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Review Article

Histopathological Evaluation of Recurrent Primary Biliary Cholangitis after Liver Transplantation

Wegahta Weldemichael, Dongwei Zhang and Jingmei Lin*

Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

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Abstract

The pathomorphological features of primary biliary cholangitis (PBC) is well-established. However, the distinction between PBC recurrence, and T cell-mediated rejection or chronic rejection remains as a challenge for pathologists. Due to the overlapping morphology, correct diagnosis requires a highly specific discrimination. Accurate diagnosis plays an essential role in patient management since different therapeutic strategies are used. This review focused on the role of pathologists in evaluating the allograft liver biopsy of patients with PBC as the leading cause of native liver cirrhosis. Furthermore, the clinicopathologic features of recurrent PBC, and T cell-mediated rejection or chronic rejection were discussed in detail, with emphasis in distinguishing the histopathology, morphologic variant, and diagnostic pitfalls.

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Introduction

Primary biliary cholangitis (PBC) is a chronic progressive inflammatory disease that affects the small bile ducts, leading to fibrosis and cirrhosis. Its etiology remains largely unknown and is most likely immune-related. Furthermore, this usually involves middle-aged women, with a peak in the 40–60 age group. Ursodeoxycholic acid (URSO) is presently the first-line drug for treating PBC. Several studies have revealed that this agent can improve the biochemical liver indices and prolong the transplant-free survival. However, approximately 40% of PBC patients do not respond to URSO, and progress to decompensated cirrhosis, which lead to transplantation or death after 10–20 years.[1] Recently, obeticholic acid and bezafibrate have been considered for treating patients without adequate response to URSO.[2] Liver transplantation is the only curative treatment for PBC patients. However, the number of liver transplantations dropped over the years, which is likely due to its early diagnosis and more effective treatment.[3]

PBC recurrence

Clinical presentation of recurrent PBC

The frequency of PBC recurrence has been reported to reach up to 46% after liver transplantation, with a median time of 3.0–5.5 years.[4] The discrepancy of its recurrence rate in various studies was due to the difference in follow-up time and allograft biopsy time, and the determination of whether this was protocol driven versus event driven.[3] Younger age at the time the diagnosis of PBC is established, young recipient age, tacrolimus usage, and biochemical evidence of cholestasis after liver transplantation are associated with PBC recurrence.[3]

Compared to cases of PBC in the native liver, the clinical manifestations of recurrent PBC in allografts is less specific. Fatigue and pruritis, which are the most common disease-related symptoms in the native setting, have been reported in approximately 10% of patients with recurrent PBC.[5] Laboratory liver tests indicate cholestasis due to the elevated recurrent PBC. However, they lack specificity. Furthermore, this may be mirrored by other conditions, including extrahepatic outflow obstruction, drug-associated cholestasis, T cell-mediated rejection, and chronic rejection. Anti-mitochondrial antibody is a pathognomonic marker for PBC in the native liver, which may precede the clinical presentation, biochemical profile, and histopathologic features. However, anti-mitochondrial antibody is not a good marker for PBC recurrence, because this remains positive after liver transplant in most patients, largely decreasing its specificity.[6] Allograft dysfunction and loss have been reported in patients with PBC recurrence.[7] The incidence of PBC recurrence may be underestimated due to the absence of abnormal liver enzymes and lack of symptoms. PBC can recur after a second and third liver transplant.

Histopathology of recurrent PBC

Like the native liver, destruction of the interlobular and septal bile ducts is the histological hallmark of recurrent PBC. This is commonly referred to as nonsuppurative destructive cholangitis and is also known as florid duct lesion, which is characterized by portal lymphoplasmacytic inflammatory infiltrates surrounding a damaged interlobular or septal bile duct (Fig. 1a and b). This is often associated with poorly formed non-caseating portal granulomas or the loose collection of

Keywords: Primary biliary cholangitis; Liver transplantation; Recurrence; Rejection.

Abbreviations: PBC, primary biliary cholangitis; URSO, ursodeoxycholic acid.

***Correspondence to:** Jingmei Lin, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, 350 West 11th Street, Indianapolis, IN 46202, United States. ORCID: https://orcid.org/0000-0003-2094-0262. Tel: +1 (317) 491-6159, Fax: +1 (317) 491-6419, E-mail: jinglin@iupui.edu

