Liver transplantation in adults: Clinical manifestations and diagnosis of acute T-cell mediated (cellular) rejection of the liver allograft

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INTRODUCTION

Acute liver allograft rejection is an important cause of allograft dysfunction. Acute rejection episodes can have an impact on long-term graft survival, even among patients who recover. The use of potent immunosuppressive agents for induction and maintenance therapy for liver transplantation has reduced the incidence of acute rejection, which is defined as liver allograft dysfunction associated with specific pathologic changes in the graft.

Acute rejection can be categorized into T cell-mediated (cellular) rejection (TCMR) and antibody-mediated (previously known as humoral) rejection. However, antibody-mediated rejection infrequently occurs in liver transplantation recipients (ie, 1 percent of recipients), while acute TCMR has been commonly reported [1,2].

This topic will review the clinical manifestations and diagnosis of acute TCMR. Treatment of acute TCMR and a review of transplantation immunobiology are discussed separately. (See "Liver transplantation in adults: Treatment of acute T cell-mediated (cellular) rejection of the liver allograft" and "Transplantation immunobiology".)

The approach to immunosuppression following liver transplantation is discussed separately. (See "Liver transplantation in adults: Initial and maintenance immunosuppression".)

Long-term management of liver transplantation recipients and nonimmunologic complications of transplantation are discussed separately. (See "Liver transplantation in adults: Long-term management of transplant recipients" and "Infectious complications in liver transplantation".)

EPIDEMIOLOGY

Incidence — With the availability of calcineurin inhibitors and antiproliferative agents, acute T-cell mediated (cellular) rejection (TCMR) has been reported in approximately 10 to 30 percent of liver transplantation recipients [3-7]. As an example, in a study of two large cohorts of liver transplant recipients, at least one biopsy-proven acute rejection episode occurred in 27 percent of transplant recipients in the Adult-to-Adult Living Donor Liver Transplantation (A2ALL) cohort and in 16 percent of transplant recipients in Scientific Registry of Transplant Recipients (SRTR) cohort [3].

Risk factors — Risk factors for developing acute TCMR can be broadly classified as the following [8]:

- Recipient-related factors – Etiology of underlying liver disease has been associated with risk of developing acute TCMR. In a study of two large cohorts of liver transplant recipients (the A2ALL and SRTR database), risk of rejection was higher for recipients with primary biliary cholangitis (hazard ratio [HR] 2.10, 95% CI 1.31-3.36, and HR 1.37, 95% CI 1.22-1.53, respectively) or hepatitis C virus infection (HR 2.22, 95% CI 1.57-3.16 and HR 1.11, 95% CI 1.05-1.18, respectively) [3]. Other risk factors for acute TCMR have included recipient age >55 years, cytomegalovirus infection, and subtherapeutic levels of cyclosporine or tacrolimus (for acute rejection occurring more than 180 days posttransplant) [3,9-12].

- Preservation-related factors – Prolonged cold ischemic time has been associated with risk of developing acute TCMR [11].

- Transplant-related factors – Transplant-related risk factors include sensitization (ie, presence of donor-specific human leukocyte antigen [HLA] alloantibodies) and fewer HLA-DR matches [9,12].

Protective factors — Studies suggested that the following may lower the risk of acute TCMR:

- Living-related donor liver transplantation – For recipients of living donor liver transplantation, having a biologically related liver donor was associated with lower risk of acute rejection. In the A2ALL and SRTR cohorts, liver transplantation from a biologically related donor was associated with lower risk of acute rejection compared with a

nonbiologically related donor (HR 0.57, 95% CI 0.43-0.76, and HR 0.78, 95% CI 0.66-0.91, respectively) [3].

