Liver Transplant Pathology

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Histopathologic evaluation plays an integral role in the overall assessment of the liver transplant. Pathologists are often asked to evaluate donor liver biopsies to assist in the determination of whether a marginal donor liver is suitable for transplantation. In addition, histopathologic assessment of allograft liver biopsies plays an important role in identifying the cause of allograft dysfunction and therefore in initiation of the appropriate therapeutic intervention. A detailed histopathologic evaluation is mandated, including histologic comparison with any previous biopsies as well as incorporation of all pertinent clinical, laboratory, and imaging findings with histologic assessment.

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5.1 Evaluation of Donor Biopsies

Donor biopsies are often evaluated to determine the extent of steatosis. There are two different forms of steatosis—macrovesicular and microvesicular—with the macrovesicular form divided into large droplet and small droplet. Large droplet macrovesicular steatosis is generally defined as one large fat vacuole that occupies more than half of the cell and displaces the nucleus to the cell periphery (Fig. 5.1). In comparison, small droplet macrovesicular steatosis is defined as fat vacuoles that are smaller than half of the cell and do not displace the nucleus (Fig. 5.2). The term microvesicular steatosis is used when innumerable tiny lipid vesicles are diffusely distributed throughout the cytoplasm, giving it a foamy appearance [1–3]. The extent of steatosis is estimated as the percentage of liver parenchyma that is replaced by steatosis (Fig. 5.3). It is typically the extent of large droplet macrovesicular steatosis that is clinically significant because more or less than 30 % of this type of steatosis has been shown to be an independent risk factor for reduced short-term graft survival. The exact amount of steatosis that precludes an organ for transplantation is rather center-dependent and depends on various donor and recipient factors. Small droplet macrovesicular steatosis and microvesicular steatosis do not predictably result in graft dysfunction, and in many centers such as ours they are not used to determine graft usage. In our practice, we estimate the amount of fat in routine hematoxylin and eosin (H&E) staining (either requested as frozen section or rush permanent evaluation), and we do not perform any special fat stains. It is important that the biopsy specimen is freshly obtained and that frozen sections are evaluated immediately or the biopsy is placed in formalin for fixation, since exposure to air or saline can significantly alter the morphology and hamper the evaluation of the biopsy.

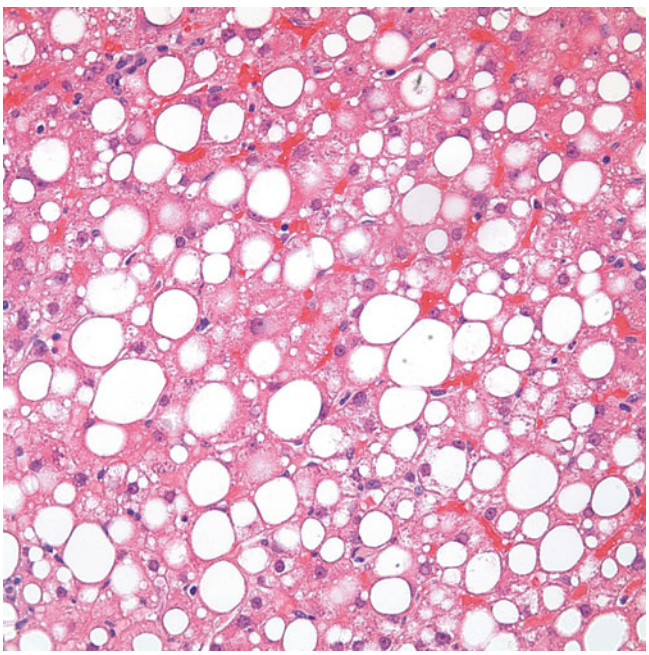

Fig. 5.1 Large droplet macrovesicular steatosis is shown as fat droplets occupying greater than half of the cytoplasm and displacing the nucleus

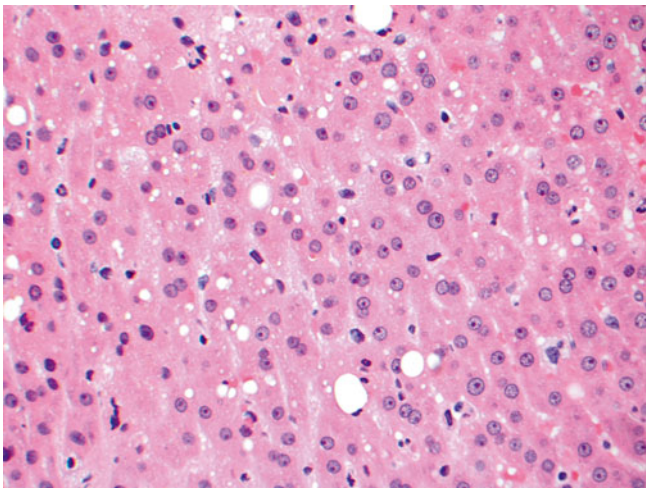

Fig. 5.2 Small droplet macrovesicular steatosis is shown as small fat droplets that occupy less than half of the cytoplasm and do not displace the nucleus. The presence of this type of steatosis in a donor organ generally does not preclude that organ from being used for transplantation. A few large droplet macrovesicular vesicular steatosis is also seen here

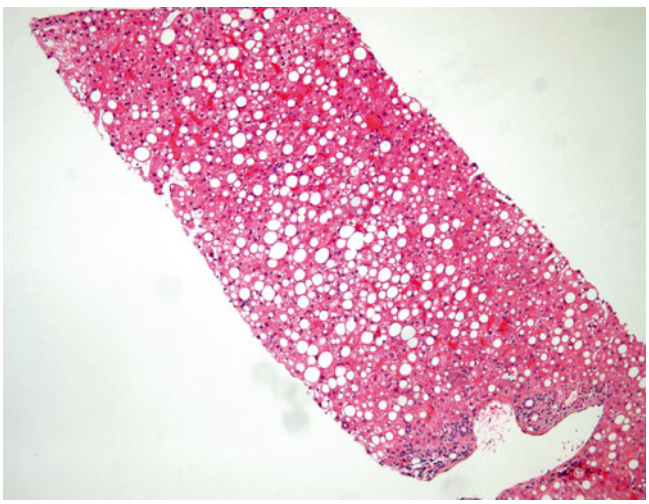

Fig. 5.3 Donor biopsy. This potential donor liver biopsy shows extensive large droplet macrovesicular steatosis (>30 % of parenchyma). This amount of large droplet macrovesicular steatosis in a potential donor liver would generally make this liver unsuitable for transplantation

5.2 Allograft Rejection

Acute cellular rejection (ACR) is the most common type of rejection and the most common complication in the early post-transplant period. The diagnosis is based on three main histopathologic features: (1) mixed but predominantly mononuclear portal inflammation containing activated lymphocytes, neutrophils, and eosinophils; (2) subendothelial inflammation of portal and/or central veins (i.e., endotheliitis); and (3) bile duct inflammation and damage (Figs. 5.4, 5.5, and 5.6). The minimum diagnostic criteria for ACR are generally accepted as the presence of at least two of these features [4]. However, because these findings may vary considerably in different areas of the graft, it is recommended that a minimum of five portal tracts and at least two sections at different levels be examined when evaluating allograft biopsies [5].

Once the diagnosis of acute rejection has been established based on the above criteria, the Banff schema (Table 5.1) is applied to grade the severity of acute rejection [6]. The schema assesses the severity of inflammation, combined with morphologic evidence of rejection-related ischemia, which is the final mechanism of allograft failure in ACR. A descriptive grading of rejection is rendered based on an overall evaluation of the parameters listed in Table 5.1.

In general, mild and moderate acute rejections are distinguished based on the extent of the portal inflammation, whereas the presence of perivenular inflammation and associated hepatocellular necrosis is used to distinguish severe acute rejection from the lower grades (Fig. 5.7). In most mild cases of ACR, the inflammatory infiltrate is limited to the portal tracts. The presence of prominent interface hepatitis indicates either a more severe form of ACR, a late form of ACR (see later description), or another concomitant cause of hepatitis. If more than one inflammatory condition is affecting the allograft (e.g., acute rejection and viral hepatitis), it is extremely difficult if not impossible to determine the relative contribution of each injury to the severity of the changes.

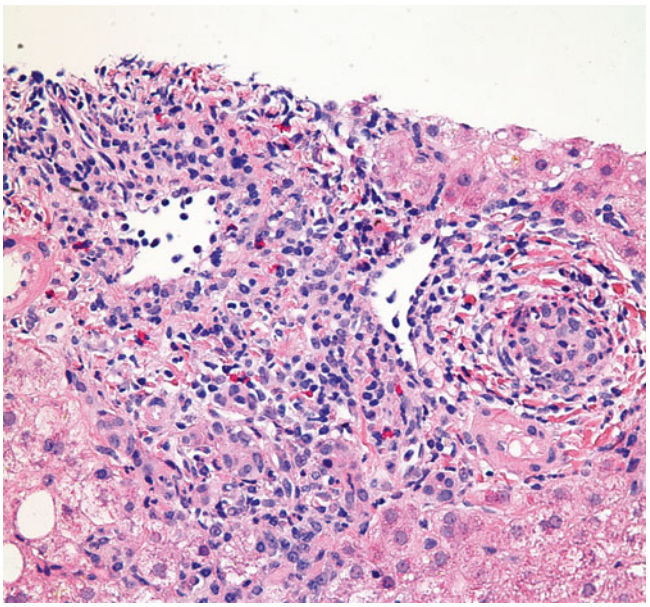

Fig. 5.4 Acute cellular rejection. The portal inflammatory infiltrate is mixed and consists predominantly of lymphocytes, including large activated immunoblasts with large nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. Other inflammatory cells include eosinophils, plasma cells, macrophages, and occasional neutrophils. This portal infiltrate may range from mild to severe and can involve a few to all sampled portal tracts

