Liver Pathology in Transplantation

19

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Abbreviations

ABMR	Antibody-mediated rejection
APC	Antigen-presenting cell
EBV	Epstein-Barr virus
GVHD	Graft-versus-host disease
H & E	Hematoxylin and eosin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
MHC	Major histocompatibility complex
NASH	Non-alcoholic steatohepatitis
PTLD	Posttransplant lymphoproliferative disorder
TCMR	T-cell-mediated rejection
Treg	Regulatory T cell

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19.1 Introduction

Liver transplantation is a treatment for almost all kinds of severe liver diseases that are otherwise incurable. More than 27,000 liver transplants were performed in 2015 worldwide, and about 20% of the donors were living donors [1]. In Japan, Southeast Asia, and Middle East, living donor liver transplantation is more common than transplantation from deceased donors due to problems with obtaining cadaveric organs. In cadaveric liver transplantation, the use of a whole allograft to replace the native diseased liver is the most common procedure. In live donor liver transplantation, the left lobe or left lateral segment of the live donor is usually used for pediatric patients. For neonates or very small children, use of a monosegment graft may be selected [2]. In some adult-to-adult living donor liver transplantation, the use of right lobe graft may be necessary to avoid small-for-size graft-associated liver dysfunction, but it might expose the live donor to considerable surgical risk. A cadaveric graft is also sometimes split into two grafts to save two recipients at a time. These partial grafts often need complicated surgical procedures and tend to have a greater risk of postoperative vascular and biliary anastomotic stricture or obstruction than livers resected for non-transplant settings.

E. Hashimoto et al. (eds.), *Diagnosis of Liver Disease*, https://doi.org/10.1007/978-981-13-6806-6_19

Steady improvements in surgical techniques and immunosuppressive regimens to minimize postoperative complications have allowed lots of recipients (patients) to live decades after liver transplantation. Still, most patients experience various postoperative problems in the liver allograft. The main clinical practice of transplant pathology is to find the causes of graft dysfunction after transplantation. Major complications of liver allografts include (1) preservation/reperfusion injury, (2) postsurgical anastomotic complications, (3) allograft rejections, (4) complications related to immunosuppression, and (5) recurrence of the original liver disease.

Before discussing pathology of these complications, it would be useful to know that there is a time course of postoperative complications after liver transplantation. Most allograft complications were seen during specific posttransplant periods. In general, preservation/reperfusion injury manifests within the first week posttransplant period. Surgical complications are commonly seen in the first several weeks, except that biliary complications may also be seen months after transplantation. Typical acute allograft rejection is seen between 5 and 30 days posttransplantation [3]. Acute rejection can actually develop at any point thereafter especially when it is treatment-resistant or associated with nonadherence to immunosuppressive drugs. Incidence of recurrence of original liver diseases increases with time after transplantation. Recurrence of hepatotropic viral hepatitis may become evident within a few months after transplantation, while recurrence of autoimmune disease is usually noticed more than 6 months posttransplantation. In clinical practice, characteristic histological features may be found only focally or the findings may be subtle. Clinicopathological correlations are therefore imperative. The liver transplantation procedure, the timing of biopsy, the laboratory data, the types and dose of immunosuppressive drugs, and the findings of previous biopsy should all be considered before making a diagnosis of liver allograft biopsy.

19.2 Preservation/Reperfusion Injury

Preservation/reperfusion injury is associated with liver graft damage before implantation of the graft into the recipient's body. The main targets of the injury are hepatocytes and sinusoidal endothelial cells. Two types of ischemia are related to graft damage. Hepatocytes are sensitive to warm ischemia, which occurs before or during organ harvesting/procurement [4]. Cold ischemia, which is related to perfusion of hypothermic preservation solution and temporal storage of the graft in ice, causes sinusoidal endothelial damage [5]. After reperfusion, the formation and release of reactive oxygen species followed by Kupffer cell activation and other immune cell reaction worsen injury of both hepatocytes and endothelial cells.

Histologically, preservation/reperfusion injury is characterized by hepatocyte swelling (Fig. 19.1). Swelling of mitochondria and vacuoles in the hepatocytes is observed in electron microscopy [6]. Platelet adhesion occurs in the sinusoids but difficult to recognize in H&E stain [5]. Steatotic hepatocytes are more susceptible to preservation/reperfusion injury [7]. Most transplant surgeons will not use donor livers with severe fatty change (>60% of macrovesicular steatosis) because of poor patient outcome (Fig. 19.2) [8]. Primary graft non-function is a clinical term and is considered as the most severe form of preservation/reperfusion injury where the graft does not function at all after transplantation.

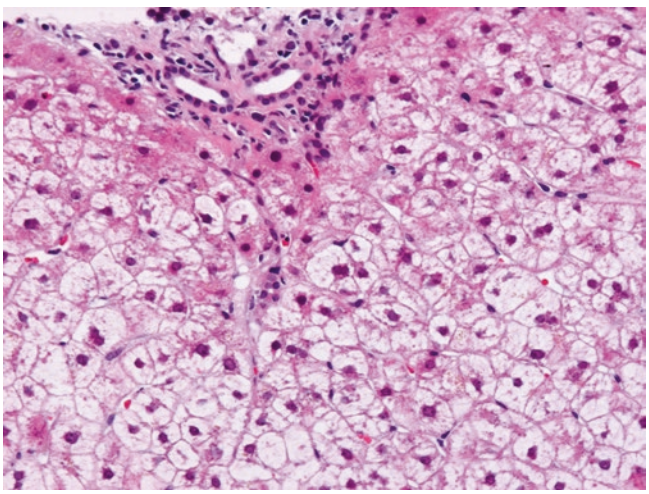

Fig. 19.1 Ischemia/reperfusion injury showing diffuse hepatocyte swelling without portal or lobular inflammation

