Antibody-Mediated Rejection After Liver Transplant

Michael Lee, MD

KEYWORDS

• Liver • Antibody-mediated rejection • Transplant

KEY POINTS

- Antibody-mediated rejection of the allograft liver is a diagnosis that requires both clinical and histologic correlation.
- The criteria for diagnosing acute antibody-mediated rejection include serum donor–specific antibodies, C4d staining, specific histologic findings, and exclusion of other entities.
- There are several treatment options for acute and chronic antibody-mediated rejection.

INTRODUCTION

The first liver transplant was successfully performed in the late 1960s[1]; however, medical knowledge about operative techniques, postoperative complications, organ preservation, immunosuppressive therapies, and graft rejection were in its infancy and the 1-year survival rate was less than 30% for the first decade with this new experimental procedure.[2,3] With improvements in surgical technique, addressing the complications that commonly arose in the first year posttransplant, and the introduction of cyclosporine in the 1980s,[4] the survival rate markedly improved with 5-year and 10-year survival rates at 70% and 50% respectively.[5–7] According to the World Health Organization, there are more than 20,000 liver transplants performed worldwide across 104 countries, which is representative of 90% of the population.[8] There was a rapid surge in liver transplants over the course of the next 2 decades, which gradually slowed because the frequency of the operation outpaced the availability of donor organs. This shortage was addressed by using cadaveric livers, splitting livers for multiple recipients, living related liver transplantation, and extending the donor criteria to organs that were once considered unsuitable.[9,10]

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Department of Pathology and Cell Biology, Columbia University, 630 West 168th Street, VC14-238, New York, NY 10032, USA
E-mail address: mjl2197@cumc.columbia.edu

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gastro.theclinics.com

PATHOBIOLOGY

The introduction of a foreign organ into a patient creates an environmental milieu for a robust immunologic response. This vigorous immune response is predominantly T cell–mediated and all nucleated cells in the liver, including hepatocytes, endothelium, and bile ducts, are targets.[11–14] The transplanted liver contains numerous major histocompatibility antigens that are present on every nucleated cell. There are also many minor histocompatibility antigens involved in the immunologic reaction, but to a lesser extent.[15,16] All cell types in the liver (hepatocytes, endothelial cells, biliary epithelium) express strong and high levels of class I human leukocyte antigens (HLA). HLA class II antigens are variably expressed, ranging from negative to focally positive on central, sinusoidal, and portal capillary endothelial cells. Portal vein endothelial cells are usually negative for HLA class II antigens.[17–21] However, liver microvascular endothelial cells can be stimulated to strongly express HLA class II antigens under the appropriate environmental impetus, which includes coexistent disorders (ie, medication effect from gamma-interferon, recurrent hepatitis C, autoimmune hepatitis, T cell–mediated rejection [TCMR]).[17,22,23] This ability leads to strong expression of HLA class II (on the magnitude of DR>DP>DQ) in all liver tissue cells (hepatocytes, biliary epithelium and the endothelium of all compartments).[17–21] Increased expression of HLA class II antigens provides a larger target for donor-specific antibodies (DSAs) and subsequent disorder.[17,24–26]

There are 2 types of rejection in organ transplant patients: TCMR and antibody-mediated rejection (AMR). TCMR is predominantly caused by CD4-positive and CD8-positive T cells, and leads to portal inflammation, endotheliitis, and bile duct injury. These features are graded on the Banff classification system using the grading criteria for a global assessment (indeterminate, mild, moderate, and severe) along with a quantitative scoring system known as the Rejection Activity Index. Six months is often used as a time marker for classification of early versus late TCMR even though the histologic features occur along a spectrum rather than in clear, time-defined categories. Both early and late TCMR show the classic histologic features described earlier but the latter also shows central perivenulitis with associated necrosis, less bile duct injury, and a more homogeneous inflammatory infiltrate of histiocytes, lymphocytes, and plasma cells with mild interface activity.[17,24]

AMR is caused by preformed antidonor antibodies, ABO incompatibilities, or de-novo antibodies that develop after transplant.[27–31] Preformed antidonor antibodies either bind to ABO antigens or to HLA class I and class II antigens expressed on endothelial cells. DSAs bind to endothelial cells and initiate a cascade of events complement fixation, activation, and C4d deposition, which stimulate endothelial procoagulant and chemotactic factors and culminates in cytotoxicity mediated by macrophages, NK cells, and neutrophils.[17,32–34] Endothelial cell damage causes margination of leukocytes and the histologic manifestations of fibrin microthrombi,[17,35–38] and capillary dilatation with subsequent repair and healing by myofibroblasts. This fibrosis and architectural remodeling causes shunting of blood flow, hypoxia, and impaired function.[39–41]

CLINICAL FEATURES

The incidence of AMR is low because of innate liver resistance, immunologic screening pretransplant, improved immunosuppressant therapies, and plasmapheresis.[42–44] The exact incidence of AMR is unknown because the diagnosis is difficult to establish, which has likely contributed to skepticism about whether AMR occurs in the post–liver transplant setting. Studies over the last 2 decades show that