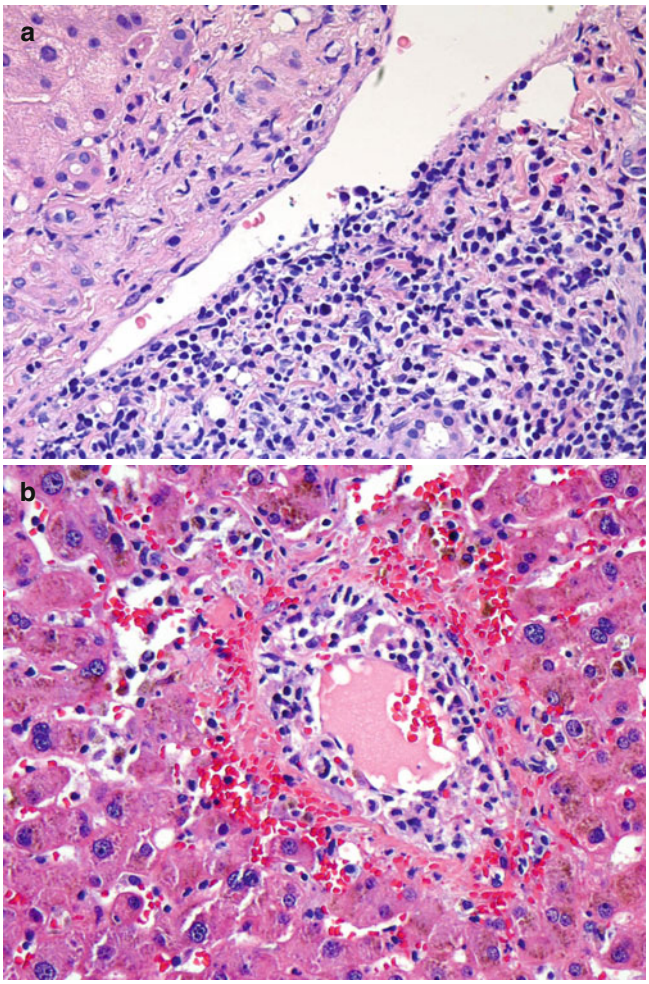

Fig. 5.5 (**a**, **b**) Acute cellular rejection. Endotheliitis. The prominent subendothelial lymphocytic infiltrate is lifting up and detaching the overlying endothelium from the basement membrane. Endotheliitis most commonly involves portal veins (**a**) but can also be seen in central veins (**b**). Endotheliitis is considered the most specific diagnostic feature of acute cellular rejection (Image **b** Courtesy of Charles Lassman, MD, PhD)

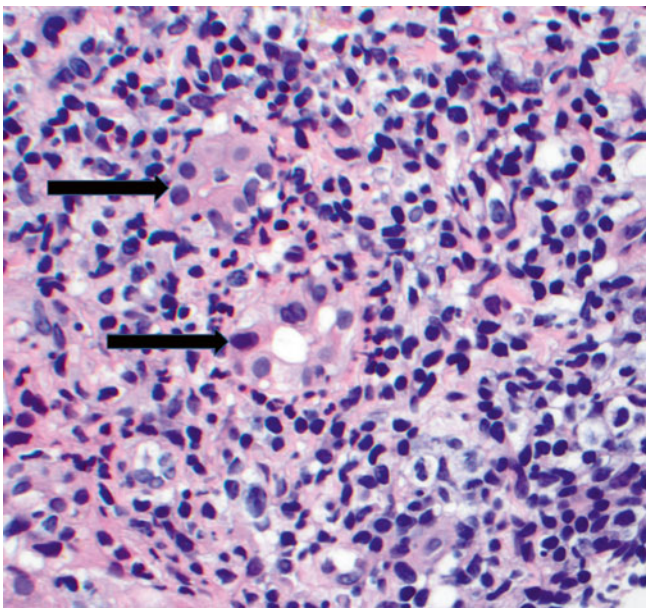

Fig. 5.6 Acute cellular rejection. Bile duct injury (*arrows*) is shown as lymphocytic infiltration of the duct epithelium accompanied by epithelial cell injury with nuclear enlargement, overlapping nuclei, loss of nuclear polarity, cytoplasmic vacuolization, and luminal disruption

Table 5.1 Banff schema for grading liver allograft acute rejection

Global assessment	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 to the portal spaces
Moderate	Rejection infiltrate, expanding most or all the triads
Severe	As above for moderate, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis

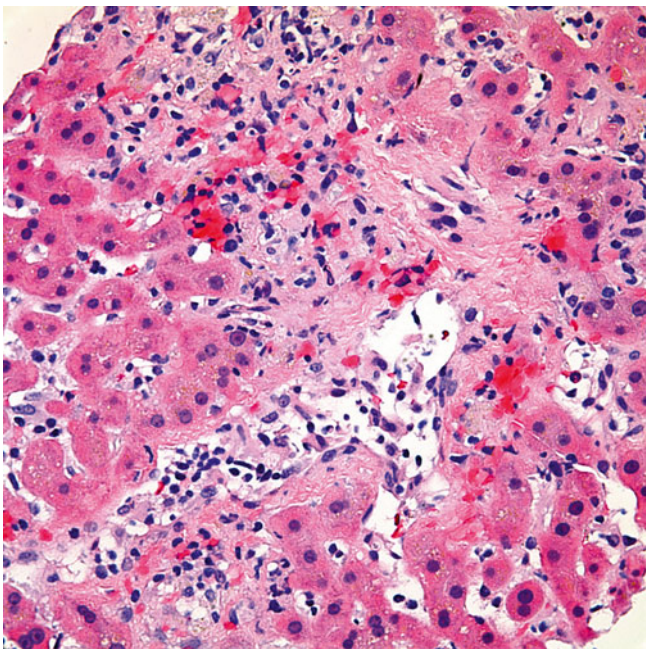

Fig. 5.7 Acute cellular rejection. The presence of perivenular inflammation and associated hepatocellular necrosis in this case would make this a severe case of acute cellular rejection. Central vein endotheliitis is also present; however, its presence is not necessary for a diagnosis of severe acute cellular rejection

5.2.1 Late Acute Rejection

This form of rejection refers to a type of cellular rejection that occurs several months after transplantation and may show different histologic features as compared with typical ACR described earlier. Alternative names include centrizonal/parenchymal rejection, hepatitic variant of rejection, or atypical rejection. It is characterized by a hepatitic pattern of liver injury and can mimic hepatitis closely [7, 8]. Perivenular inflammation (central perivenulitis) is commonly seen, which may or may not be associated with centrilobular hepatocyte injury and necrosis (Fig. 5.8). Late acute rejection is considered a diagnosis of exclusion, and complete serologic studies (including rare forms of viral hepatitis such as hepatitis E) must be performed to rule out other etiologies of hepatitis. Of note, hepatitis E is an uncommon but increasingly recognized cause of acute and chronic hepatitis in the developed countries and should be considered in any post–liver transplant patient with a hepatitic pattern of injury. In general however, if central perivenulitis is present in less than 50 % of the lobules, the diagnosis of late acute rejection is favored [9].

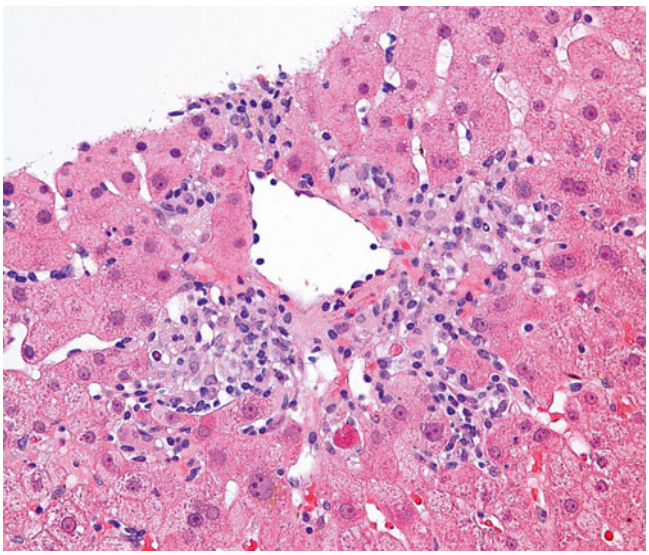

Fig. 5.8 Central perivenulitis is characterized by an inflammatory infiltrate surrounding the central vein, which may or may not be associated with centrilobular hepatocyte injury, dropout, and necrosis. In the presence of characteristic portal changes of rejection, central perivenulitis is a sign of severe acute cellular rejection, whereas isolated central perivenulitis is a histologic finding that may be seen in late acute rejection

5.2.2 Plasma Cell Hepatitis (PCH)

PCH is an immune-mediated post-transplant histologic pattern of injury. It is characterized by the presence of plasma cell–rich portal and lobular inflammatory infiltrates, including central perivenulitis, which closely resembles autoimmune hepatitis in the native liver (Fig. 5.9) [10]. While the pathophysiology is somewhat unclear, PCH is generally considered a form of rejection and is a negative prognostic factor for graft and patient outcomes. Patients with this pattern of injury are more likely to be resistant to increased immunosuppression and have an increased risk of fibrosis and graft loss [11–13].

