Interpretation of Biopsy Findings in the Transplant Liver

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With several thousand liver transplants being performed each year and many patients being managed in their local medical centers, much of the interpretation of transplant liver biopsy specimens has moved from the transplant hospital to the community setting. This article discusses both typical and more peculiar changes that occur in the transplant liver biopsy specimen. Accurate interpretation requires clear knowledge of these possible changes as well as knowledge of clinical data, such as time elapsed since transplantation and the patient's primary disease.

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INDEX WORDS: Liver, biopsy, pathology, rejection, hepatitis C, hepatitis B, primary biliary cirrhosis, transplantation, cytomegalovirus hepatitis, Epstein-Barr virus, lymphoproliferative disorder, primary sclerosing cholangitis

The histological diagnosis of posttransplant liver disorders by needle biopsy is often straightforward, but problems may arise in the diagnosis of nonspecific inflammatory lesions not diagnostic of rejection, in the determination of whether more than one process is present (eg, combination of hepatitis and rejection), or in the diagnosis of entities that have histological findings that overlap with rejection.

ACUTE CELLULAR REJECTION
(REJECTION WITHOUTBILEDUCT LOSS)

Acute cellular rejection is a relatively common occurrence over the first 3 to 4 months after orthotopic liver transplantation and may be present as soon as 4 to 5 days after transplantation. The three diagnostic criteria for rejection are (1) duct damage, (2) presence of mixed portal inflammatory infiltrates, and (3) venous endotheliitis. To make a definitive diagnosis of rejection, two of these three features must be present.

Duct damage is usually identified by abnormalities of ductal nuclei, such as nuclear loss, irregularity of distribution along the circumference of the duct, and irregularity of shape. The normal duct, in contrast, has a histological appearance similar to that of a string of pearls, with evenly spaced, round, uniform, and closely packed nuclei.

The mixed inflammatory infiltrates within the portal zones consist predominantly of lymphocytes, but eosinophils and neutrophils should also be present, and plasma cells can also be seen (Fig 1). The neutrophils are often present in the periductal region as seen in pericholangitis. The lymphocytic infiltrate usually has a component of larger, reactive-appearing lymphocytes, and the infiltrate may spill out of the portal zone into the lobule, but hepatocytic, single-cell (spotty) necrosis is infrequent. Mononuclear cells or neutrophils (or both) are often found in the duct walls.

Endotheliitis consists of an infiltrate of mononuclear cells within the venous wall, usually immediately underneath the endothelial surface, if it is still intact (Fig 2). These cells often adhere to the luminal surface of the vessel and may appear to lift the surface endothelium away from the underlying vascular wall. In our experience, the endotheliitis may be absent from an otherwise persisting acute rejection if the patient has recently been treated for rejection. In these cases, the portal inflammatory changes and duct damage must be characteristic for a definitive diagnosis of ongoing acute rejection.

Several descriptive and numerical grading systems for acute cellular rejection have been proposed in the past. Table 1 presents the grading system adopted by the pathologists at the National Institute of Diabetes, Digestive, and Kidney (NIDDK) Liver Transplant Database. This system may have some advantage in that it has been tested and found to be a reliable and reproducible method of assessing acute cellular rejection.

The Banff schema is a newer system suggested by consensus of a larger international group of pathologists and clinicians (Table 2). This schema also includes a numerical scoring system, or rejection activity index (RAI), of 0 through 9, wherein each element of portal inflammation, bile duct inflammation and damage, and venous endotheliitis is graded on a scale of 0 to 3. This scoring system in preliminary studies has not been shown to be superior to the simpler global assessment.

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Centrilobular Pattern of Rejection

