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High-Resolution CT Findings of Bronchiolitis Obliterans Syndrome after Hematopoietic Stem Cell Transplantation

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Abstract

PURPOSE—To describe the HRCT findings occurring in bronchiolitis obliterans syndrome following hematopoietic stem cell transplantation and to determine the relationship between pulmonary function tests and air-trapping detected on expiratory CT.

MATERIALS AND METHODS—The HRCT scans of 33 patients who underwent hematopoietic stem cell transplantation and subsequently developed bronchiolitis obliterans syndrome were evaluated by two observers blinded to pulmonary function test results. Scans were ranked for degree of air-trapping and scored for findings of bronchial wall thickening, bronchiectasis, and centrilobular opacities. Air-trapping rank was correlated with the degree of airflow obstruction as determined by pulmonary function tests.

RESULTS—The ranking of air-trapping correlated significantly with FEV1 ($p=0.001$), FEV1/FVC ($p<0.001$), RV ($p<0.001$), DLCO ($p=0.023$), but not FVC ($p=0.14$) or TLC ($p=0.07$). Bronchial wall thickening occurred in 73.0%, predominantly in lower lobes ($p=0.007$), but was mild. Bronchiectasis occurred in 42.4% and centrilobular opacities in 39.4%.

CONCLUSION—In bronchiolitis obliterans syndrome developing after hematopoietic stem cell transplantation, air-trapping is the principal finding on CT, and its severity correlates with pulmonary function tests. Bronchial wall thickening is common, but almost always mild; bronchiectasis and centrilobular opacities occur in less than half of cases and are also mild.

INTRODUCTION

Bronchiolitis obliterans syndrome (BOS), a form of irreversible airflow obstruction (AFO), is the most common long-term, non-infectious pulmonary complication of allogeneic hematopoietic stem cell transplantation (HSCT) (1), also known as hematopoietic cell transplantation (HCT) and bone marrow transplantation (BMT). Although early estimates of the prevalence of AFO ranged from 6–20% of long-term survivors of HSCT and up to 10% among those with chronic graft-versus-host disease (GVHD) (2–10), a more recent 10-year

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ADVANCES IN KNOWLEDGE

1. Air-trapping is the principal HRCT feature in bronchiolitis obliterans syndrome occurring in hematopoietic stem cell recipients. Bronchial wall thickening is mild, and bronchiectasis and centrilobular opacities occur in less than half of cases.

IMPLICATIONS FOR PATIENT CARE

1. In a patient who has had hematopoietic stem cell transplantation and who has graft-versus-host disease, HRCT can detect air-trapping reflecting bronchiolitis obliterans syndrome, even when pulmonary function tests reveal only mild airflow obstruction.

analysis using longitudinal pulmonary function tests (PFTs) found the prevalence of HSCT related AFO to be 26%, and up to 30% of patients with GVHD (1).

Because symptoms of BOS are non-specific (dry cough, shortness of breath, and dyspnea on exertion), early diagnosis of BOS can be difficult (11). Patients are at higher risk for developing BOS if they are older, have poor lung function before transplantation, or develop more severe GVHD (1). The degree of AFO and its rate of development can vary, potentially making it difficult to recognize (1,12). Once symptoms and abnormalities on PFTs have developed, BOS is often severe, with resultant dyspnea, decreased quality of life (13), and increased mortality (1).

Although a few papers have reported some HRCT findings of BOS in HSCT recipients (14–16), the series have been small, and the relationships between HRCT findings and the degree of physiologic impairment by PFTs have not been assessed. To demonstrate these relationships and to provide a more complete assessment of HRCT findings than has been possible with small numbers of patients, we analyzed the HRCT scans and compared them with the PFTs in 33 adult patients who developed BOS following HSCT, the largest series reported thus far for this condition.

