Respiratory Medicine (2013) 107, 276–283

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Airway dilation in bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation

Lee Gazourian [a,*], Anna Maria F. Coronata [a], Angela J. Rogers [a,b], Gerald L. Weinhouse [a], Robert J. Soiffer [c], Joseph H. Antin [c], Jerome Ritz [c], Vincent T. Ho [c], Rebecca M. Baron [a], George R. Washko [a]

[a] *Department of Medicine, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA 02115, United States*
[b] *Channing Laboratory, Brigham and Women's Hospital, Boston, MA 02115, United States*
[c] *Department of Medical Oncology, Division of Hematologic Malignancies, Dana Farber Cancer Institute, Boston, MA 02115, United States*

Received 22 February 2012; accepted 1 November 2012
Available online 26 November 2012

KEYWORDS
Computed tomography;
Bone marrow transplantation;
Bronchiolitis obliterans syndrome;
Airway disease

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.

* Corresponding author. +1 617 732 5188 (mobile).
E-mail address: lgazourian@partners.org (L. Gazourian).

http://dx.doi.org/10.1016/j.rmed.2012.11.002

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

this plot, one can derive the SRWA of a theoretical airway of standard lumen size (i.e. 10 mm lumen circumference) from a number of different airway sites. This single measure then represents a single quantitative assessment of airway remodeling for each subject Fig. 1.

Patients with a Pre-BOS and Post BOS HRCT which allowed for direct anatomical matching of pre and post airways we measured lung volume, wall thickness, internal lumen perimeter (PI), and wall area percent (WA%) using Airway Inspector (www.airwayinspector.org). WA%: A commonly reported CT based metric of airway morphology reported in both the COPD and asthma literature. It is calculated as 100*wall area/total bronchial area.[16,17] CT based measures of lung volume were calculated as described previously.[18]

The presence of bronchiectasis, mosaic attenuation, ground glass opacities, centrilobular nodules or nodules and bronchial wall thickening was recorded from the clinical reports for all HRCT scans used in our analysis.

For correlative studies both pre and post diagnosis BOS HRCT scans were analyzed if there was a corresponding PFT within 30 days of the HRCT scan. If multiple HRCT scans were available within 30 days of PFTs, the one closest to the date of PFT was utilized. For longitudinal studies, HRCT scans were included if the patient had at least two HRCT scans available. A pre diagnosis HRCT scan was defined as being conducted prior to transplantation or after HSCT but >120 days before the diagnosis of BOS. A post diagnosis HRCT scan was defined as being obtained post diagnosis or within 60 days of diagnosis of BOS, only non-contrast HRCT scans were included in the correlative analysis. Within the cohort of subjects for the longitudinal analysis contrast enhanced scans were included in the analysis only if both the baseline and follow up scan were acquired in this fashion.

This study was approved by the Institutional Review Board at Dana Farber Cancer Institute/Harvard Cancer Center, Boston, MA.

Statistical analysis

Data are presented as medians. Univariate analysis was performed to investigate the relationship between CT measures of airway remodeling and both spirometry and more detailed measures of lung function. Results are presented as Spearman correlation coefficients. Additional multivariate regression analysis was performed to further investigate the association between CT assessed airway morphology and lung function. These models were adjusted for age, sex, and lung volume (obtained from either plethysmography or helium dilution). Measures of pulmonary function were expressed as a percent of predicted for correlative investigation. Paired *t* tests were used for within group comparisons to examine the change in airway morphology from baseline to time of diagnosis. Wilcoxon sign rank test was used to compare direct measurements of individual airways in a subset of 5 patients. *p* values less than 0.05 were considered statistically significant. Analyses were performed with SAS v. 9.1. (Carey, NC).

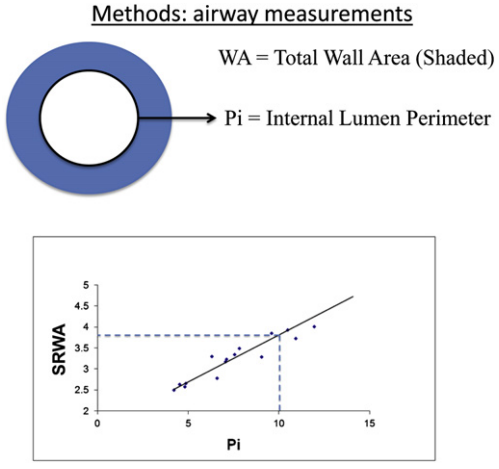

Figure 1 Methods for airway measurements.