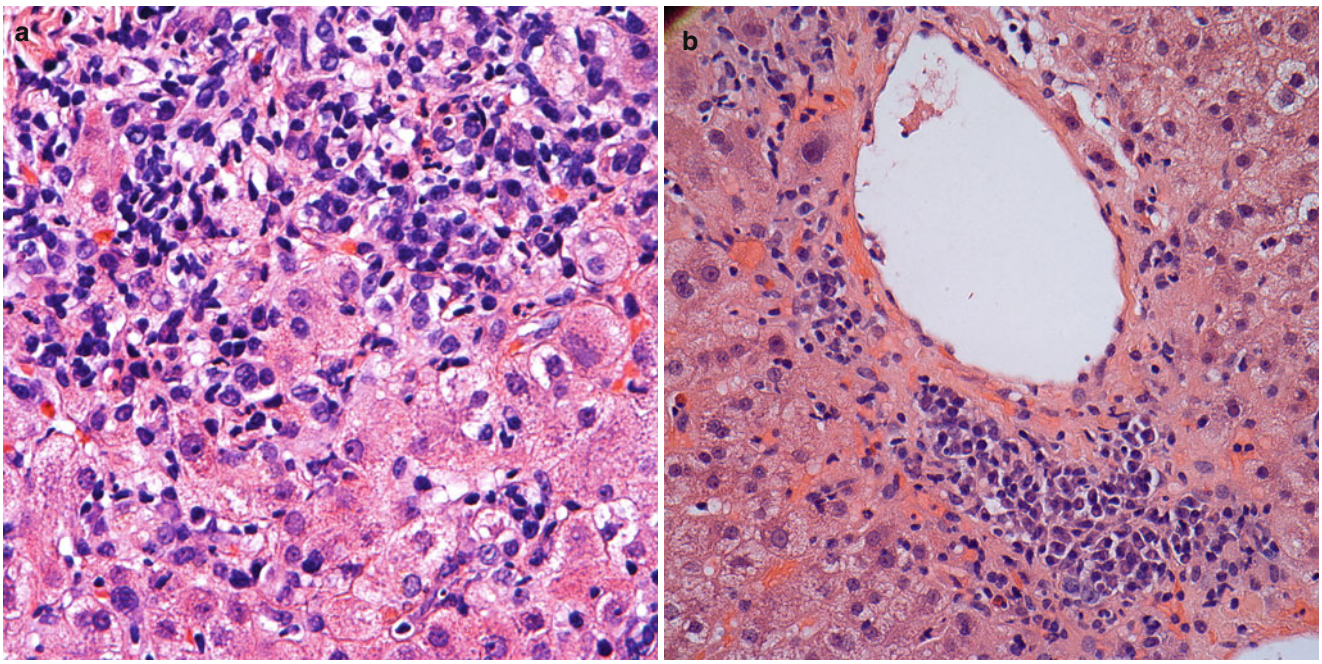

Fig. 5.9 (**a**, **b**) Plasma cell hepatitis. Numerous plasma cells are seen among the portal and periportal inflammatory infiltrate (**a**) as well as in pericentral areas (**b**) of this post-transplant liver biopsy. This pattern of injury is generally considered a form of rejection and imparts a negative prognostic factor for graft function and patient outcome

5.2.3 Chronic Rejection (CR)

In comparison to other solid organ transplants (such as heart, lung, and kidney) in which CR may affect 30–50 % of allograft recipients, CR affects only 3–5 % of liver transplant recipients. Although late CR is considered an irreversible, progressive disease that leads to graft loss, early CR is considered potentially reversible [14]. Early CR is identified by degenerative changes of the biliary epithelium, even before duct loss. These include uneven spacing of biliary epithelial cells, loss of nuclear polarity, and increased cytoplasmic eosinophilia (Fig. 5.10). Late CR is characterized by bile duct loss involving greater than 50 % of portal tracts (Fig. 5.11). Other lobular features that may be seen in later phases of CR include clusters of pigmented foamy macrophages, canalicular cholestasis, pericentral hepatocyte atrophy, and/or ballooning and perivenular fibrosis (Figs. 5.12, 5.13, and 5.14). While foam cell obliterative arteriopathy is the characteristic feature of CR, this finding is only rarely seen in needle core biopsies (Fig. 5.15). The minimum diagnostic criteria for histopathologic diagnosis of CR are defined as follows [15]: (1) the presence of bile duct atrophy/senescence affecting most of the bile ducts, with or without bile duct loss (early CR), (2) foam cell obliterative arteriopathy (OA) with accumulation of foamy, lipid-laden histiocytes within the myointimal layer, or (3) loss of interlobular bile ducts in at least 50 % of the portal tracts (late CR).

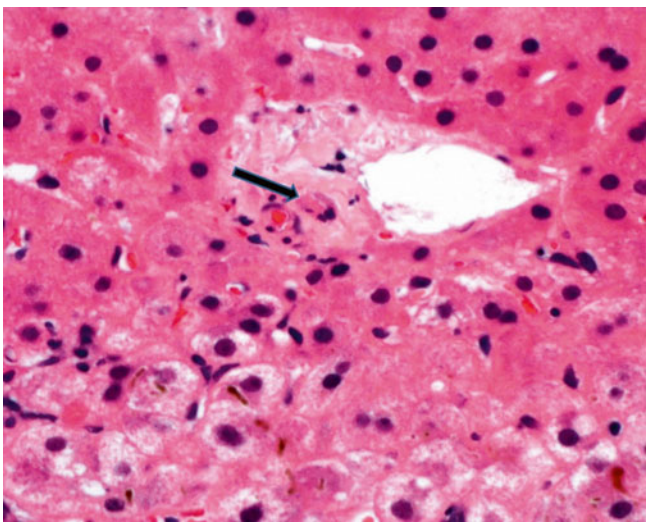

Fig. 5.10 Early chronic rejection with bile duct atrophy/senescence (*arrow*) characterized by uneven epithelial spacing, loss of nuclear polarity, nuclear atypia, and increased cytoplasmic eosinophilia. Note that there is no ductular reaction or portal infiltrate (*Courtesy of* Charles R. Lassman, MD, PhD)

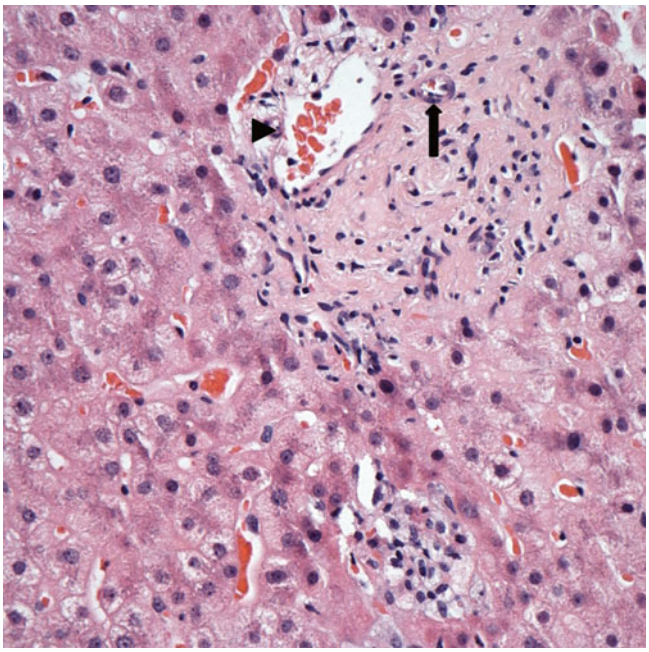

Fig. 5.11 Chronic rejection. This biopsy showed loss of bile ducts in the majority of portal tracts. The portal tract here shows a branch of hepatic artery (*arrow*) and portal vein (*arrowhead*) but no interlobular bile duct. Immunostain for cytokeratin 7 or 19 may be used to help confirm the bile duct loss

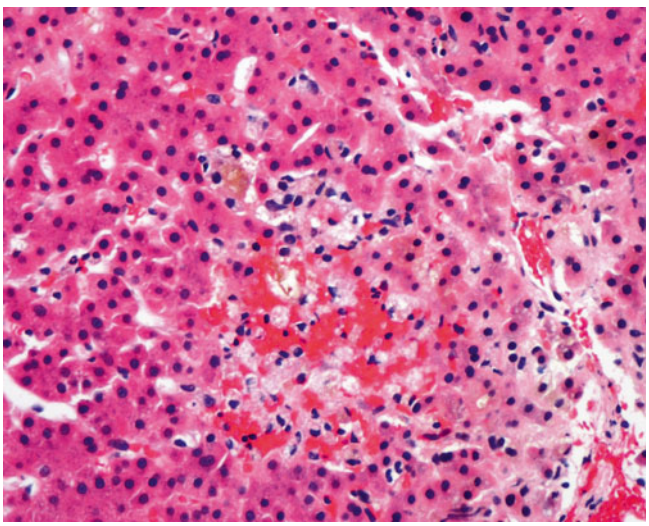

Fig. 5.12 Chronic rejection. Cluster of pigmented macrophages within the lobule with cholestasis may be seen in chronic rejection

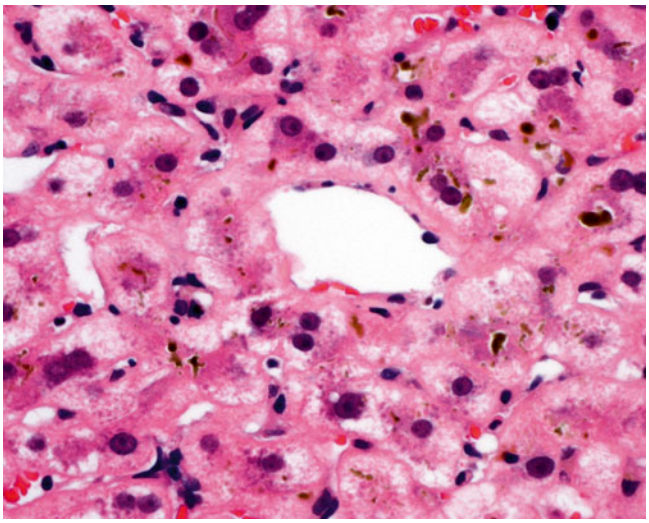

Fig. 5.13 Chronic rejection. Pericentral cholestasis is seen with canalicular bile plugging and cholate stasis with feathery degeneration

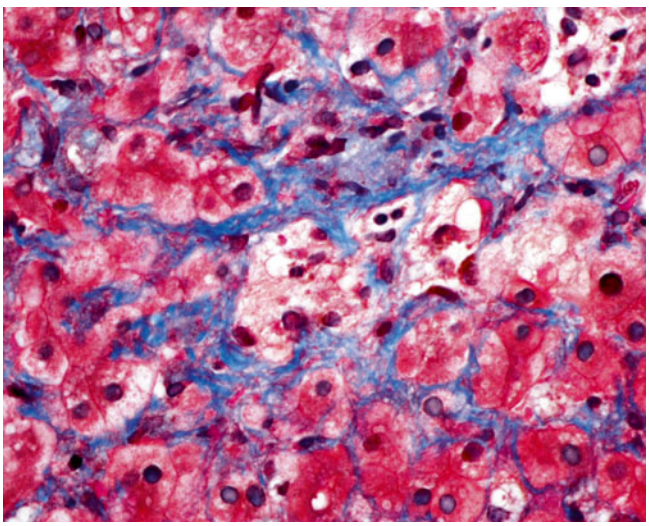

Fig. 5.14 Late chronic rejection. Trichrome stain highlights perivenular fibrosis in this case of late chronic rejection

