virus, PBC, PSC, nonalcoholic steatohepatitis, and AIH are difficult to study because of the small number of long-term survivors with biopsies and chronic immunosuppression, as well as introduction of new medical therapies. Regardless, nearly all recurrent diseases can potentially cause allograft cirrhosis.

Practical Problems and Approach to Biopsy Interpretation

Most late causes of liver allograft injury are first detected because of abnormalities in routinely monitored liver tests; clinical signs and symptoms are much less common. When signs or symptoms do occur, they are similar to those seen in the general population with the same causes of liver injury. Examples include fever and upper right quadrant pain in ascending cholangitis; fatigue, nausea, vomiting, and jaundice in viral hepatitis; relapsing bacteria in hepatic infarcts, *etc.*

Many late posttransplantation biopsies show portal-based chronic inflammation with variable interface activity. Subtle histopathological differences relied upon to distinguish among several possible specific causes of dysfunction are not always present or reliable. Occasionally, rendering a definitive diagnosis may not be possible in the early stages of a disorder. A caveat of "features suggestive of early" emphasizes a tentative diagnosis.

Laboratory tests used to establish a diagnosis before transplantation may not have the same significance after transplantation. Antimitochondrial antibodies and antinuclear antibodies often persist after transplantation in patients with PBC or AIH, albeit at lower titers, even without histopathological evidence of recurrent disease. Patients without AIH before transplantation can develop autoantibodies either as a complication of otherwise typical rejection[11,12,29] or in association with new-onset AIH.[30-36] "Non–organ-specific" autoantibodies have been detected in up to 71% of patients after liver transplantation,[37] emphasizing the need for clinicopathological correlation.

More than 1 insult can contribute to late posttransplantation dysfunction. Biopsy analysis can help to determine the main component of injury, but careful clinicopathological correlation is needed. Levels of immunosuppression can influence biopsy findings and the severity of recurrent viral hepatitis, AIH, and rejection. For example, late-onset acute rejection (LAR) is often precipitated by inadequate immunosuppression and recipients with AIH and other autoimmune disorders usually require more immunosuppression to prevent rejection and disease recurrence. Too much immunosuppression can trigger cholestatic HCV hepatitis. Lymphoid depletion followed by rapid withdrawal of immunosuppression can precipitate aggressive HCV recurrence.[38]

Biopsy interpretation should include an assessment of adequacy, systematic examination, and thorough clinicopathological correlation. Adequacy is ultimately the subjective opinion of the pathologist, but in general, at least 6 small portal tracts should be sampled. The findings should then be correlated with the original disease, immunosuppression, liver tests, viral serology, and immunology and radiology findings.

Generalized Criteria

Criteria used to distinguish rejection from AIH can be melded into generalized criteria applicable to other causes

Table 1. Incidence, Risk Factors, and Clinical Observations

Diagnosis	Incidence at 5 Years of Recurrent Disease	Risk Factors for Disease Recurrence and/or Severe Recurrent Disease	Clinical/Immunological/Radiological Observations
Recurrent AIH	~30%	Suboptimal immunosuppression; type I > type II disease; severe inflammation in native liver before transplantation; longer duration of follow-up HLA DR3 or DR4 recipient status may reflect more severe disease	Usually need higher baseline immunosuprression (see text) HLA DR3 and/or DR4 genotype often present
De novo AIH	<5%	May be more common in children, but this assumption has been questioned recently	Same as above
Recurrent HBV	100% if HBV DNA is positive; less frequent if HBV DNA is negative	Anti-HBc–positive donor Inadequate anti-HBV treatment HBV mutants	Recurrent HBV disease not usually a significant problem because of treatment with effective antiviral drugs
Recurrent HCV	Nearly universal in those with HCV replication before transplantation	HCV RNA in blood helpful in differential diagnosis (>30,000,000 IU/L); increased risk of cholestatic hepatitis Significant acute or chronic rejection usually occurs only in association with relatively low HCV RNA levels (<5,000,000 IU/L)	Greater viral burden and more rapid progression of fibrosis than in general population Severity of hepatitis often worse with genotype 1 viruses Variable disease progression Subset of recipients with late-onset rapid progression
Recurrent PBC	20%-30%; increases with time	Tacrolimus as baseline immunosuppression; living-related donor; steroid and other immunosuppression withdrawal May recur as AIH	Initial diagnosis often made via biopsy in asymptomatic recipient with or without increased liver tests
Recurrent PSC	20%-30%; increases with time	Male sex; donor–recipient sex mismatch Intact colon at time of transplantation Patients at increased risk of rejection	Cholangiographically confirmed biliary strictures occurring >90 days after liver transplantation Mural irregularity, diverticulum-like outpouchings, and an overall appearance resembling PSC Patient and allograft survival not adversely affected up to 5 years; later outcome uncertain
Acute rejection	Variable; <30% of causes of late dysfunction	Inadequate immunosuppression Treatment with immune-activating drugs (*e.g.*, interferon) History of autoimmune liver disease	Much less common than early after transplantation May be more difficult to treat, perhaps related to delay in diagnosis.
Chronic rejection	~3 %	Inadequate immunosuppression Treatment with immune-activating drugs (*e.g.*, interferon) Refractory acute rejection Chronic rejection in a previous failed allograft	Important cause of late dysfunction Most cases occur within first year Does not appear to increase with time after transplantation, but more follow-up is needed.
Idiopathic posttransplantation hepatitis	5%-60%; wide variation		5%-15% of patients followed for a minimum of 10 years will develop progressive fibrosis resulting in established cirrhosis Incidence varies widely among centers

Abbreviations: AIH, autoimmune hepatitis; HBV, hepatitis C virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

of late liver allograft dysfunction,[39-56] including: (1) histopathological evidence of liver injury showing a pattern compatible with the diagnosis (liver tests are usually elevated in a pattern consistent with the diagnosis); (2) positive serological, molecular biological, immunological, or radiographic evidence of pathogen or possible cause of injury; and (3) other causes of similar histopathological changes and elevated liver tests, if present, have been reasonably excluded.

Table 1 shows approximate incidences, risk factors, and clinical, immunological, and radiological observations for common causes of late dysfunction. Specific diagnoses can be rendered when these observations are combined with histopathological findings (Table 2), tim-

Table 2. Histopathologic Features Most Commonly Detected With Various Causes of Late Liver Allograft Dysfunction