- Aspirin – Aspirin, through its anti-inflammatory properties, has been associated with lower risk of acute rejection [13,14]. In a cohort study including 2365 liver transplant recipients, low-dose aspirin (ie, 75 to 100 mg daily) was associated with higher rates of rejection-free survival after one, three, and five years compared with no aspirin (89, 87, and 84 percent versus 82, 81, and 80 percent, respectively; HR for risk of rejection among aspirin users: 0.77, 95% CI 0.63-0.94) [13]. In addition, aspirin was associated with lower risk of hepatic artery thrombosis after one year (1 versus 4 percent; HR 0.23, 95% CI 0.13-0.40). Aspirin was not associated with increased bleeding complications (13 versus 19 percent). While these data are promising, additional studies are needed to confirm efficacy and safety before using aspirin prophylaxis routinely in liver transplant recipients.

CLINICAL FEATURES

Clinical presentation and timing — Most episodes of acute T-cell mediated (cellular) rejection (TCMR) occur within three to six months after liver transplantation, although some episodes occur beyond six months [15,16]. In addition, acute rejection after 12 months post-transplant is typically related to medication noncompliance, reduction in immunosuppression, or other factors interfering with calcineurin inhibitor trough levels (eg, drug-drug interaction).

Most patients who have acute TCMR are asymptomatic. However, some patients present with fever, malaise, abdominal pain, hepatosplenomegaly, and rarely, increasing ascites. Because most patients are asymptomatic, acute TCMR is suspected primarily by an increase in liver biochemical tests [17]. (See 'When to suspect acute rejection' below.)

Laboratory manifestations — Patients with acute TCMR present with abnormal liver biochemical tests which may include elevations of any of the following: serum aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin levels. (See 'When to suspect acute rejection' below.)

Imaging features — Imaging findings in patients with acute TCMR (eg, liver allograft enlargement) are not specific for the diagnosis, and imaging studies are generally performed to exclude other causes of elevated liver biochemical tests and allograft dysfunction (eg, biliary complications). (See "Liver transplantation in adults: Endoscopic management of biliary adverse events".)

DIAGNOSTIC EVALUATION

When to suspect acute rejection — Acute T-cell mediated (cellular) rejection (TCMR) is suspected in liver transplantation recipients who have elevations in at least one liver biochemical test within six months after transplant. Liver biochemical tests include serum aminotransferases (ALT, AST), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin levels. However, abnormalities in liver biochemical tests are not specific for distinguishing acute TCMR from other causes of liver allograft dysfunction and do not correlate with the severity of the rejection episode [17,18].

For patients with suspected acute TCMR, further evaluation is typically performed within one week and includes:

- Liver allograft biopsy (see 'Assessing liver histology' below)
- Liver ultrasound with Doppler study to exclude biliary strictures or vascular thrombosis (hepatic artery and portal vein). We routinely obtain both a Doppler ultrasound and a liver allograft biopsy on the same day.

  For patients with biliary tract abnormalities on ultrasound, further imaging with magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic cholangiography is typically performed. (See "Liver transplantation in adults: Endoscopic management of biliary adverse events".)

Liver transplant recipients with suspected acute TCMR require care and input from a multidisciplinary team including specialists from transplant hepatology, transplant surgery, and pathology.

Establishing the diagnosis

Assessing liver histology — The diagnosis of acute TCMR is made by examining liver allograft histology. The liver biopsy specimen is used for grading the severity of rejection and excluding other causes of elevated liver biochemical tests. (See 'Defining severity of rejection' below.)

Patient preparation for and complications of percutaneous liver biopsy are discussed separately. (See "Approach to liver biopsy".)

Acute TCMR occurs due to recipient T-cells that react to donor histocompatibility antigens present within donor tissue [19]. The pathologic changes that occur in the liver allograft in the setting of acute TCMR include (picture 1A-C) [15,20]:

- Portal inflammation – Portal inflammation consists of a mixed inflammatory infiltrate (predominately mononuclear activated lymphocytes, but may also contain neutrophils and eosinophils).

- Bile duct inflammation or damage – Bile duct inflammation or damage is characterized by nonsuppurative cholangitis involving bile duct epithelium. The affected ducts are infiltrated by inflammatory cells and may show changes ranging from mildly reactive to degenerative changes or focal luminal disruption. The inflammatory process may occur between epithelial cells, inside the basement membrane, or even within the lumen.