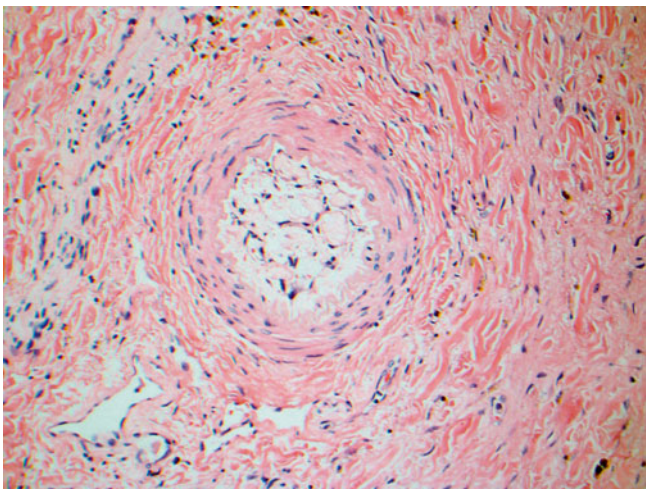

Fig. 5.15 Chronic rejection. Foam cell obliterative arteriopathy is the hallmark feature of chronic rejection and is characterized by intimal thickening with accumulation of lipid-laden foamy macrophages that can cause luminal narrowing and obstruction. This lesion is rarely seen in biopsy material

5.2.4 Antibody-Mediated Rejection (AMR)

AMR is becoming increasingly recognized in liver allografts. However, it remains a controversial area because its diagnostic criteria and histologic features have not been fully established. In general, AMR may be considered if other etiologies of allograft dysfunction have been excluded and if donor-specific antibodies (DSAs) are discovered in the patient's serum. Histologic features that have been reported include portal edema and neutrophilic inflammation with ductular reaction (i.e., features similar to those of bile duct obstruction), hepatocellular necrosis (i.e., features of ischemic injury) as well as portal vein endothelial cell hypertrophy, portal eosinophilia, and eosinophilic central venulitis (Fig. 5.16). Diffuse C4d deposition in the portal vein and sinusoids, demonstrated by immunohistochemistry and/or immunofluorescence, has been described in cases with clinical suspicion of AMR in the presence of DSAs (Fig. 5.17) [16–18]. However, the C4d stain remains a nonspecific stain, and its clinical utility remains unclear because positivity has also been reported in cases of ACR, CR, recurrent hepatitis B and C, biliary obstruction, vascular thrombosis, and even normal allograft livers [19]. The Banff schema consensus guidelines for diagnosis of AMR and C4d interpretation in liver allograft are expected to be released in the near future.

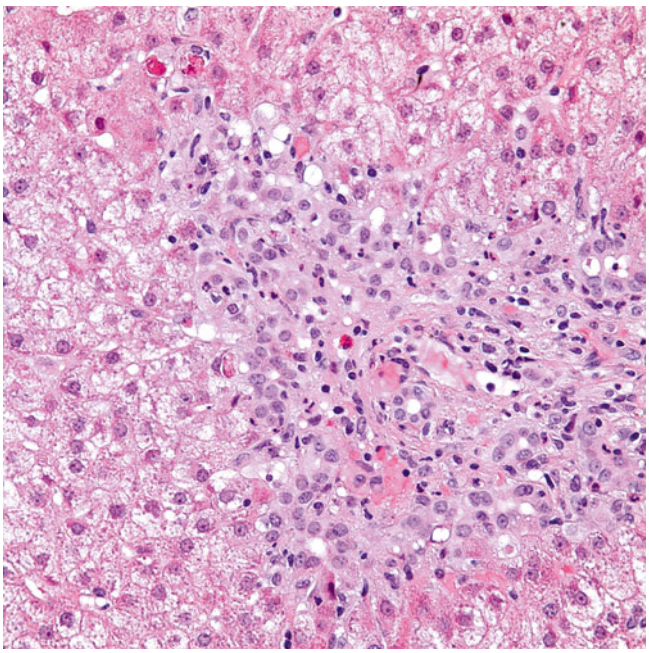

Fig. 5.16 Antibody-mediated rejection. The portal tract shows expansion by ductular reaction and edema, resembling features of bile duct obstruction. In this case, biliary obstruction was ruled out by imaging studies while the patient showed persistent signs of allograft dysfunction along with positive serum DSAs, and was determined to have AMR

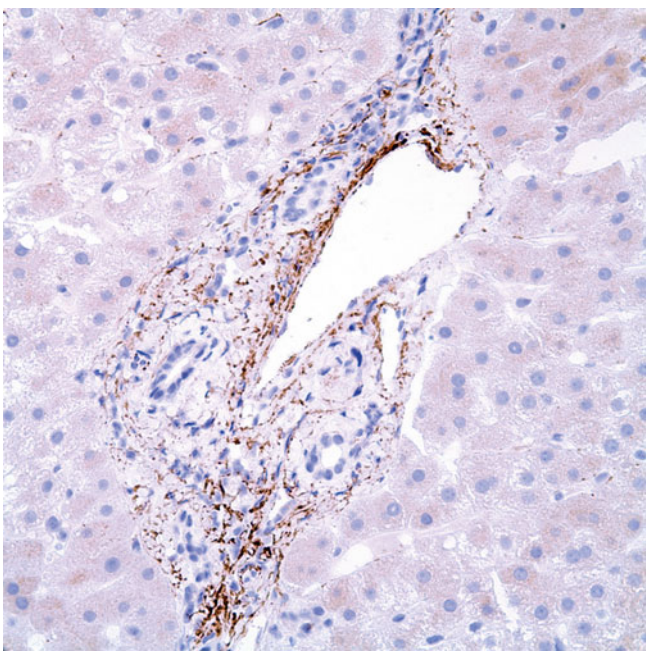

Fig. 5.17 Antibody-mediated rejection. Diffuse C4d immunohistochemical staining of greater than 50 % of portal veins/capillaries has been reported in cases with clinical suspicion of AMR in the presence of serum DSAs

5.3 Recurrent Disease

Recurrent disease is a major cause of graft dysfunction. Examples of some of the more common recurrent diseases follow.

5.3.1 Recurrent Hepatitis C

Recurrent hepatitis C is a major differential diagnosis of ACR, including late acute rejection. Early recurrence is characterized by a predominance of lobular activity with frequent apoptotic bodies (Figs. 5.18 and 5.19). Later there is a transition to predominantly portal infiltrates and interface hepatitis typical of chronic hepatitis C in native livers. The histologic feature that is very useful in determining whether acute rejection is present in the setting of recurrent hepatitis C is endotheliitis. However, it may not be present in late acute rejection. Table 5.2 contains histologic features helpful in differentiating ACR from recurrent hepatitis C.

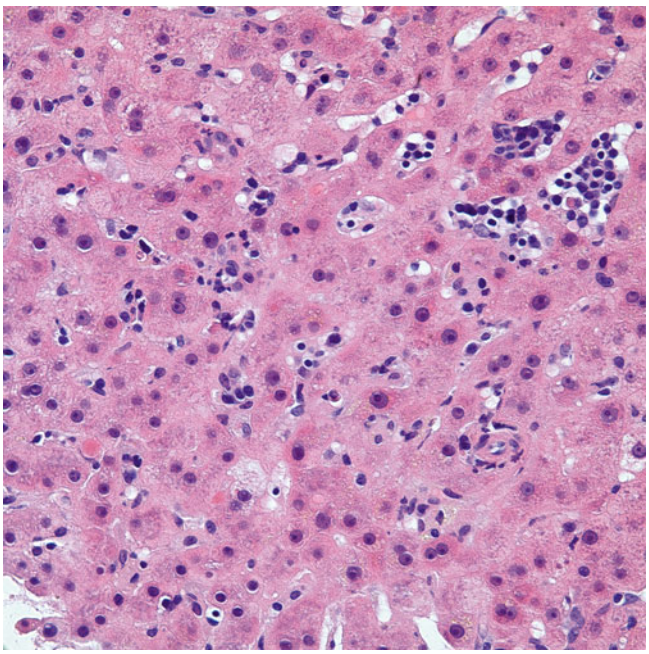

Fig. 5.18 Recurrent hepatitis C viral infection. Early recurrence manifests primarily as a lobular hepatitis with scattered clusters of lymphocytes

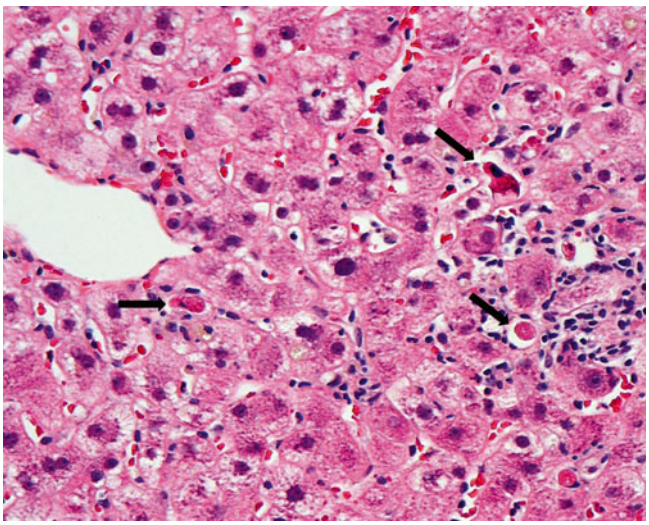

Fig. 5.19 Recurrent hepatitis C viral infection. Apoptotic hepatocytes (*arrows*) are a common feature of early recurrence

Table 5.2 Histologic features of acute rejection versus those of recurrent hepatitis C and primary biliary cirrhosis (PBC)

Histologic feature	Acute cellular rejection	Recurrent hepatitis C	Primary biliary cirrhosis
Portal inflammation	Mixed, with activated lymphocytes, plasma cells, neutrophils, and frequent eosinophils	Predominantly lymphocytic; may be nodular. Eosinophils are inconspicuous or few	Lymphoplasmacytic, sparse or dense; may be centered on bile duct
Bile ducts	Lymphocytic infiltration with epithelial injury. A very good indication of ACR, if it involves >50 % of portal tracts	Even if lymphocytic infiltration is present, it is mild and/or focal	Variable infiltration by lymphocytes and variable injury from mild to florid duct lesions
Portal vein endotheliitis	Present	Absent or mild and focal	Absent
Interface activity	Variable (often seen in moderate to severe ACR and in late ACR)	Minimal in early recurrence. Present in later phases	Ductular reaction and/or interface activity is often present
Lobular activity/injury	May be present in severe ACR but also in late ACR	Predominant in early recurrence, variable later	Variable; generally minimal
Apoptotic hepatocytes	Absent to occasional	Frequent	Absent to occasional
Central perivenulitis (with or without central vein endotheliitis)	May be present in severe ACR or late ACR	Absent or focal/mild, without endotheliitis	Generally uninvolved

5.3.2 Fibrosing Cholestatic Hepatitis (FCH)

This is a rare and aggressive form of viral hepatitis infection that occurs in patients with severe immunosuppression. It has been described in patients with both hepatitis B and C. Histologically, FCH is characterized by marked hepatocellular injury in the form of lobular disarray and ballooning changes in addition to prominent intracellular and canalicular cholestasis, ductular reaction, and periportal and pericellular/sinusoidal fibrosis (Fig. 5.20) [20–23]. There is generally a paucity of portal and lobular inflammatory infiltrate. This is a diagnosis of exclusion and requires clinicopathologic correlation with a markedly elevated viral load and exclusion of bile duct obstruction by imaging studies.

