Late-Onset Noninfectious Pulmonary Complications After Allogeneic Hematopoietic Stem Cell Transplantation

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KEYWORDS

• Bronchiolitis obliterans • Interstitial lung disease • Lung graft-versus-host disease
• Pulmonary vascular disease • Pleural effusion • Organizing pneumonia
• Thoracic air leak syndrome • Pleuroparenchymal fibroelastosis

KEY POINTS

- Late-onset noninfectious pulmonary complications (LONIPCs) occurring after allogeneic hematopoietic stem cell transplantation may involve all anatomic regions of the lung.
- Most instances of LONIPC are associated with extrathoracic graft-versus-host disease.
- Bronchiolitis obliterans syndrome is the most frequently encountered LONIPC. Early diagnostic strategies are needed for the development of a novel treatment options.
- Interstitial lung diseases are overlooked with regard to LONIPCs and include several histologic entities.

INTRODUCTION

Hematologic malignancies are the main clinical indications for allogeneic hematopoietic stem cell transplantation (HSCT). In previous years, the evolution of this procedure—including the reduction of the intensity of conditioning regimen and the development of new stem cell sources—have allowed a growing number of patients to access this type of treatment. Furthermore, advances in the prevention, diagnosis, and treatment of infectious complications have contributed to the reduced early mortality related to infections occurring after allogeneic HSCT. Although patient survival after allogeneic HSCT has increased, late complications involving several organ systems have emerged.

Late-onset noninfectious pulmonary complications (LONIPCs) occur in up to 20% of allogeneic HSCT recipients[1–3] and can involve all lung anatomic regions: bronchi, parenchyma, vessels, and pleura, leading to various clinical entities. LONIPCs are characterized by highly associated mortalities and morbidities.[2,4–6] Each entity of LONIPC is not specific for allogeneic HSCT and can be either idiopathic or diagnosed in other settings, including connective tissue disorders, lung transplantation, and disease due to environmental toxins or drugs. Regardless of the context,

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knowledge of these pulmonary diseases should help clinicians to better understand and manage postallogeneic HSCT patients who develop LONIPCs.

After HSCT, 2 clinical situations lead to the diagnosis of LONIPC: (1) the development of respiratory symptoms (eg, dyspnea, cough, sputum, and wheezing) or (2) the deterioration of lung function based on sequential posttransplant screening pulmonary function tests (PFT). Of note, many events occurring after HSCT such as infection or generalized fatigue may mask dyspnea. A patient who is deconditioned from the HSCT procedure may complain only when resuming a physical activity long after the onset of lung disease. In any case, thoracic imaging (radiograph and lung computed tomography [CT] scan) will guide the diagnosis. Attention should be paid to the fact that abnormalities of the chest wall (eg, subcutaneous tissue, diaphragm, and spine) that may occur after HSCT may be associated with a defect in lung function in the absence of LONIPCs. If an LONIPC is suspected, respiratory infection should be ruled out before retaining the LONIPC diagnosis. Finally, although lung biopsy is the gold standard for classifying LONIPCs, fewer and fewer patients undergo lung surgery due to the associated complications in allogeneic HSCT recipients and the advances in diagnosing and preventing differential infectious diagnoses.[7–9] Lung biopsy should be discussed on a multidisciplinary case-by-case basis. Thus, most LONIPCs diagnoses rely mainly on PFT and CT scan data. In this article, the author reviews the current knowledge about different LONIPCs.

BRONCHIOLITIS OBLITERANS

Postallogeneic HSCT bronchiolitis obliterans (BO) was first described in the early 1980s.[10] It is now recognized as the most frequent LONIPC and the only one that has been definitively linked to pulmonary chronic graft-versus-host disease (cGVHD).[8,11,12]

Diagnostic Criteria for Bronchiolitis Obliterans Syndrome

A diagnosis of bronchiolitis obliterans (BO) relies on histologic analysis of a surgical lung biopsy showing an obliterative bronchiolitis characterized by thickening of the bronchiolar wall via inflammatory fibrosis; this thickening is located between the epithelium and the smooth muscle, narrowing the airway lumen[13,14] (**Fig. 1**). Given the invasiveness of lung biopsy, the diagnosis of bronchiolitis obliterans syndrome (BOS) based on PFT is now endorsed.[8,12]

Clinical signs of BOS are nonspecific and vary among patients. Cough and dyspnea are the most common symptoms; patients may also experience wheezing or repeated lung infections. Lung auscultation may either be normal or reveal wheezing, subcrepitant, or squeaking sounds suggestive of small airway obstruction. Patients may be asymptomatic during the early stages of the disease. Thus, a diagnosis of BOS relies mainly on post-HSCT PFT demonstrating new onset airflow obstruction.

Before 2005, the definition of BOS was variable from one study to another, which explains the wide disparity of the published data.[15–21] In 2005, the National Institutes of Health (NIH) established standardized criteria for the diagnosis of cGVHD in clinical trials.[11] In these consensus guidelines, a diagnosis of BOS required at least one other distinctive manifestation of chronic GVHD in a separate organ system and a workup to rule out an infection in the respiratory tract. The functional diagnosis criteria for BOS were as follows: ratio of forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <0.7 and FEV1 <75% of the predicted value and residual volume (RV) >120% of the predicted volume.[11] The increased RV reflects the air trapping due to the obstruction of the small airways. Air trapping can also be visualized on a high-resolution lung CT

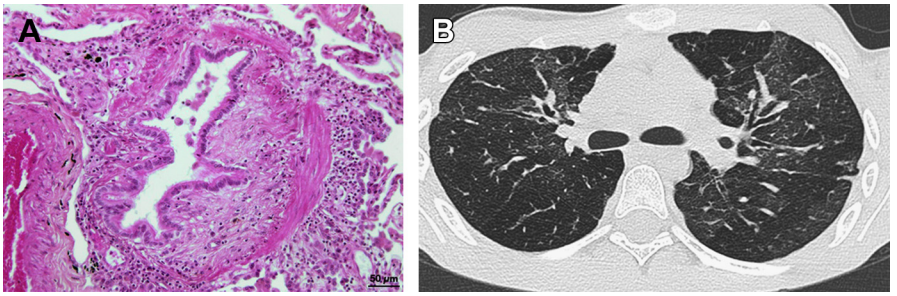

Fig. 1. Histologic features and CT scan of BO. (*A*) The bronchiolar wall is thickened by eccentric fibrosis between the epithelium and the muscle narrowing the bronchiolar lumen (hematoxylin-eosin-saffron, original magnification ×200) (provided by Dr Véronique Meignin). (*B*) High-resolution CT expiratory images of the lung from a patient with a BOS showing mosaic attenuation.