MATERIALS AND METHODS

This study was approved by the institutional review board and was conducted through a clinic that specializes in HSCT-related pulmonary complications. Patients were identified between September 15, 1990, and March 4, 2005, and clinical data were prospectively collected. Patients were included who experienced irreversible new-onset airflow obstruction and met criteria based on PFTs, consisting of an annualized rate of FEV₁ decline exceeding 5% per year with the lowest documented post-transplant FEV₁/FVC ratio less than 0.8 (1). This latter criterion differs slightly from the criteria recently published by National Institutes of Health (FEV₁/FVC < 0.7 and FEV₁ < 75% predicted) (17), but was the institutional standard used at the time the current study was initiated. Consistent with the National Institutes of Health criteria, all patients also had active chronic GVHD at a site other than the lung at the time HRCT was performed, with the diagnosis of GVHD based on published criteria for clinical, histological, and laboratory findings (18–20). Patients who may have had other causes for AFO, such as asthma, tobacco-related chronic obstructive pulmonary disease, or active respiratory tract infection (sinusitis, bronchitis, or pneumonia) were not included.

Pulmonary function tests

The PFTs used in our analysis included the set performed at baseline before transplantation and the set performed at the time the patient presented to the clinic for evaluation of respiratory symptoms. One patient did not have baseline PFTs available for analysis because her transplant was performed at another institution. All PFTs were performed according to the American Thoracic Society Guidelines, using a Sensormedics V-Max 22 (Sensormedics Co, Yorba Linda, CA). Lung volumes were measured by body plethysmography (21). All measured values for one-second forced expiratory volume (FEV₁), forced vital capacity (FVC), total lung capacity (TLC), and residual volume (RV) were expressed as percentages of predicted values using standard published equations (22). The carbon monoxide diffusion capacity (DL_{CO}) measurements were corrected for hemoglobin and expressed as percentages of predicted values calculated using a standard published equation (23,24).

High-resolution CT

HRCT scans were performed at the time the post-transplant PFTs were obtained. All but two of the HRCT scans were obtained on a GE LXi four-slice scanner (GE Medical Systems,

Milwaukee) at 140 kVp and 220 mAs. Two patients had three scans performed on a GE single-slice scanner (GE Cti). Scans were obtained with the patient supine during full inspiration with 1.25-mm (1.25-mm LXi, 1-mm Cti) collimation at 10-mm intervals, at end-expiration using 1.25-mm collimation at 20-mm intervals, and with the patient prone with 1.25-mm collimation at 10-mm intervals. Inspiratory and prone scans were reviewed on a GE Centricity 2.0 PACS Workstation with lung window settings of 1200HU window width and -700HU level for inspiratory scans, and 900-HU width and -700HU level for expiratory scans. The higher contrast of the expiratory window made air-trapping more apparent. Soft tissues were examined using 350-HU width and 50-HU level.

The HRCT scans were reviewed retrospectively by two radiologists who were blinded to the corresponding PFT results. Each scan was initially assessed by M.L.D.G. and J.D.G. for radiographic abnormalities. Separately, the expiratory scans for all patients were printed on film (using window settings of 900-HU width and -700-HU level), hung simultaneously on view boxes, and ranked by consensus for degree of air-trapping by J.P.K. and J.D.G. Air-trapping was identified by persistent lucency of lung parenchyma during expiration in regions of the lung not expected to demonstrate physiologic air trapping (25).

Each lobe in each patient was also graded for bronchial wall thickening, bronchiectasis, and centrilobular opacities. Grading of each lobe used a simple numeric scale with 0 representing the absence of disease, 1 mild disease, 2 moderate disease, and 3 severe disease, as has been used in earlier CT analyses (26). A total score for each patient was calculated for bronchial wall thickening, bronchiectasis, and centrilobular opacities by summing the scores of all the lobes. The highest possible score was thus 15. In addition, each scan was examined for lymphadenopathy, pleural thickening, pleural fluid, presence of ground-glass opacities, and consolidation.

Statistical analysis

All statistical analyses were performed using STATA 8.0 (StataCorp, 2003). Two-tailed p-values <0.05 were considered statistically significant. Correlation between the air-trapping ranking and PFTs was assessed using separate univariate linear regression models for each PFT parameter. One-way analysis of variance was performed to determine if the observed PFT parameter variation among the HRCT categories was greater than the expected variation. Summed scores for the upper and lower lobes for bronchial wall thickening, bronchiectasis, and centrilobular opacities were compared using the Mann-Whitney U-test.

