INTRODUCTION

The increasing number of transplant centers has resulted in providing lung transplantation as a therapeutic option for many patients with end-stage pulmonary diseases. However, despite improvements in immunosuppression, surgical techniques, and diagnostic accuracy, post-transplant complications remain problematic. One of the key elements to patient survival is the prompt and appropriate intervention of allograft dysfunction. While there are a number of ways to monitor the recipient, tissue examination still remains the mainstay in assessing allograft alterations. Perhaps it is important to distinguish between rejection and non-rejection processes such as infection, since treatment is often opposite. Graft syndromes typically occur in their particular context, and it is the understanding of the adaptation of the lung allograft to the host environment which is critical in arriving at the correct diagnosis. The intent of this chapter is to review the histopathology and pathophysiology of lung allograft rejection and other non-rejection processes which may also contribute to graft dysfunction. The efficacy of types of biopsies in specific situations will also be discussed.

EARLY POST-TRANSPLANT ALLOGRAFT COMPLICATIONS

During the first week post-transplant, virtually all allografts are subject to the so-called 're-implantation response' characterized by bilateral opacification on chest radiograph and histologic demonstration of interstitial and alveolar edema and margination of neutrophils (Figure 1). The process is thought to be related to fluid overload secondary to disruption of the hilar lymphatics, organ ischemia during harvesting and transport, and division of nerves and bronchial arteries. It usually resolves by the end of the first week after transplantation, before acute cellular rejection generally takes place.

Following the immediate post-transplant period a variety of other complications are encountered, many of which are related to the donor organs. Preservation (harvest) injury manifests pathologically as diffuse alveolar damage (DAD) with interstitial edema, hyaline membranes, and granulation tissue (Figure 2). While the process is thought to be secondary to organ ischemia, we have seen DAD in cases with minimal ischemic times in living-related transplants, thus implicating other etiologic factors. In contrast to the usual DAD is the occasional development of a temporally homogeneous patchy (as opposed to diffuse)
process. Clinically, its distinction from acute cellular rejection is the main differential diagnosis. This is not difficult in most cases with mild to moderate degrees of reversible DAD. However, in severe or prolonged cases, uncertainty in the clinical impression often necessitates a biopsy. Pathologically, severe DAD demonstrates extensive injury, to involve not only the interstitium but also the airways to produce acute bronchitis and bronchiolitis with luminal ingrowth of loose granulation tissue. Although some cases may demonstrate concurrent DAD and rejection, attempts should be made to distinguish features of DAD from alveolar damage secondary to severe acute cellular rejection (see below) and chronic airway rejection. While the intraluminal granulation tissue of DAD has often been referred to as ‘bronchiolitis obliterans’, it differs from the chronic rejection-related bronchiolitis obliterans, which exhibits dense eosinophilic collagen characteristic of irreversible intraluminal scar.

Early in the history of heart–lung transplantation, tracheal dehiscence was a relatively common complication. Due to improved surgical techniques this complication is now a rarity. While the acute complications of tracheal dehiscence are now under control, chronic bronchomalacia, involving the main stem bronchi and their branches due to the sacrificed bronchial artery circulation, is still a problem.

Other causes for early post-transplant complications include donor organ infection and thromboembolic disease. Sources of the embolic material include the brain, bone marrow, cartilage, and deep venous thrombi. The consequences of embolic disease are probably as varied as in the non-transplant setting. Reports of rapidly fatal embolic diseases are noted at one end of the spectrum, while small incidental thromboemboli are not uncommonly found in biopsy specimens. Finally, a progressively downhill respiratory course lacking a demonstrable etiology is classified as primary graft failure. At our institution the incidence of primary graft failure has been approximately 6% since 1982.

**ACUTE LUNG REJECTION**

In solid organ allografts, rejection may take the form of hyperacute, acute or chronic rejection. Hyperacute rejection is an immediate rejection response following implantation, and results in graft failure. While it has been reported in the animal lung transplant model, rigorous documentation in human lung transplants has not been made. Morphologic findings by themselves are not specific and therefore an integrated approach with clinical findings, histology, serology, and immunofluorescence is required. Specifically, the following are the considered criteria for diagnosis: (a) early graft failure without alternative etiology; (b) consistent gross, histologic, and immunofluorescence findings; (c) a high percentage of panel-reactive antibodies prior to transplantation; and (d) demonstration of donor-specific antibodies in the eluate of the failed allograft.

Acute cellular rejection (ACR) typically manifests after a week post-transplant and is one of the main clinical differential diagnoses of graft dysfunction along with harvest injury and infection. It should be noted, however, that ACR may occur any time post-transplant, especially when there is an alteration in the effectiveness of immunosuppression. ACR is mediated by an immunologic mechanism targeting the donor histocompatibility antigens expressed on bronchial-associated lymphoid tissue (BALT), bronchial epithelium, and vascular endothelium. The relationship between the infiltrating cellular population and MHC class II antigen expression is somewhat unclear. HLA-DR and DQ expression is found in the transplanted bronchial epithelium, but there is no correlation between the level of expression and episodes of rejection. Furthermore, normal pulmonary epithelium and endothelium may also express MHC class II antigens. The major infiltrating cell population consists of T lymphocytes with occasional \( B \)-cells of recipient origin as demonstrated by \( Y \) chromosomal probe analysis. In early ACR, most of the infiltrating \( T \) lymphocytes belong to \( \text{CD}4^+ \) (helper) phenotype whereas, later, the population of \( \text{CD}8^+ \) (suppressor/cytotoxic) \( T \)-cells increases. Recently the role of \( B \)-cells in persistent and immunosuppression-resistant ACR has