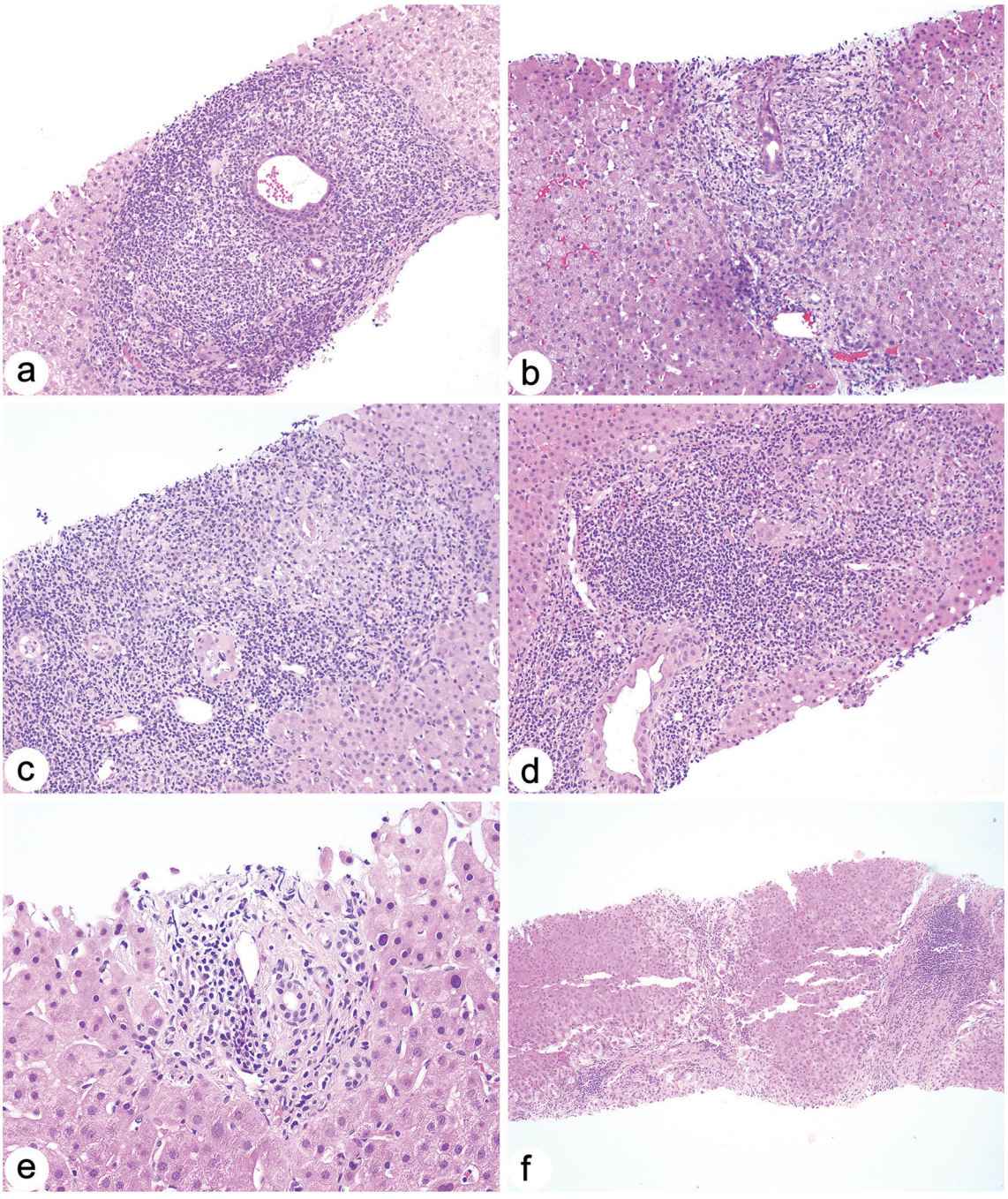

Fig. 1. Recurrent primary biliary cholangitis in liver allograft core biopsies. (a and b) Two examples of florid duct lesion are presented (×200). There were poorly formed non-caseating granuloma (c) and loose collections of epithelioid histocytes (d) in the portal tracts (×200). Minimal nonspecific portal inflammation can be observed in the liver biopsy obtained from a patient with recurrent PBC (e) (×200). Cirrhosis with features of cholate stasis and a dense lymphoid aggregate were appreciated in the allograft liver biopsy with recurrent PBC (f) (×100).

epithelioid histocytes (Fig. 1c and d). Florid duct lesions are pathognomonic, which is useful for distinguishing recurrent PBC from other biliary diseases, but this presents in merely approximately 14% of liver biopsies.[8] Interface activity and lobular inflammation are not the classic features of recurrent PBC, although these can be appreciated in focal and mild forms. Necrosis is not a feature of recurrent PBC, and this has generally raised concerns for infection, ischemia, or other etiologies.

PBC recurrence, like its native form, is a chronic progression, and the bile duct injury can be patchy. Therefore, depending on the stage of the disease and the location where the needle biopsy was taken, a wide range of morphologies can be observed in liver allograft biopsies. With time, damaged ducts disappear, and ductopenia ensues as the pattern of cholestasis progressing to cirrhosis. In addition to

pathognomonic florid duct lesions, other morphologies can be observed in biopsies obtained from patients with PBC recurrence, including patterns of chronic hepatitis, lymphocytic cholangitis, loss of bile duct, ductopenia, granulomatous hepatitis, cirrhosis, and even a nearly normal appearing histology (Fig. 1e and f). It is important for pathologists to be familiar with the variable morphological spectrum of PBC recurrence before making a diagnosis.

In addition to PBC recurrence, other common causes of bile duct damage in allograft liver include T cell-mediated rejection, chronic rejection, cytomegalovirus, and hepatitis C virus infection. The diagnosis of PBC recurrence is largely based on the histopathological features, in the absence of hepatic artery thrombosis and anastomosis stricture.