Results

Eighty-eight of the 1854 subjects (4.7%) met our criteria for BOS, 37 of which had one or more HRCT scans of sufficient quality for analysis (total of 59 scans) Fig. 2. Of these 37 subjects, 33 had CT scans and PFTs within 30 days of each other, meeting our inclusion criteria for cross sectional analysis. The CT scans from the remaining 4 subjects were excluded from correlative analysis with lung function but were included in subsequent longitudinal radiologic examination. Of the 37 subjects, 17 had a pre and post diagnosis HRCT scan available for pooled airway analysis using the calculated SRWA Pi10 mm. Of the 37 subjects, 5 had a pre and post diagnosis HRCT available for direct matched airway analysis. We identified 6 patients who meet our criteria for controls the median interval between the pre-transplant and post transplant HRCT scan was 323 days (range: 15—1826).

Baseline characteristics of the 37 subjects with HRCT scans are reviewed in Table 1. The median age of the 37 subjects was 48 years (range: 20—67) at the time of HSCT. The median interval between HSCT and diagnosis of BOS was 517 days (range: 48—1582).

All subjects received either a myeloablative ($n = 21$) or reduced intensity conditioning ($n = 16$) allogeneic HSCT

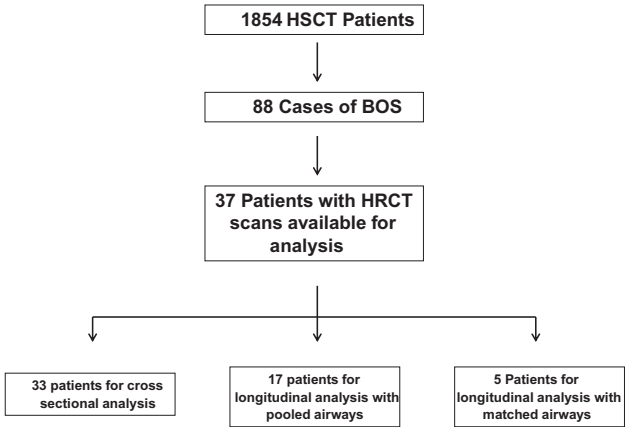

Figure 2 Flow chart detailing patient inclusion criteria for analysis.

Table 1 Baseline characteristics of 37 patients with HRCT scans.

Age in years	48 (range: 20–67)
Days from HSCT to diagnosis of BOS	517 (range: 48–1582)
Gender (female)	19 (51.4)
Race (Caucasian)	31 (83.8)
History of smoking	18 (48.6)
BOS confirmed by pathology[a]	7 (18.9)
Chronic GVHD	36 (97.3)
History of asthma	7 (18.9)
History of COPD	1 (2.7)
Conditioning regimen for HSCT[b]	
Myeloablative conditioning	21 (56.8)
Reduced intensity conditioning	16 (43.2)
Donor source	
Matched unrelated	20 (54.1)
Matched related	9 (24.3)
Mismatched unrelated	8 (21.6)
Disease transplanted	
AML	17 (45.9)
NHL	7 (18.9)
MDS	5 (13.5)
CML	4 (10.8)
ALL	2 (5.4)
HD	1 (2.7)
AA	1 (2.7)
Reason for post BOS diagnosis scans	35 (92.1)
Clinical follow up	11 (31.4)
Cough/SOB/fever/hypoxemia	19 (54.3)
Abnormal prior imaging	1 (2.9)

[a] Of the 7 patients with BOS confirmed on pathology 2/7 did not meet FEV_1/FVC criteria for inclusion but all 7 subjects met FEV_1 inclusion criteria.
[b] Myeloablative conditioning regimens: cytoxan + total body irradiation 1400cGY; high dose Busulfan + cyclophosphamide. Reduced intensity conditioning regimen: fludarabine + low dose busulfan.

from matched unrelated donors ($n = 20$) or matched related donors ($n = 9$), or mismatched unrelated donors ($n = 8$). Transplantation was performed for acute myelogenous leukemia ($n = 17$), non-Hodgkin lymphoma ($n = 7$), myelodysplastic syndrome ($n = 5$), chronic myeloid leukemia ($n = 4$), acute lymphoblastic leukemia ($n = 2$), Hodgkin lymphoma ($n = 1$) and Aplastic anemia ($n = 1$). A history of any smoking prior to transplantation was reported by 48.6% of subjects and 21.6% carried a pre HSCT diagnosis of either COPD ($n = 1$) or asthma ($n = 7$). All subjects with a pre HSCT history of COPD or asthma had non-reversible obstructive deficits on bronchodilator challenge.

