The role of the pulmonary function laboratory in the management of hematologic diseases

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BACKGROUND

Pulmonary complications can occur in 40-60% of patients with hematologic disorders. Although acute manifestations such as infection and hemorrhage are a major concern because of their life-threatening nature, chronic respiratory complications often also increase morbidity and mortality in such patients.[1] In this context, pulmonary function tests (PFTs) are vital for evaluating respiratory symptoms and for informing the management and follow-up of patients.

OVERVIEW

A 52-year-old male never-smoker (Case 1) presented with complaints of progressive dyspnea and dry cough 15 months after an allogeneic hematopoietic stem cell transplantation (HSCT) for acute myeloid leukemia. In relation to the preserved pre-HSCT values, FVC and FEV_1, expressed as percentages of the predicted value, had both decreased (to 63% and 49%, respectively). The new onset obstructive ventilatory defect (FEV_1/FVC ratio=0.60) indicated post-HSCT bronchiolitis obliterans. This diagnosis was supported by the presence of air trapping in plethysmography (RV, 147% of predicted) and expiratory HRCT scan. A 24-year-old female never-smoker with sickle cell disease (Case 2) presented with dyspnea (with a modified Medical Research Council scale score of 3) after recurrent episodes of acute chest syndrome (new segmental opacity on chest radiograph accompanied by fever, cough, and phlegm). Spirometry revealed a proportional reduction in FVC (to 69% of predicted) and FEV_1 (to 66% of predicted), together with a reduction in TLC (to 70% of predicted), indicative of a restrictive pattern. A mild reduction (to 70% of predicted) in DL_{CO} corrected for hemoglobin (9.6 mg/dL) and HRCT revealed chronic scarring of the lung parenchyma (pulmonary fibrosis) due to repeated episodes of acute chest syndrome with pulmonary infarction. Notably, echocardiography findings were unremarkable.

With improved management leading to a reduction in infection-related mortality, noninfectious complications are becoming increasingly common after HSCT.[2] Bronchiolitis obliterans syndrome (BOS) is a subtype of a broader category of chronic graft-versus-host disease (GVHD) involving the lungs that usually develops after the first 100 days and typically within the first 2 years after HSCT. Although BOS is characterized by the new onset of an obstructive ventilatory defect usually associated with dyspnea, cough, or wheezing, many patients are asymptomatic early in the disease process. Historically, biopsy-proven bronchiolitis obliterans was considered the only diagnostic pulmonary manifestation of chronic GVHD; that is, without the need for further testing or evidence of other organ involvement.[3] However, because of the risks of invasive lung biopsy, PFT findings can be used as "clinical" diagnostic criteria for BOS in the right clinical context.[4] Therefore, baseline and regular follow-up PFTs are recommended after HSCT (Chart 1). In sickle cell disease, chronic dyspnea is usually multifactorial. Common causes of such dyspnea include anemia, deconditioning, asthma, pulmonary hypertension, venous thromboembolism, and pulmonary fibrosis. Although the benefit of universal screening PFTs and echocardiography in asymptomatic individuals has yet to be determined, they should be performed in individuals with respiratory symptoms and other risk factors.[5]

CLINICAL MESSAGE

Several hematologic diseases and their treatments can chronically affect pulmonary function by causing direct damage to the lung tissue, impairing pulmonary immune responses, or affecting pulmonary vascular function. These are diverse, heterogeneous conditions that frequently course with respiratory symptoms and complications. The use of PFTs can shed light on the underlying mechanisms and guide the management of these conditions.

AUTHOR CONTRIBUTIONS

All of the authors contributed equally to this manuscript.

CONFLICTS OF INTEREST

None declared.

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Chart 1. Hematologic disorders and related treatments that can cause chronic respiratory manifestations, together with general recommendations for pulmonary function testing and the main findings indicative of each respiratory complication.

	General considerations	PFT recommendation	PFT findings
HSCT	• BOS is characterized by new-onset airflow limitation after allogeneic HSCT and is the pulmonary manifestation of chronic GVHD. • GVHD occurs when immune cells transplanted from a nonidentical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction that causes disease in the recipient. • The confirmation of a diagnosis of BOS requires surgical lung biopsy, which is rarely performed in HSCT recipients. As a result, BOS is commonly diagnosed on the basis of the findings on PFT and chest imaging. • The magnitude of dyspnea and reduction in FEV_1 (% pred) are the parameters considered in the organ-specific score to grade the severity of pulmonary involvement in chronic GVHD.	• The current recommended work-up for BOS includes spirometry, and, in the presence of suggestive alterations, supporting features from plethysmography, expiratory CT, or both. • Screening spirometry is recommended pre-HSCT, at day 100 after transplantation, at diagnosis of chronic GVHD, at 1 year after transplantation, and at 6-month intervals for the first 2 years after the initial diagnosis of chronic GVHD. • More frequent PFT monitoring is recommended in patients diagnosed with BOS and in those with a significant decline in lung volumes but not yet meeting the criteria for BOS.	• In the presence of a distinctive* manifestation of GVHD in another organ or organs, a clinical diagnosis of BOS is sufficient to establish the diagnosis of chronic GVHD when all the following criteria are met: 1. FEV_1/FVC ratio < 0.70 or < 5th percentile of pred 2. FEV_1 post bronchodilator < 75% of pred with >10% decline in 2 years 3. Absence of infection in the respiratory tract 4. One of two supporting features**: a. evidence of air trapping on expiratory CT, small airway thickening, or bronchiectasis on HRCT b. evidence of air trapping by RV or RV/TLC ratio > 95th percentile of pred • Restrictive ventilatory defect is not characteristic of BOS but can reflect extra-pulmonary conditions like advanced sclerotic GVHD of the chest wall or intrapulmonary processes not related to GVHD, such as cryptogenic organizing pneumonia or pulmonary fibrosis.
Sickle Cell Disease	• Acute chest syndrome and PH are the most common causes of death. • The probable etiology of PH includes hemolysis, impaired nitric oxide bioavailability, chronic hypoxemia, thromboembolism, and parenchymal/vascular injury due to sequestration of sickle erythrocytes. • Venous thromboembolism and pulmonary arterial thrombosis are also increased secondary to a hypercoagulable state. • Pulmonary fibrosis is occasionally seen after recurrent episodes of acute chest syndrome with pulmonary infarction.	• There is variable practice related to routine PFT recommendation. • Some experts recommend against performing routine screening PFTs for asymptomatic children and adults. • However, diagnostic PFTs should be performed in the presence of any of the following: • respiratory symptoms • impaired exercise capacity • history of syncope or recurrent acute chest syndrome	The most common PFT abnormality is • restrictive ventilatory defect (↓TLC with or without accompanying ↓FEV_1 and ↓FVC with an FEV_1/FVC ratio > 0.70). Mechanisms of restrictive physiology could be ineffective inspiration due to chest wall discomfort, prior rib infarctions or vertebral disease. It could also be caused by pulmonary fibrosis related to more frequent episodes of acute chest syndrome. • Isolated ↓DL_{CO} (corrected for hemoglobin) can be a marker of early ILD or, more commonly, can be associated with PH.