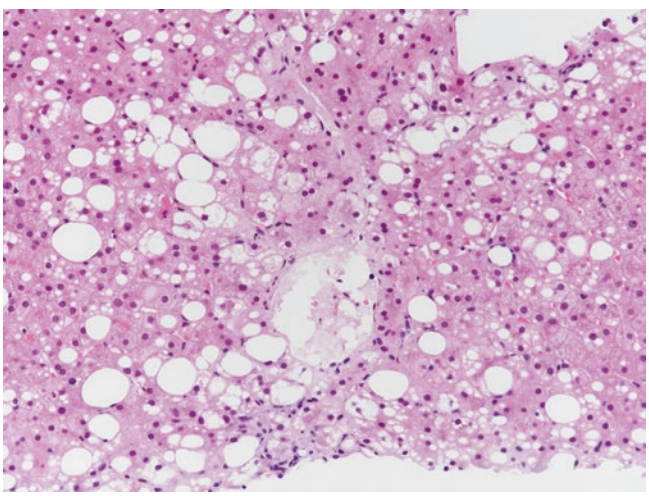

Fig. 19.2 Donor candidate with 60% of macrovesicular steatosis, which was not used for liver transplantation

19.3 Postsurgical Anastomotic Complications

Early complications of the vascular anastomoses can be associated with serious graft damage and can lead to graft failure if untreated. In principle, vascular anastomotic complications should be detected radiologically. Biopsy finding is relatively nonspecific, and it is often impossible to pinpoint affected vessels. Acute hepatic artery thrombosis, for example, can cause centrilobular hepatocyte coagulative necrosis (Fig. 19.3), but almost identical finding can be seen in grafts with acute portal vein thrombosis or severe venous outflow block. Hepatic vein stenosis, or outflow block, is usually associated with centrilobular congestion and hemorrhage (Fig. 19.4). Unlike hepatic artery thrombosis, the hepatocytes are atrophic and show thin cord-like arrangement. However, in partial graft, especially right lobe graft, focal congestion is sometimes seen without demonstrable large hepatic vein stenosis. Therefore, clinicopathological correlation is always necessary for interpretation of congestion of the allograft. Portal vein stenosis or obstruction found several months after transplantation tends to show more nonspecific findings, including periportal fibrosis, occlusion of small portal vein branches, focal sinusoidal dilatation, steatosis, or regenerative hyperplasia (Fig. 19.5) [9].

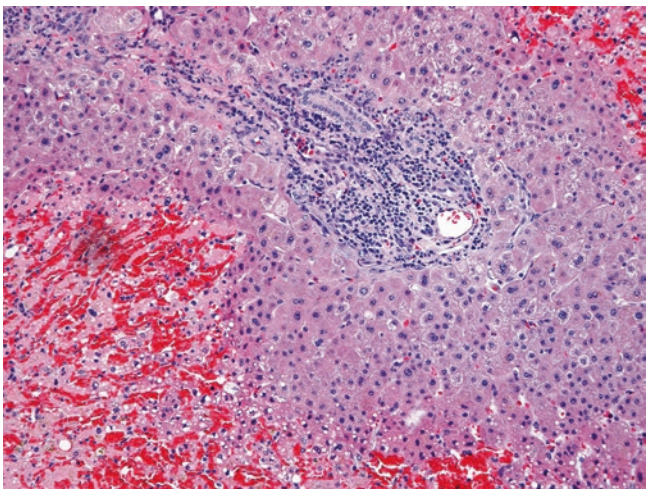

Fig. 19.3 Hepatic artery thrombosis. Centrilobular infarction is seen in the lower left corner. Portal inflammation suggests concurrent mild acute rejection

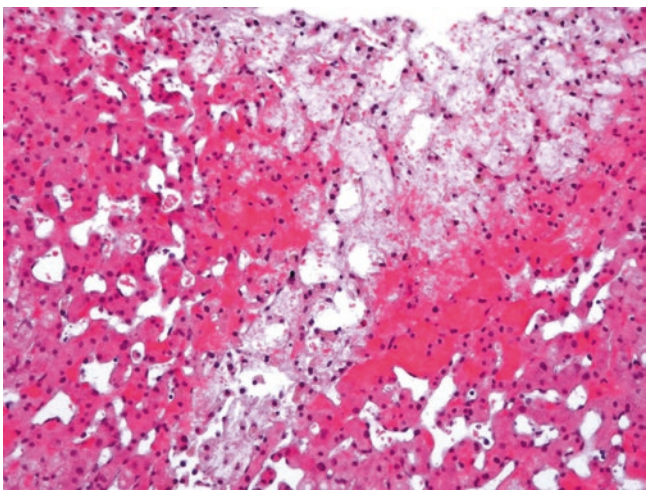

Fig. 19.4 Hepatic vein stenosis showing centrilobular congestion, dilatation of the sinusoids, and hepatocyte dropout

Biliary tract complication is more commonly seen than vascular complication after liver transplantation. Biliary reconstruction is usually performed by duct-to-duct anastomosis or hepaticojejunostomy and sometimes needs complicated procedures due to abnormal anatomy. Anastomotic biliary stricture usually occurs within the first several months posttransplantation, while non-anastomotic stricture tends to become apparent months or years after surgery. The large bile duct and surrounding peribiliary glands are supplied by a subepithelial layer of fine capillaries (peribiliary plexus) originated from the terminal branchings of the hepatic artery. Any insults associated with biliary tract ischemia can lead to disruption of bile flow. Major causes of biliary tract complication include preservation/reperfusion injury, hepatic artery thrombosis, antibody-mediated rejection, bacterial infection, cytomegalovirus infection, and recurrence of primary sclerosing cholangitis.