Baseline and follow up measures of pulmonary function are presented in Table 2. As expected, after the diagnosis of BOS there was a statistically significant decline in the FEV_1, FVC, FEV_1/FVC ratio, DLco and a significant decrease in TLC compared with similar values obtained prior to HSCT (all $p < 0.01$).

Of the 37 subjects in our study, 35 subjects had HRCT scans conducted after meeting inclusion criteria for BOS.

Table 2 Changes in pulmonary function after hematopoietic stem cell transplantation in our cohort of 37 subjects. Data is expressed as the average percent predicted (PP) and the standard deviations are in parenthesis. The pre HSCT PFT's were conducted prior to the patients HSCT, the post BOS PFT's are the first set of pulmonary function tests that meet our diagnostic criteria for BOS.

	Pre HSCT	Post BOS	Δ (Pre-Post)
FVC PP	93.7 (17.0)	68.8 (16.9)	24.9%
FEV_1 PP	92.8 (15.9)	55.9 (16.0)	36.9%
FEV_1/FVC	77.3 (9.6)	61.8 (10.0)	15.5%
TLC PP	95.9 (19.9)	80.4 (15.7)	15.5%
DL_{CO} PP	84.4 (22.0)	63.7 (19.9)	20.7%

We reviewed the clinical reports for these CT scans for abnormal findings. Bronchiectasis was documented in 14 (40%), mosaic attenuation in 5 (14.3%), ground glass opacities in 6 (17.1%), centrilobular nodules or nodules in 8 (22.9%), bronchial wall thickening in 2 (5.7%) and 26 (74.3%) had at least one abnormal finding reported.

For the correlative studies, all HRCT scans with pulmonary function testing available ±30 days the SRWA Pi10 mm was calculated. Table 3 depicts the relationship between the SRWA Pi10 mm and multiple lung function parameters. Fig. 3A and B depict the direct relationship between the SRWA Pi10 mm and FEV_1% predicted ($n = 33$, $r = 0.636$, $p < 0.0001$) and the inverse relationship for RV/TLC% predicted ($n = 28$, $r = -0.736$, $p < 0.0001$) respectively, as these two values were most significantly correlated with SRWA Pi10 mm. In subsequent models adjusted for age, sex and total lung capacity the SRWA Pi10 mm remained a significant predictor of FEV_1% predicted ($p < 0.0001$) and RV/TLC% predicted ($p < 0.0001$).

Of the 37 subjects with HRCT scans available we identified 5 with HRCT images which allowed direct comparison of anatomically matched individual airways at both time points. In these selected airways, there was a trend for an increase in the lung volume, internal lumen perimeter (PI), and a decrease in wall area percent (WA%) ($p = 0.06$, Fig. 4B).

Table 3 Correlation coefficients (r Values) of the univariate regression analysis for square root of wall area at Pi10 with pulmonary function tests, HRCT scan and PFT's were conducted ± 30 days of each other. $n = 25$–33.

PFT	r value	p value
FVC PP	0.546	0.001
FEV_1 PP	0.636	<0.0001
FEV_1/FVC%	0.343	NS
FEF_{25-75}%	0.578	0.0004
VC PP	0.595	0.002
IC PP	0.602	0.002
ERV PP	−0.353	NS
TLC PP	0.219	NS
RV PP	−0.561	0.002
RV/TLC PP	−0.736	<0.0001
DL_{CO} PP	−0.175	NS