T cell-mediated rejection

T cell-mediated rejection, which is also known as acute cellular rejection, is defined as inflammation of the allograft, elicited by a genetic disparity between the donor and recipient, primarily affecting the interlobular bile ducts and vascular endothelia.[9] This is a common complication after liver transplantation. Its incidence varies in studies from different medical centers. The recent incidence of T cell-mediated rejection is declining, and is estimated to be 10–40%,[10] which is likely due to better pathological interpretation of the liver allograft and enhanced immunosuppression. Most of these occur within the first six weeks after liver transplantation, although these can occur anytime.[11] A multivariate analysis revealed that young recipient age, normal levels of serum creatinine and aspartate transaminase, the presence of edema, donor/recipient HLA-DR mismatch, long cold ischemic time, patients with autoimmune disorders (*e.g.* PBC, primary sclerosing cholangitis, and autoimmune hepatitis), and older donor age are associated with acute cellular rejection.[12]

Clinical presentation of T cell-mediated rejection

The clinical symptoms or laboratory findings in T cell-mediated rejection are often subtle and are either sensitive or specific. The clinical suspicion of T cell-mediated rejection requires the histological confirmation of the liver allograft to exclude other possible etiologies.

Histopathology of T cell-mediated rejection

Histological assessment is the "gold standard" for diagnosing liver allograft rejection. The following three features have been useful: (1) mixed portal inflammation, (2) bile duct damage, and (3) endotheliitis.[13] Minimally, at least two features are required.

T cell-mediated rejection-associated portal inflammation consists of a mixed and heterogeneous inflammatory population, which includes lymphocytes, blasts, plasma cells, neutrophils, macrophages and eosinophils (Fig. 2a). The interface activity may or may not be conspicuous. The presence of eosinophils is commonly observed, and the presence of abundant eosinophils may likely represent a severe form of T cell-mediated rejection (Fig. 2b).[14] The aggregates of neutrophils are not rare. Most of the lymphocytes in T cell-mediated rejection are CD8+ T lymphocytes.[15] Although immunophenotyping is not recommended, this can be useful to differentiate T cell-mediated rejection from posttransplant lymphoproliferative disorder, which is a B lymphocyte predominant lesion.

Interlobular bile duct damage, which is usually cuffed and disrupted by a dense inflammatory infiltrate with architectural disarray, is an important histologic feature. The features of these epithelial degenerative changes include cytoplasmic vacuolization and eosinophilia, pyknosis, disruption of the basement membrane, atrophy, nuclear enlargement and pleomorphism, and apoptosis (Fig. 2c). The spectrum of inflammatory cells that involve bile duct damage mimics that of the portal inflammation of PBC recurrence. Aggregates of neutrophils within or around the bile ducts are not rare.[16] Ductular reaction is usually insignificant, in contrast to that observed in perfusion-reperfusion injury, cholangitis, or extrahepatic bile duct obstruction. However, interlobular bile duct damage is not specific in T cell-mediated rejection, and this is also present in other liver diseases, such as hepatitis B and C virus infection, PBC recurrence, primary sclerosing cholangitis, and autoimmune hepatitis.[17] The diagnosis of T cell-mediated rejection is favored when more than 50% of the interlobular bile duct is involved, in addition to other rejection histologic features.

Endotheliitis is characterized by endothelial injury and subendothelial inflammatory infiltrates in the portal and central veins. The morphological spectrum ranges from focal minimal lymphocyte attachment to the endothelial lumen to intense subendothelial infiltration. The endothelial cells may be swollen and are usually incoherent from the basement membrane or lifted in dense inflammation (Fig. 2d). Relatively speaking, endotheliitis is the most specific feature in T cell-mediated rejection. However, its specificity remains limited, because endotheliitis is well-known to exist in native liver diseases, such as hepatitis B and C virus infection, PBC, alcoholic liver disease, and nonalcoholic steatohepatitis.[18]

Central perivenulitis is a spectrum of endotheliitis that involves the central veins, and centrilobular or perivenular hepatocytes. Histologically, central perivenulitis is characterized by endothelial disruption, subendothelial inflammatory cell infiltrates, and variable perivenular hepatocyte dropout and necrosis, with or without variable extents of perivenular fibrosis (Fig. 2e and f). Central perivenulitis is commonly observed in T cell-mediated rejection and chronic rejection.[18] According to the Banff Schema, central perivenulitis with necrosis is required for a diagnosis of moderate-to-severe T cell-mediated rejection.[13] In addition to rejection, the other etiologies that lead to central perivenulitis include ischemia, hepatitis B and C virus infection, autoimmune hepatitis, and drug toxicity (azathioprine). Isolated central perivenulitis is defined as the presence of centrilobular inflammation and necrosis in the absence of a portal triad. If other causes can be excluded, extensive studies support that the presence of central perivenulitis or isolated central perivenulitis is a manifestation of T cell-mediated rejection.[19]

The Banff schema includes a descriptive grading system and a rejection activity index.[9] Depending on the extent and distribution of inflammation and injury, T cell-mediated rejection can be further graded as indeterminate, mild, moderate and severe (Table 1). Simply speaking, a minority of portal tract involvement and lack of necrosis are emphasized for mild form. If necrosis is limited in a minority of perivenular areas, this is moderate, in contrast to the severe form, in which necrosis involves the majority of perivenular areas.