Biopsy is relatively sensitive to biliary complications. Portal and periportal edema, neutrophilic portal inflammation, ductular reaction, and hepatocanalicular cholestasis are the typical features of acute biliary complications (Fig. 19.6). Although neutrophils are most commonly seen in the periductal areas, there may be some intraductal inflammation

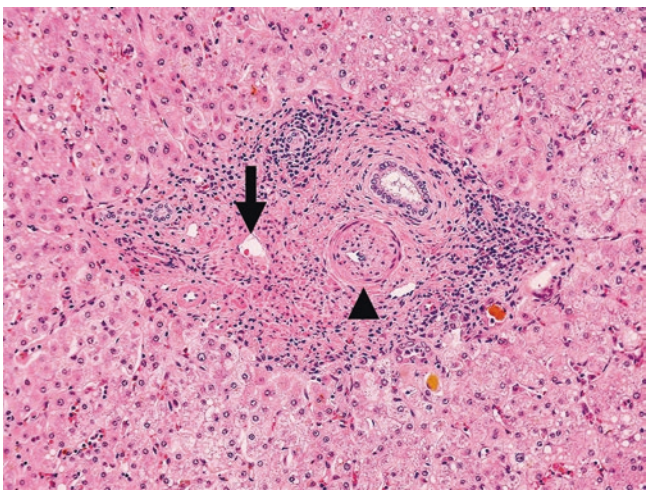

Fig. 19.5 Long-standing portal vein obstruction showing narrowing of the portal tract lumen (arrow) and intimal thickening of the hepatic artery (arrowhead)

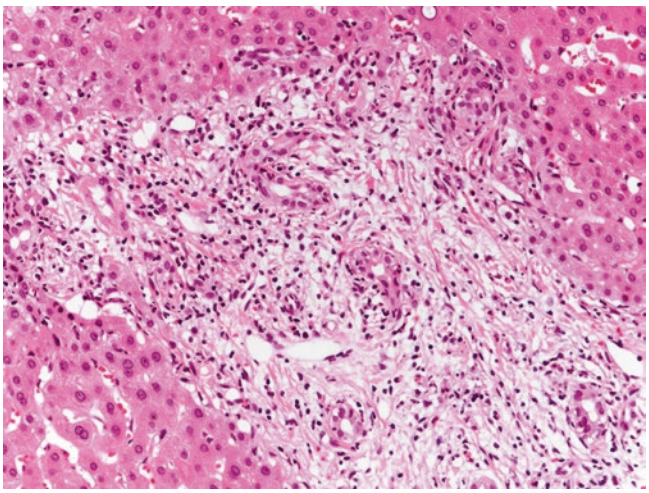

Fig. 19.6 Acute biliary obstruction showing portal edema and neutrophilic portal inflammatory cell infiltration

and neutrophil margination of the sinusoids. Prolonged biliary tract stricture is associated with mixed polymorphonuclear and mononuclear cell infiltration and periductal and periportal fibrosis, and these microscopic features appear similar to chronic hepatitis. Bile duct damage and cholestatic periportal hepatocytes can be the key to differentiate chronic biliary complications from chronic hepatitis. Loss of interlobular bile duct and ductules can occur in severe chronic biliary stenosis, and histology is sometimes indistinguishable from that of chronic ductopenic rejection. Both severe chronic biliary stenosis and late phase of chronic rejection are refractory to treatment and important causes of graft and patient loss.

19.4 Allograft Rejections

19.4.1 Mechanisms of Allograft Rejection

Allograft means a transplant graft from a genetically nonidentical donor of the same species. Liver transplantation using xenograft (graft from other species/animals) has not been successful in human liver transplantation. Allograft rejection is an immunological reaction against allograft antigens. The main target of this reaction is major histocompatibility complex (MHC), a set of cell surface proteins which is related to peptide antigen presentation. The human MHC is also called the human leukocyte antigen (HLA). In transplant settings, MHC expressed by donor cells act as target of rejection unless the recipient has the same MHC. In the first several days or weeks after transplantation, the donor MHC antigens can be directly presented by donor antigen-presenting cells (APCs) (direct pathway). Direct pathway is believed to be related to acute rejection in early course of transplantation. Subsequently recipient APCs start to engulf donor-derived antigens shed from the graft, and donor antigens were presented by the recipient APCs (indirect pathway). Because most of the donor APCs were killed by allograft rejection in early course of transplantation, indirect pathway is believed to be associated with late acute rejection and chronic rejection. It is also known that whole donor MHC-peptide complex can be transferred to recipient APCs through exosomes released from the graft cells and is used to cause immune reaction (semi-direct pathway) [10]. The role of semi-direct pathway in liver transplantation is not well understood.

19.4.2 Classification of Allograft Rejection

Rejection in liver transplantation can be classified into three main types based on the time course: hyperacute rejection, which starts from minutes after transplantation; acute rejection, which usually fully develop several days after transplantation; and chronic rejection, which may become apparent months or years after transplantation. However, there is no clear chronological definition for these immune reactions. Pathophysiologically, rejection is classified into two categories: antibody-mediated rejection (ABMR) and T-cell-mediated rejection (TCMR). This classification of rejection is well-recognized in kidney transplantation and other solid organ transplantations. In liver transplantation, however, histomorphological evaluation of liver allograft ABMR is often difficult, and there remains so much uncertainty about the role of ABMR. By contrast, histology of acute and chronic rejection is well-documented and has been widely used for management of liver allograft rejection. The terms of acute and chronic rejection are therefore mainly used in this chapter.