Histopathological Features	Autoimmune Hepatitis*	Acute Rejection	Chronic Rejection	Chronic Viral Hepatitis Types B and C	Primary Biliary Cirrhosis	PSC/BD Strictures
Distribution, severity, and composition of portal inflammation	Usually diffuse; predominantly mononuclear of varying intensity; often prominent plasma cell component	Usually diffuse; variable intensity; mixed "rejection-type" (see text) infiltrate	Patchy; usually minimal or mild lymphoplasmacytic	Patchy; variable intensity; predominantly mononuclear; nodular aggregates	Noticeably patchy and variable intensity; predominantly mononuclear; nodular aggregates and granulomas	Usually patchy to diffuse depending on stage; mild neutrophilic, eosinophilic, or occasionally mononuclear predominant
Presence and type of interface activity	Prominent and defining feature is usually necroinflammatory-type; often plasma cell–rich	Focally present and mild necroinflammatory type	Minimal to absent	Variable; usually not prominent: necroinflammatory- and ductular-type	Important feature later in disease development: ductular and necroinflammatory-type with copper deposition	Prominent and defining feature: ductular-type with portal and periportal edema
Bile duct inflammation and damage	Variable; if present, involves a minority of bile ducts	Present and usually involves a majority of bile ducts	Focal ongoing lymphocytic bile duct damage; inflammation wanes with duct loss	Variable; if present, involves a minority of bile ducts	Granulomatous or focally severe lymphocytic cholangitis is diagnostic in proper setting	Periductal lamellar edema; "fibrous cholangitis"; acute cholangitis; multiple intra-portal ductal profiles
Biliary epithelial senescence changes and small bile loss	Absent or involves only a minority of ducts/portal tracts, but may be focally severe	Absent or involves only a minority of ducts	Senescence/atrophy/atypia involve a majority of remaining ducts (see text)	Absent or involves only a minority of ducts	Small bile duct loss associated with ductular reaction	Small bile duct loss associated with ductular reaction
Perivenular mononuclear inflammation and/or hepatocyte dropout	Variable; can involve a majority of perivenular regions, similar to rejection (see text); may be plasma cell–rich.	Variable, if defining feature should involve a majority of perivenular regions; may also show subendothelial inflammation of vein (see text)	Usually present, but variable	Variable but generally mild; if present, involves a minority of perivenular regions	Variable but generally mild; if present, involves a minority of perivenular regions	Absent
Lobular findings and necroinflammatory activity	Variable severity; rosettes may be present and/or prominent	Variable; if present, concentrated in perivenular regions	Variable; if present, concentrated in perivenular regions	Disarray variable; variable severity; necroinflammatory activity	Mild disarray; parenchymal granulomas; periportal copper deposition and cholatestasis are late features	Disarray unusual; neutrophil clusters; ± cholestasis
Pattern of fibrosis during progression toward cirrhosis	Usually macronodular; posthepatitic pattern	Rare	Uncommon, if present usually a venocentric pattern; may evolve to biliary pattern over time	Usually macronodular, hepatitic pattern; may be micronodular (see text)	Biliary pattern	Biliary pattern

NOTE. The histopathological findings in this table should be combined with clinical, serological, radiographic, and important exclusionary criteria listed in Table 2 to arrive at a final diagnosis.
Abbreviation: PSC/BD, primary sclerosing cholangitis/bile duct.
*The same findings apply to recurrent and *de novo* autoimmune hepatitis.

ing and pattern of liver test elevations, and important exclusionary criteria (Table 3). A discussion of histological findings in late posttransplant biopsies and their differential diagnosis follows.

Late-Onset Acute Rejection. LAR, which occurs more than several months after transplantation, may show slightly different features than typical acute rejection seen early after transplantation (Fig. 1). Fewer blastic lymphocytes, slightly greater interface activity, less venous subendothelial inflammation, and slightly more lobular activity cause biopsies with LAR to resemble chronic hepatitis.[4,57] LAR can also present as isolated perivenular inflammation and hepatocyte dropout (so-called "central perivenulitis")[58-60] and evolve into typical chronic rejection with ductopenia.[61] Subendothelial inflammation of portal or central veins is not a required finding in such cases. LAR, however, is still most commonly characterized by: (1) predominantly mononuclear portal inflammation containing lymphocytes, neutrophils, and eosinophils; (2) venous subendothelial inflammation of portal or central veins or perivenular inflammation; and (3) inflammatory bile duct damage. Previously proposed criteria[2] should be used for grading unless LAR presents as isolated central perivenulitis. For these cases, the following descriptors are recommended:

- minimal/indeterminate: perivenular inflammation involving a minority of central veins with patchy perivenular hepatocyte loss without confluent perivenular necrosis

Table 3. Inclusionary and Exclusionary Criteria for the Diagnosis of Recurrent and New-Onset Chronic Necroinflammatory Diseases After Liver Transplantation and Timing of First Onset and Pattern of Liver Test Elevation

Diagnosis	Original Disease	Serology/Molecular Testing*	Timing and Liver Injury Test Profile†	Important Exclusionary Criteria
Recurrent AIH	AIH	Autoantibodies (ANA, ASMA, ALKM) usually in high titers (>1:160); elevated serum immunoglobulin G	>6 months hepatocellular	Acute and chronic rejection, HBV, HCV infection, as determined via third-generation ELISA and/or serum PCR
De novo AIH	Other than AIH	Same as above	>6 months hepatocellular	Same as above
Recurrent HBV or HCV	HBV- or HCV-induced cirrhosis	HBV or HCV infection using standard, third-generation serological criteria and/or positive molecular testing for HBV or HCV nucleic acids	Usually 6-8 weeks, but as early as 10 days Usually hepatocellular but may be cholestatic	Acute and chronic rejection AIH
Recurrent PBC	PBC	Positive AMA, but little additional benefit because AMA remains elevated in the majority of patients after transplantation	>1 yr Cholestatic	Biliary tract obstruction/strictures
Recurrent PSC	PSC	NA	Usually >1 yr Cholestatic	HA thrombosis/stenosis, chronic (ductopenic) rejection, abnormal surgical anatomy, anastomotic strictures alone, nonanastomotic strictures occurring <90 d after liver transplantation, and ABO incompatibility
Acute rejection	NA (see text for risk factors)	NA	Any time Usually hepatocellular; may be mixed if superimposed on chronic rejection	Inadequate immunosuppression usually, but not always present (see text) Important exclusions: biliary tract obstruction/strictures, HBV, HCV, AIH
Chronic rejection	NA (see text for risk factors)	NA	Any time, but usually <1 yr Cholestatic; rarely hepatocellular in veno-occlusive variant (see text)	Inadequate immunosuppression usually, but not always present (see text) Important exclusions: biliary tract obstruction/strictures, HBV, HCV, AIH
Idiopathic posttransplantation hepatitis	Nonviral and non-autoimmune hepatitis	Negative testing for HBV and HCV infection and autoantibodies	>1 yr Usually hepatocellular	Acute and chronic rejection, all other causes of chronic hepatitis, and biliary tract obstruction/strictures reasonably excluded; all attempts should be made to determine a cause

NOTE. See Table 1 for compatible histopathological findings.

Abbreviations: AIH, autoimmune hepatitis; ANA, antinuclear antibodies; ASMA, anti–smooth muscle antibodies; ALKM, anti-liver–kidney microsomal antibodies; HBV, hepatitis B virus; HCV, hepatitis C virus; PCR, polymerase chain reaction; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

*Timing = usual timing of first onset.

†Sustained elevation for more than 1 month. Hepatocellular = alanine aminotransferase and/or aspartate aminotransferase > alkaline phosphatase and/or γ-glutamyltranspeptidase. Cholestatic = alkaline phosphatase and/or γ-glutamyltranspeptidase > aspartate aminotransferase and/or alanine aminotransferase.

- mild: as above, but involving a majority of central veins
- moderate: as above, with at least focal confluent perivenular hepatocyte dropout and mild moderate inflammation, but without bridging necrosis
- severe: as above, with confluent perivenular hepatocyte dropout and inflammation involving a majority of hepatic venules with central-to-central bridging necrosis.

"Minimal" and "mild" cases, as described above, may resolve spontaneously.[60] More severe perivenular changes probably warrant more aggressive treatment, but studies of long-term outcome according to therapy are needed to validate such an approach.