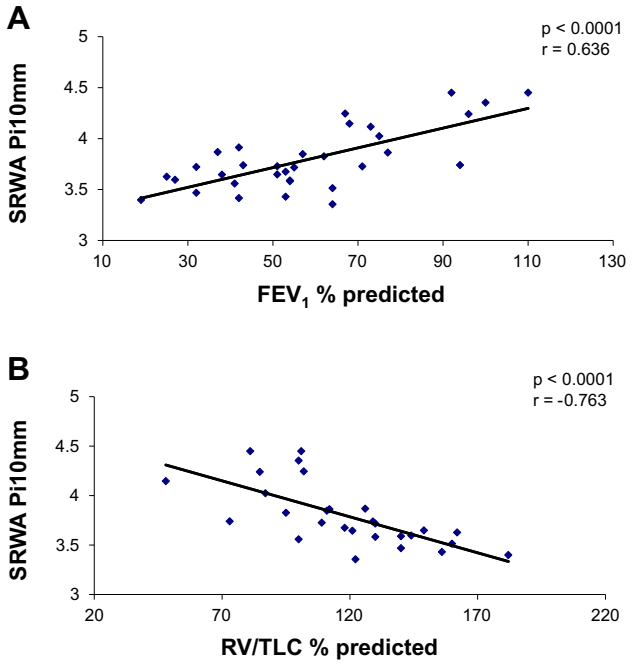

Figure 3 A and B. Graphs of the relationship between square root of wall area at Pi10 mm and each of the pulmonary function parameters. Pulmonary function parameters are expressed as a percentage of the predicted normal value. Each graph is shown with a fitted regression line. The correlations (r) and p values (p) were (A) FEV_1 $n = 33$ ($r = 0.636$, $p < 0.0001$) and (B) RV/TLC $n = 28$ ($r = -0.736$, $p < 0.0001$).

Within our cohort of 37 subjects with HRCT scans 17 subjects meeting our criteria for longitudinal analysis were identified. For longitudinal studies HRCT scans were included if the patient had at least two HRCT scans available; a pre diagnosis HRCT scan defined as being conducted prior to transplantation or after HSCT but >120 days from the diagnosis of BOS and an HRCT scan post diagnosis or within 60 days of diagnosis of BOS. The SRWA Pi10 mm significantly decreased from the pre-diagnosis HRCT scan compared to the post diagnosis HRCT scan ($p < 0.001$). There was no significant change in 6 control subjects who had a pre transplant and post transplant HRCT scan available for analysis Fig. 5A.

Of the 17 subjects with HRCT scans conducted before and after meeting inclusion criteria for BOS. We reviewed the clinical reports for these CT scans for abnormal findings. Bronchiectasis was documented in 6 of the 17 post diagnosis CT scans (35%) while all 17 subjects had a decline in the SRWA Pi10 mm from the pre to post BOS HRCT scan (100%).

We identified 8 subjects who had an HRCT scan >100 days after HSCT, but before the diagnosis of BOS. This analysis allowed us to determine of the change in SRWA Pi10 mm is independent of pre-transplant conditioning regimen. As shown in Fig. 5B, the SRWA Pi10 mm was less in the HRCT after the diagnosis of BOS as compared with the HRCT that preceded the diagnosis of BOS ($p < 0.001$).

Based upon prior investigations of subjects with COPD, we expected the Pi10 to be inversely related to a subject's degree of expiratory airflow obstruction (FEV_1% predicted). For example, in smokers, those with greater degrees of expiratory airflow obstruction tended to have increased SRWA suggestive of airway wall thickening.[16] In fact, the directions of our correlations were opposite to this suggesting that similar to what we observed in the 5 subject in whom we could measure anatomically matched airways, airways were dilating or that their walls were thinning proportionally to the severity of BOS.

Discussion

To our knowledge, this is the first study to use direct quantitative measurement of the airway diameter before and after the diagnosis of BOS. In our investigation of clinically acquired HRCT scans, we found that airway remodeling in BOS is characterized by central airway dilation. The degree of this dilation, as assessed by the SRWA Pi10 mm, was significantly associated with impairments in lung function.

Previous investigation has demonstrated that airway caliber is directly related to lung volume; specifically the airways dilate with increasing lung volume.[19] Our subset of 5 subjects anatomically with matched individual airways also demonstrated a trend for an increase in lung volume, increased PI and a decrease in WA%. However, our model adjusted for age, sex and total lung capacity the SRWA Pi10 mm remained a significant predictor of FEV_1% and RV/TLC%. This data suggests that airway dilation is *not* solely explained by a change in lung volume. In addition, in patients who develop BOS, our longitudinal data suggest that the central airway morphology observed at the time of the clinical diagnosis of BOS was due to airway dilation as evidenced by the decline SRWA Pi10 mm from baseline measures.

