Early Onset Noninfectious Pulmonary Syndromes after Hematopoietic Cell Transplantation

Lisa K. Vande Vusse, MD, MSc[a,b,*], David K. Madtes, MD[a]

KEYWORDS

• Idiopathic pneumonia syndrome • Cryptogenic organizing pneumonia
• Hematopoietic cell transplantation

KEY POINTS

- Idiopathic pneumonia syndrome (IPS) is an uncommon but deadly complication of transplantation with many clinical phenotypes.
- A better understanding of IPS pathobiology and the role of occult infection is needed to develop effective therapies.
- Some drugs given for conditioning or graft-versus-host disease prevention and treatment have known potential pulmonary toxicities.
- Venous thromboembolism and pulmonary hypertension can cause pulmonary symptoms with normal chest imaging after a hematopoietic cell transplant.

INTRODUCTION

More than a million hematopoietic cell transplants (HCTs) have been performed worldwide to treat a spectrum of benign and malignant diseases.[1,2] Survival rates after HCT are increasing over time because of advances in donor and recipient selection, pretransplant conditioning, infection and graft-versus-host disease (GVHD) prevention and treatment, blood transfusion management, and critical care.[3–6] Nonrelapse mortality within 200 days of allogeneic HCT decreased from 30% to 16% comparing years 1993–1997 to 2003–2007, respectively, at one high-volume US transplant center.[4] Despite improved overall survival, noninfectious lung injuries remain an important cause of morbidity and mortality after HCT. A recent "call to arms" urges concerted efforts toward identifying effective preventive and therapeutic strategies.[7]

This article focuses on noninfectious pulmonary complications that manifest within the first few months after HCT. The first section reviews epidemiology, pathogenesis, treatment, and outcomes of the diffuse lung injuries collectively referred to as idiopathic pneumonia syndrome (IPS) and its clinically relevant subtypes, including diffuse alveolar hemorrhage (DAH) and cryptogenic organizing pneumonia. The second section reviews pulmonary toxicities of drugs commonly used for conditioning or GVHD prophylaxis and treatment. The final section summarizes the limited knowledge of less common pulmonary syndromes that occur after HCT, including pulmonary alveolar

Disclosures: The authors have no disclosures to report.
[a] Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Mailstop D5-360, Seattle, WA 98109, USA; [b] Division of Pulmonary and Critical Care Medicine, University of Washington, 1959 NE Pacific Street, Seattle, WA 98195, USA
* Corresponding author. Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Mailstop D5-360, Seattle, WA 98109.
E-mail address: lkvandev@u.washington.edu

Clin Chest Med 38 (2017) 233–248
http://dx.doi.org/10.1016/j.ccm.2016.12.007

proteinosis, venous thromboembolism, and pulmonary hypertension.

IDIOPATHIC PNEUMONIA SYNDROME

Definition

The National Institutes of Health sponsored a workshop in 1991 with the goal of unifying research on lung complications of transplantation.[8] The standard IPS definition proposed by this group required evidence of widespread alveolar injury and absence of active lower respiratory tract infection (LRTI). LRTI could be excluded by either nonresponse to broad-spectrum antibiotics or at least one bronchoscopy with bronchoalveolar lavage (BAL) testing negative for an extensive panel of known pulmonary pathogens. Transbronchial biopsy was recommended when clinically permissible. Many clinical syndromes were included in this IPS definition, including acute respiratory distress syndrome (ARDS), acute interstitial pneumonitis, delayed pulmonary toxicity syndrome, peri-engraftment respiratory distress syndrome, DAH, cryptogenic organizing pneumonia, and bronchiolitis obliterans syndrome. The working group acknowledged the clinical heterogeneity within this definition and recommended multidisciplinary investigation to improve our understanding of IPS pathobiology and motivate novel treatments.

The emergence of new diagnostic technologies and newly recognized pulmonary pathogens resulted in updates to the original IPS definition.[9,10] The most recent published revision requires the exclusion of heart failure, acute kidney injury, and iatrogenic fluid overload as cause for the widespread alveolar injury.[11] The modified definition in **Box 1** incorporates an evolved understanding of pulmonary pathogens[12–16] and an appreciation that inflammatory lung injury and hydrostatic pulmonary edema can coexist.[17]

Box 1
Modified definition of idiopathic pneumonia syndrome

1. Widespread alveolar injury, as evidenced by
   a. Multilobar opacities on chest imaging
   b. Symptoms and signs of pneumonia
   c. Abnormal pulmonary physiology
      i. Increased alveolar to arterial oxygen difference
      ii. New or increased restrictive pulmonary physiology
2. Absence of active LRTI
   a. Negative tests for
      i. *Bacteria*: stains and cultures for bacteria, acid-fast bacilli, *Nocardia*, *Legionella*, *Mycoplasma*
      ii. *Viruses*: culture, DFA, and PCR for respiratory viruses (adenovirus, influenza, parainfluenza, metapneumovirus); shell vial culture (CMV, RSV); DFA for CMV, VZV, HSV; cytopathology for viral inclusions
      iii. *Fungi*: stain and culture; serum and BALF galactomannan ELISA for Aspergillus species; PCR for Zygomycetes and other non-*Aspergillus* invasive molds in some clinical settings
   b. Consider tests for possible pulmonary pathogens: HHV6, rhinovirus, coronavirus
   c. Consider lung biopsy if clinical condition permits and less invasive diagnostics are insufficient
3. No alternate explanatory cause for pulmonary dysfunction, such as heart failure, acute kidney injury, or iatrogenic fluid overload

Abbreviations: BALF, BAL fluid; CMV, cytomegalovirus; DFA, direct fluorescent antibody staining; ELISA, enzyme-linked immunosorbent assay; HHV6, human herpesvirus 6; HSV, herpes simplex virus; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

Adapted with permission of the American Thoracic Society. Copyright (c) 2016 American Thoracic Society. Panoskaltsis-Mortari A, Griese M, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. Am J Respir Crit Care Med 2011;183(9):1263. The Am J Respir Crit Care Med is an official journal of the American Thoracic Society.

Epidemiology

Our knowledge of IPS epidemiology in the contemporary era is limited by the age of the currently available evidence and heterogeneous definitions used (**Table 1**). Two large retrospective cohort studies applied the standard IPS definition and found results similar to earlier studies of noninfectious interstitial pneumonitis and idiopathic interstitial pneumonitis. Incidence of IPS in these populations that included children and adults was 5.7% after autologous HCT[18] and 8% after allogeneic HCT.[18,19] Median time to IPS onset was 21 days, ranging from 7 to 34 days. Risk factors included high-grade GVHD, age, total-body-irradiation (TBI) dose, and transplant indication. Mechanical ventilation was used in 62% to 69% of IPS cases, and mortality rates were approximately 75% in the hospital or within 30 days of discharge. Recent studies added prior HCT and