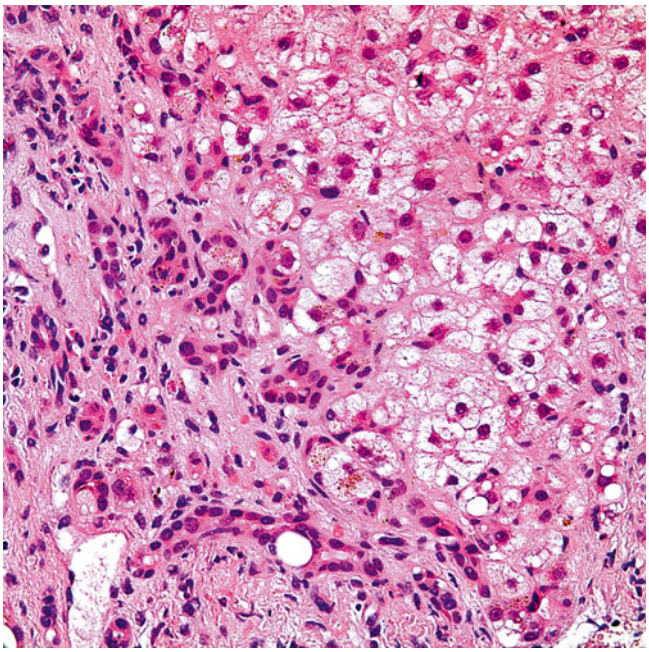

Fig. 5.20 Fibrosing cholestatic hepatitis (FCH). Irregular portal expansion with ductular reaction and diffuse parenchymal ballooning changes and cholestasis can be seen. Note the presence of ductular reaction and the relative paucity of inflammatory infiltrate. Histologically, FCH may mimic bile duct obstruction. However, the latter is not generally accompanied by extensive hepatocellular injury/ballooning and instead may show prominent portal edema

5.3.3 Primary Biliary Cirrhosis (PBC)

The histopathologic findings of recurrent PBC are identical to those seen in native livers. Given the presence of bile duct injury and/or loss in cases of recurrent PBC (Fig. 5.21), the differential diagnosis between acute and chronic rejection can be challenging. (See Tables 5.1 and 5.2 for histologic features that are helpful in this distinction.)

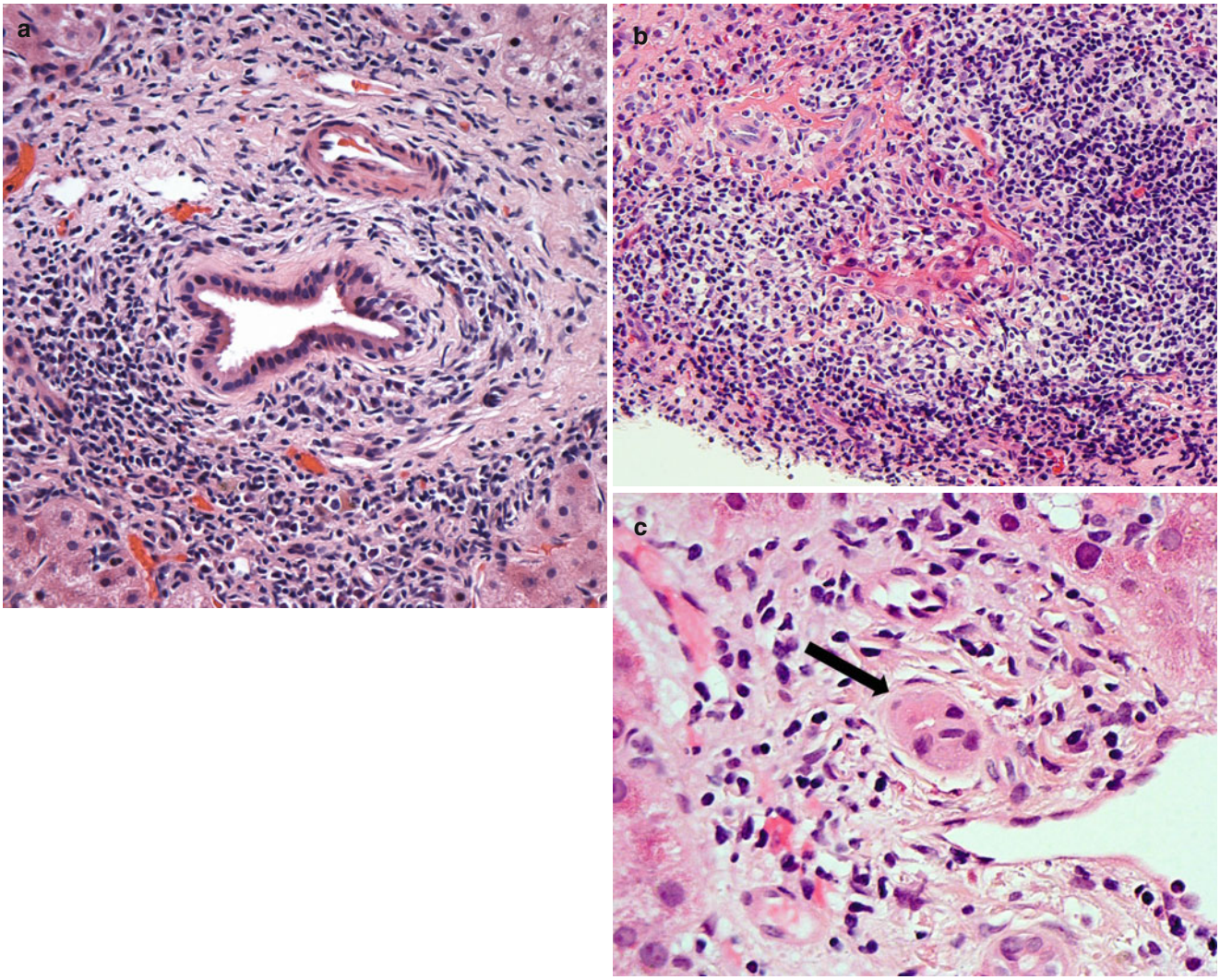

Fig. 5.21 (**a–c**) Recurrent primary biliary cirrhosis (PBC). Note the robust portal inflammatory infiltrate and florid duct lesions (**a**, **b**) in this case of recurrent PBC, 2 years post-transplant. Note the atrophic bile duct (*arrow*) with minimal inflammation in a different case of a late recurrent PBC (**c**). The distinction from acute and early chronic rejection can be difficult in such cases. See Tables 5.1 and 5.2 for some histologic clues (*Photo Courtesy of* Charles Lassman, MD, PhD)

5.3.4 Primary Sclerosing Cholangitis (PSC)

Recurrent PSC cannot be reliably distinguished from other forms of biliary obstruction on biopsy specimens, and cholangiography is essential in establishing a diagnosis. In addition, distinguishing PSC from chronic rejection can be

Table 5.3 Histologic features of chronic rejection (CR) versus those of recurrent hepatitis C, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC)

Histologic feature	Chronic rejection	Recurrent hepatitis C	Primary biliary cirrhosis	Primary sclerosing cholangitis
Portal inflammation	Minimal inflammation	Nodular lymphocytic infiltrate	Variable, from minimal to robust	Variable
Bile ducts	Early CR: atrophy and senescence Late CR: absent	Normal to mild lymphocytic infiltration	May be normal, atrophic, or absent; inflammatory lesions may be present	May be normal, atrophic, or absent; Periductal fibrosis or collagenous scars may be present
Portal fibrosis	None or minimal fibrous expansion	Variable, portal fibrosis progressing to bridging fibrosis and cirrhosis	Variable, portal fibrosis progressing to bridging fibrosis and cirrhosis	Variable, portal fibrosis progressing to bridging fibrosis and cirrhosis
Interface activity	None or minimal	Present	Variable	Variable
Ductular reaction	Absent	May be present	Generally present	Generally present
Lobular activity/ injury	Late CR: Kupffer cell aggregates, cholestasis, perivenular fibrosis may be seen in late CR	Variable: apoptotic cells are usually present; small lymphocytic aggregates may also be present	May be similar to CR with Kupffer cell aggregates and cholestasis	May be similar to CR with Kupffer cell aggregates and cholestasis

challenging because both PSC and chronic rejection may result in atrophy and loss of interlobular bile ducts. However, features of PSC that are not typically seen in chronic rejection include portal inflammation, ductular reaction, and portal fibrosis (see Table 5.3).

5.4 Infections

5.4.1 Cytomegalovirus Hepatitis (CMV)

CMV can infect hepatocytes, endothelial cells, and bile duct epithelial cells. Infected cells have an enlarged nucleus with an eosinophilic inclusion surrounded by a clear halo [24].