19.4.2.1 Hyperacute Rejection

Hyperacute rejection is a pure form of ABMR, mediated by preformed donor-specific anti-donor HLA antibodies (DSAs). Although recipients with high titers of DSA are at risk for ABMR, this type of rejection is rare in liver transplantation even the donor has DSAs. This relative resistance of liver allograft against ABMR, however, does not mean that hyperacute rejection does not occur at all. If hyperacute rejection develops, preformed DSAs bind donor endothelial cells and sinusoidal cells, and activation of complement causes thrombosis. Most of the vasculature within the graft is rapidly thrombosed, and massive necrosis of the liver parenchyma develops within hours after transplantation (Fig. 19.7a, b). Re-transplantation is the only way to save the recipient. Patients with high titers of DSA are therefore often precluded from cadaveric transplantation. In living donor liver transplantation, preoperative plasmapheresis and

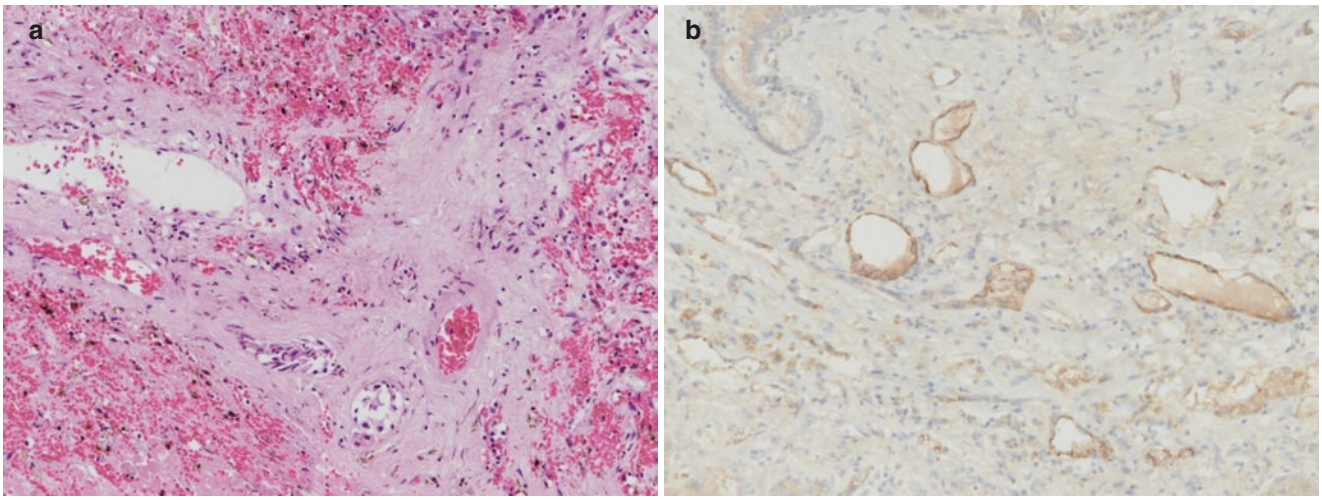

Fig. 19.7 (**a**) Hyperacute rejection showing massive hepatocyte necrosis. (**b**) Hyperacute rejection showing capillary C4d deposition, which suggests complement activation after antibody binding

administration of anti-CD20 antibody are performed to prevent ABMR for high-risk patients.

19.4.2.2 Acute Rejection

Acute cellular rejection (ACR) is often used as synonym for acute rejection because acute rejection is believed to be primarily caused by TCMR. This cellular process is supported by histological assessment. Acute rejection is characterized by (1) T-cell predominant but mixed portal and/or perivenular inflammation, (2) bile duct inflammation and damage, and (3) subendothelial inflammation of portal and/or terminal hepatic venules (Fig. 19.8a–d) [11]. To make the diagnosis of acute rejection, at least two of the above findings are required. Patients often show fever, abdominal pain, and reduced portal vein and bile flow. Blood test shows nonspecific liver injury (e.g., elevation of transaminase), and liver biopsy is necessary to confirm the diagnosis. Grading of acute rejection is proposed by the Banff Working Group on Liver Allograft Pathology, and acute rejection is graded as indeterminate, mild, moderate, and severe [11]. A basic concept of Banff grading is that grade is more than mild if more than half of the portal triads or perivenular areas are affected by inflammatory process. Most acute rejection is classified as mild or moderate and easily controlled by bolus of steroid and increased immunosuppression. More than mild acute rejection is often accompanied by eosinophilic infiltration and CD8+ cell-predominant infiltration and can be treatment-resistant [12, 13]. A diagnosis of severe acute rejection is made when parenchymal necroinflammation is observed in a majority of periportal and/or perivenular areas. Some therapy-resistant rejection may be treated by rabbit antihuman thymocyte immunoglobulin.

Involvement of ABMR in acute rejection of liver transplantation is thought to be uncommon. Patients with high-titer DSAs have a higher risk of developing ABMR. To make a definitive diagnosis of acute ABMR, positive serum DSA and microvascular deposition of C4d (degradation product of complement C4) are required in addition to histopathological pattern of injury consistent with acute ABMR such as endothelial swelling, capillary dilatation, and microvasculitis (Fig. 19.9a, b) [11]. ABMR can also be observed after ABO-incompatible transplantation if preoperative preventive management is inadequate (Fig. 19.10).

Late acute rejection, which is defined as acute rejection seen after 6 months posttransplantation, is likely attributable to indirect or semi-direct alloantigen presentation. Late acute rejection shows more monotonous lymphocytic infiltration and less bile duct and endothelial injury. In addition, lobular inflammation (periportal or perivenular) is more commonly seen even though clinical presentation does not suggest severe acute rejection. When there is marked plasma cell infiltration, the diagnosis of plasma cell-rich rejection (formerly known as "de novo autoimmune hepatitis") may be made (Fig. 19.11). Although patients with late acute rejection often initially have little or no symptoms, it is important to recognize and treat late acute rejection. Late acute rejection is a risk to patient and graft survival. Unlike typical (early) acute rejection, late acute rejection often recurs or persists and can cause liver cirrhosis or chronic rejection [14–16].