The histological changes of centrilobular mononuclear infiltrates and hepatocyte necrosis can be caused by a variety of lesions, including preservation injury, drug reaction, and viral hepatitis. If microscopic evidence of portal rejection is found, the lesion most likely represents a form of parenchymal rejection. In these cases, the central veins show surrounding hepatocyte necrosis, often accompanied by a mononuclear infiltrate, usually with a prominent plasma cell component. The lesion lacks the hepatocyte ballooning typical of ischemia. Although parenchymal rejection is frequently seen in conjunction with portal inflammation, it may be seen in isolation (Fig 3). This centrilobular pattern of rejection is most commonly associated with tacrolimus (Prograf, FK-506) therapy in our experience but can be seen with cyclosporine as well. It is not thought to represent a form of idiosyncratic drug reaction or toxicity because the lesion decreases in intensity or disappears in response to increased levels of immunosuppression, including increased doses of tacrolimus or steroid therapy.
Table 1. NIDDK Liver Transplant Database
Rejection Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rejection</td>
<td></td>
</tr>
<tr>
<td>Rejection without bile duct loss (acute cellular rejection)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Rejection in some, but not all, of the triads</td>
</tr>
<tr>
<td>Moderate</td>
<td>Rejection involving most or all of the triads, associated with centrilobular hepatocyte ballooning or necrosis and dropout</td>
</tr>
<tr>
<td>Severe</td>
<td>Rejection in some or all of the triads, associated with centrilobular hepatocyte ballooning or necrosis and dropout</td>
</tr>
<tr>
<td>Rejection with bile duct loss (chronic rejection)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Bile duct loss present*</td>
</tr>
<tr>
<td>Moderate</td>
<td>Bile duct loss present with at least one of the following findings: centrilobular cholestasis, centrilobular fibrosis, hepatocellular ballooning or necrosis and dropout</td>
</tr>
<tr>
<td>Severe</td>
<td>Bile duct loss present with at least two of the following findings: centrilobular cholestasis, centrilobular fibrosis, hepatocellular ballooning or necrosis and dropout</td>
</tr>
</tbody>
</table>

* In general, four portal tracts must be present to be considered adequate, and >50% of the ducts must be absent to make the definitive diagnosis.
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Resolving Acute Rejection

Resolving acute rejection exhibits a number of histological features that make it a mimic of other lesions. The liver may show persistence of damaged ducts with features such as loss of epithelium or some irregularity of nuclear size and shape as well as a sparse, often predominantly neutrophilic periductal infiltrate (peri-cholangitis). These changes may be present for 1 to 2 weeks after the acute episode of rejection has been treated, and clinical correlation is necessary so that a mistaken diagnosis of early chronic rejection, persisting acute rejection, or other biliary tract problem is not made.

CHRONIC REJECTION

Chronic rejection may present in two forms: (1) rejection with bile duct loss, or vanishing bile duct syndrome, and (2) vascular rejection,⁸ which is an obliterator lesion of arteries that results in ischemic changes in the liver parenchyma. These lesions may appear independent of each other but mostly commonly occur together.⁹,¹⁰

The histological changes of chronic rejection, especially the duct lesions, may be subtle, so care must be taken to examine portal tracts for the presence of ducts and for early signs of severe duct damage. Bile duct loss is best identified by locating the hepatic artery within the portal zone and its associated portal vein, then examining for the presence of the interlobular bile duct (Fig 4). The duct should be found near the small arteriole rather than at the periphery of the portal zone, where proliferating ductules may be seen. Severely damaged ducts often have an eosinophilic appearance of the cytoplasm and appear attenuated, or smaller than normal. Ductal nuclei may be flattened and decreased in number, sometimes to the point of only a rare nucleus remaining in the duct. The nuclei present are irregularly separated by cytoplasm so that the ducts lose their uniform string-of-pearls appearance (Fig 5). This type of change can be an important feature of the early stages of chronic rejection before significant bile duct loss, so it is important to examine for these findings.¹¹ Cholestasis may be prominent, but the presence of foamy, pale Kupffer’s cells in the sinusoids may be a key finding that could give a clue to the histopathologist that a chronic cholestatic problem is present. The portal infiltrate is usually scant and generally consists of lymphocytes, without the neutrophils or eosinophils seen in acute rejection.

The hallmark feature of the vascular form of chronic rejection on liver biopsy is the secondary ischemic effect as demonstrated by hepatocyte ballooning or necrosis and dropout. These changes usually involve the centrilobular hepatocytes, but the entire lobule can be affected. The typical vascular lesions of this form of chronic rejection cannot usually be found on biopsy specimens because the small arteries seen are generally not involved in the process. Instead, this process affects

Table 2. Banff Global Assessment of Acute Cellular Rejection

<table>
<thead>
<tr>
<th>Rejection Grade</th>
<th>Histological Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indeterminate</td>
<td>Nonspecific findings that do not fulfill the criteria for acute cellular rejection</td>
</tr>
<tr>
<td>Mild (grade I)</td>
<td>Involvement of &lt;50% of the triads, limited to portal tracts</td>
</tr>
<tr>
<td>Moderate (grade II)</td>
<td>Involvement and expansion of most or all of portal tracts</td>
</tr>
<tr>
<td>Severe (grade III)</td>
<td>Same as moderate rejection with moderate-to-severe centrilobular inflammation and necrosis, inflammatory spillover into periportal areas</td>
</tr>
</tbody>
</table>

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the large arteries in the hilum and larger portal zones. These large arteries become occluded by foam cells in the intima or media, fibrosis, and thrombosis (Fig 6).