To date the quantitative assessment of HRCT in BOS associated with HSCT is limited. There is a more extensive literature in the lung transplant population, but like the HSCT population the vast majority of these studies are also subjective rather than quantitative evaluations of HRCT findings in BOS. The subjective studies in the BOS lung transplantation population have provided mixed results with regards to predictive ability of visual assessments of air trapping and bronchial dilation in the diagnosis of BOS.[20–27] However, there are two studies assessing the quantitative analysis of mean lung attenuation in patients with BOS secondary to lung transplantation. Knollmann et al. demonstrated that those with greater amounts of gas trapping on expiratory CT were more likely to progress to clinically overt BOS.[28,29]

Commonly reported HRCT findings in BOS after HSCT include bronchiectasis, bronchial wall thickening, mosaic attenuation and centri-lobular nodules.[9–13] Of the 35 HRCT scans conducted after the diagnosis of BOS bronchiectasis was reported in 14 (40%), centri-lobular nodules/nodules in 8 (22.9%), mosaic attenuation in 5 (14.3%), bronchial wall thickening in 2 (5.7%). Previous small studies of the HRCT findings in BOS have reported the prevalence of bronchiectasis to be between 11% and 71% of patients with BOS; the criteria used to define bronchiectasis were the lumen diameter being greater than that of the adjacent pulmonary artery.[10–13] The largest study by Gunn et al. documented bronchiectasis to be present in 42% of their cohort, and we found 40% of our cohort to have clinically identified