- Venous endothelial inflammation – Venous endothelial inflammation (ie, endotheliitis) involving the portal veins or terminal hepatic venules is often seen in patients with acute TCMR. Endotheliitis is characterized by the attachment of lymphocytes and other immunocytes to the luminal surface of the endothelium. The inflammatory process may affect only a small segment of the cross-section of the vessel. Lymphocytes also aggregate under the damaged endothelium, which is then lifted from the basement membrane.

The adequacy of a biopsy specimen is ultimately left to the judgment of the pathologist. Liver allograft biopsy technique typically includes performing two passes with the biopsy needle to obtain samples that each have a minimum of five portal triads [21,22]. (See "Interpretation of nontargeted liver biopsy findings in adults", section on 'General principles'.)

Defining severity of rejection — A classification system for acute TCMR was developed by a panel of expert hepatologists who agreed on a nomenclature and histopathologic criteria for grading acute rejection (ie, Banff classification) [15]. After assessing the allograft biopsy specimen for histologic evidence of acute TCMR, three specific features (portal inflammation, bile duct inflammation, and venous endothelial inflammation) are more critically evaluated and scored on a scale from zero to three. Thus, a maximum score of nine is possible, and the sum of scores from each category is called the rejection activity index (RAI) [15].

Rejection severity is determined by RAI values (table 1). Mild rejection has been regarded as RAI ≤4, although the classification of RAI values has varied among studies [15-17,20,23-27].

Although management of patients with histologic evidence of acute TCMR is guided by severity of rejection, a higher RAI has not been correlated with failure to respond to antirejection treatment. In a study of 231 patients with acute TCMR confirmed by histology, higher RAI scores were not associated with inadequate response to glucocorticoid therapy [23].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of elevated liver biochemical tests in liver transplantation recipients includes other causes of allograft dysfunction such as ischemic reperfusion injury, vascular thrombosis, biliary strictures, infection, and recurrence of primary liver disease. Occasionally, more than one disorder may occur in transplant recipients, and thus, features of both disorders may be found on liver allograft biopsy.

Timing of the clinical presentation may help to narrow the potential causes of elevated liver biochemical tests in transplant recipients. During the first few days and up to one month after transplantation, elevated liver tests may reflect surgical complications or issues such as hepatic artery thrombosis, ischemic reperfusion injury, biliary anastomotic leakage or stricture, primary graft nonfunction, or consequences of hemodynamic instability. Imaging (eg, Doppler ultrasonography) and liver biopsy are typically obtained to differentiate these disorders from acute TCMR. (See 'Diagnostic evaluation' above.)

Elevated liver biochemical tests and allograft dysfunction that occur within the first month following transplant may be caused by:

- Ischemic reperfusion injury – Abnormalities in liver biochemical tests in the immediate post-transplantation period (<4 weeks) may reflect graft injury that usually manifests with elevation of the alkaline phosphatase and GGT, without an increase in total bilirubin [17]. By contrast, elevation of aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) together with rising bilirubin level and/or GGT should raise concern for acute T-cell mediated (cellular) rejection (TCMR).

- Prolonged intrahepatic cholestasis – Prolonged intrahepatic cholestasis (ie, duration >1 week) typically presents in the initial posttransplantation period and is marked by elevations in total bilirubin and alkaline phosphatase in the absence of extrahepatic biliary obstruction on imaging [28,29]. On liver allograft biopsy, portal tract and bile duct inflammation is often accompanied by bile duct plugging and bile staining within the hepatocytes [30]. Subcellular organelle damage produced by cold ischemia may play an etiologic role, leading to bile flow dysfunction [31].

- Cyclosporine toxicity – Cyclosporine toxicity is a potential cause of liver allograft dysfunction; however, cyclosporine is infrequently used for immunosuppression for liver transplant recipients. For patients who take cyclosporine, toxicity should be suspected when elevated liver biochemical tests are seen in conjunction with elevations in serum creatinine. (See "Cyclosporine and tacrolimus nephrotoxicity".)