19.4.2.3 Chronic Rejection

Ductopenic rejection is a synonym of chronic rejection. Chronic rejection usually evolves from severe or persistent acute rejection. In some cases, it starts with intractable cholestasis with minimal inflammatory cell infiltrate. Owing to improvements of immunosuppression, this is a relatively uncommon problem in liver transplantation, but

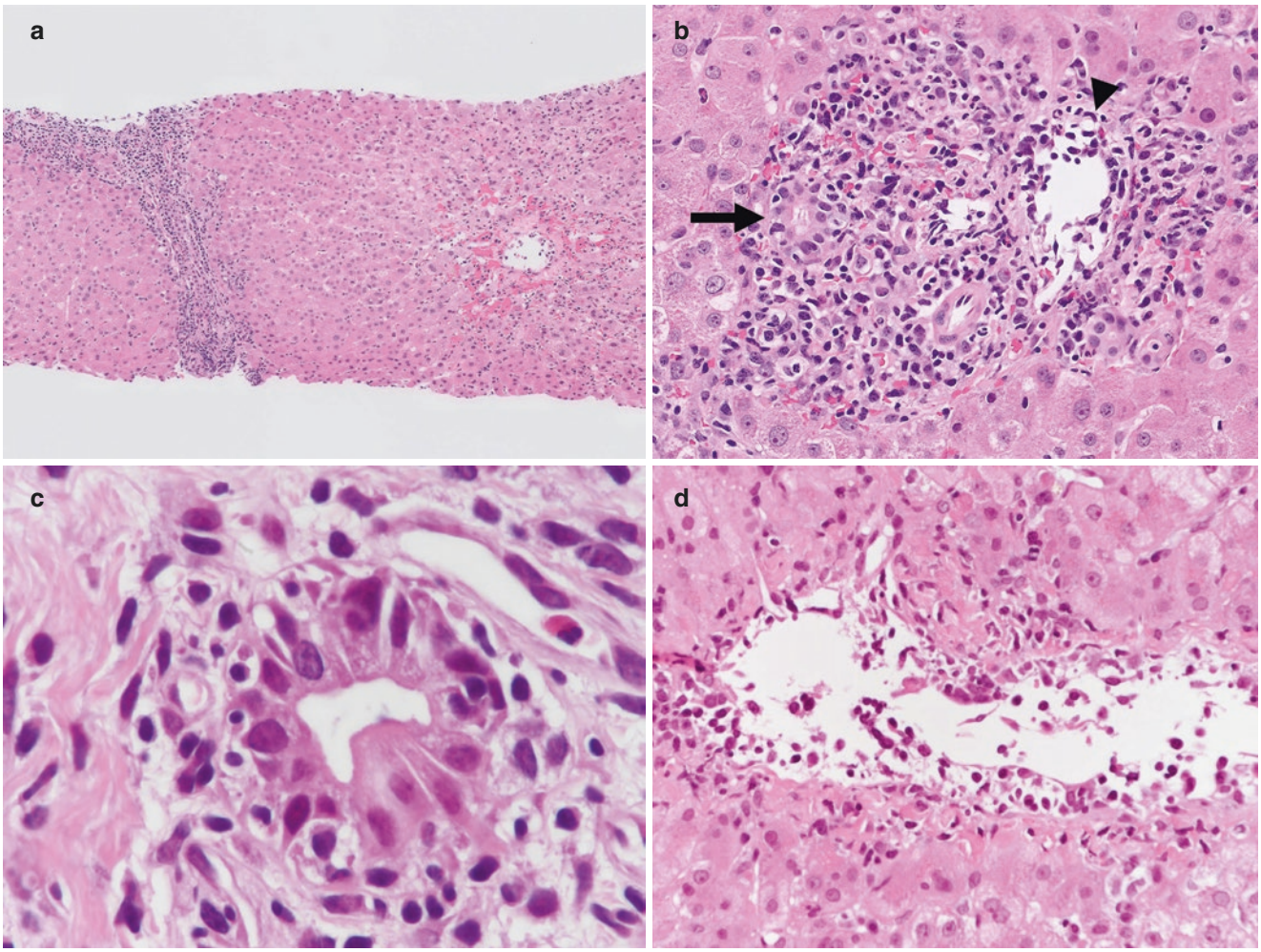

Fig. 19.8 (**a**) Low-power view of moderate acute rejection showing portal inflammation (left side) and perivenular inflammation (right side). Perivenular inflammation is accompanied by hemorrhage. (**b**) Acute rejection demonstrating bile duct inflammation damage (arrow, left side) and venous endothelial inflammation (arrow head, right). (**c**) Acute rejection showing degenerated biliary epithelium with inflammatory cell infiltration. (**d**) Acute rejection demonstrating endothelial detachment of the hepatic venule by subendothelial lymphocytic infiltration