RESULTS

Patient characteristics

The mean age of the 33 patients was 45.6 ± 13.8 years (range 11.8 to 66.8 years) at the time HRCT was obtained. All patients received either a myeloablative (n=28) or nonmyeloablative (n=5) allogeneic stem cell transplant from matched related donors (n=18), matched unrelated donors (n=8), or mismatched unrelated donors (n=7). Transplants were performed for myelodysplastic syndrome (n=8), chronic myeloid leukemia (n=11), acute myelogenous leukemia (n=8), multiple myeloma (n=2), aplastic anemia (n=1), biphenotypic anemia (n=1), agnogenic myeloid metaplasia (n=1), and non-Hodgkin's lymphoma (n=1). Comparison of PFTs obtained at baseline before transplantation and at the time of HRCT demonstrated a considerable decrease in FVC, FEV₁, and FEV₁/FVC ratio, and an increase in RV (Table 1). All but six of the 33 patients also met the new NIH criterion for BOS (FEV₁/FVC < 70%) (17). The remaining six patients had milder obstruction, with FEV₁/FVC < 80%, which was the inclusion criterion in effect when our study began.

The median interval between transplantation and HRCT was 838 days (range: 264 to 4603 days). The mean time between the performance of the PFTs and subsequent HRCT scans was $2.5 \text{ days} \pm 5.8 \text{ days}$.

HRCT findings

Air-trapping—Air-trapping manifested as persistent lucency of regions of lung parenchyma during expiration (Figure 1). Figure 2 depicts the relationship between the air-trapping ranking and PFTs. Correlations between the air-trapping ranking and PFTs were significant for all parameters except FVC and TLC. The strongest correlations were with FEV₁ ($r=-0.52$, $p=0.002$), FEV₁/FVC ratio ($r=-0.57$, $p<0.001$), and RV ($r=0.62$, $p<0.001$). To refine our correlation analysis, we re-analyzed the results for only the 27 patients who meet the current NIH criteria for BOS. This resulted in improvement in the correlation (FEV₁ $r=-0.62$, FEV₁/FVC ratio = -0.65 , RV = 0.66 .)

Bronchial wall thickening, bronchiectasis, and centrilobular opacities—Although bronchial wall thickening (Figures 1, and 3) was observed in 24 (73%) of the patients, it was generally mild, with a median score of 2 (range 0–14). One patient had severe bronchial wall thickening (score 14). Overall, significantly more bronchial wall thickening was observed in the lower lobes ($p=0.007$).

Bronchiectasis and centrilobular opacities were present in 14 (42.4%) and 13 (39.4%) of patients, respectively (Table 2). Both were generally mild, with a median score of 0 (ranges 0–9 and 0–13 respectively.) One patient had a large number of centrilobular opacities (centrilobular opacity score = 13). As in all patients, this patient did not have clinical or microbiologic evidence of infection and there were no other signs of infection on CT. There was also no significant lobar predilection for bronchiectasis or for centrilobular opacities. There were no significant correlations between the scores for bronchiectasis, centrilobular opacities, or bronchial wall thickening and PFTs.

Lymphadenopathy was not found in any of the patients. Subcentimeter mediastinal lymph nodes were present in five patients and were calcified in one patient. In one patient the thymus was diffusely enlarged. No patients had marked pleural thickening. One patient had induration of subcutaneous tissues, attributable to GVHD. There were no findings to suggest cryptogenic organizing pneumonia in any patient.

DISCUSSION

In this study, we provide a comprehensive description of HRCT findings and their relationship to PFTs for HSCT-related BOS. The principal finding in HSCT-related BOS is air-trapping, and the degree of air-trapping, as reflected by HRCT ranking, correlates closely with FEV₁, FEV₁/FVC, and RV on PFTs. Every patient had at least mild air-trapping. Other findings are bronchial wall thickening, bronchiectasis, and centrilobular opacities, but contrary to other smaller series(14,16), these findings and cryptogenic organizing pneumonia(27), were neither common nor severe in our cohort.

BOS is a serious and often fatal complication of HSCT (28–31) that is thought (although has not been proved) to be caused by GVHD, in which the host lung epithelium activates donor T lymphocytes, which target the bronchioles of the recipient (32). Infection may play a secondary role in damaging bronchioles. HSCT recipients are prone to infection because of impaired humoral and cell-mediated immunity (32).