- Antibody-mediated rejection – Antibody-mediated rejection is an infrequent cause of allograft injury and loss after ABO-compatible liver transplantation that can mimic or

overlap with acute TCMR. Proposed features of antibody-mediated rejection in patients following liver transplantation include donor-specific human leukocyte antigen (HLA) alloantibodies in serum, microvascular endothelial cell injury on biopsy, and linear C4d positivity in liver sinusoids, in the absence of other causes of liver injury [20,32,33].

- Recurrent hepatitis C virus (HCV) infection – Some histologic features, such as bile duct injury and portal lymphocytic infiltration, are found in both recurrent HCV infection and acute TCMR. However, the availability of safe and highly effective therapy with direct acting antivirals has revolutionized the approach to HCV management in liver transplant candidates and recipients. The diagnosis and management of recurrent HCV infection following liver transplantation is discussed separately. (See "Hepatitis C virus infection in liver transplant candidates and recipients".)

- Massive hemorrhagic necrosis – A very rare complication after liver transplantation is acute graft necrosis and failure in the absence of vascular obstruction. Histologic features include widespread hemorrhage and infarction. This syndrome has been described as massive hemorrhagic necrosis [34].

- Graft-versus-host disease – Graft-versus-host disease (GVHD) after liver transplantation has been rarely reported but usually presents within the first month after transplantation [35]. Common clinical features have included skin rash, diarrhea, and cytopenia. The diagnosis can be made on rectosigmoid biopsies showing histologic features of increased crypt epithelial apoptosis, crypt loss, and neutrophilic infiltration. A biopsy of the skin rash can also be used to evaluate for GVHD. (See "Cutaneous manifestations of graft-versus-host disease (GVHD)".)

Causes of liver allograft dysfunction that are typically seen later in the post-transplantation period (ie, after six months) include infections (eg, cytomegalovirus, Epstein-Barr virus) and recurrence of primary liver disease (eg, primary biliary cholangitis). (See "Infectious complications in liver transplantation".)

Recurrence of nonviral chronic liver disease (eg, primary biliary cholangitis, primary sclerosing cholangitis) typically occurs >1 year following liver transplantation. (See "Liver transplantation in primary biliary cholangitis".)

Recurrent viral hepatitis (eg, hepatitis B virus infection) may occur at any time after transplant. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Liver transplantation".)

SUMMARY AND RECOMMENDATIONS

- **Background** – Acute liver allograft rejection is an important cause of allograft dysfunction. Acute rejection episodes can have an impact on long-term graft survival, even among patients who recover. The use of potent immunosuppressive agents for induction and maintenance therapy for liver transplantation has reduced the incidence of acute rejection, which is defined as liver allograft dysfunction associated with specific pathologic changes in the graft. (See 'Introduction' above.)

- **Incidence** – With the availability of calcineurin inhibitors and antiproliferative agents, acute T-cell mediated (cellular) rejection (TCMR) has been reported in approximately 10 to 30 percent of liver transplantation recipients. (See 'Incidence' above.)

- **Clinical features** – Most liver transplant recipients with acute TCMR are asymptomatic and present with elevated liver biochemical tests within three to six months following transplantation. (See 'Clinical features' above.)

- **Diagnostic evaluation** – Acute TCMR is suspected in liver transplantation recipients who have elevations in at least one liver biochemical test within six months after transplant. Liver biochemical tests include serum aminotransferases (ALT, AST), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin levels. (See 'When to suspect acute rejection' above.)

  Patients with suspected acute TCMR are evaluated with liver allograft biopsy and liver ultrasound with Doppler study.

  The diagnosis of acute TCMR is made by examining liver allograft for histologic evidence of acute rejection. The liver biopsy specimen is also used for grading the severity of rejection and excluding other causes of elevated liver biochemical tests. The pathologic changes that occur in the liver allograft include portal inflammation, bile duct inflammation and damage, and venous endothelial inflammation. (See 'Assessing liver histology' above.)