Chronic Rejection. Portal tracts and perivenular regions are primarily affected in chronic rejection, and changes are divided into "early" and "late" stages.[1] In a biopsy specimen, the minimum diagnostic criteria are: (1) biliary epithelial senescence changes affecting a majority of the bile ducts with or without bile duct loss; or (2) foam cell obliterative arteriopathy; or (3) bile duct loss affecting >50% of the portal tracts.[1]

Biliary epithelial senescence changes include cell and nuclear enlargement, multinucleation, uneven nuclear spacing, and cytoplasmic eosinophilia.[62] Some small bile ducts may be only partially lined by biliary epithelial cells. Perivenular hepatocyte dropout and central perivenulitis are typical of early chronic rejection.[63] Variable perivenular fibrosis occasionally progressing to veno-centric cir-

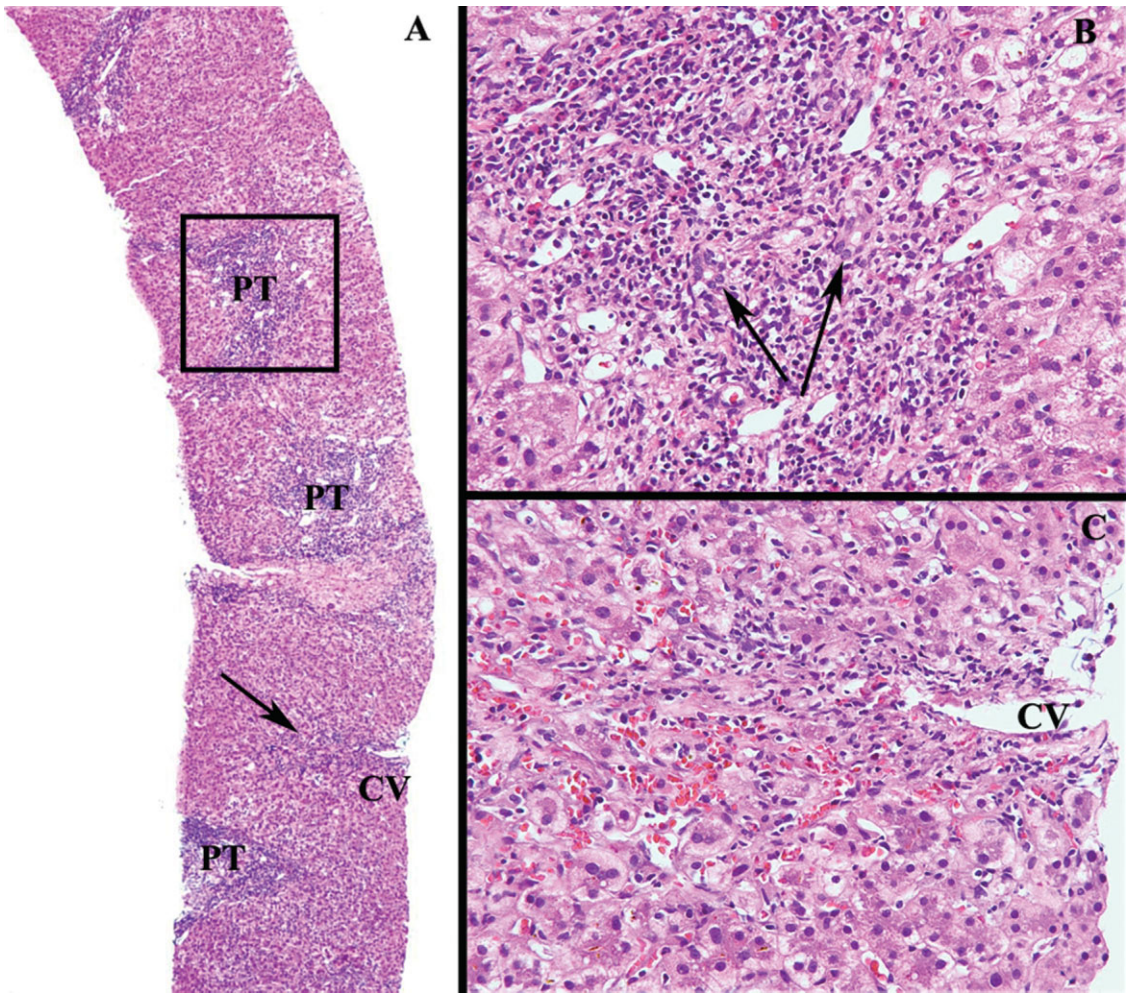

Fig. 1. Composite of late-onset acute rejection occurring more than 1 year after transplantation in a patient with low levels of baseline immunosuppression. (A) Low-magnification view (×20) shows prominent portal inflammation distributed evenly throughout the portal tracts, as well as perivenular mononuclear inflammation. Note also the irregular interface zone around the inflamed portal tracts. (B) Higher magnification (×200) of the portal tract outlined by the rectangle in panel A better illustrates the irregular interface zone and fewer blastic lymphocytes, which causes the biopsy to resemble chronic hepatitis. However, the prevalence and severity of lymphocytic cholangitis (**arrows**) are much worse than would be expected in chronic hepatitis and point toward acute rejection as the correct diagnosis. (C) Higher magnification (×200) of the central vein designated by the arrow in panel A better illustrates the perivenular mononuclear inflammation, or "central perivenulitis." Abbreviations: PT, portal tract; CV, central vein.

rhosis is typical of late chronic rejection.[64] Chronic rejection rarely results in a "posthepatitic" pattern of cirrhosis. If this pattern is present, other insults should be reasonably excluded.

The safest approach to a chronic rejection diagnosis in any setting is to review prior biopsies and correlate the histopathological findings closely with the clinical course. The typical scenario usually includes persistent/unresponsive acute rejection and/or inadequate immunosuppression.

Recurrent Diseases and New-Onset Diseases

Hepatitis C Virus. The predominant features of HCV include mononuclear portal inflammation, often arranged into nodular aggregates, necroinflammatory and ductular-type interface activity, and mild macrovesicular steatosis. Except for an association between steatosis and HCV genotype 3,[65] no histopathological features reliably distinguish among different viral genotypes. Lymphocytic cholangitis, if present, involves a minority of bile ducts without ductopenia. Lobular disarray and necroinflammatory activity are usually mild. Confluent or bridging necrosis with recurrent HCV alone is unusual. Central perivenulitis, if present, involves a minority of central veins.

There are two histopathological patterns of severe chronic HCV: (1) aggressive conventional hepatitis with prominent interface activity and (2) fibrosing cholestatic hepatitis. Features of fibrosing cholestatic hepatitis in-

clude centrilobular hepatocyte swelling and degeneration; cholestasis, hepatocyte apoptosis, and portal expansion because of a ductular reaction; fibrosis; and a mild mixed portal inflammation.[66] Fibrosing cholestatic hepatitis is associated with massive HCV replication (*e.g.*, >40-50 million IU/mL[67,68]).

Recurrent and New-Onset or* De Novo *Autoimmune Hepatitis. AIH is difficult to distinguish, histologically and conceptually, from rejection. Immune responses against self-antigens constitute an autoimmune response, whereas those against foreign antigens constitute rejection. Donor livers undoubtedly contain non–major histocompatibility complex antigens not expressed in the native liver, and theoretically all forms of AIH after transplantation could be classified as rejection.[34,42] Serological and histological findings used to distinguish AIH from rejection may reflect the nature, density, and location of antigenic targets. There are no conventional clinical tests that differentiate an autoimmune response from rejection, and distinctions based on clinical and histopathological findings may not reflect the true pathogenesis. Some new-onset AIH cases might be attributable to polymorphic expression of glutathione S-transferase T1[69]; transplantation of a mismatched graft into a nonexpressing recipient could trigger rejection that closely resembles AIH.

The International Autoimmune Hepatitis Group[70] scoring system and criteria for the diagnosis of AIH in native livers have not been tested in allografts; however, they do provide useful guidelines. AIH is established through a combination of serological, molecular biological, and histopathological findings. Non–organ-specific autoantibodies, a requisite for diagnosis, typically include anti–smooth muscle antibodies and antinuclear antibodies, as well as antibodies to liver kidney microsome type 1.[71] Their occurrence implies activation of immune mechanisms possibly involved primarily in disease pathogenesis or collateral responses to liver cell destruction and nonselective antigen release. Autoantibodies after liver transplantation do not establish the diagnosis of AIH, nor are they accurate parameters of inflammatory activity. Their principal value is to direct attention to the possibility of AIH.

