Bronchiolitis Obliterans Syndrome and Other Late Pulmonary Complications After Allogeneic Hematopoietic Stem Cell Transplantation

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KEYWORDS

• Obliterative bronchiolitis • Bronchiolitis obliterans syndrome • Organizing pneumonia
• Allogeneic hematopoietic stem cell transplant • Graft-versus-host disease • Interstitial lung disease
• Pleuroparenchymal fibroelastosis

KEY POINTS

- Late-onset noninfectious pulmonary complications, which may involve all anatomic regions of the lung, contribute to excess morbidity and mortality in survivors of allogeneic hematopoietic stem cell transplantation.
- Bronchiolitis obliterans syndrome, characterized by new-onset airflow obstruction on spirometry, is recognized as a pulmonary manifestation of chronic graft-versus-host disease.
- Early recognition and treatment of bronchiolitis obliterans syndrome are required to reduce long-term lung function impairment.
- Interstitial lung diseases include several histologic entities and are often overlooked in hematopoietic stem cell transplant recipients.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is an established treatment with curative intent for hematologic malignancies and several nonmalignant conditions. Advances in this procedure over the past 2 decades—including reduced intensity of conditioning regimens and the development of new stem cell sources—have allowed a growing number of patients to access this type of treatment. Less toxic conditioning, improved graft-versus-host disease, and anti-infectious prophylaxis and improved supportive care have contributed to reduced early mortality after allogeneic HSCT.[1]

The success of allogeneic HSCT, however, remains tempered by significant organ-specific complications, including acute and chronic

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pulmonary disease. Because survivorship after HSCT has improved, the burden of disease has shifted from early complications to late complications relating to chronic graft-versus-host disease (cGVHD) and concomitant immunosuppression. Up to 20% of allogeneic HSCT recipients experience a late pulmonary complication.[2,3] Long-term survivors of HSCT who are cured of their original malignancy continue to experience a higher incidence of pulmonary disease contributing to increased morbidity and mortality compared with non-HSCT patients with cancer.[4,5] The prevention and treatment of late pulmonary complications have been acknowledged by the transplant community as a significant unmet need in this population.[6]

This review discusses the late-onset noninfectious pulmonary complications (LONIPCs) of allogeneic HSCT, which encompass all aspects of the bronchopulmonary anatomy, including airways, parenchyma, pleura, and vasculature. Bronchiolitis obliterans syndrome (BOS) is the most well-characterized late complication and the only entity formally recognized as a manifestation of cGVHD, although much work remains to be done in defining, detecting, and treating this disease. There is increasing appreciation of parenchymal disease, including organizing pneumonia (OP) and other interstitial lung diseases (ILDs), as well as pleural and pulmonary vascular complications. Knowledge of these pulmonary diseases should help clinicians to better understand and manage postallogeneic HSCT patients who develop late pulmonary complications.

Several diagnostic considerations specific to the HSCT recipient are worth noting.[7] LONIPCs in HSCT recipients are often difficult to recognize and may come to attention with the development of respiratory symptoms (eg, dyspnea, cough, sputum, and wheezing) or the deterioration of lung function demonstrated by posttransplant screening pulmonary function tests. Generalized fatigue and infection are common after HSCT and may mask dyspnea. A patient who is deconditioned may complain only when resuming a physical activity long after the onset of lung disease. A defect in lung function may reflect chest wall restriction or neuromuscular weakness from HSCT rather than true lung disease. Respiratory infections are common after HSCT and should be ruled out in the diagnostic workup. Finally, although surgical lung biopsy is the gold standard for classifying LONIPCs, surgery is avoided because of potential morbidity.[8–10] Lung biopsy should be considered on a case-by-case basis.

BRONCHIOLITIS OBLITERANS SYNDROME

Obliterative Bronchiolitis

New-onset, severe airflow obstruction in association with cGVHD in 4 young, nonsmoking allogeneic HSCT recipients was reported in 1984.[11] Lung biopsy specimens showed obliterative bronchiolitis (OB), characterized by peribronchiolar fibrosis and varying degrees of intraluminal fibrous obliteration and circumferential narrowing of the terminal small airways (**Fig. 1**).[7] The clinical correlate of physiologic airflow obstruction is now known as *bronchiolitis obliterans syndrome* (BOS).[12]

Although the pathogenesis of OB is largely unknown, it is postulated that an insult to the small airway epithelium, such as aspiration or viral infection, induces an inflammatory infiltrate driven by alloreactive T cells, leading to an aberrant repair response that ultimately results in fibrosis. Many factors—including conditioning regimen, donor source, prior pneumonitis—have been implicated in the development of BOS, but only chronic GVHD has been consistently associated

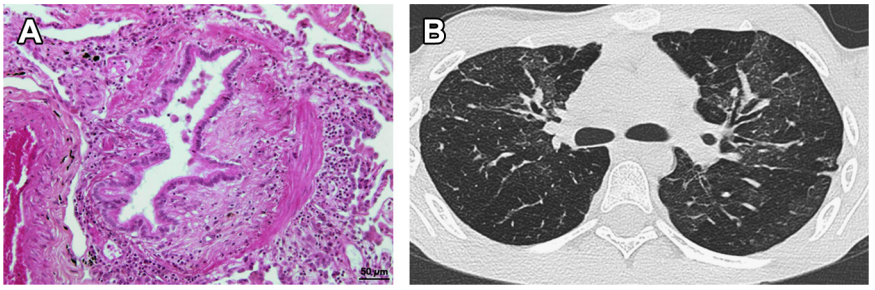

Fig. 1. Histologic features and CT scan pattern of bronchiolitis obliterans. (*A*) The bronchiolar wall is thickened by eccentric fibrosis between the epithelium and the muscle narrowing the bronchiolar lumen (hematoxylin-eosin-safran, original magnification ×200). (*B*) HRCT expiratory images of the lung from a patient with a BOS showing mosaic attenuation. ([*A*] *Courtesy of* Dr Véronique Meignin, Pathology Department, Hospital Saint Louis, Paris, France; and *From* Bergeron A. Late-onset noninfectious pulmonary complications after hematopoietic stem cell transplantation. Clin Chest Med 2017;38(2):249–62.)