- **Determining severity of rejection** – For patients with acute TCMR of the liver allograft, rejection severity is determined by the rejection activity index (RAI) (table 1). (See

'Defining severity of rejection' above and "Liver transplantation in adults: Treatment of acute T cell-mediated (cellular) rejection of the liver allograft".)

- **Other complications of liver transplantation** – Long-term management of liver transplantation recipients and nonimmunologic complications of transplantation are discussed separately. (See "Liver transplantation in adults: Long-term management of transplant recipients" and "Infectious complications in liver transplantation".)

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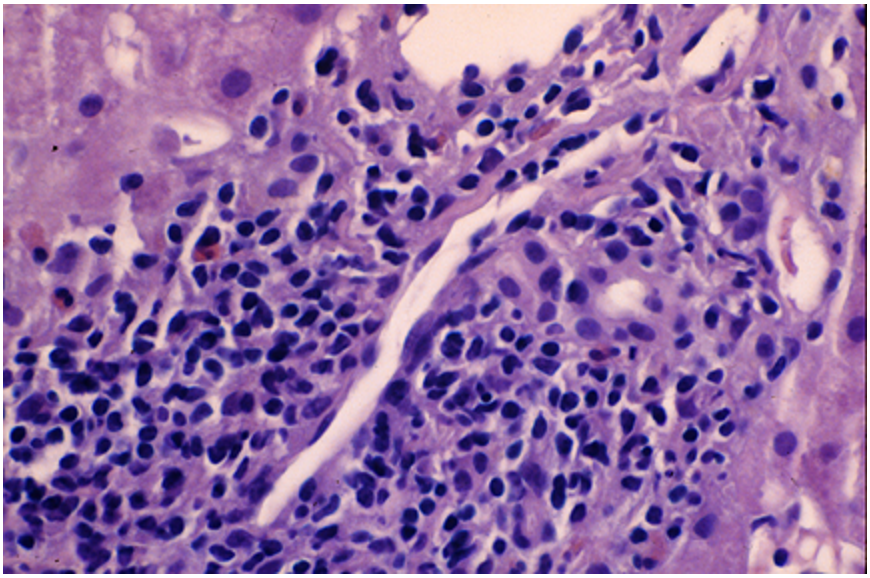
Topic 4587 Version 19.0

GRAPHICS

Acute T cell-mediated (cellular) rejection of the liver allograft

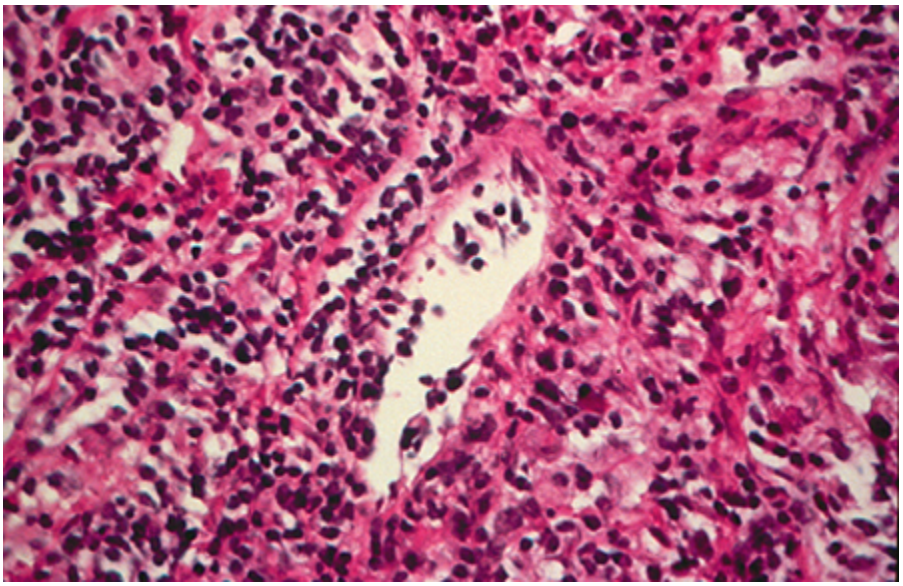


High power light micrograph of a liver biopsy from a patient with acute T cell-mediated (cellular) rejection of the liver allograft shows an expanded portal tract containing mixed inflammatory cells. There is also evidence of bile duct inflammation and endotheliitis.