The minimum diagnostic criteria for recurrent or *de novo* AIH in an allograft are: (1) interface hepatitis with portal lymphocytic infiltrates; (2) significant titers (≥1:160) of antinuclear antibodies, smooth muscle antibodies, or antibodies to liver kidney microsome type 1; (3) hyper-gammaglobulinemia; and (4) exclusion of virus-induced or drug-related hepatitis and late acute or chronic rejection. Titers ≥1:160 are unlikely to be nonspecific background reactivities and therefore compel a thorough evaluation for AIH.[70]

Initial manifestations include lobular hepatitis with hepatocyte rosetting[40] that usually evolves into the chronic phase characterized by lymphoplasmacytic portal inflammation with prominent interface activity. Plasmacytic infiltrates characterize AIH, but are not diagnostic requisites. Confluent and bridging necrosis are not uncommon, particularly in patients on suboptimal immunosuppression. Lymphocytic cholangitis, if present, involves a minority of ducts.

Central perivenulitis can occur in acute onset AIH in native livers[72-74] and in otherwise typical LAR. In native livers, perivenular hepatocyte injury associated with AIH usually wanes as interface hepatitis appears,[75] but the evolution of changes has not been studied in allografts. Panacinar hepatitis is also within the spectrum of histological findings in AIH,[70] but a cholestatic form is not recognized.

Idiopathic Posttransplantation Hepatitis. Idiopathic posttransplantation hepatitis is defined as chronic hepatitis that cannot be ascribed to a particular cause. By definition, bile duct damage and venous endothelial inflammation are not conspicuous. In adults, the prevalence is difficult to determine, because most native diseases have the potential to recur with features of chronic hepatitis. In some centers, up to 40% of adult patients subjected to biopsy more than 12 months after transplantation have unexplained chronic hepatitis.[76] A similar prevalence has been observed in the pediatric population, in which recurrent native disease is less of a problem; the frequency of "idiopathic" chronic hepatitis was 20% at 1 year of age, rising to 60% at 10 years of age.[77]

Cases presenting as central perivenulitis probably represent centrilobular-based acute rejection, or AIH if autoantibodies are also present,[57] because allograft dysfunction usually responds to increased immunosuppression.[59-61,78] Some idiopathic posttransplantation hepatitis cases may represent rejection with chronic hepatitic features.[79] However, a diagnosis of idiopathic posttransplantation hepatitis does not usually trigger treatment with increased immunosuppression. In some series, as many as 50% of such cases may develop bridging fibrosis or cirrhosis over a period of 10 years.[77] This observation supports the need for protocol biopsies and clarification of management policies in those with significant activity.[77]

Primary Biliary Cirrhosis. Recurrent PBC findings are nearly identical to those seen in native livers.[80,81] The pathognomonic lesion is noninfectious granulomatous cholangitis in the proper setting, which includes presence of antimitochondrial antibodies and absence of other causes such as infections and biliary strictures. Diagnostic

lesions are not always present. Patchy but easily recognizable and severe lymphocytic cholangitis accompanied by biliary epithelial cell eosinophilia, portal lymphoid nodules containing germinal centers, and development of a "biliary gestalt" can also be diagnostic of recurrent PBC in the proper setting. The biliary gestalt includes a ductular reaction at the interface zone combined with portal and periportal fibrosis, small bile duct loss, periportal edema (halo sign), and lysosomal pigment and copper/protein deposition in periportal hepatocytes. Plasma cell–rich periportal hepatitis may be an early marker predictive of later PBC recurrence.[82] Nonspecific lobular findings include mild spotty hepatocyte apoptosis, slight sinusoidal lymphocytosis, mild nodular regenerative hyperplasia, and Kupffer cell granulomas.

Primary Sclerosing Cholangitis. Findings are identical to those described for native livers with PSC and to other causes of biliary strictures. Subtle histopathological clues that suggest low-grade biliary strictures include mild portal edema; mild nonspecific acute and chronic "pericholangitis" often accompanied by a very mild type I ductular reaction; sinusoidal clusters of neutrophils; and centrilobular hepatocanalicular cholestasis. More significant strictures usually cause lamellar periductal edema, increased portal tract ductal profiles, and/or concentric periductal fibrosis.[83] Later-stage findings include the biliary gestalt. "Fibro-obliterative duct lesions" are not diagnostic of recurrent PSC, because they can also develop in patients with ischemic cholangitis and reflux cholangiopathy.

Differential Diagnosis

Rejection Versus Chronic Hepatitis. This commonly encountered and difficult problem has important therapeutic implications.[67] Unnecessary augmentation of immunosuppression can accelerate fibrogenesis in chronic HCV or trigger cholestatic hepatitis. Untreated acute rejection can progress to chronic rejection, particularly in interferon-treated recipients.

Mononuclear portal inflammation and lymphocytic cholangitis are features of chronic hepatitis and most cases of LAR. In LAR, however, the portal infiltrate tends to be more diffusely distributed throughout the portal tracts and throughout the biopsy rather than aggregated into nodules in occasional portal tracts, as in chronic hepatitis. In LAR and chronic rejection, lymphocytic cholangitis and/or biliary epithelial senescence changes, respectively, should involve a majority of bile ducts.[67] Central perivenulitis involving a majority of central veins also favors rejection. Damage limited to a minority of bile ducts favors acute or chronic hepatitis. Key features of acute and chronic hepatitis are lobular necroinflammatory activity and necroinflammatory and ductular-type interface zone activity, respectively, which are more prevalent and severe than in acute rejection.

Because acute and/or chronic rejection and chronic hepatitis can coexist, the predominant process should be identified. Key features of acute rejection in the context of recurrent HCV are prevalence and severity of mononuclear inflammatory bile duct damage and central perivenulitis. If either feature involves a majority of bile ducts or central veins, then acute rejection is present. However, coexistent acute rejection should be listed as the primary process only when rejection-related changes are obvious. Most such cases are graded as "moderate" according to the Banff schema.[67] Chronic rejection in the context of recurrent HCV is recognized by the same features as in allografts without recurrent HCV: small bile duct loss or biliary epithelial senescence or perivenular inflammation and fibrosis involving a majority of bile ducts or hepatic venules, respectively.

Chronic Rejection. Small bile duct damage and loss and perivenular fibrosis are relied upon for the diagnosis of chronic rejection because arteries with pathognomonic changes are rarely present in needle biopsy specimens.[1] Bile duct injury and ductopenia, however, can also be caused by biliary strictures, hepatic artery pathology, adverse drug reactions, and cytomegalovirus. Isolated ductopenia involving less than 50% of portal tracts can be seen occasionally without significant elevations of liver tests.[80] Whether these uncommon cases are an early phase or subclinical chronic rejection is uncertain. Angiography showing pruning of intrahepatic arteries with poor peripheral filling and segmental narrowing also supports a chronic rejection diagnosis.[84,85]

Perivenular fibrosis can also be caused by suboptimal hepatic venous drainage, adverse drug reactions,[86] and the various causes of veno-occlusive disease and Budd-Chiari syndrome in native livers.[87] In cases of chronic rejection identified by biliary epithelial senescence, bile duct loss, or perivenular fibrosis alone, non–rejection-related causes of ductal injury and loss or perivenular fibrosis should be reasonably excluded, particularly if the clinical scenario is not typical (Table 1).