The main pathologic feature associated with HSCT-related BOS is constrictive bronchiolitis, in which peribronchiolar fibrosis narrows the lumens of conducting bronchioles. In the severest

form, circumferential narrowing and cicatrization ultimately obliterate the lumen (33) and cause air-trapping; alveolar ducts and alveoli are generally spared (34). Since transbronchial biopsy is insensitive, and surgical lung biopsy is rarely performed in suspected BOS, the diagnosis is generally based on symptoms and demonstration of fixed AFO on PFTs.

Our findings of BOS in HSCT recipients are similar to those in lung transplant recipients, in whom chronic rejection induces obliterative bronchiolitis in up to 50% of long-term survivors (35). In lung transplants, air-trapping is the HRCT finding that correlates best with the presence of obliterative bronchiolitis (36,37). In some early (26,36,37), but not all later (38,39) lung transplant series, HRCT was considered to be potentially more sensitive and accurate than PFTs in indicating obliterative bronchiolitis because of its high sensitivity to air-trapping (36). Our findings in BOS in HSCT recipients mirror those in lung transplant recipients, with air-trapping as the predominant HRCT manifestation.

Bronchial wall thickening was found in the majority of our patients, most frequently in the lower lobes, but it was generally mild. Bronchiectasis and centrilobular opacities were present in less than half of patients, even when air-trapping was severe. This observation is contrary to that reported by two of the three smaller studies examining HRCT in HSCT recipients (14,16). Bronchiectasis often develops in other diseases that cause air-trapping, such as lung transplantation, cystic fibrosis, ciliary dysmotility, diffuse panbronchiolitis, and infectious bronchiolitis (35,40,41).

The primary goals of this analysis were to determine the HRCT findings in patients with HSCT-related BOS and to determine whether air-trapping detected on HRCT correlates with physiologic measurements of lung function. Although these goals were achieved, our study has limitations. First, the statistical analysis of the air-trapping ranking system assumes that the HRCT findings were normally distributed along the entire spectrum of air-trapping associated with this syndrome, which is unlikely. Indeed, the distributions of FEV₁ and FEV₁/FVC ratio in our population were skewed toward more severe obstruction.

Second, acute pulmonary or sinus infection can cause transient AFO. Although we were careful to exclude all patients who had microbiological evidence of infection at the time of presentation, it is possible that undetected respiratory infections may have caused some of the observed physiologic and radiographic abnormalities. As a further step to eliminate cases of AFO caused by acute infection, we excluded patients whose AFO was reversible over time. However, infection can lead to permanent AFO: constrictive bronchiolitis following viral infection (Swyer-James or McLeod syndrome) can lead to expiratory air-trapping and hyperlucent lung (42). The effects of infection are of particular concern in HSCT recipients because respiratory viral infection within the first 100 days after transplant is associated with an increased risk of AFO at one year (1) particularly for lower respiratory tract infections (43). Thus, we cannot definitively exclude respiratory infection as having some role in BOS in our patients.

Third, ranking air-trapping based on 12 or fewer non-contiguous HRCT slices through the lungs is not quantitative and is necessarily partly subjective. Visual assessment of air-trapping on HRCT is widely used so our technique reflects common practice, and the strong correlation between the ranking and the PFTs suggests that our method was reasonable. Because there was no control group or gold-standard, no attempt was made to assess the sensitivity, specificity, or accuracy of HRCT in the assessment of air-trapping, bronchial wall thickening, bronchiectasis, or profusion of centrilobular opacities. HRCT findings of only mild air-trapping are unlikely to prove specific for BOS, given that modest degrees of physiologic air-trapping can occur in patients without respiratory disease (25,36,44,45),

Finally, the HRCT protocol and method of assessing air-trapping are now out of date. Volumetric multidetector CT (MDCT) has been shown to be superior in the assessment of bronchiectasis (46) and presumably would also be superior in the assessment of air-trapping and bronchial wall thickening; when MDCT can be combined with software that performs volumetric analysis of lung density, precise quantification of air-trapping will become possible and serial studies in patients with BOS may then become useful.

