Acute, Chronic, and Humoral Rejection

Pathologic Features Under Current Immunosuppressive Regimes

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KEYWORDS

• Liver transplantation • Allograft rejection • Acute cellular rejection • T-cell–mediated rejection • Chronic rejection • Antibody-mediated rejection • Humoral rejection

Key points

- Histopathologic assessment of allograft biopsies continues to serve an important role in the diagnosis of rejection to facilitate successful patient management.
- The diagnosis of acute and chronic antibody-mediated rejection requires integration of the results of histologic examination, donor-specific antibody testing and C4d immunostaining, and exclusion of other potential etiologies of allograft dysfunction.
- Antibody-mediated rejection should be suspected if histologic findings in an allograft biopsy cannot be adequately explained by an identifiable etiology.

ABSTRACT

Under current immunosuppressive regimes, T-cell–mediated acute and chronic rejection remain common and important posttransplant complications. The definition of humoral (antibody-mediated) rejection has been greatly expanded in recent years. The histopathologic assessment of allograft biopsies continues to serve an important role in the diagnosis of rejection and to facilitate patient management. The diagnosis of both acute and chronic antibody-mediated rejection requires integration of the results of donor-specific antibody testing and C4d immunostaining, as well as exclusion of other potential etiologies of allograft dysfunction. Chronic antibody-mediated rejection should also be included in the differential diagnosis for unexplained allograft fibrosis.

OVERVIEW

Since first performed by Dr Thomas E. Starzl and colleagues in 1963, liver transplantation has evolved to become the standard of care for patients with end-stage liver diseases, acute liver failure, liver-based metabolic disorders, and selected primary hepatic malignancies.[1,2] The range of posttransplant complications is broad, and includes surgical/technical complications, allograft rejection, infections, recurrent liver diseases, and acquired liver diseases, among others. Allograft rejection remains a major complication despite advances in immunosuppressive agents and regimens that have dramatically improved patient survival since the early days of liver transplantation. The histopathologic examination of allograft biopsies is an integral tool to the diagnosis of rejection, because many of the posttransplant

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complications cannot be easily differentiated from each other clinically, radiographically, or biochemically. In this article, current immunosuppressive agents and regimens are reviewed briefly, followed by a detailed discussion of the current diagnostic criteria for T-cell–mediated rejection (TCMR; acute cellular rejection), chronic rejection, and antibody-mediated rejection (AMR; humoral rejection). Relevant differential diagnoses and clinical aspects of these entities are also discussed briefly.

CURRENT STRATEGIES OF IMMUNOSUPPRESSION FOR LIVER TRANSPLANTATION

IMMUNOSUPPRESSIVE AGENTS

Corticosteroids are most commonly used during the induction phase immediately after transplantation and in the treatment of acute rejection.[3–5] They exert their antiinflammatory effects through multiple mechanisms, including decreased transcription of proinflammatory factors, inhibition of cell-mediated immunity and antibody production via decreased production of cytokines (interleukin [IL]-1, IL-2, IL-6, IL-8, tumor necrosis factor-α), and impairment of cell migration, phagocytosis, and respiratory burst mechanisms, and so on. Adverse side effects from long-term steroid use are numerous, including increased risk of opportunistic infections, metabolic derangements (such as hyperglycemia, hypertension, hyperlipidemia, weight gain, and osteoporosis), and in patients transplanted for active hepatitis C, the possibility for early and aggressive recurrence.

Calcineurin inhibitors (CNIs), including cyclosporine and tacrolimus (FK506, Prograf), are the most commonly used drugs for long-term maintenance immunosuppression. They exert their effects by binding to proteins that inhibit the phosphatase calcineurin, which in turn prevents transcription of the *IL-2* gene and, thus, T-cell proliferation. Tacrolimus is preferred over cyclosporine in the setting of liver transplantation, because it has been shown to be more potent and efficacious, with better graft survival rates and a fewer clinically significant side effects. The main complication from long-term CNI use is nephrotoxicity, which can lead to both acute and chronic renal insufficiency. Other significant side effects include hyperglycemia with development of diabetes mellitus, headaches, neurologic symptoms, and atherosclerotic cardiovascular disease.

The antimetabolites mycophenolic acid (MPA; CellCept) and azathioprine (Imuran) are second-line agents that are used in conjunction with CNIs for maintenance immunosuppression. Both exert their effects by inhibiting synthesis of purine nucleotides in T and B cells, thus, inhibiting lymphocyte proliferation. Over the past 20 years, the use of azathioprine has progressively decreased in the setting of liver transplantation and has now largely been replaced by MPA. The main side effects of MPA are dose-dependent leukopenia and gastrointestinal symptoms such as nausea, vomiting, and diarrhea, which usually respond to dose reduction or a switch to a different MPA formulation.

The mammalian target of rapamycin inhibitors sirolimus and everolimus are used less frequently for maintenance immunosuppression and are typically limited to patients who cannot tolerate CNIs, have renal dysfunction, or with high-risk hepatocellular carcinoma. They bind to the same protein (FKBP12) that binds tacrolimus but at a different site, which leads to inhibition of the kinase mammalian target of rapamycin, and thus inhibits T-cell activation and proliferation. Sirolimus has been associated with an increased risk of hepatic artery thrombosis, hyperlipidemia, hypertension, and cytopenia.

There are various polyclonal and monoclonal antibodies that either inhibit or deplete T cells, and can be used for steroid-free regimens or for treatment of steroid-resistant rejection. The polyclonal antibodies antithymocyte globulin and antilymphocyte globulin contain antibodies to multiple T-cell antigens, which leads to lymphocyte depletion via apoptosis and/or cell lysis. In general, they are well-tolerated, but can occasionally cause allergic reactions or a serum sickness-like illness. Monoclonal antibodies include those to CD3, IL-2 receptor, and CD52, but these are not widely used at this time.

STRATEGIES AND PROTOCOLS

Immunosuppression protocols can vary widely as a result of a combination of physician preference, primary disease necessitating transplantation, and an individual patient's side effect profile to particular medications. In the period immediately after transplantation, higher levels of immunosuppression are needed temporarily as the recipient's immune system is first exposed to various alloantigens from the donor liver. This immunosuppression is usually in the form of high-dose corticosteroids, up to 1000 mg at the time of transplantation, followed by a rapid taper over the first couple of weeks and maintenance on lower doses for the first 3 to 12 months after transplantation.[4–6] There has been growing interest in antibody-based steroid-free regimens, including the use of antithymocyte globulin or monoclonal antibodies,