Differentiation between recurrent PBC *vs.* T cell-mediated rejection

Morphological overlapping remains challenging for pathologists to review biopsies obtained from liver transplant patients with a prior history of PBC. The features to distinguish T cell-mediated rejection from recurrent PBC are listed in Table 2. Among these features, florid duct lesion, portal granuloma,

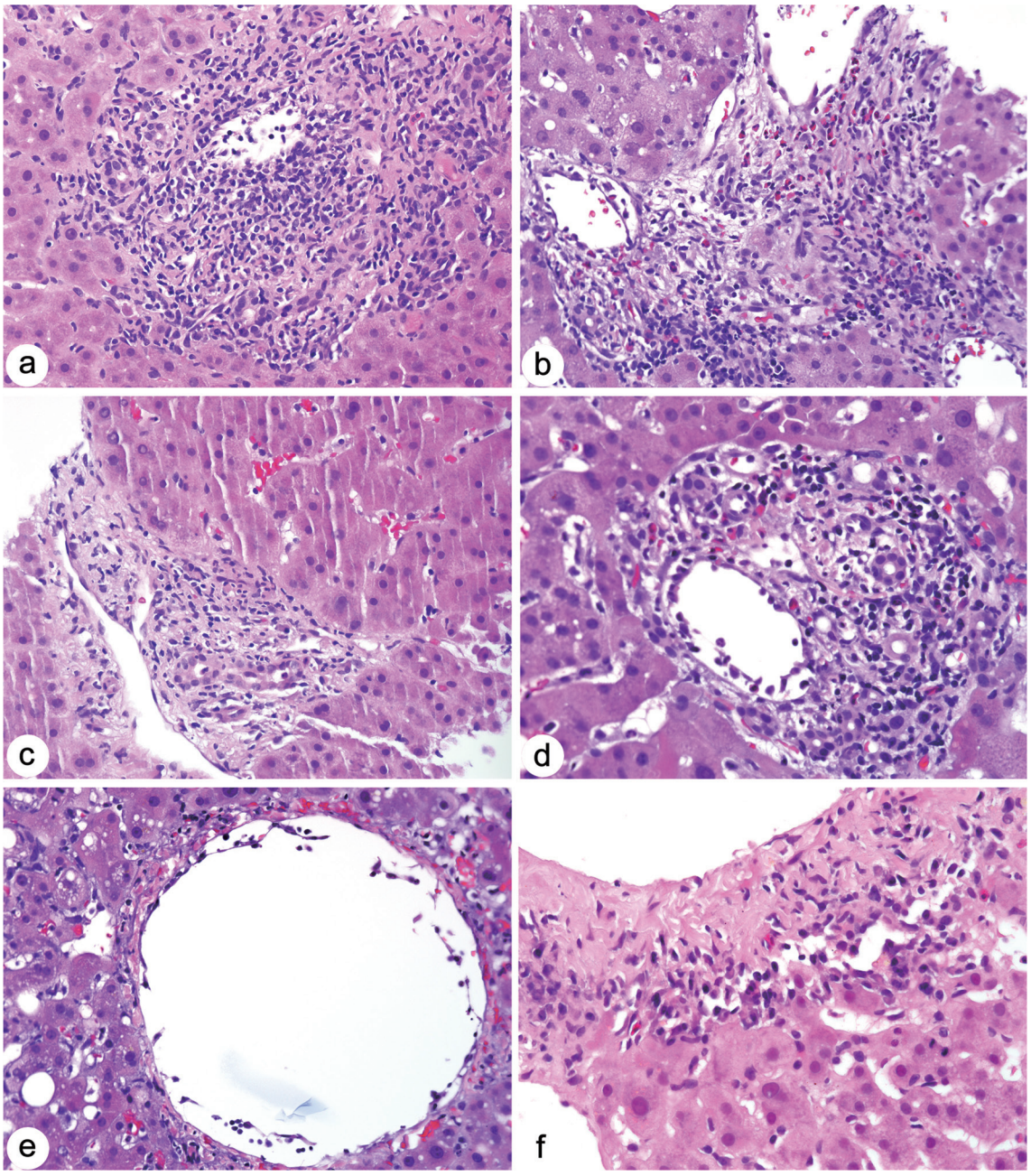

Fig. 2. T cell-mediated rejection in liver allograft. (a) Portal inflammation consists of mixed and heterogeneous inflammatory infiltrates, which include enlarged blast cells, lymphocytes, and rare eosinophils. The interlobular bile ducts were cuffed and effaced by the dense inflammation, with the evidence of endotheliitis in the portal venule (×400). (b) Abundant eosinophils and some neutrophils were noted in the portal inflammation, with the presence of bile duct damage and endotheliitis (×400). (c) The interlobular bile ducts presented with degenerative changes, including cytoplasmic vacuolization and eosinophilia, atrophy, nuclear enlargement and pleomorphism. However, the ductular reaction was not appreciated (×400). (d) The portal venule presented with evidence of endotheliitis. Inflammatory cells attached to the endothelial lumen and endothelial cells were lifted from the basement membrane (×400). The central perivenulitis (e) exhibited inflammatory cells that attached to the endothelial lumen. The centrilobular endothelial cells were disrupted and lifted from the basement membrane, with occasional centrilobular hepatocyte drop-outs (×400). (f) The subendothelial inflammatory cell infiltrate was apparent. The centrilobular endothelial cells were inconspicuous with the centrilobular hepatocyte dropout and fibrosis (×400).

