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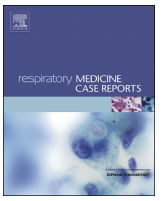

Case Report

Early and rapid development of bronchiolitis obliterans syndrome after allogeneic hematopoietic cell transplantation

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ABSTRACT

Bronchiolitis obliterans (BO) is a form of graft-versus-host disease (GVHD) in the lung and manifests as moderate to severe airflow obstruction after hematopoietic stem cell transplantation (HCT). New-onset airflow obstruction on spirometry is considered diagnostic of bronchiolitis obliterans syndrome (BOS). BOS affects about 5% of all HCT recipients. In general, BO is thought of as a late complication of HCT, usually occurring after day 100 post-transplantation. However, the onset of airflow obstruction can be rapid and is most often irreversible even with treatment. We describe a patient who rapidly developed severe airflow obstruction less than one month after transplantation following the development of upper airway symptoms. Despite aggressive immunosuppression, the patient had no improvement in airflow obstruction. We hypothesize that early screening and treatment may help prevent BOS after HCT.

1. Introduction

Chronic GVHD affects about 50% of patients who undergo HCT [1]. GVHD of the lung most commonly manifests as BOS and affects as many as 5% of all patients after HCT and up to 14% of patients with GVHD [2]. Potential risk factors for the development of BOS include older recipients or donors, unrelated donors, acute and/or chronic extrapulmonary GVHD, and respiratory viral infection within 100 days of HCT [2–7]. BOS is diagnosed when all of the following criteria are met: airflow obstruction by FEV1/FVC <0.7, FEV_1 $<75\%$ predicted with $\geq 10\%$ decline in FEV_1 within two years that does not correct with bronchodilators, absence of respiratory tract infection, and evidence of air trapping either by pulmonary function test (PFT) (residual volume (RV) $>120\%$ of predicted RV or RV/total lung capacity (TLC) above the 90th percentile) or by expiratory computed tomography (CT). If there is evidence of extrapulmonary chronic GVHD, only the first three criteria are required for diagnosis [8].

Although BOS and other manifestations of chronic GVHD typically occur after day 100, early BOS, though rare, may not be identified easily since routine pulmonary function screening starts around day 100. Here, we report a patient undergoing HCT who rapidly developed severe shortness of breath 22 days after HCT due to BOS.

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2. Case presentation

A 39-year-old female presented to our institution for possible HCT to treat an aggressive follicular lymphoma, histologic grade 2. She was referred for evaluation for high-dose chemotherapy with HCT after recurrence within a year despite first line chemotherapy. Because she did not have a suitable related donor, she was listed for a matched unrelated donor (MUD); an autologous HCT was thought to have too high a risk of relapse given her aggressive course. She underwent four additional cycles of salvage chemotherapy with rituximab and bendamustine prior to undergoing HCT.

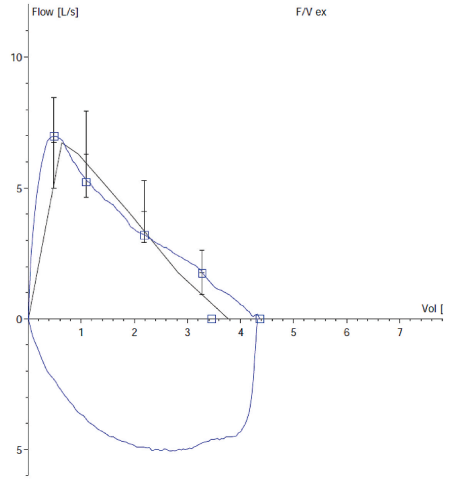
Her pre-transplantation evaluation showed no renal, hepatic, or cardiac abnormalities. A *trans*-thoracic echocardiogram revealed normal wall motion with an ejection fraction of 55–60%. Pulmonary function testing before transplantation (Fig. 1A) revealed excellent lung function with the patient in Lung Function Score Category I, the stratum with the lowest risk for early respiratory failure and mortality.

She subsequently received an unrelated donor peripheral blood progenitor cell transplant after myeloablative conditioning with carmustine, bortezomib, rituximab, etoposide, cytarabine, and melphalan. Her hospital course was unremarkable with the exception of fluid retention requiring intravenous furosemide. Prior to discharge, she developed a fever and was treated with metronidazole, cefepime, and vancomycin, which were discontinued shortly thereafter when her bacterial cultures were negative. Chest radiograph was clear. She was discharged home 16 days post-HCT.