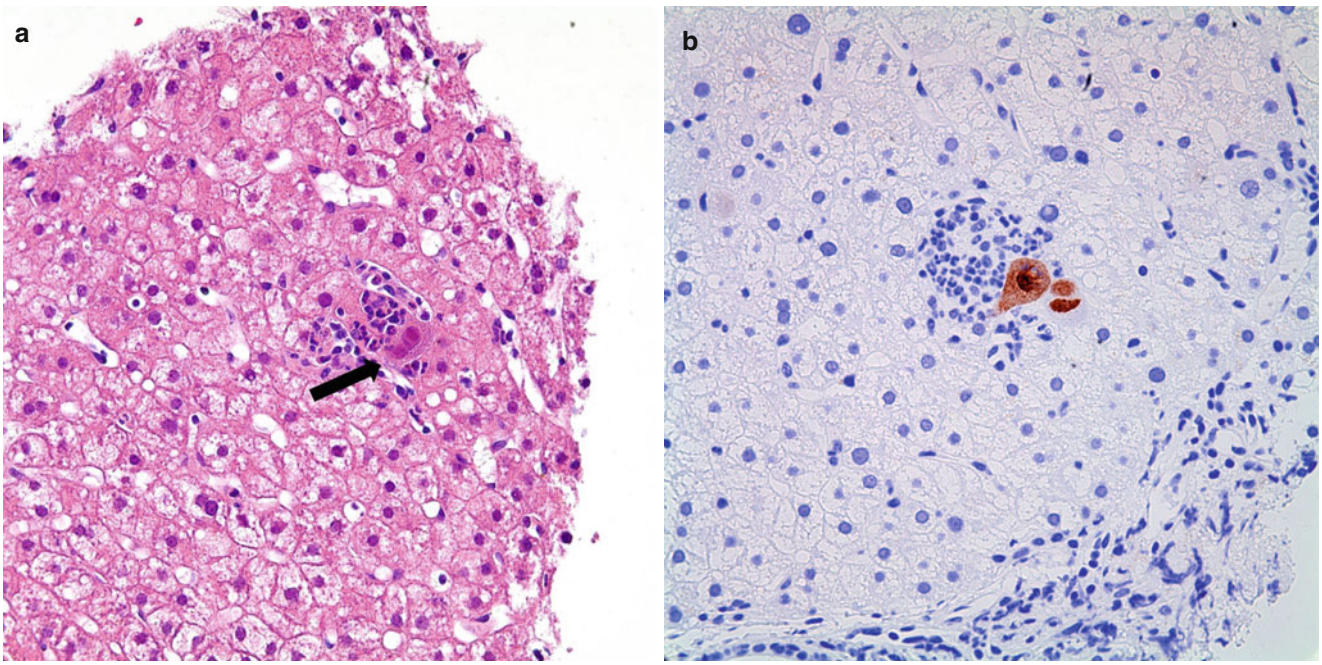

Fig. 5.22 (**a**, **b**) CMV infection. Note the infected cell with an eosinophilic nuclear inclusion (*arrow*) seen adjacent to a cluster of inflammatory neutrophils forming a characteristic neutrophilic "microabscess" (**a**). Immunohistochemistry highlights CMV- infected cells (**b**). Characteristic CMV inclusions might not be present on H&E stain, and therefore immunohistochemical staining for CMV should be considered in any allograft liver biopsy with a clinical and/or histologic suspicion for CMV infection

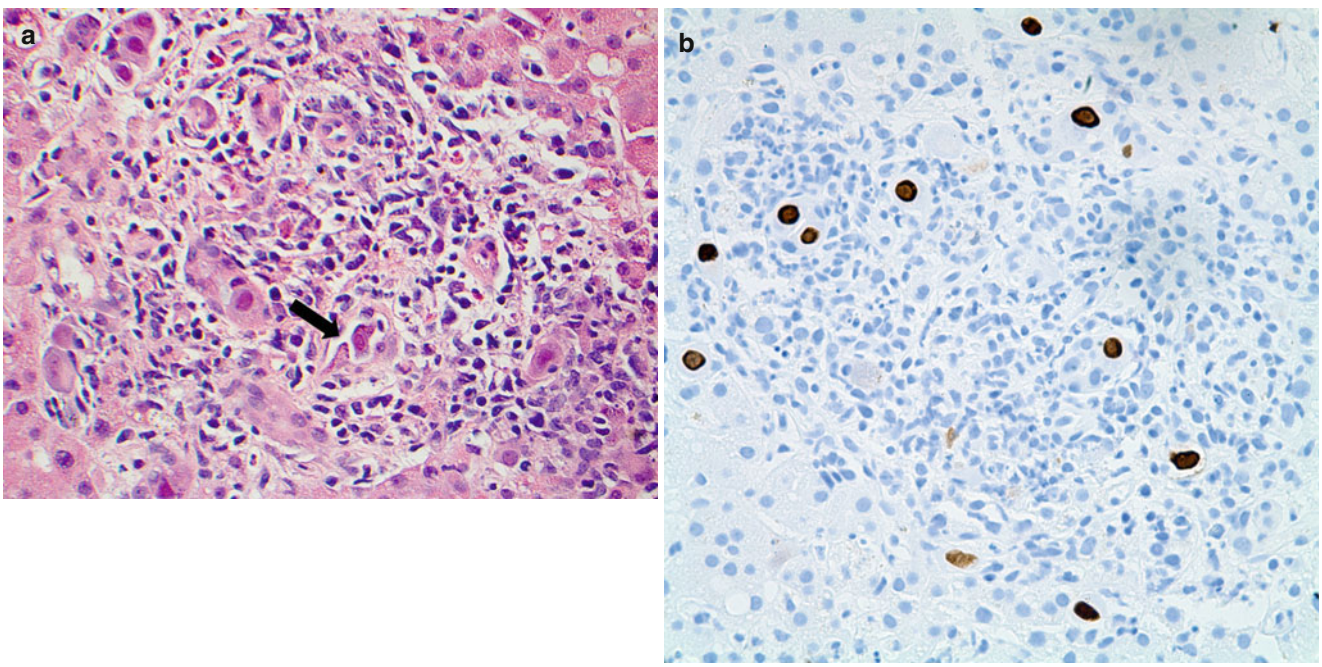

Fig. 5.23 (**a**, **b**) CMV infection. CMV may infect any many cell types including endothelial cells, bile duct epithelial cells, or hepatocytes. In this case, many CMV-infected cells are seen in this portal tract (**a**) and are highlighted by immunohistochemistry (**b**). Note the presence of both cytoplasmic and nuclear eosinophilic inclusions (*arrow* in **a**)

The cytoplasm often also contains eosinophilic granular inclusions. Adjacent liver sections may show clusters of neutrophils forming characteristic neutrophilic "microabscesses" (Figs. 5.22 and 5.23). In fact, this finding in isolation is considered a reasonable indication for performing immunohistochemical analysis to evaluate for CMV.

5.4.2 Adenovirus Hepatitis

Adenoviral infection is characterized by patchy nonzonal coagulative necrosis. Typically, hepatocytes peripheral to the necrosis demonstrate smudgy nuclei with chromatin margination (Fig. 5.24).

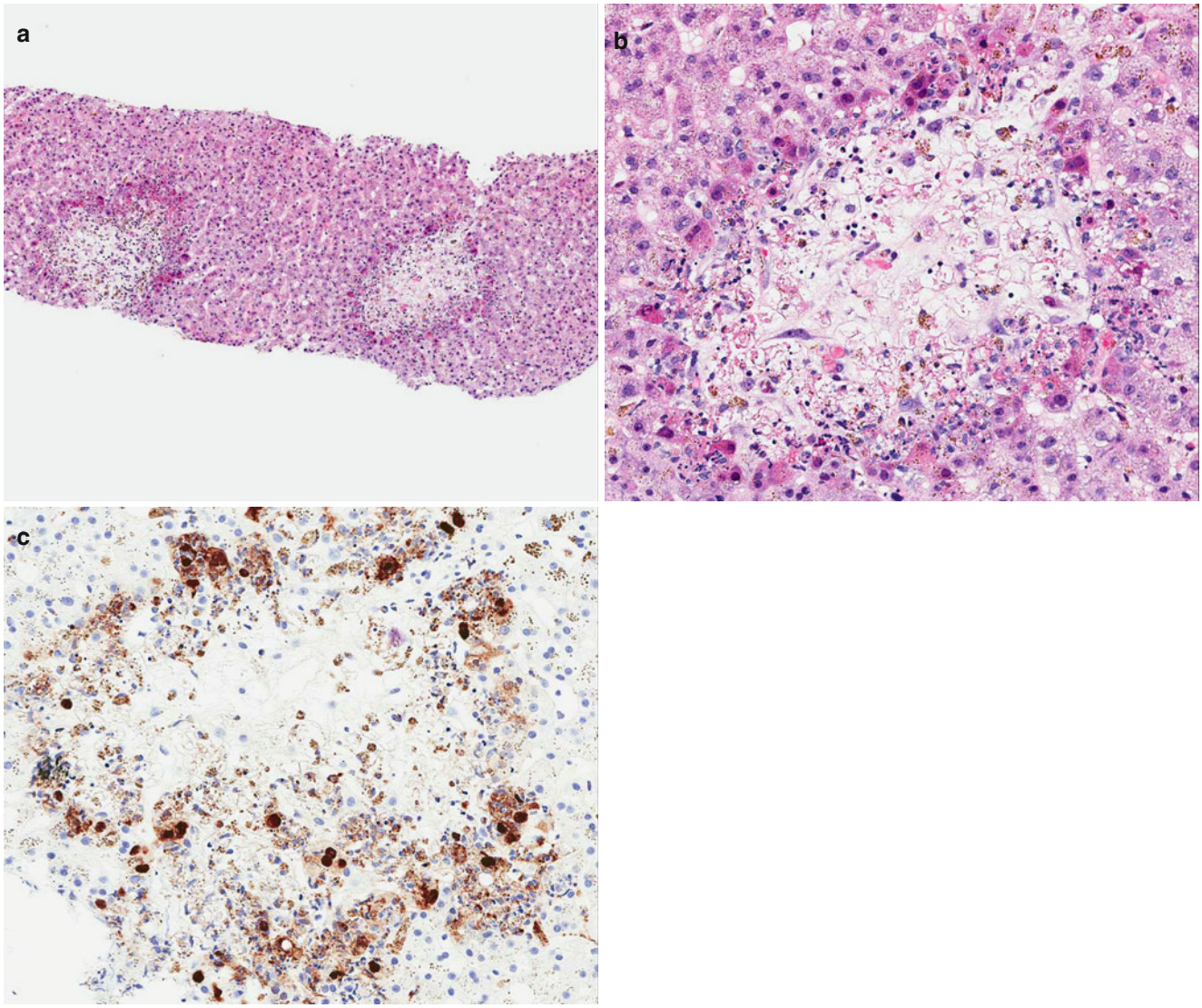

Fig. 5.24 (**a–c**) Adenovirus infection. This infected allograft liver shows patchy hepatocellular necrosis. Note that there is no zonal distribution for the areas of necrosis (**a**). The adenovirus-infected cells are seen at the edges of the necrotic area and show smudged nuclei and chromatin margination (**b**). Immunohistochemical analysis highlights the adenovirus inclusions within infected cells surrounding the necrotic area (**c**)

5.4.3 Herpes Simplex (HSV) and Varicella-Zoster (VZV) Hepatitis

HSV and VZV infections occur secondary to reactivation from latency any time post-transplant. These infections are similar histologically and show variable degrees of hepatocellular necrosis (up to massive) with the typical nuclear features of herpes infection, including multinucleation with molding of nuclei, margination of chromatin, and glassy nuclear inclusions (Fig. 5.25).

