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Airway dilation in bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation

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Computed tomography;
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Summary
Rationale: Bronchiolitis obliterans syndrome (BOS) is a late, non-infectious pulmonary complication following hematopoietic stem cell transplantation (HSCT). There is minimal data published on quantitative radiologic characterization of airway remodeling in these subjects.
Objectives: To examine quantitative measurements of airway morphology and their correlation with lung function in a cohort of patients who underwent HSCT and developed BOS.
Methods: All adult patients who underwent allogeneic HSCT at the Dana-Farber Cancer Institute/Brigham and Women's Hospital ($n = 1854$) between January 1st 2000 and June 30th 2010 were screened for the development of BOS. Clinically acquired high resolution CT (HRCT) scans of the chest were collected. For each subjects discrete measures of airway wall area were performed and the square root of wall area of a 10-mm luminal perimeter (Pi10) was calculated.
Measurements and main results: We identified 88 cases of BOS, and 37 of these patients had available HRCT. On CT scans obtained after BOS diagnosis, the Pi10 decreased (consistent with airway dilation) as compared with pre-BOS values ($p < 0.001$). After HSCT the Pi10 correlated

Abbreviations: BOS, bronchiolitis obliterans syndrome; HSCT, hematopoietic stem cell transplantation; HRCT, high resolution computed tomographic; FEV_1, forced expiratory volume in 1 s; DL_{CO}, carbon monoxide diffusion capacity; FEV_1/FVC, ratio of forced expiratory volume in one second to forced vital capacity; RV, residual lung volume; COPD, chronic obstructive pulmonary disease; PFTs, pulmonary function tests; FEF_{25-75}, forced expiratory flow between 25 and 75%; VC, vital capacity; IC, inspiratory capacity; ERV, end residual volume; TLC, total lung capacity; RV/TLC, ratios of residual lung volume to total lung capacity; SRWA Pi10 mm, square root of wall area of a 10-mm luminal perimeter; PI, internal lumen perimeter; WA%, wall area percent.

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with FEV_1% predicted ($r = 0.636$, $p < 0.0001$), and RV/TLC% predicted ($r = -0.736$, $p < 0.0001$), even after adjusting for age, sex and total lung capacity ($p < 0.0001$ for both).
Conclusions: On HRCT scan BOS is characterized by central airway dilation, the degree of which is correlated to decrements in lung function. This is opposite of what has been previously demonstrated in COPD and asthma that quantitative measure of proximal airway wall thickening directly correlate with pulmonary function. Our data suggests that the pathologic process affecting the central airways is different from the pathology observed in the distal airways. Further work is needed to determine if such change can be used as a sensitive and specific tool for the future diagnosis and staging of BOS.

Introduction

Bronchiolitis obliterans syndrome (BOS) is a form of irreversible airflow obstruction and is a late, non-infectious pulmonary complication following hematopoietic stem cell transplantation (HSCT).[1] Depending on the disease definition, the prevalence of BOS in the allogeneic HSCT population ranges from approximately 2%–26%.[2–7] and it is associated with a significant increase in morbidity and mortality.[3,8]

The clinical presentation of BOS is usually insidious and may include a dry cough, shortness of breath, or dyspnea on exertion, but up to 20% of patients are asymptomatic.[7] In the absence of routine spirometric screening, reports of disease prevalence likely underestimate the true burden of BOS, since symptomatic patients are typically already suffering from moderate to severe airflow obstruction.[7]

Published studies of high-resolution computed tomography (HRCT) in BOS after HSCT have reported subjective evaluations of radiographic findings.[9–13] The largest study ($n = 33$) by Gunn et al.[13] demonstrated that the visually assessed degree of air trapping on expiratory high resolution computed tomographic (HRCT) scan correlated with the forced expiratory volume in 1 s (FEV_1), carbon monoxide diffusion capacity (DL_{CO}), ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC), and residual lung volume (RV). There is an extensive literature available in the CT characterization of airway disease in other obstructive conditions, such as chronic obstructive pulmonary disease (COPD) and asthma. Therefore, we examined the clinically acquired data on almost 2000 patients who underwent allogeneic HSCT at our institution to identify the subset who were diagnosed with BOS. We hypothesized that the measurements of airway dimensions in patients with BOS would correlate with the degree of pulmonary dysfunction.

Methods

Subjects

All patients who underwent an allogeneic HSCT at the Dana-Farber Cancer Institute/Brigham and Women's Hospital ($n = 1854$) between January 1st 2000 and June 30th 2010 were screened for the development of BOS. All pulmonary function tests (PFTs) conducted between January 1st 2000 and June 30th 2010 were reviewed for the presence of expiratory airflow obstruction (FEV_1/FVC ratio ≤ 0.7). Patients identified as having an FEV_1/FVC ratio ≤ 0.7 either before or after HSCT then underwent a detailed chart review and were excluded if they had reversible airflow obstruction or an alternative explanation for their obstructive deficit. From this remaining cohort, BOS was defined as (1) new onset airflow obstruction, FEV_1/FVC ratio ≤ 0.7 and $FEV_1 < 80\%$ predicted; (2) irreversible obstruction defined as no response to bronchodilator per ATS criteria[14]; (3) if airflow obstruction was noted prior to HSCT, a $\geq 15\%$ decline in FEV_1 from baseline; or (4) BO confirmed by pathology irrespective of meeting the spirometric definition of BOS.

Control subjects were identified from the same patient population and were included in the study if they had pre and post transplant pulmonary function testing demonstrating no significant change in pulmonary function per ATS criteria[14] and a pre and post transplant non-contrast HRCT scan available for analysis.

The medical records of all subjects meeting criteria for BOS were examined for both measures of pulmonary function and high resolution CT (HRCT) scans of the chest. All PFTs were performed according to the American Thoracic society guidelines.[14] For correlative studies, CT scans and PFTs were used if they were within 30 days of each other. Lung function data collected included FEV_1, FVC, forced expiratory flow between 25 and 75% (FEF_{25-75}), vital capacity (VC), inspiratory capacity (IC), end residual volume (ERV), total lung capacity (TLC), RV, DL_{CO} and the ratios of RV to TLC (RV/TLC) all expressed as a percentage of predicted values. FEV_1/FVC is expressed as a ratio.[14] Lung volumes were assessed using He dilution or plethysmography.

CT scans

All CT scans were performed for routine clinical care and were included in this investigation if they had sufficient high-resolution images for analysis. Scans were obtained with the patient supine during full inspiration with or without intravenous contrast enhancement. Images were reconstructed using a high spatial frequency algorithm with 1.00–1.5-mm slice thickness at 10–20 mm intervals. Discrete measures of airway wall area were performed in a total of 16 randomly selected airways with 4 in each quadrant; (ie, the right and left upper and lower lobes) using Airway Inspector (www.airwayinspector.org). From these measures, the square root of wall area of a 10-mm luminal perimeter (SRWA Pi10 mm) was calculated.[15,16] The Pi10 is derived by plotting the square root of airway wall area vs. the airway lumen perimeter. From