Before making a definitive diagnosis of chronic rejection with duct loss, at least four or five complete portal tracts should be examined. In smaller or less adequate samples, the diagnosis of chronic rejection should be considered when centrilobular ballooning and cholestasis are present, especially if some or most of the ducts that are present appear attenuated. Correlation with serum tests, such as alkaline phosphatase or bilirubin, is recommended because these values should be elevated. Table 1 presents the recommended grading system for chronic rejection as used by the NIDDK transplant database.3,8

ABO INCOMPATIBILITY AND HYPERACUTE REJECTION

A form of hyperacute rejection can be observed after transplantation of liver grafts from ABO-incompatible donors and is thought to be related to the presence of ABO blood group antigens on hepatocellular compo-
nants (e.g., vascular endothelium). Antigen-antibody interaction leads to complement activation with resultant microvascular occlusion by platelet-fibrin thrombi. This fibrin deposition can be observed histologically, 2 to 6 hours posttransplant, along with a centriflobular neutrophilic infiltrate, single-cell necrosis, and hemorrhage. The lesion progresses over days to weeks to show centriflobular geographic coagulative necrosis and hemorrhage. Portal inflammation is variable, generally less severe than central lesions, and consists of a neutrophilic infiltrate and hemorrhage (reminiscent of preservation injury). Immunofluorescent microscopy reveals IgM, C1q, and fibrinogen deposition in sinusoidal walls and vascular endothelium.

In addition to the hyperacute form of rejection, ABO incompatibility has been implicated in an increase in nonanastomotic biliary strictures and dilations. These strictures, in contrast to most other forms of biliary tract complication, are diagnosed within the first few weeks after transplantation. The biliary abnormalities can be visualized by cholangiography. By light microscopy, a neutrophilic pericholangitis might be the only evidence.

Fig 5. Chronic ductopenic rejection, early stage. Bile ducts lack the usual string-of-pearls appearance and instead show irregular nuclei with variable size and occasional nuclear dropout (arrow).

Fig 6. Chronic vascular rejection. Large artery showing luminal narrowing by intimal and medial (arrow) collection of foam cells.
of obstruction. Rising bilirubin and alkaline phosphatase levels may help to distinguish this entity from preservation injury, which also can show a pericholangitis (see later).

**PRESERVATION INJURY**

Preservation injury, or *reperfusion injury*, occurs in the immediate posttransplant period and is thought to be secondary to ischemia in the allograft. The histological features generally are those of centrilobular hepatocyte swelling and cholestasis (Fig 7).\(^1\)\(^\text{-}\)\(^5\) Follow-up biopsy specimens often show persisting hepatocyte abnormalities, including swelling or dropout in the central zone for up to 2 to 3 weeks after transplantation, but the changes should diminish in severity with each subsequent biopsy specimen. After this time period, any persistence of hepatocellular swelling or increasing severity of the histological lesion should raise the possibility of a new or superimposed ischemic process. The cholestatic changes are often the last to disappear.

In cases of severe preservation injury, hepatocellular necrosis, mostly present in the centrilobular zone, may be prominent. In some instances, if the necrotic hepatocytes had contained fat, a resultant accumulation of large fat droplets within the sinusoids may occur, a lesion that has been termed *lipopeliosis* (Fig 8).\(^6\)

Another significant change that can occur with severe preservation injury is portal and periportal injury, which results in ductular proliferation and pericholangitis. In these instances, the proliferating ductules may develop bile plugs, which can persist for a month or two (personal observation). This ductular injury with bile stasis is similar to the lesion seen with sepsis.\(^7\) So clinical correlation may be important for the correct identification of this process as preservation injury rather than sepsis.