5.4.4 Epstein Bar Virus (EBV) Hepatitis

EBV infection is also seen as a reactivation from a previous infection. It might present as a range of histologic changes from mild EBV hepatitis seen as portal and sinusoidal lymphocytic infiltrate to post-transplant lymphoproliferative disorder (PTLD) (see later description). In situ hybridization testing for EBV-encoded RNA (EBER) is helpful.

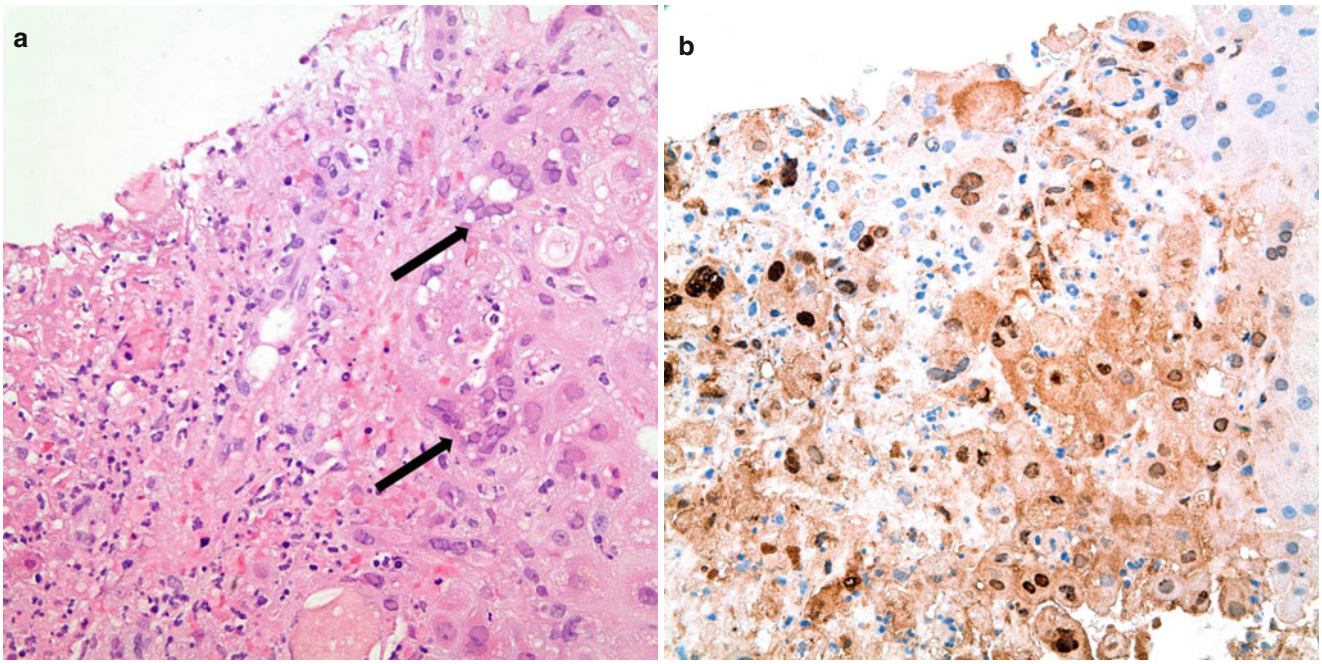

Fig. 5.25 (**a**, **b**) HSV infection. Infected hepatocytes (*arrows*) demonstrate multinucleation and nuclear chromatin margination. Focal necrosis is also present (**a**). Immunohistochemical study demonstrates numerous infected hepatocytes (**b**)

5.5 Other Complications

5.5.1 Preservation/Reperfusion Injury

This is one of the most common causes of allograft dysfunction within the first several weeks after transplantation. It is a general term that refers to the injury that may happen at any time, starting from the donor organ's acquisition, harvesting, and implantation into the recipient. It includes the cold ischemic time of the donor organ as well as injury related to postperfusion. Histologically, it is typically seen as pericentral sinusoidal congestion with neutrophilic infiltration of lobules accompanied by necrotic/apoptotic hepatocytes (Fig. 5.26).

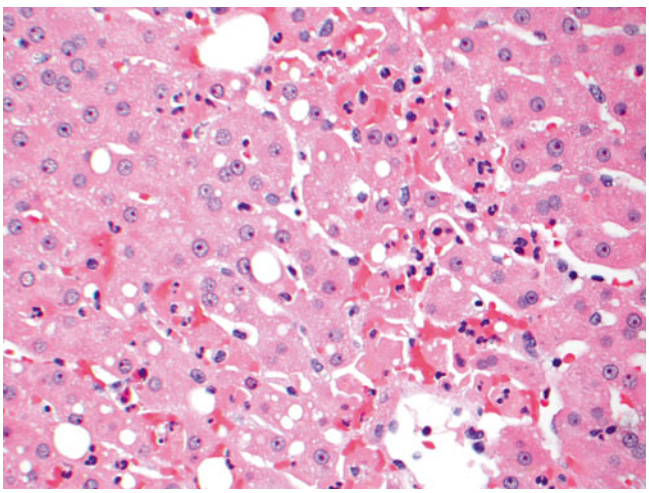

Fig. 5.26 Preservation/reperfusion injury is seen as sinusoidal congestion with neutrophilic inflammation and associated patchy hepatocyte necrosis/apoptosis

5.5.2 Vascular Thrombosis

This is one of the most serious post-transplant technical complications and most often involves the hepatic artery. It most frequently occurs during the first several weeks post-transplant and less frequently 1–3 years after transplantation. Vascular compromise may be seen as pericentral hepatocellular damage, manifested as hepatocellular ballooning with cholate stasis and cholestasis (Fig. 5.27). In more severe cases, pericentral hepatocellular necrosis is present (Fig. 5.28). Other causes of pericentral necrosis in liver allografts include ischemic shock from hypovolemia or sepsis. Patients with sepsis or intra-abdominal infection have a characteristic pattern of injury, so-called subacute nonsuppurative cholangitis, also known as cholangitis lenta (Fig. 5.29) [25, 26].

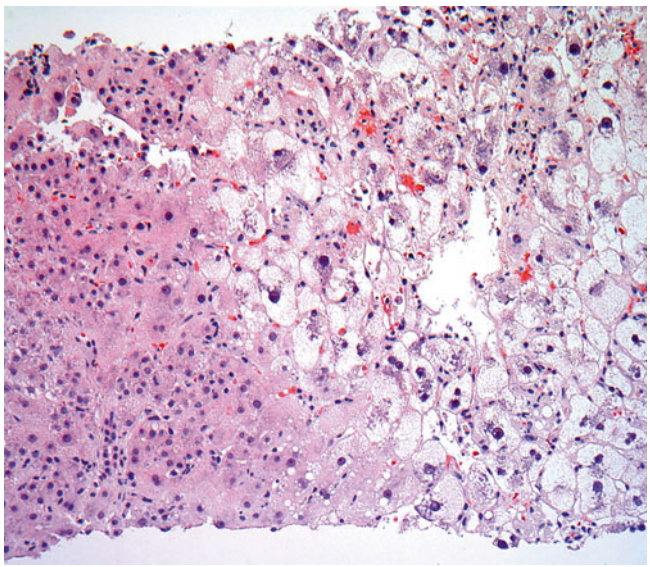

Fig. 5.27 Vascular thrombosis. Pericentral hepatocellular ballooning is seen in this patient with hepatic artery thrombosis

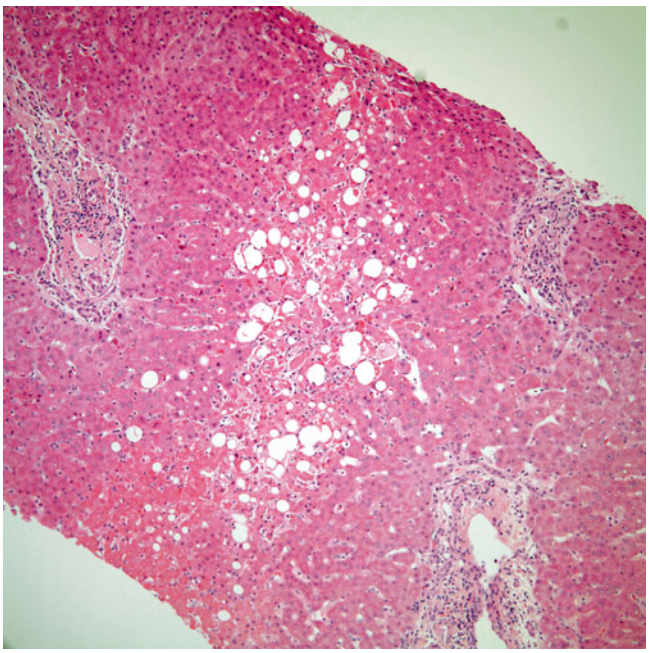

Fig. 5.28 Vascular thrombosis. This biopsy displays pericentral hepatocyte necrosis/apoptosis in a patient with hepatic artery thrombosis