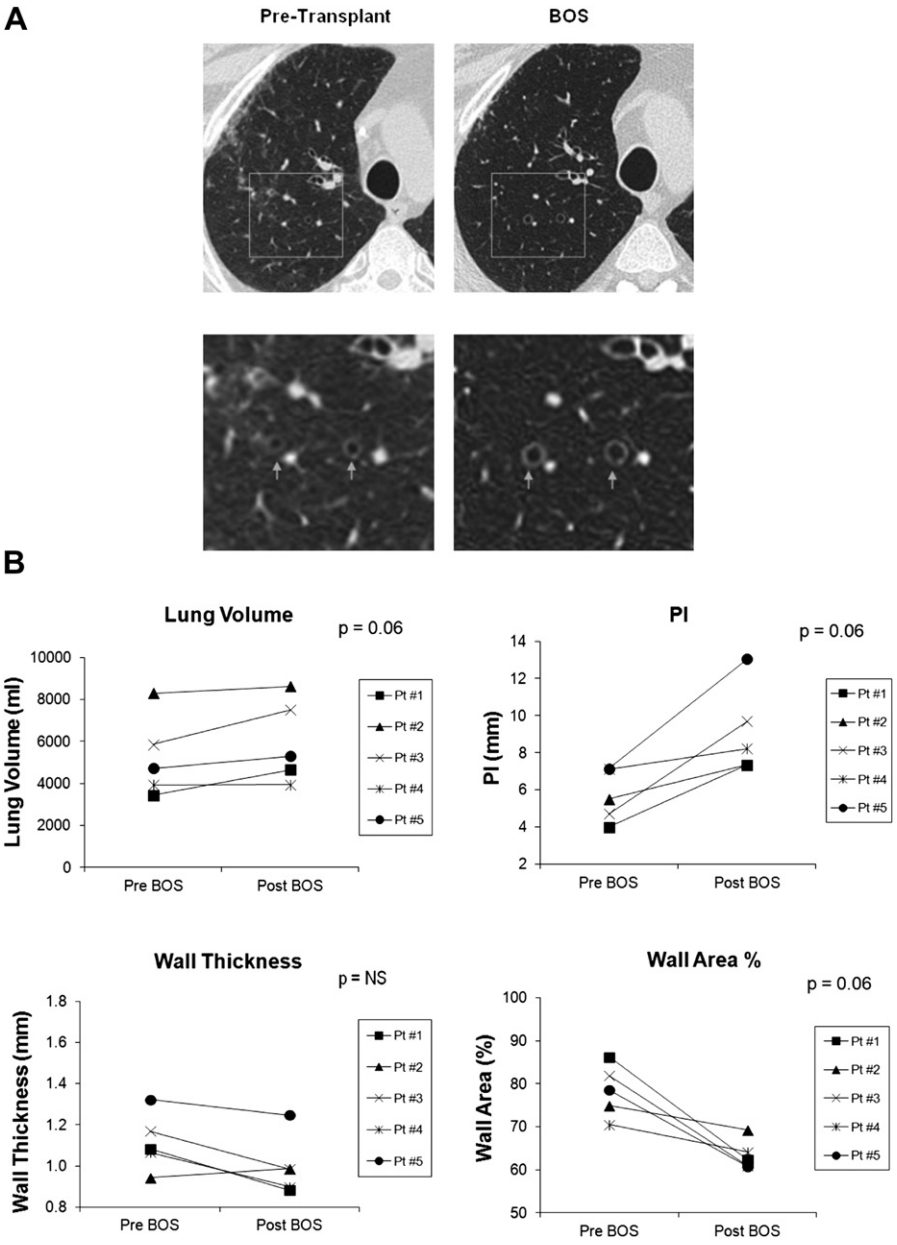

Figure 4 A. Representative images from HRCT scans of patient #5 before transplantation and after the diagnosis of BOS. Arrows demonstrate airway dilation. B. Change in lung volume, internal lumen perimeter (PI), wall thickness and wall area % (WA%) from before and after the diagnosis of BOS in 5 patients with anatomically matched airways on HRCT scans.

bronchiectasis. These data suggest that our cohort is representative of prior BOS cohorts. In addition, we were able to document a decline in the SRWA Pi10 mm in all 17 subjects meeting our criteria for longitudinal analysis. While the clinical reports only identified bronchiectasis in 6 of the 17 subjects (35%). These data suggest that either bronchiectasis is underreported or that quantitative airway measurements may be more sensitive in detecting airway dilation.

Studies in COPD and asthma have demonstrated that quantitative measure of proximal airway wall thickening correlate with pulmonary function.[17,30,31] However, our results are the opposite of those found in patients with COPD where a decrease in FEV_1 is associated with an increase of the airway wall area.[31] Our analysis suggests that the change in lumen diameter associated with the development of BOS is not solely explained by the increase in lung volume in our cohort of subjects with BOS. These findings support the hypothesis that airway remodeling, resulting in bronchial dilation, is occurring in patients with BOS.

One possible explanation for the difference between the findings in COPD and asthma can be explained by the pathologic findings in BO described by Yousem. Yousem[32] reviewed the largest series of 17 patients with graft versus host disease of the lung. He suggested that there is a spectrum and progression of airways pathology from lymphocytic bronchitis/bronchiolitis affecting both large and small airways to the lymphocytic bronchitis/

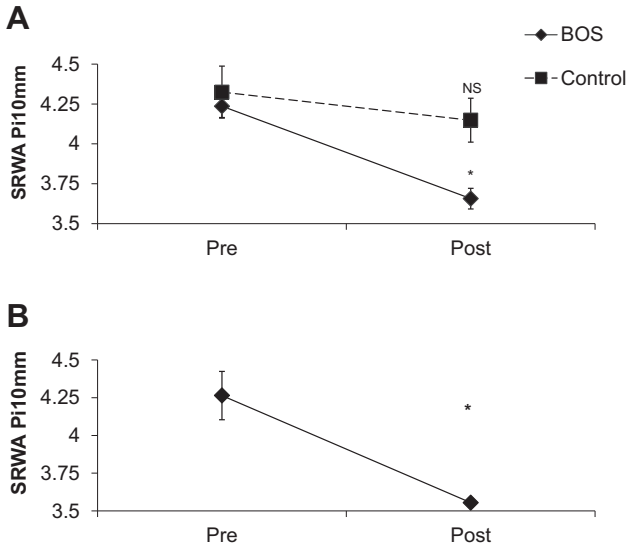

Figure 5 A. Seventeen patients with HRCT scans obtained both before and after the diagnosis of BOS ($p < 0.001$) and 6 control patients who did not develop airflow obstruction with HRCT scans obtained both before and after transplant (p = NS). B. Eight patients with HRCT scans obtained more than 100 days after HSCT as well as an HRCT after the diagnosis of BOS ($p < 0.003$).

bronchiolitis with intraluminal granulation tissue and cicatricial bronchiolitis obliterans found in the distal airways. He hypothesized that the bronchiolitis obliterans represented the late and potentially irreversible stage of the disease; subsequent case series and reports have confirmed Yousem's findings.[33,34] The early lymphocytic bronchitis/bronchiolitis found in patients with cGVHD of the lung may result in airway remodeling and dilation and that the greater the degree of proximal airway dilation is simply an indicator of more peripheral airway disease and obliteration. This is further supported by the findings of Glanville et al.[35] who demonstrated that lymphocytic bronchiolitis is associated with an increased risk of BOS after lung transplantation and by Sugino et al.[36] who demonstrated, using histopathological bronchial reconstruction, proximal airway dilation in a case series of patients with bronchiolitis obliterans.