**NONSPECIFIC CHANGES**

Many liver transplant patients have mild abnormalities on liver biopsy specimens that are not associated with or do not seem to progress into significant clinical abnormalities.\(^8\) These abnormalities include focal, mild infiltration of mononuclear cells, usually lymphocytes, in the portal zones or in the lobule, foci of pericholangitis (neutrophils surrounding a ductule), or rare lymphocytes within the wall of a bile duct. These findings are not considered diagnostic of rejection when the changes are scattered about the portal zones but are not all present in the same zone or when they are solitary or isolated features. Such isolated findings are probably clinically insignificant, and most would not make a diagnosis of minimal acute cellular rejection (personal communications with other transplant pathologists). Other nonspecific features can include mild periportal fibrosis, rare spotty hepatocyte necrosis, and scattered parenchymal aggregates of Kupffer’s cells (microgranulomas).\(^9\)

**CYTOMEGALOVIRUS HEPATITIS**

The incidence of cytomegalovirus (CMV) hepatitis is decreasing in the posttransplant setting related to effective therapy with ganciclovir. When infection does
occur, it usually manifests as scattered foci of several necrotic hepatocytes in association with either small clusters of neutrophils (microabcesses) or with Kupffer's cell hyperplasia. Typical intranuclear or cytoplasmic inclusions are often present. Rarely, CMV can involve the biliary tree.

**OBSTRUCTION**

Obstruction typically causes a more prominent ductular proliferation and periductular neutrophilic infiltration than seen with acute rejection. A few scattered lymphocytes and eosinophils may also be present; however, if the mononuclear inflammatory infiltrate is the prominent finding, the lesion could more likely represent acute cellular rejection. The presence of uniform, diffuse portal tract edema and canalicul cholestasis supports a diagnosis of obstruction, but canalicul cholestasis may not always be present in early obstruction. In addition, some forms of cholestatic hepatitis (caused by hepatitis B virus [HBV] or hepatitis C virus [HCV]) can have prominent cholestasis and bile ductular proliferation, but these lesions also show extensive cellular degenerative changes or necrosis of hepatocytes (see later under recurrent disease). Correlation with clinical findings may be helpful in cases with features overlapping with rejection or hepatitis.

A form of sclerosing cholangitis with obstructive features can occur in the posttransplant setting. This complication is seen in ABO-incompatible allografts, in chronic vascular rejection with foam cell arteritis, in arterial thrombosis affecting the biliary tree, or in other forms of arterial fibrointimal hyperplasia. The histological features are similar to those of primary sclerosing cholangitis with the additional findings of the various arteriopathic changes as described previously.

**RECURRENT PRIMARY DISEASE IN THE ALLOGRAFT**

**Hepatitis B or C**

Viral hepatitis may recur as early as 1 month posttransplant but typically recurs later. Recurrent hepatitis B or C in most cases first presents with spotty, single-cell, hepatocyte necrosis usually accompanied by some degree of lymphocytic infiltration of sinusoids or portal tracts (or both). The typical lymphoid aggregates of HCV hepatitis may not be present in early stages of recurrence, and the lymphocytes tend to lack the spectrum of small to larger, reactive-appearing changes seen in acute cellular rejection.

The differentiation between hepatitis and rejection by histology is often straightforward, but at times, histological features of these two processes may overlap, or both may be occurring simultaneously. The findings of spotty parenchymal necrosis and predominantly mononuclear infiltrates in the portal zones without significant duct damage to the interlobular bile ducts are the most important features that differentiate chronic hepatitis from acute cellular rejection. Overlapping features include the presence of eosinophils in the portal infiltrates, infiltration of the biliary epithelium by mononuclear cells, and damage to the biliary epithe-
Liium, although the damage tends to be milder in hepatitis (HCV rather than HBV tends to cause the overlapping ductal lesions). In addition, any proliferating ductules are more likely to be associated with a mixed inflammatory periductular infiltrate, ductal damage, or infiltration by lymphocytes regardless of the cause of the proliferation, so the interlobular ducts are the ones that should be examined for evidence of inflammation or damage that occurs in rejection. Endotheliitis may also be seen in viral hepatitis, so its presence may not be indicative of a superimposed rejection in the setting of recurrent hepatitis. Ancillary tests, such as immunohistochemical staining for hepatitis B core antigen (HBcAg), may be helpful for the identification of active HBV infection. We have found the HBcAg to be a more effective means of identifying HBV than the hepatitis B surface antigen (HBsAg). No reliable, commercially produced stains for HCV are available, but polymerase chain reaction for HCV can confirm its presence.22