the formation of lymphoid aggregates, portal mononuclear inflammatory infiltrates, diffuse bile duct injury, and lack of endotheliitis are helpful features to differentiate PBC recurrence from T cell-mediated rejection. Ductular reaction is a useful feature that is prominent in PBC recurrence, but not in T cell-mediated rejection. Periportal fibrosis and periportal copper depositions can also be commonly observed in PBC recurrence. Although endotheliitis is not completely exclusive in PBC, its presence favors T cell-mediated rejection, especially when other rejection features are present.

Occasionally, the histological findings are limited to render a definitive distinction between recurrent PBC and T

Table 1. Banff grading of T cell-mediated rejection in liver allograft

Grade	Criteria
Indeterminate	Portal and/or perivenular inflammatory infiltrates that failed to meet the criteria for the diagnosis of T cell-mediated rejection
Mild	Rejection-type infiltrates that involved a minority of portal tracts or perivenular areas, which were generally mild, with the absence of necrosis
Moderate	Rejection-type infiltrates that involved most or all portal tracts, with necrosis limited to a minority of perivenular areas
Severe	Like the above for moderate, with spillovers into the periportal areas, moderate-to-severe central perivenulitis, and major perivenular hepatocyte necrosis

Adapted from the 2016 Comprehensive Update of the Banff Working Group on Liver Pathology.

cell-mediated rejection. In such cases, communication with transplant clinicians is helpful. Clinicians might already have an impression based on the serum levels of the immunosuppressant or the timing of post transplantation, although late T cell-mediated rejection can occur.

Plasma cell-rich rejection

Plasma cell-rich rejection, which is also known as posttransplant plasma cell hepatitis or *de novo* autoimmune hepatitis, is a histologic variant of rejection. This is a unique form of immune-mediated graft injury with abundant plasma cells (estimated at >30%).[9] This was initially described in pediatric liver recipients without a history of autoimmune hepatitis, and adults who had liver transplantation for PBC. Since then, this has been identified in recipients with variable primary liver diseases.[20] This is a rare entity that occurs in merely 2–4% of liver transplant recipients.[21] Plasma cell-rich rejection tends to occur at more than six months after the transplant. Patients often present with elevated transaminases, fever, fatigue, graft tenderness, and hepatomegaly.

Histologically, plasma cell-rich rejection is characterized by portal and/or perivenular inflammatory cell infiltrates that comprise of abundant plasma cells. The Banff Working Group recommends more than 30% of plasma cell involvement to distinguish this from T cell-mediated rejection.[9] The portal tracts are expanded by a heterogenous inflammatory cell infiltrate that comprises of abundant plasma cells, lymphocytes, and rare eosinophils and neutrophils (Fig. 3a). The interface activity and lobular inflammation are variable. Bile duct damage and endotheliitis are usually observed to involve variable extents of portal tracts (Fig. 3b and c). Central perivenulitis with perivenular hepatocyte dropout and necrosis are common (Fig. 3d). The diagnosis of plasma cell-rich rejection is based on the histologic findings. The patient should not have a history of autoimmune hepatitis in the native liver.

Plasma cell-rich rejection is considered as an immune-mediated graft injury. However, its exact pathogenesis remains unclear. This mimics the histologic features of T cell-mediated rejection with prominent plasma cells. Some patients exhibit donor-specific antibodies and positive C4d immunostaining in the endothelial lining of cells, suggesting a component of antibody-mediated rejection.[22] Autoimmunity is another etiology, since autoantibodies can be detected in more than half of pediatric and adult recipients.[23] The most common antibody is anti-smooth muscle antibodies and antinuclear antibodies, followed by anti-mitochondrial antibodies, or anti-liver-kidney microsome antibodies.

The differential diagnosis of plasma cell-rich rejection includes PBC recurrence, T cell-mediated rejection, and chronic hepatitis. The overlapping feature of abundant plasma cells in portal inflammation makes the distinguishment from recurrent PBC challenging. The presence of florid duct lesion, portal granuloma, and lack of endotheliitis are helpful for diagnosing PBC recurrence. T cell-mediated rejection presents with mixed portal infiltrates that predominantly contain

Table 2. Features for distinguishing recurrent primary biliary cirrhosis from T cell-mediated rejection and chronic rejection