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Chart 1. Hematologic disorders and related treatments that can cause chronic respiratory manifestations, together with general recommendations for pulmonary function testing and the main findings indicative of each respiratory complication. (Continued...)

	General considerations	PFT recommendation	PFT findings
Amyloidosis	Lung involvement is mainly caused by systemic AL amyloidosis due to deposition of protein derived from immunoglobulin light chain fragments. It is a potential complication of any plasma cell dyscrasia that produces monoclonal Ig light chains. • In the systemic form, Ig light chains are produced in the bone marrow and deposited in the lung interstitium, vasculature, lymph nodes, pleura, phrenic nerves, or diaphragm. • In the localized form, precursor amyloidogenic proteins are locally produced and most frequently deposited in lung parenchyma (nodules and cysts) and/or airways	• PFTs are usually performed to assess the presence, type, and severity of respiratory impairment. • PFTs are also often performed prior to lung biopsy to document baseline function.	• PFTs are generally not affected by the presence of limited amyloid nodules or cysts (localized amyloidosis). • Restrictive ventilatory defect (↓TLC) associated with ↓DL_{CO} and exertional desaturation is typical of amyloidosis ILD. • ↓TLC with preserved DL_{CO} (and especially K_{CO}) is indicative of diaphragmatic/phrenic dysfunction. • Patients with mild airway narrowing usually present normal PFT results. However, severe airway wall thickening can induce airflow obstruction and air trapping. Of note, blunted inspiratory and expiratory limbs of the flow volume loop might be the only abnormal spirometric finding.
Histiocytosis	• Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon tobacco-related cystic ILD caused by a disorder of myeloid dendritic cells.	• Same as mentioned above for amyloidosis	• In general, spirometry and plethysmography results are preserved. • Nevertheless, obstructive and restrictive ventilatory defects can be observed in some patients. • DL_{CO} is usually reduced disproportionately in relation to the changes in lung volume.
Leukemias & Lymphomas	• Although classic Hodgkin lymphoma accounts for ≈10% of all lymphomas, more than 75% of treated patients experience long-term survival at risk for pulmonary complications: pulmonary fibrosis, bronchiectasis, chronic pleural effusions, and recurrent pneumonia. Factors that contribute to lung injury include bleomycin use, radiation therapy, and smoking. • Patients with myeloproliferative neoplasms and chronic myeloid leukemia have been shown to develop PH. Potential mechanisms include CTEPH, portal hypertension, extramedullary hematopoiesis, drug toxicity, and occlusion of the pulmonary capillary bed due to aberrant, excessive, or immature cells.	• There is a lack of data on the value of screening with PFTs following treatment for Hodgkin lymphoma. Baseline PFTs should be considered for patients who have undergone chest wall radiation with or without bleomycin treatment. Follow-up PFTs and imaging are recommended for those with chronic or progressive respiratory symptoms (dyspnea, fatigue, wheezing, or cough). • Unexplained respiratory symptoms in patients with myeloproliferative neoplasms require further evaluation, including chest imaging, echocardiography, PFTs, and testing for cardiac biomarkers such as NT-proBNP.	• Restrictive ventilatory defect (↓TLC) with ↓DL_{CO} is indicative of ILD. If DL_{CO} and K_{CO} are within normal limits, an extrapulmonary cause of restriction should be considered. • Isolated ↓DL_{CO} should raise the suspicion of PH. • An obstructive or mixed ventilatory defect is suggestive of bronchiectasis.

HSCT: hematopoietic stem cell transplantation; BOS: bronchiolitis obliterans syndrome; GVHD: graft-versus-host disease; PFT: pulmonary function testing; % pred: % of predicted; PH: pulmonary hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; NT-proBNP: N-terminal pro-brain natriuretic peptide; ILD: interstitial lung disease; and K_{CO}: carbon monoxide transfer coefficient. *Manifestations that are not ordinarily found in acute GVHD but are not considered sufficient to establish an unequivocal diagnosis of chronic GVHD without further testing or evidence of additional organ involvement. **If a patient already has "definite" diagnostic signs and/or symptoms of chronic GVHD by organ involvement elsewhere, then these supporting features are unnecessary. If BOS is the only clinical manifestation in a patient without a prior diagnosis of chronic GVHD, a lung biopsy is required to establish the diagnosis of chronic GVHD.

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