Biliary Strictures Versus Acute and Chronic Rejection. Significant biliary strictures are usually recognized by the biliary gestalt and are reinforced by preferential elevation of γ-glutamyltranspeptidase and alkaline phosphatase. However, a thorough clinicopathological correlation is needed to distinguish among many underlying causes, such as recurrent PSC, ischemic cholangitis due to injury from prolonged preservation or non–heart-beating donors, imperfect biliary anastomoses, inadequate arterial

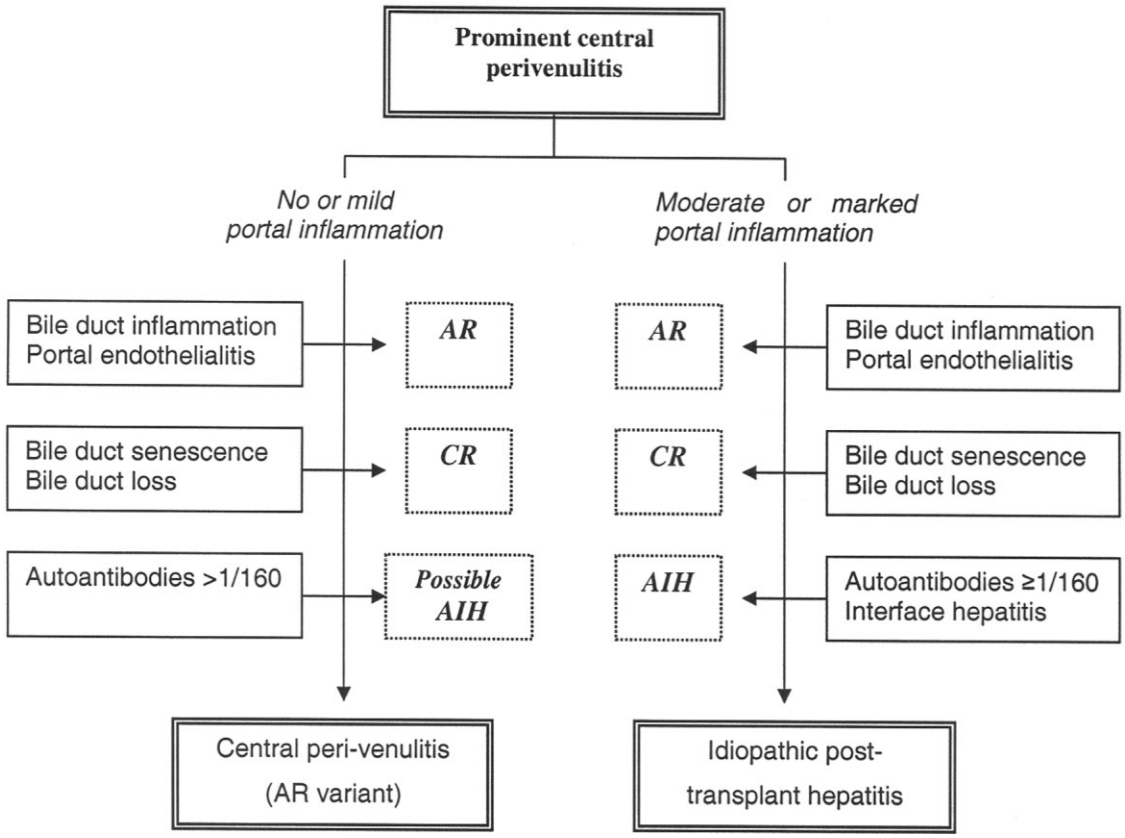

Fig. 2. Approach to biopsies showing posttransplantation central perivenulitis. In cases with no or minor portal inflammation, the differential diagnosis includes acute rejection, chronic rejection, and prediagnostic autoimmune hepatitis. If none of these changes is present, and vascular imaging is normal, the lesion is likely to represent a form of acute rejection. Cases with a more extensive portal inflammatory infiltrate have a similar differential diagnosis. It remains unclear whether idiopathic posttransplantation hepatitis is a form of rejection, and how it is related to pure central perivenulitis. Follow-up biopsies also frequently provide important diagnostic findings. Abbreviations: AR, acute rejection; CR, chronic rejection; AIH, autoimmune hepatitis.

flow, and antibody-mediated rejection.[4,88-92] Periportal hepatocyte copper deposition signals chronic bile flow impediments.

Mononuclear portal inflammation usually favors acute rejection, whereas neutrophilic or eosinophilic portal inflammation, late after transplantation, favors biliary strictures. However, chronic low-grade biliary strictures can occasionally cause predominantly mononuclear portal inflammation. Ductopenia in some portal tracts accompanied by a ductular reaction should raise the suspicion of biliary strictures. Cholangiography and/or angiography may be required to distinguish between chronic rejection and biliary strictures. Acute rejection occurring more than 6 months after transplantation is unusual in adequately immunosuppressed recipients. Therefore, checking baseline immunosuppressive drug levels and the liver test profile often point to the need for cholangiography before increased immunosuppression.

Acute and Chronic Rejection Versus Primary Biliary Cirrhosis. In acute rejection, portal inflammation and lymphocytic cholangitis are usually more diffusely distributed throughout the portal tracts and the biopsy and typically involve small bile ducts (<20 μm). Portal inflammation and lymphocytic cholangitis in recurrent PBC are typically patchy and involve medium-sized bile ducts (>40-50 μm). In the absence of a pathognomonic lesion, recurrent PBC is most commonly recognized by the biliary gestalt occurring in the absence of mechanical biliary strictures. This gestalt is unusual in rejection. Central perivenulitis is not a feature of PBC.

Central Perivenulitis. LAR can manifest primarily as central perivenulitis.[59-61,63,93-96] Because of its association with severe acute rejection[2] and transition to early chronic rejection,[63] central perivenulitis is sometimes portrayed as a poor prognosis lesion, but this is not necessarily correct.[59,60] As in native livers, central perivenulitis in allografts has several causes (Fig. 2), including various forms of rejection (pure perivenular rejection and early chronic rejection), early autoimmune hepatitis,[72,74,97] compromised afferent or efferent blood flow,[73,87,98] and adverse drug reactions. Perivenular rejection can be missed clinically and

present later as ascites because of a Budd-Chiari syndrome or veno-occlusive disease.[63,64,93,96,99]

An acute rejection diagnosis is obvious when central perivenulitis occurs in association with other portal-based changes typical of acute rejection; the severity is graded according to standard criteria.[2] Acute rejection is also the most likely diagnosis when central perivenulitis involves a majority of central veins with minimal or absent portal inflammation, except if the original disease was AIH. In this situation, isolated central perivenulitis may represent early recurrent AIH[34,42,74,75] or new-onset AIH. In native livers presenting with acute AIH central perivenulitis, chronic portal inflammation and interface activity usually develop over time.[72,74,97] Therefore, in allografts, re-examination of the native liver histopathology, serological studies for autoantibodies, and close follow-up for the development of changes more typical of chronic hepatitis[75] are warranted. Because increased immunosuppression effectively treats either rejection or AIH, any differences in assigned diagnoses may be semantic. Hepatic vein outflow obstruction and ischemia can also cause centrilobular necrosis, but any associated lymphocytic inflammation is usually minimal.

Mild focal central perivenulitis can coexist with other causes of late dysfunction. In such cases, central perivenulitis probably represents a focal alloreaction, because similar changes are rarely—if ever—seen with the same disorders in native livers. Therefore, we recommend mentioning its presence or suggesting a diagnosis of "indeterminate for rejection," unless a majority of central veins are involved.

Distinguishing Among the Various Causes of Chronic Hepatitis. Determining a specific cause of chronic hepatitis is not always possible, but subtle differences can suggest a specific etiology. Plasma cell and aggressive interface activity and confluent perivenular or bridging necrosis are suggestive of AIH, macrovesicular steatosis is suggestive of HCV, and viral inclusions are seen only in hepatitis B virus. Because potentially distinguishing features are inconsistently present and not entirely reliable, determining the underlying cause of acute and/or chronic hepatitis should be based on a complete clinicopathological evaluation (Tables 2 and 3). Steatohepatitis can coexist with other causes of injury.

Cholestatic or Biliary Disease Versus Chronic Hepatitis. A single granulomatous duct destructive lesion is diagnostic of PBC in the proper setting. Infectious causes of granulomatous cholangitis should be excluded, but they are uncommon. Portal granulomas without granulomatous cholangitis have been reported in native livers with HCV.[100] In the absence of pathognomonic lesions, recurrent PBC or PSC is most commonly distinguished from chronic hepatitis by a biliary gestalt.