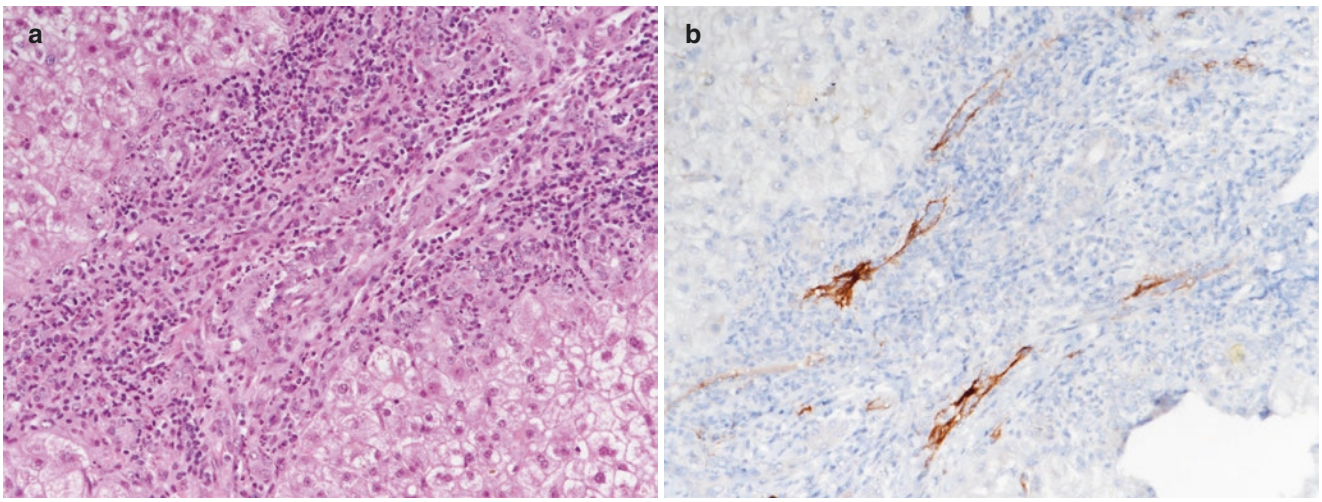

Fig. 19.9 (**a**) Acute rejection with ABMR component. Mixed infiltrate is neutrophil predominant although neither biliary complication nor infection is not evident in this case. (**b**) Acute rejection with ABMR component showing C4d deposition in the sinusoids

it still consists of more than 10% of causes of pediatric retransplantation [17]. The most characteristic histological feature is interlobular bile duct loss and duct degeneration (atypia or senescence-like morphology) seen in more than half of the portal tracts (Fig. 19.12a, b). In typical cases, fibrous expansion of portal tracts is not conspicuous, and other portal structures such as arterioles often become atrophic and difficult to identify. Keratin 7 (cytokeratin 7) immunostaining is very useful to confirm the degeneration and loss of bile ducts and ductules (Figs. 19.12b and 19.13). Ductular reaction is usually absent, and there is aberrant expression of keratin 7 in the periportal and perivenular hepatocytes.

Unlike other solid organ allografts, the liver allograft with chronic rejection may response to rejection therapy and recovers its function to some extent. Staging of chronic rejection is therefore proposed by the Banff Working Group [11]. Early chronic rejection, which does not show severe cholestasis or bile duct loss in ≥50% of portal tracts, is potentially reversible or likely to response to potent immunosuppressive therapy. Late chronic rejection, in contrast, shows advanced histology with severe progressive cholestasis and is potentially irreversible. Venous obliteration is a feature of late chronic rejection (Fig. 19.14). Obliterative arteriopathy (Fig. 19.15) is another feature of late chronic rejection but usually dif-

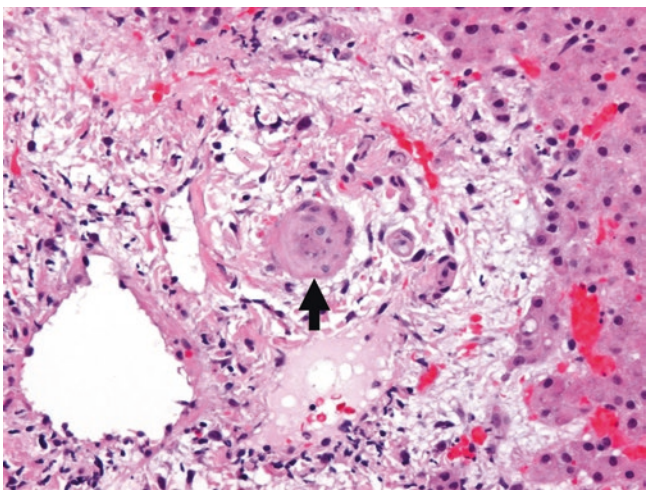

Fig. 19.10 ABO-incompatible acute ABMR showing portal edema, endothelial swelling (center, arrow) of the hepatic artery, and thromboses of the capillary (right side). There is not a component of TCMR

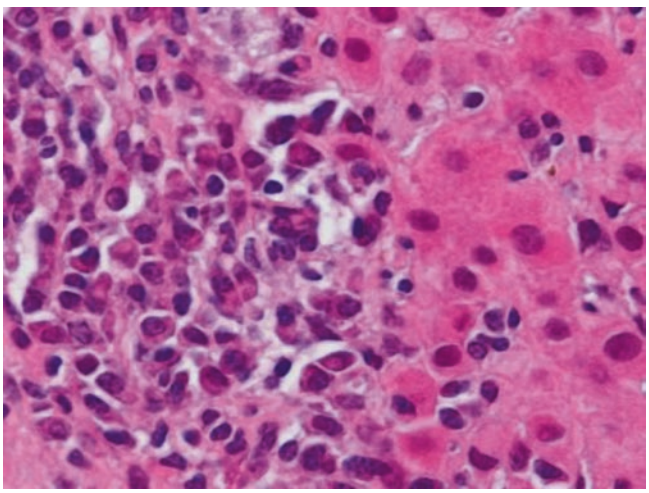

Fig. 19.11 Plasma cell-rich rejection (variant of late acute rejection) showing interface activity by lymphoplasmacytic infiltration