A form of rapidly progressive liver dysfunction after transplantation for hepatitis B has been described that may lead to liver failure over the course of several weeks.23,24 This variant has been termed fibrosing cholestatic hepatitis and usually occurs between 3 and 13 months after transplantation. The liver shows architectural abnormalities with hepatocyte enlargement or atrophy and occasional ground-glass cytoplasm (Fig 9). There is extensive periportal fibrosis, progressing to septal fibrosis. Cholestasis can be marked with both canalicular and central bile plugs. Clinically, these patients show rapid deterioration and develop encephalopathy with a concurrent prolongation of prothrombin time and hyperbilirubinemia. There may be only slight elevations of hepatic transaminases. Staining of liver samples reveals large amounts of cytoplasmic HBsAg. In patients transplanted for hepatitis B, treatment is directed at decreasing recurrence rates and decreasing antigen load. Use of hepatitis B immunoglobulin has led to a marked decrease in disease recurrence.25 More recently, the use of antiviral agents such as lamivudine has been shown to decrease detectable HBV DNA in patients after liver transplantation, including the aggressive fibrosing cholestatic variant.26

A form of fibrosing cholestatic hepatitis C after transplantation has also been described.27 The histological changes are similar to those in cholestatic hepatitis B with periportal fibrosis progressing to cirrhosis, and the patients tend to present with a similar picture of progressive hyperbilirubinemia. In addition, a cholestatic variant of recurrent hepatitis C with severe necrosis can occur, which lacks the prominent fibrosis of the previous entity.28

Primary Biliary Cirrhosis

Sufficient evidence is present to date to confirm that primary biliary cirrhosis (PBC) can recur in the transplanted liver.29-33 Serologically, almost all patients have a drop in antimitochondrial antibody titer after transplantation, followed by a reappearance of the antibody in the serum. The titers may be higher or lower than pretransplantation and do not tend to be as sensi-
tive a marker for disease recurrence as are the histological changes on biopsy specimens. The microscopic features of early recurrence are essentially identical to those seen in the primary disease. These changes include the presence of portal-based epithelioid granulomas, which often center around the interlobular bile duct; duct damage; and prominent portal mononuclear infiltrates with formation of lymphoid aggregates (Fig 10). The granulomas are probably the most specific finding for recurrent PBC. In our experience, the disease tends to recur about 1 year or more after transplantation.

Several other lesions in the transplanted liver have overlapping histological features with PBC. For example, chronic hepatitis C is associated with a diffuse infiltration of mononuclear lymphocytes into the portal zones with lymphoid aggregates and focal mononuclear infiltrates of the duct wall. There tends to be more inflammatory involvement of the lobules associated with focal parenchymal necrosis and no portal-based granulomas in chronic hepatitis. PBC may cause a hepatitis-like pattern in the lobule, including features such as lymphoid infiltrates of the sinusoids and even focal, spotty hepatocyte necrosis. Serum viral markers can be done when necessary to exclude the possibility of acquired hepatitis B or C in such cases.

Chronic rejection with ductopenia is usually discussed in the literature as the most difficult entity to differentiate from recurrent PBC. Ductopenic chronic rejection, however, is usually associated with concurrent chronic vascular rejection with occlusive vascular lesions; thus, the biopsy specimen shows effects of ischemia (centrilobular hepatocyte ballooning or necrosis) not seen in PBC. In the instances when ischemic changes are not present, other histological differences, such as prominent cholestasis, the lack of prominent portal mononuclear infiltrates or granulomas, the rapid disappearance of bile ducts in serial biopsy specimens, and significant duct damage with attenuation of the duct epithelium, hallmark the features of chronic rejection.

Acute cellular rejection may also have overlapping features with recurrent PBC. Both entities may show a mixture of lymphocytes and eosinophils in the portal tracts and lymphocytic infiltrates of interlobular bile ducts. Neutrophilic periductular infiltrates, well-developed endothelitis, and the lack of granulomas, however, favor acute cellular rejection. Additionally, PBC tends to recur about 1 year after transplantation, when acute rejection is unlikely, provided that adequate immunosuppression is given.