Features	Recurrent primary biliary cirrhosis	T cell-mediated rejection	Chronic rejection
Portal inflammation	Mild-to-severe lymphoplasmacytic inflammation	Mild-to-severe, mixed heterogenous inflammation	None or mild inflammation
Florid duct lesion	Likely present, pathognomonic	Absent	Absent
Portal noncaseating granulomas	Likely present	Absent	Absent
Bile duct damage	Present, diffuse and severe	Present, Ranging from mild to severe	Present, Ranging from mild to severe
Ductular reaction	Present, ranging from none/mild at the early stage to moderate at late stage	Absent or minimal	Absent or minimal
Periportal copper deposition	Likely present	Absent	Absent
Portal endotheliitis	Absent	Likely present	Not prominent
Central perivenulitis	Absent	Likely present	Likely present
Serum level of immunosuppressants	High	Low	Low

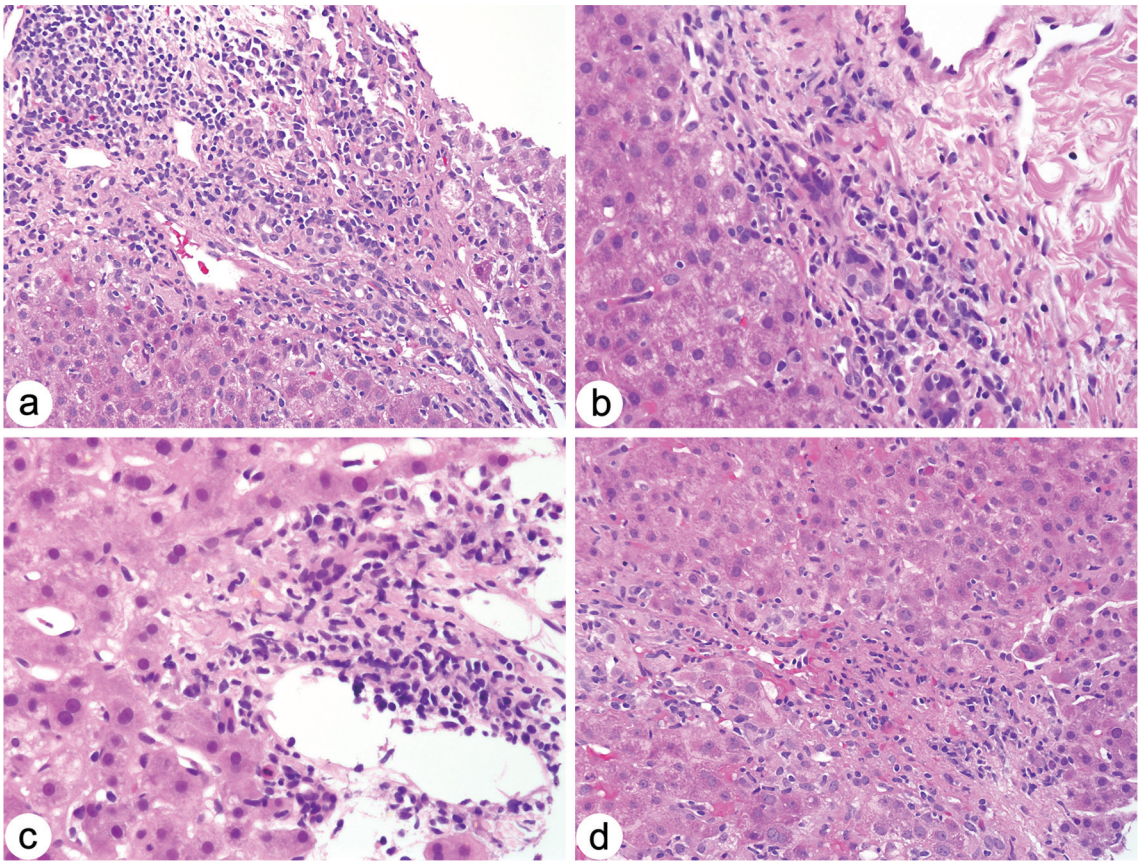

Fig. 3. Plasma cell-rich rejection in liver allograft biopsies. (a) The portal inflammation consisted of a plasma cell-rich inflammatory infiltrate (×400). (b) The interlobular bile duct presented with degenerative changes, including nuclear enlargement and pleomorphism. However, the ductular reaction was not appreciated (×400). (c) The endothelial cells were disrupted and lifted from the basement membrane, compatible with endotheliitis (×400). (d) The centrilobular region showed inflammatory infiltrates and centrilobular hepatocyte dropouts (×400).

lymphocytes with fewer plasma cells (<30%). This tends to occur within the first six months after liver transplantation. Plasma cell-rich rejection and recurrent autoimmune hepatitis can both present plasma cell-rich infiltrates. Although these cannot be distinguished based on the histology alone, the fact that plasma cell-rich rejection affects the patient with no prior history of autoimmune hepatitis in the native liver would be decisive. Similarly, the distinction between plasma cell-rich rejection, and recurrent or *de novo* chronic hepatitis B and C infection can be made based on the history and hepatitis virus panel. Occasionally, hepatitis A or cytomegalovirus can present with plasma cell infiltrates. A viral serology panel should be performed when the biopsy presents the features of plasma cell-rich hepatitis.

Once the diagnosis is made, patients are usually treated with increased immunosuppression, such as corticosteroids or tacrolimus. Thus, the prognosis would be generally favorable. This may progress to chronic rejection or graft failure, when inappropriately treated.