Cholestatic viral hepatitis can be difficult to distinguish from biliary strictures with or without hepatic artery thrombosis. Portal edema and portal—rather than periportal—neutrophilia are common in biliary strictures. Cholangiolar proliferation and acute cholangiolitis without portal edema is more characteristic of cholestatic hepatitis. Lobular disarray and hepatocellular swelling and apoptosis are more usual for cholestatic viral hepatitis.

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Oyedele Adeyi, Princess Margaret Hospital, University of Toronto, Toronto, Canada
Chris O. C. Bellamy, University of Edinburgh, Edinburgh, Scotland, UK
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Ierachmiel Daskal, Albert Einstein Healthcare Network, Jefferson Health System, Philadelphia, PA
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Paulo Fontes, University of Pittsburgh Medical Center, Pittsburgh, PA
John Fung, Cleveland Clinic Foundation, Cleveland, OH
Bruno Gridelli, ISMETT, Palermo, Italy
Maria Guido, Istituto di Anatomia Patologica, Padova, Italy
Hironori Haga, Kyoto University Hospital, Kyoto, Japan
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Charles Lassman, David Geffen School of Medicine at the University of California–Los Angeles, Los Angeles, CA
Saverio Ligato, Hartford Hospital, Hartford, CT

John G. Lunz III, University of Pittsburgh Medical Center, Pittsburgh, PA
Amadeo Marcos, University of Pittsburgh Medical Center, Pittsburgh, PA
Marta Ida Minervini, ISMETT, Palermo, Italy
Johan Mölne, Sahlgrenska University Hospital, Göteberg, Sweden
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Imad Nasser, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
Desley Neil, Queen Elizabeth Hospital, University of Birmingham, UK
Erin Ochoa, University of Pittsburgh Medical Center, Pittsburgh, PA
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Phil Ruiz, University of Miami Medical Center, Miami, FL
Mylène Sebagh, Universite Paris XI, Hopital Paul Brousse, Villejuif, France
Marco Spada, SMETT (Istituto Mediterraneo per Trapianti e Terapie Alta Specializzazione), Palermo, Sicily
Aurelio Sonzogni, Ospedali Riuniti, Bergamo, Italy
Athanassios C. Tsamandas, University of Patras School of Medicine, Patras, Greece
Annika Wernerson, Karolinska University Hospital, Stockholm, Sweden
Tong Wu, University of Pittsburgh Medical Center, Pittsburgh, PA
Funda Yilmaz, Ege University School of Medicine, Bornova, Izmir, Turkey

References

1. Demetris A, Adams D, Bellamy C, Blakolmer K, Clouston A, Dhillon AP, 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;31:792-799.
2. Anonymous. Banff schema for grading liver allograft rejection: an international consensus document. HEPATOLOGY 1997;25:658-663.
3. Hunt J, Gordon FD, Jenkins RL, Lewis WD, Khettry U. Sarcoidosis with selective involvement of a second liver allograft: report of a case and review of the literature. Mod Pathol 1999;12:325-328.
4. Pappo O, Ramos H, Starzl TE, Fung JJ, Demetris AJ. Structural integrity and identification of causes of liver allograft dysfunction occurring more than 5 years after transplantation. Am J Surg Pathol 1995;19:192-206.
5. Pappo O, Yunis E, Jordan JA, Jaffe R, Mateo R, Fung J, et al. Recurrent and de novo giant cell hepatitis after orthotopic liver transplantation. Am J Surg Pathol 1994;18:804-813.
6. Starzl TE, Demetris AJ. Liver transplantation: a 31-year perspective. Part III. Curr Probl Surg 1990;27:187-240.
7. Ciubotariu R, Liu Z, Colovai AI, Ho E, Itescu S, Ravalli S, et al. Persistent allopeptide reactivity and epitope spreading in chronic rejection of organ allografts. J Clin Invest 1998;101:398-405.
8. Suciu-Foca N, Harris PE, Cortesini R. Intramolecular and intermolecular spreading during the course of organ allograft rejection. Immunol Rev 1998;164:241-246.
9. Vanderlugt CL, Miller SD. Epitope spreading in immune-mediated diseases: implications for immunotherapy. Nat Rev Immunol 2002;2:85-95.
10. Rose NR. Mechanisms of autoimmunity. Semin Liver Dis 2002;22:387-394.
11. Dubel L, Farges O, Johanet C, Sebagh M, Bismuth H. High incidence of antitissue antibodies in patients experiencing chronic liver allograft rejection. Transplantation 1998;65:1072-1075.
12. Duclos-Vallee JC, Johanet C, Bach JF, Yamamoto AM. Autoantibodies associated with acute rejection after liver transplantation for type-2 autoimmune hepatitis. J Hepatol 2000;33:163-166.
13. Varani S, Muratori L, De Ruvo N, Vivarelli M, Lazzarotto T, Gabrielli L, et al. Autoantibody appearance in cytomegalovirus-infected liver transplant recipients: correlation with antigenemia. J Med Virol 2002;66:56-62.
14. Lytton SD, Berg U, Nemeth A, Ingelman-Sundberg M. Autoantibodies against cytochrome P450s in sera of children treated with immunosuppressive drugs. Clin Exp Immunol 2002;127:293-302.
15. Benichou G. Spreading of T cell responses to autoantigens after allotransplantation and its potential involvement in the rejection process. Graft 2003;6:18-20.
16. Demetris AJ, Murase N, Delaney CP. Overlap between allo- and autoimmunity in the rat and human evidence for important contribtuions for dendritic and regulatory cells. Graft 2003;6:21-32.
17. Heeger PS. T cell autoreactivity by design:a theoretical framework for understanding tolerance, autoimmunity, and transplant.rejection. Graft 2003;6:33-41.
18. Wilkes DS. Autoimmune responses to grafted lungs: immune responses to native collagen—type V collagen. Graft 2003;6:42-49.
19. Berenguer M, Rayon JM, Prieto M, Aguilera V, Nicolas D, Ortiz V, et al. Are posttransplantation protocol liver biopsies useful in the long term? Liver Transpl 2001;7:790-796.
20. Burra P, Mioni D, Cecchetto A, Cillo U, Zanus G, Fagiuoli S, et al. Histological features after liver transplantation in alcoholic cirrhotics. J Hepatol 2001;34:716-722.
21. Berenguer M, Aguilera V, Prieto M, Carrasco D, Rayon M, San Juan F, et al. Delayed onset of severe hepatitis C-related liver damage following liver transplantation: a matter of concern? Liver Transpl 2003;9:1152-1158.
22. Sebagh M, Rifai K, Feray C, Yilmaz F, Falissard B, Roche B, et al. All liver recipients benefit from the protocol 10-year liver biopsies. HEPATOLOGY 2003;37:1293-1301.
23. Slapak GI, Saxena R, Portmann B, Gane E, Devlin J, Calne R, et al. Graft and systemic disease in long-term survivors of liver transplantation. HEPATOLOGY 1997;25:195-202.
24. Rosenthal P, Emond JC, Heyman MB, Snyder J, Roberts J, Ascher N, et al. Pathological changes in yearly protocol liver biopsy specimens from healthy pediatric liver recipients. Liver Transpl Surg 1997;3:559-562.
25. Maor-Kendler Y, Batts KP, Burgart LJ, Wiesner RH, Krom RA, Rosen CB, et al. Comparative allograft histology after liver transplantation for cryptogenic cirrhosis, alcohol, hepatitis C, and cholestatic liver diseases. Transplantation 2000;70:292-297.
26. Heneghan MA, Zolfino T, Muiesan P, Portmann BC, Rela M, Heaton ND, et al. An evaluation of long-term outcomes after liver transplantation for cryptogenic cirrhosis. Liver Transpl 2003;9:921-928.
27. Wong T, Nouri-Aria KT, Devlin J, Portmann B, Williams R. Tolerance and latent cellular rejection in long-term liver transplant recipients. HEPATOLOGY 1998;28:443-449.
28. Gane E, Portmann B, Saxena R, Wong P, Ramage J, Williams R. Nodular regenerative hyperplasia of the liver graft after liver transplantation. HEPATOLOGY 1994;20:88-94.