Primary Sclerosing Cholangitis

Recurrent primary sclerosing cholangitis (PSC) can be difficult to differentiate histologically and radiographically from other causes of sclerosing cholangitis. Therefore a definitive diagnosis of recurrent disease can be problematic. Patients with PSC, however, have a much higher incidence of biliary strictures than in other, non-PSC control groups. Longer follow-up with good histological documentation of ductopenia of small ducts and sclerosis of large ducts may
Table 3. Differential Diagnosis Summary

<table>
<thead>
<tr>
<th>Histological Feature</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed portal inflammation with bile duct damage or inflammation (mononuclear, eosinophils, neutrophils)</td>
<td>Acute cellular rejection (rarely viral hepatitis if associated with parenchymal necrosis)</td>
</tr>
<tr>
<td>Predominantly mononuclear infiltrates (± eosinophils)</td>
<td>Viral hepatitis, consider rejection in some settings</td>
</tr>
<tr>
<td>Predominantly neutrophilic infiltrates around ducts, duct damage</td>
<td>Resolving rejection, obstruction, nonspecific if mild and focal, component of preservation injury</td>
</tr>
<tr>
<td>Bile ductular proliferation with bile plugs</td>
<td>Sepsis, preservation injury (obstruction less likely)</td>
</tr>
<tr>
<td>Bile ductular proliferation without bile plugs</td>
<td>Severe early preservation injury, acute cellular rejection, obstruction, severe viral hepatitis</td>
</tr>
<tr>
<td>Cholestasis: bile plugs mostly around central vein</td>
<td>Preservation injury (can last up to 4 weeks), obstruction, chronic rejection</td>
</tr>
<tr>
<td>Centrilobular hepatocyte necrosis and/or swelling, minimal inflammation; ± congestion and/or fibrosis</td>
<td>Preservation injury (2-3 weeks posttransplant); ischemia, vascular rejection (after 3 weeks)</td>
</tr>
<tr>
<td>Centrilobular hepatocyte necrosis and mononuclear inflammation</td>
<td>Parenchymal rejection, rule out HBV or HCV, ischemia less likely</td>
</tr>
<tr>
<td>Diffuse hepatocyte ballooning</td>
<td>Ischemia versus hepatitis</td>
</tr>
<tr>
<td>Spotty parenchymal necrosis</td>
<td>Usually hepatitis</td>
</tr>
<tr>
<td>Spotty parenchymal necrosis with neutrophilic microabscesses</td>
<td>CMV</td>
</tr>
<tr>
<td>Spotty parenchymal necrosis with predominantly portal mononuclear infiltrates, ± parenchymal mononuclear infiltrates</td>
<td>HBV, HCV, rarely CMV</td>
</tr>
<tr>
<td>Focal parenchymal mononuclear clusters</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Isolated bile duct proliferation or necrosis of parenchyma</td>
<td>May be former biopsy site or local ischemia/other injury</td>
</tr>
</tbody>
</table>

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; CMV, cytomegalovirus.

be necessary to establish whether primary disease recurs.

EPSTEIN-BARR VIRUS–RELATED LYMPHOPROLIFERATIVE DISORDER

Epstein-Barr virus (EBV) infection does not cause a significant form of hepatitis as do the other herpesviruses, but it is associated with the so-called lymphoproliferative disorder. This lesion can be differentiated from infectious mononucleosis by the more intense mononuclear infiltrates. The pattern of infiltrates can be of several types, including the polymorphous type (composed of a spectrum of small to large B cells); a plasma cell–rich type; and a monotonous infiltrate of lymphocytes arrested at one stage of development, usually either the small or large noncleaved lymphocyte.38,39 The atypical mononuclear proliferation expands the portal zones or invades the hepatic lobule (or both) and is often associated with necrosis of the adjacent liver. Identification of EBV by in situ hybridization or other methods can be key in confirming the diagnosis. In addition, immunoglobulin gene rearrangement and EBV DNA analysis may be done to determine the clonality.39 Therapy entails decreasing the immunosuppressive regimen and treatment with ganciclovir.

Atypical lymphoid or plasma cell hyperplasias and infectious mononucleosis–like infiltrates have also been identified as EBV related, which may possibly
represent early forms of lymphoproliferative disorder in the transplant setting. These lesions are typically polyclonal, but some have small monoclonal or oligoclonal bands. These lesions tend to occur early after transplantation predominantly in children and often involve tonsils or lymph nodes more than other extranodal sites.18,39

SUMMARY

Table 3 reviews some of the histological features seen as discussed here and their differential diagnoses in liver transplant biopsy specimens. Any histological features that do not clearly fit one particular entity could represent a combination representing more than one process, such as combined rejection and hepatitis or other recurrent disease, so that a single diagnosis may not be immediately apparent. In these instances, as in any complicated transplant setting, clinical correlation and follow-up are vital to elucidate the diagnosis of any significant lesions present that may require further therapy.

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