Courtesy of Donald Jensen, MD.

Graphic 80063 Version 4.0

Acute T cell-mediated (cellular) rejection of the liver allograft

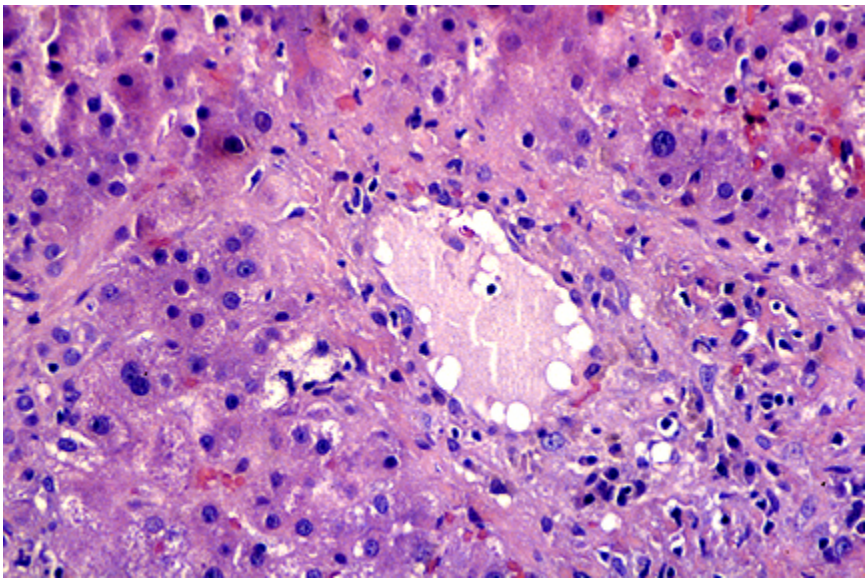


Medium power view of a liver allograft biopsy in a patient with acute T-cell-mediated (cellular) rejection shows dense lymphocytic infiltrate and endotheliitis.

Courtesy of Robert Odze, MD.

Graphic 60368 Version 3.0

Endotheliitis in acute T-cell mediated (cellular) rejection of the liver allograft



Light micrograph of a liver allograft biopsy from a patient with acute T-cell mediated (cellular) rejection shows endotheliitis involving a central hepatic vein.

Courtesy of Donald Jensen, MD.

Graphic 79840 Version 2.0

Histologic rejection activity index for liver transplantation

Category	Criteria	Score
Mixed portal inflammatory infiltrate	Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads	1
	Expansion of most of all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils and eosinophils	2
	Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma	3
Bile duct epithelial inflammation and damage	A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear:cytoplasmic ratio of the epithelial cells	1
	Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity and cytoplasmic vacuolization of the epithelium.	2
	As above for 2, with most or all of the ducts showing degenerative changes or focal lumenal disruption	3
Venous endothelial inflammation	Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules	1
	Subendothelial infiltration involving most or all of the portal and/or hepatic venules with or without confluent hepatocyte necrosis/dropout involving a minority of perivenular regions	2
	As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis	3

The sum of the scores from each category is called the rejection activity index (RAI). Rejection severity is determined by RAI values. Mild acute T-cell mediated rejection has been classified as RAI ≤4. Refer to content on defining severity of T-cell mediated rejection of the liver allograft.

Adapted from: Demetris AJ, Batta KP, Dhillon AP, et al. Hepatology 1997; 25:658.

Graphic 74243 Version 5.0

Contributor Disclosures

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