29. Shinkura N, Ikai I, Egawa H, Yamauchi A, Kawai Y, Inomata Y, et al. Presence of anti-FKBP12 autoantibodies in patients with liver allografts: its association with allograft rejection. Transplantation 1997;64:1336-1342.
30. Salcedo M, Vaquero J, Banares R, Rodriguez-Mahou M, Alvarez E, Vicario JL, et al. Response to steroids in de novo autoimmune hepatitis after liver transplantation. HEPATOLOGY 2002;35:349-356.
31. Gupta P, Hart J, Millis JM, Cronin D, Brady L. De novo hepatitis with autoimmune antibodies and atypical histology: a rare cause of late graft dysfunction after pediatric liver transplantation. Transplantation 2001; 71:664-668.
32. Heneghan MA, Portmann BC, Norris SM, Williams R, Muiesan P, Rela M, et al. Graft dysfunction mimicking autoimmune hepatitis following liver transplantation in adults. HEPATOLOGY 2001;34:464-470.
33. Hernandez HM, Kovarik P, Whitington PF, Alonso EM. Autoimmune hepatitis as a late complication of liver transplantation. J Pediatr Gastroenterol Nutr 2001;32:131-136.
34. Aguilera I, Wichmann I, Sousa JM, Bernardos A, Franco E, Garcia-Lozano JR, et al. Antibodies against glutathione S-transferase T1 (GSTT1) in patients with de novo immune hepatitis following liver transplantation. Clin Exp Immunol 2001;126:535-539.
35. Jones DE, James OF, Portmann B, Burt AD, Williams R, Hudson M. Development of autoimmune hepatitis following liver transplantation for primary biliary cirrhosis. HEPATOLOGY 1999;30:53-57.
36. Kerkar N, Hadzic N, Davies ET, Portmann B, Donaldson PT, Rela M, et al. De-novo autoimmune hepatitis after liver transplantation. Lancet 1998;351:409-413.
37. Salcedo M, Vaquero J, Banares R, Mahou MR, Alvarez E, Hernandez-Albujar A, et al. Serum autoantibodies after liver transplantation. Prevalence and associated immunologic disorders [Abstract]. J Hepatol 2003; 34:47.
38. Marcos A, Eghtesad B, Fung JJ, Fontes P, Patel K, Devera M, et al. Use of alemtuzumab and tacrolimus monotherapy for cadaveric liver transplantation: with particular reference to hepatitis C virus. Transplantation 2004;78:966-971.
39. Wright HL, Bou-Abboud CF, Hassanein T, Block GD, Demetris AJ, Starzl TE, et al. Disease recurrence and rejection following liver transplantation for autoimmune chronic active liver disease. Transplantation 1992;53:136-139.
40. Ayata G, Gordon FD, Lewis WD, Pomfret E, Pomposelli JJ, Jenkins RL, et al. Liver transplantation for autoimmune hepatitis: a long-term pathologic study. HEPATOLOGY 2000;32:185-192.
41. Birnbaum AH, Benkov KJ, Pittman NS, McFarlane-Ferreira Y, Rosh JR, LeLeiko NS. Recurrence of autoimmune hepatitis in children after liver transplantation. J Pediatr Gastroenterol Nutr 1997;25:20-25.
42. Czaja AJ. Autoimmune hepatitis after liver transplantation and other lessons of self-intolerance. Liver Transpl 2002;8:505-513.
43. Duclos-Vallee JC, Sebagh M, Rifai K, Johanet C, Ballot E, Guettier C, et al. A 10 year follow up study of patients transplanted for autoimmune hepatitis: histological recurrence precedes clinical and biochemical recurrence. Gut 2003;52:893-897.
44. Faust TW. Recurrent primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis after transplantation. Semin Liver Dis 2000;20:481-495.
45. Gonzalez-Koch A, Czaja AJ, Carpenter HA, Roberts SK, Charlton MR, Porayko MK, et al. Recurrent autoimmune hepatitis after orthotopic liver transplantation. Liver Transpl 2001;7:302-310.
46. Hurtova M, Duclos-Vallee JC, Johanet C, Emile JF, Roque-Afonso AM, Feray C, et al. Successful tacrolimus therapy for a severe recurrence of type 1 autoimmune hepatitis in a liver graft recipient. Liver Transpl 2001;7: 556-558.
47. Milkiewicz P, Hubscher SG, Skiba G, Hathaway M, Elias E. Recurrence of autoimmune hepatitis after liver transplantation. Transplantation 1999;68:253-256.
48. Molmenti EP, Netto GJ, Murray NG, Smith DM, Molmenti H, Crippin JS, et al. Incidence and recurrence of autoimmune/alloimmune hepatitis in liver transplant recipients. Liver Transpl 2002;8:519-526.
49. Reich DJ, Fiel I, Guarrera JV, Emre S, Guy SR, Schwartz ME, et al. Liver transplantation for autoimmune hepatitis. HEPATOLOGY 2000;32:693-700.
50. Sanchez-Urdazpal L, Czaja AJ, van Hoek B, Krom RA, Wiesner RH. Prognostic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. HEPATOLOGY 1992; 15:215-221.
51. Devlin J, Donaldson P, Portmann B, Heaton N, Tan KC, Williams R. Recurrence of autoimmune hepatitis following liver transplantation. Liver Transpl Surg 1995;1:162-165.
52. Prados E, Cuervas-Mons V, de la Mata M, Fraga E, Rimola A, Prieto M, et al. Outcome of autoimmune hepatitis after liver transplantation. Transplantation 1998;66:1645-1650.
53. Ratziu V, Samuel D, Sebagh M, Farges O, Saliba F, Ichai P, et al. Long-term follow-up after liver transplantation for autoimmune hepatitis: evidence of recurrence of primary disease. J Hepatol 1999;30:131-141.
54. Sempoux C, Horsmans Y, Lerut J, Rahier J, Geubel A. Acute lobular hepatitis as the first manifestation of recurrent autoimmune hepatitis after orthotopic liver transplantation. Liver 1997;17:311-315.
55. Vogel A, Heinrich E, Bahr MJ, Rifai K, Flemming P, Melter M, et al. Long-term outcome of liver transplantation for autoimmune hepatitis. Clin Transplant 2004;18:62-69.
56. Miyagawa-Hayashino A, Haga H, Egawa H, Hayashino Y, Sakurai T, Minamiguchi S, et al. Outcome and risk factors of de novo autoimmune hepatitis in living-donor liver transplantation. Transplantation 2004;78: 128-135.
57. Hubscher SG. Recurrent autoimmune hepatitis after liver transplantation: Diagnostic criteria, risk factors, and outcome. Liver Transpl 2001; 7:285-291.
58. Demetris AJ, Fung JJ, Todo S, McCauley J, Jain A, Takaya S, et al. Conversion of liver allograft recipients from cyclosporine to FK506 immunosuppressive therapy—a clinicopathologic study of 96 patients. Transplantation 1992;53:1056-1062.
59. Tsamandas AC, Jain AB, Felekouras ES, Fung JJ, Demetris AJ, Lee RG. Central venulitis in the allograft liver: a clinicopathologic study. Transplantation 1997;64:252-257.
60. Krasinskas AM, Ruchelli ED, Rand EB, Chittams JL, Furth EE. Central venulitis in pediatric liver allografts. HEPATOLOGY 2001;33:1141-1147.
61. Khettry U, Backer A, Ayata G, Lewis WD, Jenkins RL, Gordon FD. Centrilobular histopathologic changes in liver transplant biopsies. Hum Pathol 2002;33:270-276.
62. Lunz JG 3rd, Contrucci S, Ruppert K, Murase N, Fung JJ, Starzl TE, et al. Replicative senescence of biliary epithelial cells precedes bile duct loss in chronic liver allograft rejection: increased expression of p21(WAF1/Cip1) as a disease marker and the influence of immunosuppressive drugs. Am J Pathol 2001;158:1379-1390.
63. Neil DA, Hubscher SG. Histologic and biochemical changes during the evolution of chronic rejection of liver allografts. HEPATOLOGY 2002;35: 639-651.
64. Nakazawa Y, Jonsson JR, Walker NI, Kerlin P, Steadman C, Lynch SV, et al. Fibrous obliterative lesions of veins contribute to progressive fibrosis in chronic liver allograft rejection. HEPATOLOGY 2000;32:1240-1247.
65. Gordon FD, Pomfret EA, Pomposelli JJ, Lewis WD, Jenkins RL, Khettry U. Severe steatosis as the initial histologic manifestation of recurrent hepatitis C genotype 3. Hum Pathol 2004;35:636-638.
66. Ferrell LD, Wright TL, Roberts J, Ascher N, Lake J. Hepatitis C viral infection in liver transplant recipients. HEPATOLOGY 1992;16:865-876.
67. Demetris AJ, Eghtesad B, Marcos A, Ruppert K, Nalesnik MA, Randhawa P, et al. Recurrent hepatitis C in liver allografts: prospective assessment of diagnostic accuracy, identification of pitfalls, and observations about pathogenesis. Am J Surg Pathol 2004;28:658-669.
68. Doughty AL, Spencer JD, Cossart YE, McCaughan GW. Cholestatic hepatitis after liver transplantation is associated with persistently high serum hepatitis C virus RNA levels. Liver Transpl Surg 1998;4:15-21.
69. Aguilera I, Sousa JM, Gavilan F, Bernardos A, Wichmann I, Nunez-Roldan A. Glutathione S-transferase T1 mismatch constitutes a risk fac-

