Diagnostic Evaluation of Pulmonary Abnormalities in Patients with Hematologic Malignancies and Hematopoietic Cell Transplantation

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KEYWORDS

• Pulmonary complications • Lung infiltrates • Hematopoietic cell transplant
• Hematologic malignancy • Diagnosis • Pneumonia • Bronchoscopy

KEY POINTS

- Patients with hematologic malignancies and recipients of hematopoietic cell transplantation are highly susceptible to pulmonary complications.
- Early diagnosis of pulmonary complications is challenging. Delayed diagnosis limits opportunity for targeted treatment, and may contribute to poor outcomes, including mortality.
- An integrated clinicoradiologic approach to diagnosing pulmonary complications provides some insight into their nature, and guides the risk/benefit assessment in pursuing lung sampling.
- Diagnostic bronchoscopy should be considered promptly in these immunocompromised populations, especially in the presence of high-risk features, such as neutropenia and posttransplant status.

INTRODUCTION

Pulmonary complications (PC) of hematologic malignancies (HM) and their treatments, including hematopoietic cell transplantation (HCT), are common causes of morbidity and mortality.[1,2] Despite advances in management,[3] these patients remain highly susceptible to lung injury involving one or more anatomic compartments of the lower respiratory tract (LRT), especially the lung parenchyma. Vulnerability to parenchymal PCs is multifactorial, determined largely by the type, magnitude, and duration of impaired immune defense.[4] This risk is compounded further by treatment-related toxicities, complex comorbidities, and recurrent nosocomial exposures.

Patients at greatest risk for infectious PCs include those with prolonged neutropenia[5] and recipients of HCT.[6] Infectious and noninfectious parenchymal PCs occur in up to 70% of allogeneic HCT patients[1] (25% after autologous HCT[7]), frequently in the acute setting,[8] and represent the most common cause for admission to the intensive care unit.[9] PCs significantly increase mortality, both during treatment (eg, during induction therapy for acute leukemias[10]) and in later periods, after HCT.[1,11] This predisposition requires clinical vigilance in the formulation of a differential diagnosis, in performing prompt diagnostic investigations, and in the initiation of treatment.

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In practice, a specific cause of pulmonary disease is frequently undiagnosed ante mortem in this population.[12–14] An elusive understanding of disease mechanisms, notably inflammatory HCT-related PCs, may contribute to this disparity. However, the lack of a diagnosis also reflects delayed, if not altogether deferred, diagnostic sampling of the LRT in the setting of excessive patient risk and/or provider preference. It has been suggested that diagnostic uncertainty regarding PCs may impact mortality after HCT.[15,16] Difficulty obtaining a timely diagnosis naturally interferes with the clinician's ability to target treatment, leading to prolonged empirical management of many PCs. With the institution of these broad therapies come exposures to unnecessary toxicities, ripe conditions for the emergence of antibiotic resistance, and possibly the acceleration of poor outcomes.

Given the incidence of acute and often fatal PCs in this highly immunocompromised population, a comprehensive approach to the diagnostic evaluation of PCs in HM and HCT patients is essential. The integration of information regarding high-risk host features, abnormal chest imaging patterns, and noninvasive test results informs decisions to pursue lung sampling via minimally invasive techniques, such as fiberoptic bronchoscopy (FOB), or other modalities. The goal of this paper is to provide an overview of the considerations and practices in the diagnostic approach to the adult HM and HCT patient with respiratory signs and symptoms, with a focus on investigating PCs involving the lung parenchyma.

DIAGNOSTIC APPROACH

Context

An initial survey of the clinical landscape is essential to ascertain PC risk and to determine subsequent diagnostic steps. Timing of presentation, host characteristics, immune deficits, treatment-related factors, and past exposures may each impact the risk/benefit equation for LRT sampling in an HM or HCT patient with new pulmonary infiltrates on chest imaging. The identification of high-risk features (eg, prolonged neutropenia or known mold exposure) may also raise suspicion of a specific disease entity (eg, invasive fungal infection), early enough to expedite lung sampling while initiating presumptive therapy.

Immune defects

Understanding the timing of respiratory symptom onset relative to immunosuppressive treatments[17] can help to narrow the differential diagnosis of PCs. Defects in innate, cell-mediated, and humoral immunity, as well as splenic defects, each predispose to infection by specific organisms[18] (**Table 1**).

Table 1
Immune defects and associated pathogens in hematologic malignancies and HCT

Immune Impairment	Potential Causes	Spectrum of Respiratory Infections
Neutrophil number/function	Leukemia Lymphoma Myelodysplastic syndrome Cytoreductive therapies Corticosteroids Hematopoietic stem cell transplant	Gram-negative bacilli Gram-positive cocci Invasive molds (eg, *Aspergillus* spp, *Mucorales, Fusarium, Scedosporium*)
T lymphocytes	Lymphoma Corticosteroids T-cell depletion Drugs Calcineurin inhibitors Mammalian target of rapamycin inhibitors	Intracellular bacteria (eg, *Nocardia, mycobacteria, legionella*) Viruses (eg, respiratory viruses, latent Herpesviridae) Fungi (eg, *Pneumocystis jirovecii, Cryptococcus* spp, *Histoplasma capsulatum, Coccidioides* spp, *Aspergillus* spp, *Micorales, Fusarium, Scedosporium*) Parasites (eg, *Strongyloides* spp, *Toxoplasma* spp)
B lymphocytes and humoral immunity	Leukemia Multiple myeloma Anti–B-cell antibodies Splenectomy Plasmapheresis Drugs	Encapsulated bacterial (eg, *Pneumococcus, H influenza*) *Mycoplasma* spp