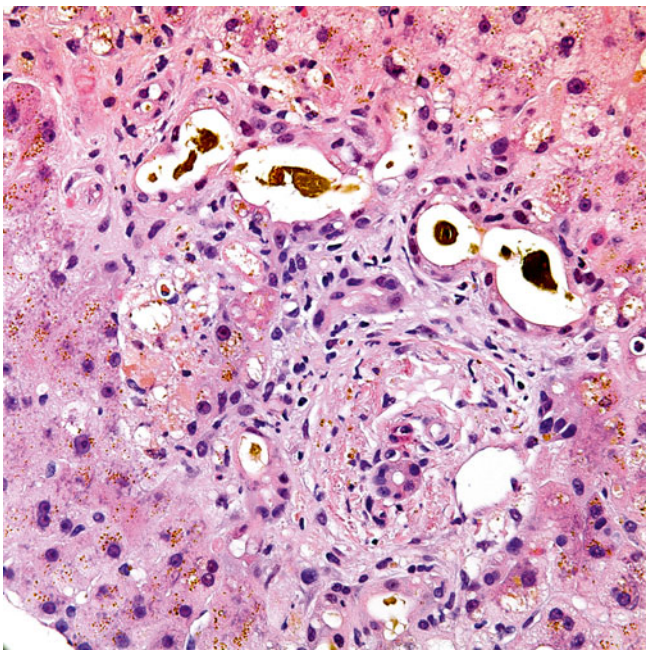

Fig. 5.29 Subacute nonsuppurative cholangitis (cholangitis lenta). This finding of dilated periportal ductules filled with inspissated bile has been generally associated with sepsis and/or intra-abdominal infection. Note that there is minimal portal inflammation and no portal edema

5.5.3 Biliary Strictures/Bile Duct Obstruction

Biliary tract complications are a common source of dysfunction in the liver allograft. Histologic features include portal expansion with edema (neutrophilic), inflammatory infiltrate of portal tracts, and bile ductular reaction (Fig. 5.30). It is important to note that biopsies may show histologic features of mechanical obstruction when the initial imaging is negative for obstruction. Furthermore, bile duct obstruction can be a focal process, and therefore histologic features may not be seen in a biopsy from a nonaffected area.

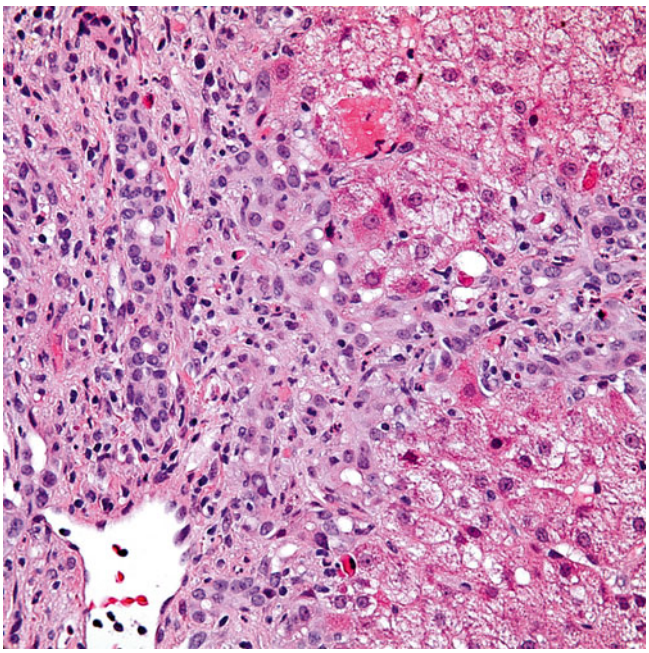

Fig. 5.30 Biliary stricture/bile duct obstruction. Features of bile duct obstruction (portal edema, ductular reaction, and neutrophilic infiltrates) are seen in this patient with a post-transplant biliary stricture

5.5.4 Adverse Drug Reaction

As in nontransplant patients, all forms of drug injury can be seen, including hepatitis and cholestasis. One type of change that is commonly seen in liver allograft is the presence of pseudo–ground-glass hepatocytes (Fig. 5.31) [27]. These deposits closely resemble the ground-glass inclusions of chronic hepatitis B infection. Immunostains for hepatitis B surface antigen may be helpful if there is any clinical concern and serologic testing is not available. Whether the drug injury alone accounts for the allograft dysfunction may not be clear.

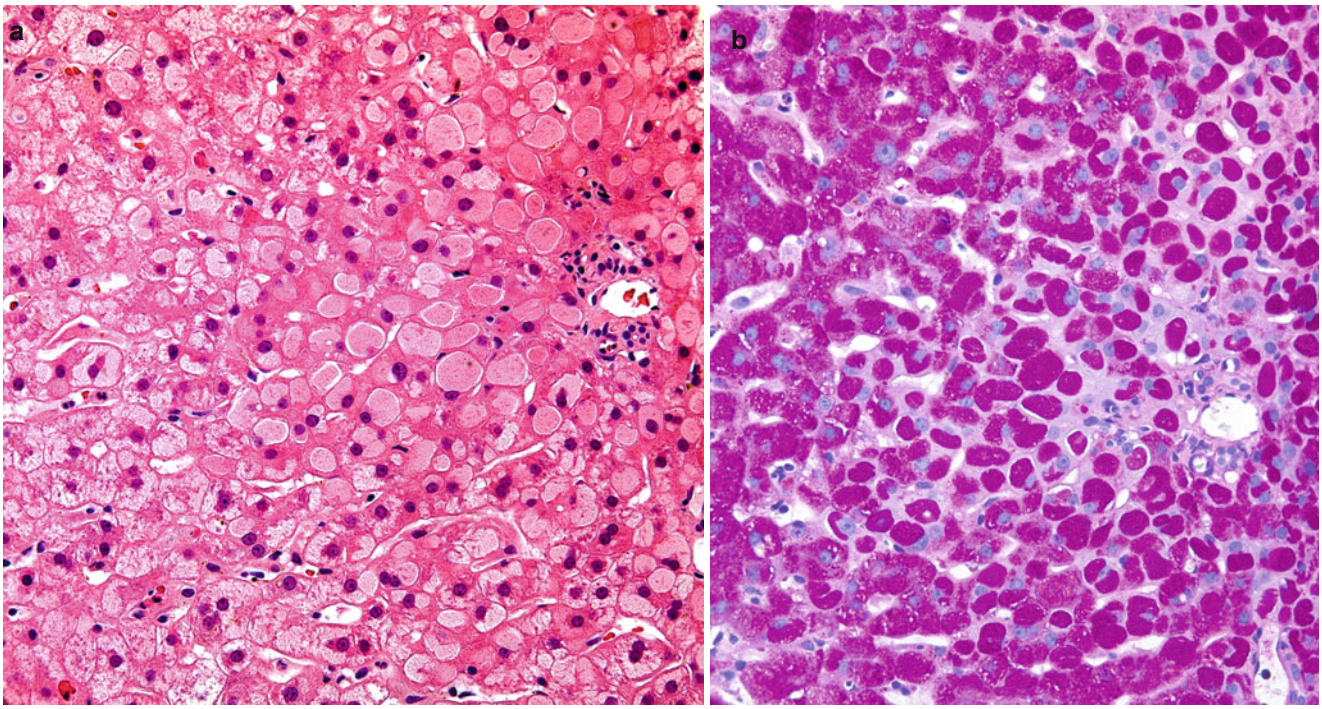

Fig. 5.31 (**a**, **b**) Pseudo–ground-glass hepatocytes. These hepatocytes show pale eosinophilic cytoplasmic inclusions that are displacing the nucleus to the side. This histologic feature may be seen in immunosuppressed patients on multiple medications and is commonly seen in allograft liver biopsies (**a**). Pseudo–ground-glass hepatocytes are associated with the accumulation of abnormal forms of glycogen, as demonstrated here by PAS stain (**b**)

5.5.5 Post-transplant Lymphoproliferative Disease (PTLD)

PTLD may present as an atypical portal and/or a lobular infiltration by mononuclear inflammatory cells, or a mass-forming lesion indistinguishable from lymphoma. It is commonly seen in the presence of EBV detected in tissue (Fig. 5.32). See Chap. 9 for more details.

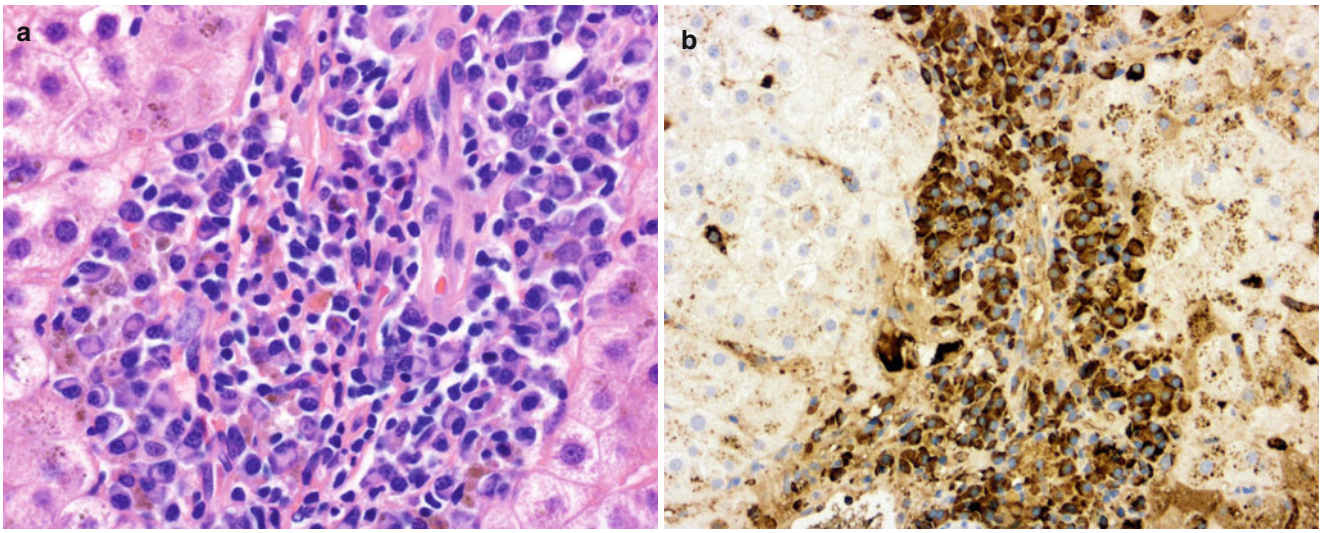

Fig. 5.32 (**a**, **b**) PTLD. Neoplastic plasmacytoid portal infiltrates are seen with little interface activity in this case of PTLD (**a**). The neoplastic cells in this case show light chain kappa restriction, as highlighted by immunohistochemistry (**b**)

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