In summary, we have demonstrated that air-trapping is the principal HRCT feature in BOS occurring in HSCT recipients, just as in lung transplant recipients, suggesting that pathogenesis and site of bronchiolar injury may be similar. Bronchial wall thickening, bronchiectasis, and profusion of centrilobular opacities were generally mild in our patients. Since HSCT recipients often present to clinics and hospitals outside of transplant centers, it is important that HRCT findings that may indicate BOS—particularly air-trapping—be recognized.

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Figure 1.

BOS with severe air-trapping (ranked 33/33). Inspiratory (a) and expiratory (b) HRCT scans in a 33-year-old woman 3 years and 11 months following a matched related donor stem cell transplant, with FEV1/FVC = 0.35. Regions of low attenuation (black arrows) are visible in the right middle lobe, right lower lobe and in the periphery of the left lower lobe indicating air-trapping. Regions with increased attenuation represent normal effect of expiration. The scores for bronchial wall thickening were 1, 2, 1, and 2 in the right middle lobe, right lower lobe, left upper lobe, and left lower lobe, respectively, with total score of 7 (including the right upper lobe which is not shown).

Figure 2.

Graphs of the relationships between air-trapping ranking and each of the pulmonary function parameters. FVC= forced vital capacity; FEV₁=one-second forced expiratory volume; TLC=total lung capacity; RV=residual volume; DL_{CO}=carbon monoxide diffusion capacity. Pulmonary function parameters are expressed as a percent of the predicted normal value. Each graph is shown with a fitted regression line and 95% confidence intervals (grey lines). The correlations (r) and p-values (p) were FVC (r=−0.264, p=0.138), FEV₁ (r=−0.52, p=0.002), FEV₁/FVC ratio (r=−0.57, p<0.001), TLC (r= 0.32, p=0.069), RV (r=0.62, p<0.001) and DL_{CO} (r=−0.39, p=0.023).

Figure 3.

BOS with moderate bronchiectasis a 66-year-old man one year following a matched related donor stem cell transplant, with $FEV_1/FVC = 0.47$. HRCT was scored as 9 for bronchiectasis, the highest score in the cohort. Bronchial dilation and bronchial wall thickening are apparent in all the visible lobes, with a bronchial/arterial ratio of > 1.0 . The score was 8 for bronchial wall thickening. The air-trapping rank was 2/33, based on expiratory scan (not shown).

Table 1

Changes in pulmonary function after hematopoietic stem cell transplant

	Mean percent of predicted $\pm$ standard deviation		
	Pretransplant	Post-transplant	Δ (pre-post)
FVC	98.9% $\pm$ 12.8	74.5% $\pm$ 15.0	-23.6% $\pm$ 14.2
FEV₁ *	93.5% $\pm$ 11.1	53.2% $\pm$ 18.3	-39.3% $\pm$ 16.6
FEV₁/FVC *	0.77 $\pm$ 0.06	0.57 $\pm$ 0.15	-0.20 $\pm$ 0.14
TLC	102.5% $\pm$ 11.2	106.3% $\pm$ 11.8	-3.72 $\pm$ 10.4
RV	106% $\pm$ 22.8	168% $\pm$ 41.5	61.1% $\pm$ 39.3
RV/TLC	0.31 $\pm$.08	0.49 $\pm$ 0.09	0.18 $\pm$ 0.09
DL_{CO}	90.5% $\pm$ 15.0	74.9% $\pm$ 14.6	-14.4% $\pm$ 17.3

FVC= forced vital capacity; FEV₁=one-second forced expiratory volume; TLC=total lung capacity; RV=residual volume; DL_{CO}=carbon monoxide diffusion capacity

* FEV₁ and FEV₁/FVC ratios are expressed as ratios of the absolute values

Table 2

HRCT scores (and range) for bronchial wall thickening, bronchiectasis, and centrilobular opacities in patients with HSCT-related BOS

	Bronchial wall thickening	Bronchiectasis	Centrilobular opacities
Patients affected	24 (73%)	14 (42.4%)	13 (39.4%)
Median overall score¹	3 (0–14)	0 (0–9)	0 (0–13)
Median upper lobe score²	1 (0–6)	0 (0–6)	0 (0–6)
Median lower lobe score²	2 (0–6)	0 (0–4)	0 (0–6)
Upper vs lower lobe	p = 0.007	p=0.453	p=0.164

¹ Maximum possible score of 15

² Maximum possible score of 6