One of the major limitations of our study is that we performed a secondary analysis of clinically acquired data. With regard to the CT imaging, the lack of volumetric reconstructions did not allow us to compare anatomically matched airways over time in our cohort. We were limited to 5 subjects who had HRCT scans that had anatomically matched airways. We feel that the trend toward significance in this small cohort is impressive, and the modest p value of 0.06 very likely results from low power. We hope to replicate these findings is a larger prospective cohort soon. Although this is a limitation of our current study, it also represents the significant potential of quantitative airway analysis and the diagnosis of BOS.

Our results and the work of Knollmann et al. suggest that quantitative HRCT scans may provide a new and promising modality for the prospective identification of BOS prior to symptoms and the development of a significant decline in pulmonary function. Further work is needed to determine the etiology of these radiologic changes in the central airways and if these observed changes can be used to predict the development of BOS.

Acknowledgments

The authors would like to thank Diana C. Pierce-Tremblay, Walter D Little, Britt Selland, Qiheng Yang and Dr. Jyothi Priya Jagannathan for their contributions to this study.

Funding

This work was supported by the following National Institutes of Health grants; Dr. Gazourian 5T32HL007118-35, 5T32HL007680-20, Dr. Washko, K23HL089353-04. The DFCI BMT data repository is supported, in part, by the Ted and Eileen Pasquarello Research Fund; NIH grants; CA142106, and PO1HL070149-02; and the Jock and Bunny Adams Education and Research Fund. Dr. Rogers and Dr. Washko were also supported by an award from the Parker B. Francis Foundation.

Conflict of interest

None of the authors have any conflicts of interest to disclose.

References

1. Au BK, Au MA, Chien JW. Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2010.
2. Dudek AZ, Mahaseth H, DeFor TE, Weisdorf DJ. Bronchiolitis obliterans in chronic graft-versus-host disease: analysis of risk factors and treatment outcomes. *Biol Blood Marrow Transplant* 2003;**9**:657–66.
3. Chien JW, Martin PJ, Gooley TA, et al. Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Respir Crit Care Med* 2003;**168**:208–14.
4. Soubani AO, Uberti JP. Bronchiolitis obliterans following haematopoietic stem cell transplantation. *Eur Respir J* 2007;**29**:1007–19.
5. Santo Tomas LH, Loberiza Jr FR, Klein JP, et al. Risk factors for bronchiolitis obliterans in allogeneic hematopoietic stem-cell transplantation for leukemia. *Chest* 2005;**128**:153–61.
6. Clark JG, Schwartz DA, Flournoy N, Sullivan KM, Crawford SW, Thomas ED. Risk factors for airflow obstruction in recipients of bone marrow transplants. *Ann Intern Med* 1987;**107**:648–56.
7. Clark JG, Crawford SW, Madtes DK, Sullivan KM. Obstructive lung disease after allogeneic marrow transplantation. Clinical presentation and course. *Ann Intern Med* 1989;**111**:368–76.
8. Worel N, Biener D, Kalhs P, et al. Long-term outcome and quality of life of patients who are alive and in complete remission more than two years after allogeneic and syngeneic stem cell transplantation. *Bone Marrow Transplant* 2002;**30**:619–26.
9. Padley SP, Adler BD, Hansell DM, Muller NL. Bronchiolitis obliterans: high resolution CT findings and correlation with pulmonary function tests. *Clin Radiol* 1993;**47**:236–40.
10. Sargent MA, Cairns RA, Murdoch MJ, Nadel HR, Wensley D, Schultz KR. Obstructive lung disease in children after

