Acute Rejection and Antibody-Mediated Rejection in Lung Transplantation

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KEYWORDS

• Lung transplantation • Acute rejection • Antibody-mediated rejection • Lymphocytic bronchiolitis

KEY POINTS

- Acute rejection is a common complication after lung transplantation.
- Acute rejection is an independent risk for the development of chronic lung allograft dysfunction.
- The diagnosis of antibody-mediated rejection after lung transplantation requires a multidisciplinary approach.
- Antibody-mediated rejection may cause acute allograft failure.

INTRODUCTION

Lung transplantation rapidly evolved from an experimental treatment in the early 1980s into the ultimate treatment option for patients with end-stage lung disease. Survival after lung transplantation has improved significantly over time, but much of this improvement has been seen in the first few months after transplantation and attributed to refinements in surgical techniques, recipient and donor selection, and immediate postoperative care.[1] However, long-term survival remains disappointing, and the median survival in the latest International Society for Heart and Lung Transplantation (ISHLT) registry was 6 years.[1] The leading cause of death beyond the first year after transplantation is chronic lung allograft dysfunction (CLAD). Bronchiolitis obliterans syndrome (BOS) is the prototypic form of CLAD and has been an important endpoint in most clinical studies.[2,3] It is believed that recurrent alloimmune and non-alloimmune insults to the lung allograft, as well as a disordered repair process, result in BOS.

The term acute cellular rejection (ACR) is sometimes used to distinguish acute rejection from antibody-mediated rejection (AMR). ACR has been a common complication after lung transplantation in spite of intensive immunosuppressive therapy. Among lung recipients with known rejection status, 28% have at least 1 episode of ACR in the first year after transplantation according to the latest ISHLT registry report, and registry data may underestimate the incidence of rejection.[1] Although ACR is often clinically silent and rarely fatal, it has been consistently recognized as an important risk factor for the development of BOS.[1,4–7] Similarly, lymphocytic bronchiolitis (LB) is an airway-focused acute rejection pathology that has been associated with the subsequent development of BOS.[8] In recent years, there has been increasing awareness of AMR after lung transplantation, and the ISHLT recently developed a consensus report to establish diagnostic criteria.[9–14] Unlike ACR, AMR has typically been associated with signs and symptoms of allograft dysfunction and has often resulted in allograft failure.[9–12]

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This article details clinical and pathologic features of ACR and AMR after lung transplantation and discusses routine management and outcomes.

DEFINITION OF ACUTE REJECTION

Transbronchial lung biopsy remains the gold standard for the diagnosis of ACR after lung transplantation. Although the procedure is invasive and carries a small risk of complications, transbronchial biopsy is necessary to establish the diagnosis of ACR, because clinical and radiographic findings are not specific or sensitive. An ISHLT pathology working group developed the original histologic criteria for the diagnosis of lung allograft rejection in 1990.[15] The criteria were revised in 1996 and again in 2007.[16,17] According to these criteria, acute rejection may affect the vasculature and the small airways of the lung allograft; consequently, rejection may manifest as ACR, involving small vessels, or lymphocytic bronchiolitis (LB), involving the small airways.[15–17] The diagnosis of ACR is based on the presence of a circumferential perivascular mononuclear cell infiltrate. The severity of ACR grade is based on the intensity of mononuclear cell infiltrates and extension into the adjacent interstitium (**Table 1**). ACR grade A0 (none) is characterized by normal parenchyma without perivascular mononuclear cell infiltrates. ACR grade A1 (minimal) is characterized by infrequent perivascular infiltrates consisting of small lymphocytes that are 2 to 3 cells thick circumferentially surrounding small vessels (**Fig. 1**, see **Table 1**). ACR grade A2 (mild) is characterized by a perivascular infiltrate consisting of activated and small lymphocytes, with some eosinophils that expand the vascular adventitia (**Fig. 2**, see **Table 1**). These may be associated with endothelialitis. ACR grade A3 (moderate) is characterized by frequent and obvious infiltrates circumferentially surrounding small vessels and extending into the adjacent interstitium and alveolar septae (**Fig. 3**, see **Table 1**). The infiltrating cells in ACR grade A3 often include eosinophils and neutrophils, and endothelialitis is often seen. ACR grade A4 (severe) is characterized by diffuse infiltrates with alveolar damage and necrotizing vasculitis (**Fig. 4**, see **Table 1**). Although imperfect, this grading scheme has been validated in studies that examined its inter-reader and intrareader reliability.[18,19]

INCIDENCE OF ACUTE REJECTION

The reported incidence of ACR in the first year after lung transplantation has varied between 10% and 45% in different reports. In the ISHLT registry, 28% of patients with known rejection status had at least 1 episode of ACR.[1] Similarly, according to the 2015 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) annual report, 15% to 20% of patients of patients developed at least 1 episode of ACR in the first year after lung transplantation.[20] However, large national and international registries may underestimate the true incidence of ACR because of methodological and reporting limitations. Some randomized

Table 1
Histologic diagnosis of acute rejection and lymphocytic bronchiolitis

Acute Rejection Grade	Severity	Features
A0	None	No mononuclear cell infiltrates; normal parenchyma
A1	Minimal	Scattered perivascular 2–3 cell thick infiltrates
A2	Mild	More frequent perivascular infiltrates expanding vascular adventitia; endothelialitis
A3	Moderate	Obvious perivascular infiltrates at scanning magnification; extending into adjacent interstitium
A4	Severe	Diffuse infiltrates; alveolar damage; necrotizing vasculitis
Lymphocytic Bronchiolitis	**Severity**	**Features**
B0	None	Normal airway, without excess inflammatory cells
B1R	Low grade	Submucosal peribronchiolar mononuclear cell infiltrates; intact respiratory epithelium
B2R	High grade	Intense peribronchiolar mononuclear cell infiltrates; epithelial damage with necrosis and ulceration