Chronic rejection

Chronic rejection is defined as an immunologic injury to the liver allograft, resulting in potentially irreversible damage to the bile ducts, arteries and veins. The recent incidence of chronic rejection ranges to approximately 3–5% at five years after liver transplantation.[24]

Clinical presentation of chronic rejection

The onset of chronic rejection would likely occur in patients with unresolved or multiple episodes of T cell-mediated rejection, recurrent hepatitis C virus infection with an alpha interferon treatment, and reduced dosage of immunosuppression due to drug toxicity, coexisting infections and post-transplant lymphoproliferative disorders, or non-compliance.[25]

Patients with chronic rejection may or may not present with signs or symptoms.[26] If symptoms are present, this would mimic those of T cell-mediated rejection. The laboratory tests would present a progressive cholestatic pattern with increased γ-glutamyl transpeptidase and alkaline phosphatase. Progressive cholestasis in a patient with T cell-mediated rejection, who is unresponsive to anti-rejection treatment, is a strong indication of chronic rejection. Biliary sludging and strictures, and hepatic infarcts can be typically observed at the late stage of allograft failure. Coagulation, malnutrition and hepatosplenomegaly would also be present due to the hepatic dysfunction. Arteriograms may present with intrahepatic arterial pruning and poor peripheral filling.

Histopathology of chronic rejection

Histologically, chronic rejection is characterized by the following: (1) biliary epithelial degenerative changes that involve the majority of interlobular bile ducts, with or without bile duct loss or ductopenia; (2) obliterative vasculopathy.[27]