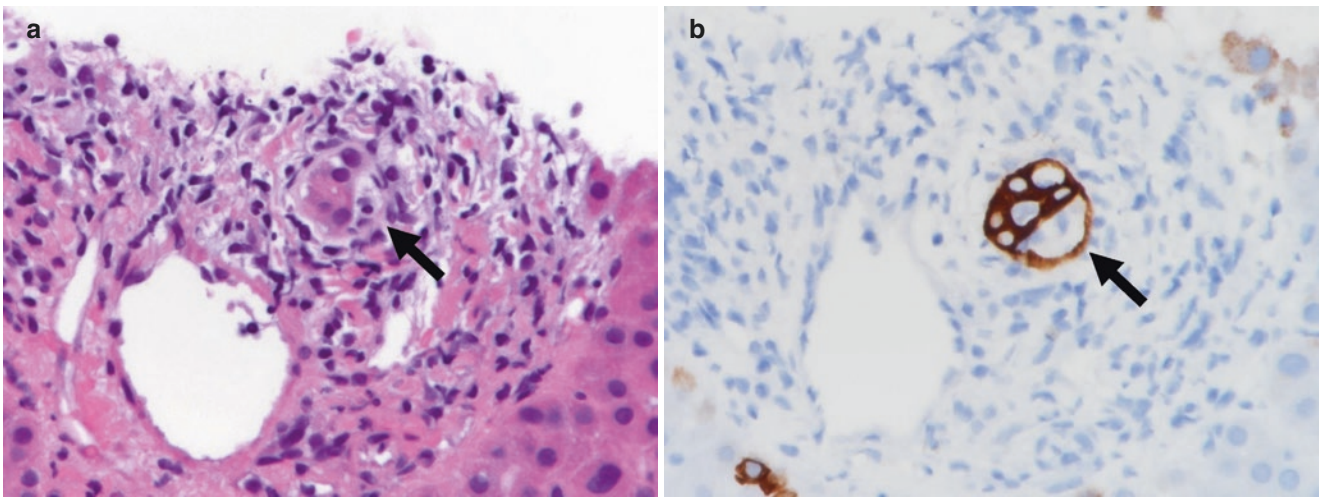

Fig. 19.12 (**a**) Early chronic rejection showing bile duct degeneration. (**b**) Early chronic rejection with keratin 7 immunostaining demonstrating luminal disruption and vacuolar changes of biliary epithelium

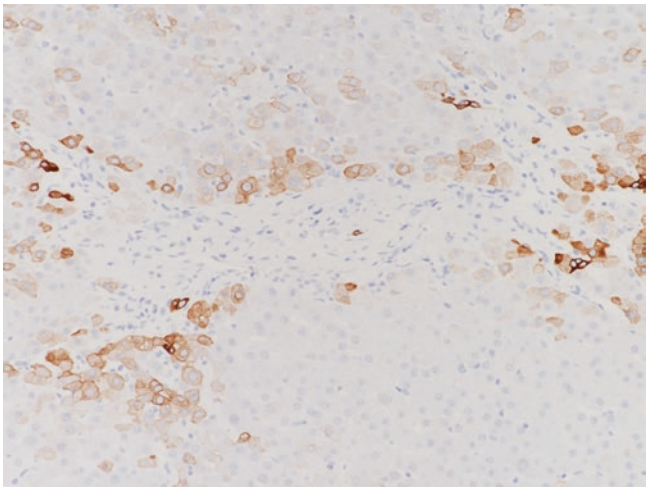

Fig. 19.13 Keratin 7 immunostaining confirms loss of bile ducts and bile ductules in late chronic rejection. Aberrant/compensatory keratin 7 expression is seen in some periportal hepatocytes

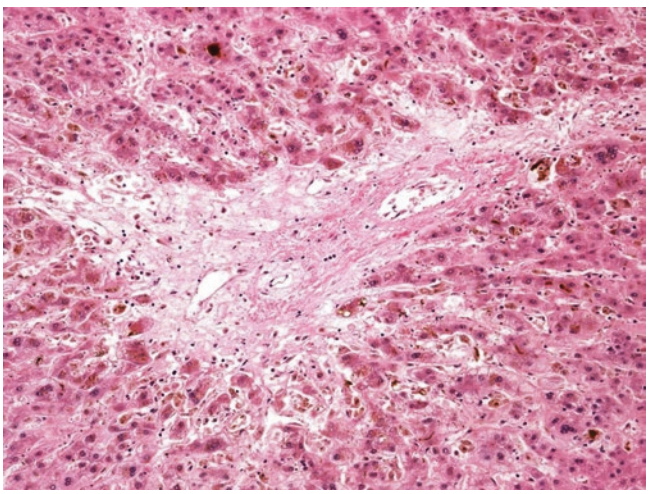

Fig. 19.14 Late chronic rejection showing fibrous obliteration of the terminal hepatic venule

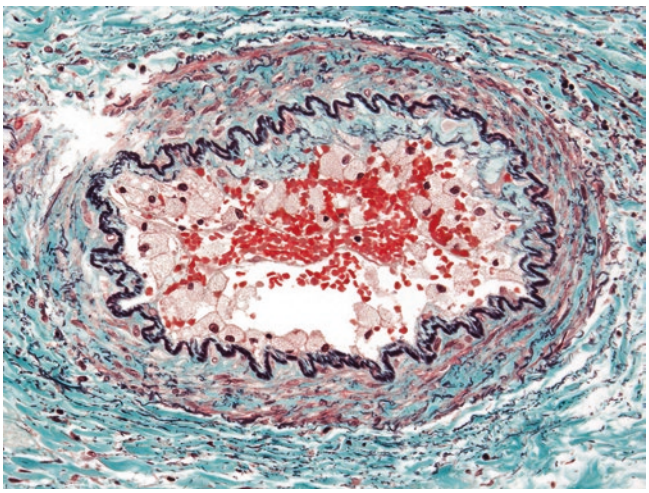

Fig. 19.15 Arterial lesion of late chronic rejection (Masson trichrome and Verhoeff elastic staining)

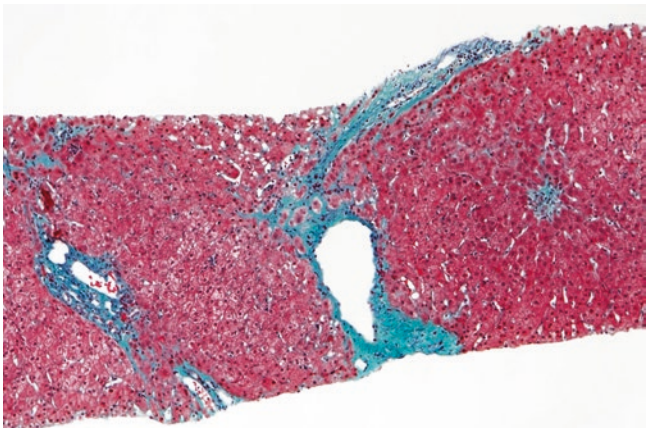

Fig. 19.16 Perivenular bridging fibrosis with minimal inflammation seen after complete withdrawal of immunosuppression

ficult to find in needle biopsy specimens. These features are usually associated with graft failure.

Graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation shows similar histology to early chronic rejection; bile duct atypia and cholestasis are common, but portal inflammation tends to be mild, and endothelial inflammation is inconspicuous. Advanced GVHD shows similar histology and clinical course to late chronic rejection.

Chronic ABMR is an evolving concept. Some type of DSAs detected after months or years after transplantation is associated with chronic rejection and poor graft survival [18, 19]. Patients with DSAs often show portal and/or perivenular fibrosis, with minimal portal inflammation that does not fulfill the criteria of acute or chronic rejection [20, 21]. Such histology was initially reported in some pediatric recipients after complete cessation of immunosuppressive drugs (Fig. 19.16) [22]. These findings suggest that inadequate immunosuppression causes insidious progression of "nonspecific" allograft fibrosis, which would be a histological feature of chronic ABMR. To detect chronic ABMR, protocol biopsy (biopsy obtained in a patient with stable graft function) years after transplantation may be necessary. However, there is currently no defined treatment strategy for possible chronic ABMR.

19.4.3 Immune Tolerance in Liver Transplantation

It is known that some liver allograft recipients keep completely normal allograft histology and liver function after gradual weaning of immunosuppressive drugs and complete cessation of those drugs. This status is called "operational tolerance." Clinically this phenomenon is not uncommon, especially among pediatric liver transplanta-

tion. The mechanisms of "operational tolerance" are not clearly understood, but regulatory T cells (Tregs) seem to have an important role for liver allograft tolerance [23]. It is also true that majority of the patients cannot achieve operational tolerance due to overt rejection during weaning. Since progressive fibrosis with or without mild inflammation suggests subclinical rejection [22], weaning of immunosuppressive drugs should be carefully carried out with follow-up biopsy. A major goal in liver (and other solid organs) transplantation is to establish the ways to evaluate and induce graft tolerance.

19.5 Complications Related to Immunosuppression

Most serious infections associated with immunosuppressive status occur within the first 2 postoperative months. Various types of viral, fungal, and bacterial infection can occur. Bacterial infection of the allograft or systemic bacterial infection can cause sepsis (systemic inflammatory response syndrome in response to an infectious process) and sepsis-associated cholestasis. Histology of sepsis is characterized by canalicular and ductular cholestasis with bile plugs and periductular neutrophil infiltration (referred to as *cholangitis lenta*) (Fig. 19.17). Major opportunistic viral infections include cytomegalovirus and Epstein-Barr virus. The latter usually does not cause hepatitis but is associated with posttransplant lymphoproliferative disorder (PTLD) involving the allograft. PTLD seen the liver biopsy is mostly overt B-cell or T-cell lymphoma. Staining of EBV (EBER in situ hybridization) can be helpful to differentiate EBV-positive lymphoma from rejection, but EBV-negative T-cell lymphoma can mimic acute rejection.

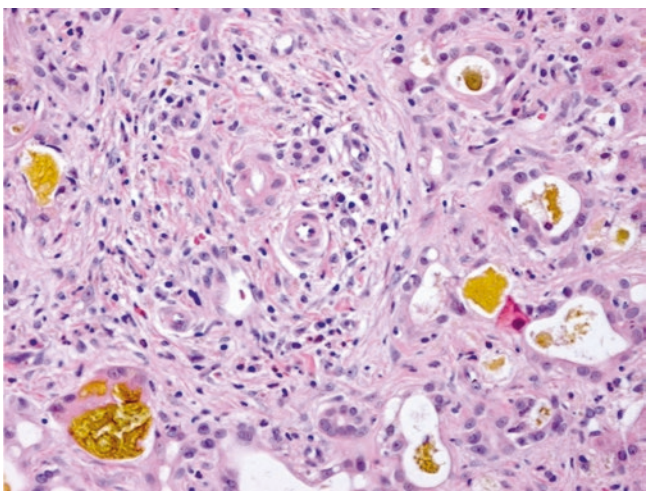

Fig. 19.17 Sepsis-related ductular cholestasis

19.6 Recurrence of the Original Liver Disease

Histology of recurrent disease is basically similar or identical to that of nontransplant settings. Timing of biopsy is an important factor for the diagnosis of recurrent disease. For example, recurrent alcoholic liver disease and recurrent NASH are usually seen in months or years after transplantation; graft steatosis in the first month posttransplantation is almost always attributed to donor-derived steatosis or parenteral nutrition.

Recurrence of hepatotropic virus infection (HBV and HCV) was once a common and serious complication after liver transplantation. Immunosuppression was often associated with accelerated course of recurrent hepatitis. After the introduction of effective and safe antiviral therapy, most cases of recurrent hepatitis can be treated without biopsy. Histology of recurrent hepatitis is rather nonspecific and can be similar to that of acute rejection. When acute rejection and recurrent HCV seem to coexist, antiviral therapy is recommended. Rejection therapy should be added only when acute rejection is graded as moderate or severe [24]. It is of note that late acute rejection can develop after treatment of recurrent HCV [25].

Autoimmune liver diseases, such as autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, recur in about 10–50% of patients [26]. Histological findings are identical to those of nontransplant diseases. After more than a year after transplantation, biopsy from patients free from symptom and normal liver tests sometimes shows early stage of the recurrent disease. Graft and patient survival are generally good after liver transplantation for autoimmune liver disease except primary sclerosing cholangitis. Like other non-anastomotic late biliary complications, effective treatment for recurrent primary sclerosing cholangitis is not available. Compared to other autoimmune diseases, recurrent primary sclerosing cholangitis is associated with decreased graft and patient survival [26].

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