allogeneic bone marrow transplantation: evaluation with high-resolution CT. *AJR Am J Roentgenol* 1995;**164**:693—6.
11. Ooi GC, Peh WC, Ip M. High-resolution computed tomography of bronchiolitis obliterans syndrome after bone marrow transplantation. *Respiration* 1998;**65**:187—91.
12. Jung JI, Jung WS, Hahn ST, Min CK, Kim CC, Park SH. Bronchiolitis obliterans after allogenic bone marrow transplantation: HRCT findings. *Korean J Radiol* 2004;**5**:107—13.
13. Gunn ML, Godwin JD, Kanne JP, Flowers ME, Chien JW. High-resolution CT findings of bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *J Thorac Imaging* 2008;**23**:244—50.
14. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;**26**:948—68.
15. Nakano Y, Wong JC, de Jong PA, et al. The prediction of small airway dimensions using computed tomography. *Am J Respir Crit Care Med* 2005;**171**:142—6.
16. Patel BD, Coxson HO, Pillai SG, et al. Airway wall thickening and emphysema show independent familial aggregation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;**178**:500—5.
17. Niimi A, Matsumoto H, Amitani R, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *Am J Respir Crit Care Med* 2000;**162**:1518—23.
18. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med* 2011;**364**:897—906.
19. Diaz AA, Come CE, Ross JC, et al. Association between airway caliber changes with lung inflation and emphysema assessed by volumetric CT in subjects with COPD. *Chest* 2011.
20. Bankier AA, Van Muylem A, Knoop C, Estenne M, Gevenois PA. Bronchiolitis obliterans syndrome in heart-lung transplant recipients: diagnosis with expiratory CT. *Radiology* 2001;**218**:533—9.
21. Choi YW, Rossi SE, Palmer SM, DeLong D, Erasmus JJ, McAdams HP. Bronchiolitis obliterans syndrome in lung transplant recipients: correlation of computed tomography findings with bronchiolitis obliterans syndrome stage. *J Thorac Imaging* 2003;**18**:72—9.
22. de Jong PA, Dodd JD, Coxson HO, et al. Bronchiolitis obliterans following lung transplantation: early detection using computed tomographic scanning. *Thorax* 2006;**61**:799—804.
23. Konen E, Gutierrez C, Chaparro C, et al. Bronchiolitis obliterans syndrome in lung transplant recipients: can thin-section CT findings predict disease before its clinical appearance? *Radiology* 2004;**231**:467—73.
24. Lee ES, Gotway MB, Reddy GP, Golden JA, Keith FM, Webb WR. Early bronchiolitis obliterans following lung transplantation: accuracy of expiratory thin-section CT for diagnosis. *Radiology* 2000;**216**:472—7.
25. Miller Jr WT, Kotloff RM, Blumenthal NP, Aronchick JM, Gefter WB, Miller WT. Utility of high resolution computed tomography in predicting bronchiolitis obliterans syndrome following lung transplantation: preliminary findings. *J Thorac Imaging* 2001;**16**:76—80.
26. Morrish WF, Herman SJ, Weisbrod GL, Chamberlain DWThe Toronto Lung Transplant Group. Bronchiolitis obliterans after lung transplantation: findings at chest radiography and high-resolution CT. *Radiology* 1991;**179**:487—90.
27. Siegel MJ, Bhalla S, Gutierrez FR, Hildebolt C, Sweet S. Post-lung transplantation bronchiolitis obliterans syndrome: usefulness of expiratory thin-section CT for diagnosis. *Radiology* 2001;**220**:455—62.
28. Knollmann FD, Ewert R, Wundrich T, Hetzer R, Felix R. Bronchiolitis obliterans syndrome in lung transplant recipients: use of spirometrically gated CT. *Radiology* 2002;**225**:655—62.
29. Knollmann FD, Kapell S, Lehmkuhl H, et al. Dynamic high-resolution electron-beam CT scanning for the diagnosis of bronchiolitis obliterans syndrome after lung transplantation. *Chest* 2004;**126**:447—56.
30. Ohara T, Hirai T, Sato S, et al. Longitudinal study of airway dimensions in chronic obstructive pulmonary disease using computed tomography. *Respirology* 2008;**13**:372—8.
31. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000;**162**:1102—8.
32. Yousem SA. The histological spectrum of pulmonary graft-versus-host disease in bone marrow transplant recipients. *Hum Pathol* 1995;**26**:668—75.
33. Yokoi T, Hirabayashi N, Ito M, et alNagoya BMT Group. Broncho-bronchiolitis obliterans as a complication of bone marrow transplantation: a clinicopathological study of eight autopsy cases. *Virchows Arch* 1997;**431**:275—82.
34. Trisolini R, Bandini G, Stanzani M, et al. Morphologic changes leading to bronchiolitis obliterans in a patient with delayed non-infectious lung disease after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001;**28**:1167—70.
35. Glanville AR, Aboyoun CL, Havryk A, Plit M, Rainer S, Malouf MA. Severity of lymphocytic bronchiolitis predicts long-term outcome after lung transplantation. *Am J Respir Crit Care Med* 2008;**177**:1033—40.
36. Sugino K, Hebisawa A, Uekusa T, Hatanaka K, Abe H, Homma S. Histopathological bronchial reconstruction of human bronchiolitis obliterans. *Pathol Int* 2011;**61**:192—201.