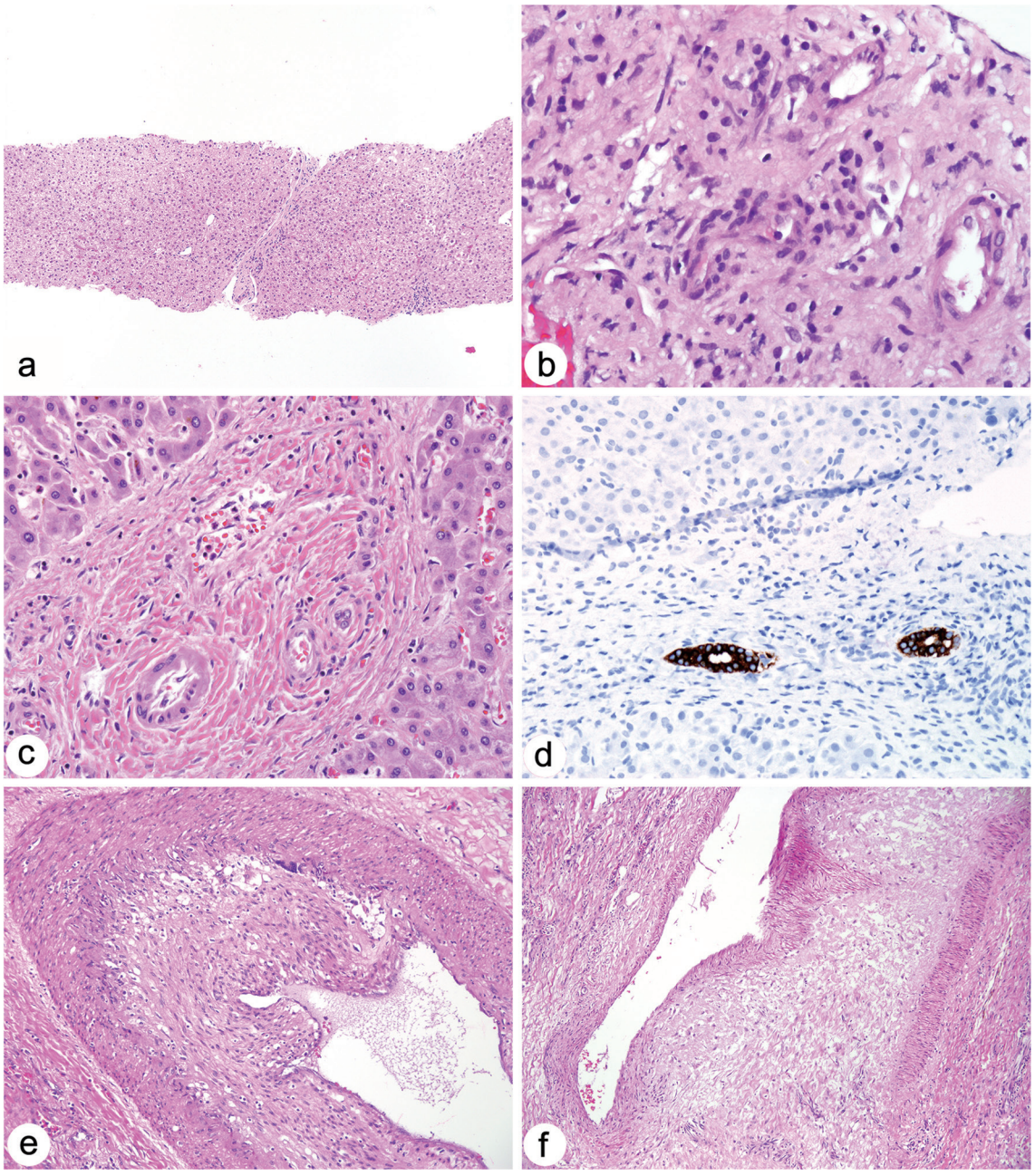

Fig. 4. Chronic rejection in liver allograft biopsies and resections. (a) The low power examination presented a vaguely nodular architecture with no inflammation (×100). (b) The interlobular bile ducts presented with degenerative changes in a background of minimal inflammation. However, the ductular reaction was not appreciated (×400). (c) The loss of bile ducts in a background of subsided "burnt out" inflammation is typical for chronic rejection. Hepatic arterioles and portal venules were present (×400). (d) The immunostaining for cytokeratin 7 confirms the presence of obscured bile ducts (×400). (e) A medium-sized hepatic artery in the hepatectomy observed from a patient who lost the liver allograft due to chronic rejection presented with intimal thickening and abundant lipid-laden foamy macrophages in a background of minimal inflammation (×200). (f) The allograft hepatectomy obtained from the same patient presented a large-sized hepatic artery with prominent intimal thickening, intimal fibrosis, and intimal lamina fragmentation, which significantly obliterated the vessel (×200).

These two features may coexist or independently occur.[19] Unfortunately, pathognomonic arterial changes are generally appreciated in the hilum of the liver, and are rarely observed in routine peripheral core biopsies. Therefore, interlobular bile duct damage, bile duct loss, and ductopenia are emphasized in routine liver allograft biopsies.

Lack of prominent portal inflammation, which is also called subsided inflammation or no inflammation, is a feature of chronic rejection (Fig. 4a). Degenerative or senescent changes in the bile ducts can present with a spectrum from cytoplasmic vacuolization and eosinophilia, pyknosis, disruption of the basement membrane, uneven nuclear spacing, atrophy, and nuclear pleomorphism (Fig. 4b).[28] Although similar changes can be observed in T cell-mediated rejection, the progressive loss of bile ducts remain as the hallmark for chronic rejection (Fig. 4c). As the disease progresses, the

loss of bile ducts in a background of subsided "burnt out" inflammatory infiltrates would be typical for chronic rejection. Ductopenia is strictly defined as the loss of bile ducts in more than 50% of portal tracts in an adequate biopsy. Loss of bile ducts can be patchy in distribution. Therefore, caution should be given during its evaluation, especially in short cores with fewer portal tracts. Adequacy is essential for liver evaluation, although there is no consensus on the minimum number of portal tracts in a biopsy specimen to make a diagnosis.[29] Largely based on experience, at least 10 portal tracts is required, and some authors suggest at least 20 portal tracts before the diagnosis of ductopenia can be rendered.[30] In some biopsies, the bile ducts are severely effaced, which causes poor morphological appreciation. In difficult cases, the immunostaining for cytokeratin 7 may help to confirm the presence of obscured interlobular bile ducts (Fig.4d).[31]

Obliterative vasculopathy is pathognomonic for chronic rejection. This is characterized by intimal thickening with a minimal inflammatory infiltrate and abundant lipid-laden foamy macrophages (Fig. 4e). Subsequently, there would be an increase in clusters of myofibroblasts, with associated variable degrees of intimal fibrosis and intimal lamina fragmentation (Fig. 4f). Obliterative vasculopathy commonly involves large- and medium-sized vessels, thereby limiting its diagnostic value in allograft core biopsies, where merely small portal arteries are available for evaluation. The loss of small arterial branches in the portal tracts may indicate early chronic rejection.[32]

Differentiation between recurrent PBC *vs.* chronic rejection

The features to distinguish chronic rejection from recurrent PBC are listed in Table 2. Among these features, florid duct lesion and granuloma-associated lymphoplasmacytic inflammation are pathognomonic, in contrast to the subsided inflammation observed in chronic rejection. Ductular reaction is a useful feature that is prominent in PBC recurrence, but this is inconspicuous in chronic rejection. Periportal fibrosis and periportal copper depositions can be commonly observed during PBC recurrence, in contrast to chronic rejection. In addition, a history of persistent or multiple episodes of T cell-mediated rejection would be useful information supportive of chronic rejection.

Conclusions

Although the histopathologic features of PBC recurrence have been well-described, its differential diagnosis remains challenging in practice for pathologists, especially in the setting of T cell-mediated rejection, plasma cell-rich rejection, and chronic rejection. The overlapping morphology, particularly the "rejection-like" features due to PBC recurrence and PBC-like features due to rejection, would compound the diagnosis. To date, routine histopathologic examination remains as the gold standard, which requires highly specific knowledge and diagnostic skills for pathologists.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Dr. Weldemichael wrote the part of primary biliary cholangitis, while Dr. Zhang wrote the part of plasma cell-rich rejection and was in charge of submitting the manuscript. Dr. Lin oversaw writing the remaining parts of the manuscript, the figures and tables, and the critical revision. All authors made a significant contribution to the study and approved the final version of the manuscript.

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