tor for de novo immune hepatitis after liver transplantation. Liver Transpl 2004;10:1166-1172.
70. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-938.
71. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. HEPATOLOGY 2002;36:479-497.
72. Pratt DS, Fawaz KA, Rabson A, Dellelis R, Kaplan MM. A novel histological lesion in glucocorticoid-responsive chronic hepatitis. Gastroenterology 1997;113:664-668.
73. Czaja AJ. Autoimmune liver disease. Curr Opin Gastroenterol 2003;19: 232-242.
74. Singh R, Nair S, Farr G, Mason A, Perrillo R. Acute autoimmune hepatitis presenting with centrizonal liver disease: case report and review of the literature. Am J Gastroenterol 2002;97:2670-2673.
75. Okano N, Yamamoto K, Sakaguchi K, Miyake Y, Shimada N, Hakoda T, et al. Clinicopathological features of acute-onset autoimmune hepatitis. Hepatol Res 2003;25:263-270.
76. Neuberger J. Chronic allograft dysfunction: diagnosis and management. Is it always progressive? Liver Transpl 2005;11:S63-S68.
77. Evans HM, Kelly DA, McKiernan PJ, Hübscher SG. Progressive histological damage in liver allografts following paediatric liver transplantation. HEPATOLOGY 2006;43:1109-1117.
78. Demetris AJ, Fung JJ, Todo S, McCauley J, Jain A, Takaya S, et al. FK 506 used as rescue therapy for human liver allograft recipients. Transplant Proc 1991;23:3005-3006.
79. Kemnitz J, Gubernatis G, Bunzendahl H, Ringe B, Pichlmayr R, Georgii A. Criteria for the histopathological classification of liver allograft rejection and their clinical relevance. Transplant Proc 1989;21:2208-2210.
80. Hubscher SG, Elias E, Buckels JA, Mayer AD, McMaster P, Neuberger JM. Primary biliary cirrhosis. Histological evidence of disease recurrence after liver transplantation. J Hepatol 1993;18:173-184.
81. Neuberger J, Portmann B, Calne R, Williams R. Recurrence of autoimmune chronic active hepatitis following orthotopic liver grafting. Transplantation 1984;37:363-365.
82. Sebagh M, Farges O, Dubel L, Samuel D, Bismuth H, Reynes M. Histological features predictive of recurrence of primary biliary cirrhosis after liver transplantation. Transplantation 1998;65:1328-1333.
83. Sebagh M, Yilmaz F, Karam V, Falissard B, Roche B, Azoulay D, et al. The histologic pattern of "biliary tract pathology" is accurate for the diagnosis of biliary complications. Am J Surg Pathol 2005;29:318-323.
84. White RM, Zajko AB, Demetris AJ, Bron KM, Dekker A, Starzl TE. Liver transplant rejection: angiographic findings in 35 patients. AJR Am J Roentgenol 1987;148:1095-1098.
85. Devlin J, Page AC, O'Grady J, Portmann B, Karani J, Williams R. Angiographically determined arteriopathy in liver graft dysfunction and survival. J Hepatol 1993;18:68-73.
86. Dhillon AP, Burroughs AK, Hudson M, Shah N, Rolles K, Scheuer PJ. Hepatic venular stenosis after orthotopic liver transplantation. HEPATOLOGY 1994;19:106-111.
87. Demetris AJ. Central venulitis in liver allografts: considerations of differential diagnosis. HEPATOLOGY 2001;33:1329-1330.
88. Harrison RF, Davies MH, Neuberger JM, Hubscher SG. Fibrous and obliterative cholangitis in liver allografts: evidence of recurrent primary sclerosing cholangitis? HEPATOLOGY 1994;20:356-361.
89. Goss JA, Shackleton CR, Farmer DG, Arnaout WS, Seu P, Markowitz JS, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. Ann Surg 1997;225:472-481.
90. Gow PJ, Chapman RW. Liver transplantation for primary sclerosing cholangitis. Liver 2000;20:97-103.
91. Graziadei IW, Wiesner RH, Marotta PJ, Porayko MK, Hay JE, Charlton MR, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. HEPATOLOGY 1999;30:1121-1127.
92. Narumi S, Roberts JP, Emond JC, Lake J, Ascher NL. Liver transplantation for sclerosing cholangitis. HEPATOLOGY 1995;22:451-457.
93. Sebagh M, Debette M, Samuel D, Emile JF, Falissard B, Cailliez V, et al. "Silent" presentation of veno-occlusive disease after liver transplantation as part of the process of cellular rejection with endothelial predilection. HEPATOLOGY 1999;30:1144-1150.
94. Turlin B, Slapak GI, Hayllar KM, Heaton N, Williams R, Portmann B. Centrilobular necrosis after orthotopic liver transplantation: a longitudinal clinicopathologic study in 71 patients. Liver Transpl Surg 1995;1: 285-289.
95. Anand AC, Hubscher SG, Gunson BK, McMaster P, Neuberger JM. Timing, significance, and prognosis of late acute liver allograft rejection. Transplantation 1995;60:1098-1103.
96. Ludwig J, Gross JB Jr, Perkins JD, Moore SB. Persistent centrilobular necroses in hepatic allografts. Hum Pathol 1990;21:656-661.
97. Te HS, Koukoulis G, Ganger DR. Autoimmune hepatitis: a histological variant associated with prominent centrilobular necrosis. Gut 1997;41: 269-271.
98. Nakazawa Y, Walker NI, Kerlin P, Steadman C, Lynch SV, Strong RW, et al. Clinicopathological analysis of liver allograft biopsies with late centrilobular necrosis: a comparative study in 54 patients. Transplantation 2000;69:1599-1608.
99. Demetris AJ, Ruppert K, Dvorchik I, Jain A, Minervini M, Nalesnik MA, et al. Real-time monitoring of acute liver-allograft rejection using the Banff schema. Transplantation 2002;74:1290-1296.
100. Farges O, Bismuth H, Sebagh M, Reynes M. Granulomatous destruction of bile ducts after liver transplantation: primary biliary cirrhosis recurrence or hepatitis C virus infection? HEPATOLOGY 1995;21: 1765-1767.