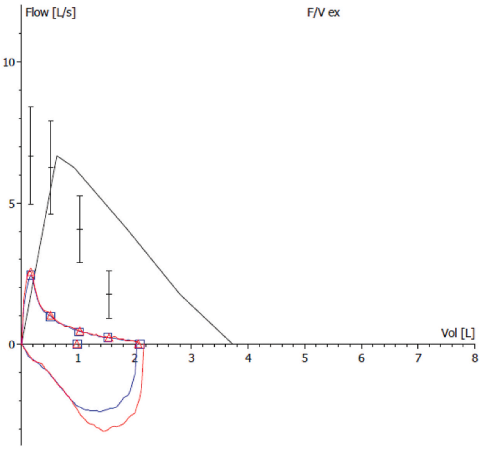
One day after discharge, she noted mild shortness of breath, cough, post-nasal drip, and sinus fullness about 17 days post-HCT. A sinus CT revealed a fluid collection and mild thickening of the left sphenoidal sinus, and she was started on a course of moxifloxacin. Her shortness of breath progressed significantly over the next several days, and she began to develop fatigue with low-grade fevers and tachycardia. A CT of the chest and a viral culture panel revealed no evidence of acute infection, though rhinovirus, coronavirus, and metapneumovirus were not included in this panel. A blood culture obtained at this time grew no bacteria or fungi. Despite her worsening shortness of breath, evaluation of her follicular lymphoma indicated that she had complete metabolic regression by PET/CT. She had no other evidence of GVHD at this time but later developed cutaneous manifestations of chronic GVHD.

She was seen by our pulmonary group 47 days post-HCT for further evaluation of her GVHD. The only additional history the patient gave was a 10-year history of mild intermittent rhinosinusitis. At the time of evaluation, her cough was productive of an opaque

A. Pre-Transplantation



B. Post-Transplantation



Spirometry

		Pred	Pre BD	%Pred
FVC	[L]	3.77	4.36	116
FEV 1	[L]	3.13	3.46	111
FEV 1 / VC MAX	[%]	82.43	79.32	96
FEF 25-75	[L/s]	3.38	3.11	92
PEF	[L/s]	6.72	6.98	104
FIVC	[L]	3.77	4.30	114
FIV1	[L]		4.09	
FIV1 / FVC	[%]		95.17	

Lung Volumes

		Pred	Measured	%Pred
VC	[L]	3.77	4.16	111
TLC	[L]	5.79	6.48	112
RV	[L]	1.96	2.32	119
RV / TLC	[%]	32.03	35.77	112
FRC-PL	[L]	3.29	4.65	141

Spirometry

		Pred	Pre BD	%Pred
FVC	[L]	3.72	2.08	56
FEV 1	[L]	3.10	0.98	32
FEV 1 / VC MAX	[%]	82.61	47.01	57
FEF 25 - 75	[L/s]	3.36	0.41	12
PEF	[L/s]	6.67	2.45	37
FIVC	[L]	3.72	2.03	54
FIV1	[L]		1.81	
FIV1 / FVC	[%]		89.56	

Lung Volumes

		Pred	Measured	%Pred
VC	[L]	3.72	2.30	62
TLC	[L]	5.71	6.63	116
RV	[L]	1.92	4.32	225
RV / TLC	[%]	32.03	65.24	204
FRC-PL	[L]	3.30	4.97	150

Fig. 1. A. Pulmonary function testing before transplantation revealed an FEV1 of 113% predicted, FVC of 116%, total lung capacity (TLC) of 117% predicted, residual volume (RV) of 129% predicted, and diffusing capacity of the lung for carbon monoxide (DLCO) of 107% predicted.
1B. Pulmonary function testing after transplantation revealed severe airflow obstruction and gas trapping with an FEV1 of 32% predicted, FVC of 56% predicted, FEV1/FVC ratio of 47%, TLC of 116% predicted, RV of 225% predicted, and DLCO of 63% predicted. DLCO corrected for alveolar volume was not significantly different from pre-transplant PFTs.

mucus, and she was short of breath while performing activities of daily living, a significant change from her ability to perform vigorous aerobic exercise for 30–45 minutes prior to HCT. Vital signs at this time revealed a resting oxygen saturation of 93%, pulse rate of 108 bpm, and otherwise normal vital signs. Physical exam revealed markedly decreased breath sounds bilaterally with expiratory wheezing but was otherwise unremarkable. Pulmonary function testing after transplantation (Fig. 1B) revealed severe airflow obstruction and gas trapping with an FEV1 of 32% predicted and FEV1/FVC ratio of 47%. She did not have improvement in FEV1 or FVC after the administration of a bronchodilator. Her hemoglobin was 14.5 g/dL, and she had an elevated eosinophil count of 1800/μL. The remainder of her complete blood count was within normal limits. A two-view chest radiograph and contrasted CT scan of the chest revealed no abnormalities. Because of the severity of airflow obstruction measured by pulmonary function testing, an expiratory CT scan to test for mosaic attenuation was not felt to be necessary. An echocardiogram performed shortly thereafter revealed preserved systolic ejection fraction but mild diastolic dysfunction.

3. Discussion

We present a patient with severe airflow obstruction that did not reverse with bronchodilators within 100 days of HCT with a MUD transplant. Although there are a small number of other reports of BOS occurring this early in the course of HCT, the development of BOS this early is not well described [9,10]. Initial microbiologic and imaging surveys were negative, although the viral culture assay may have missed common respiratory pathogens. While she did not have extrapulmonary chronic GVHD at the time of BOS, she shortly thereafter developed cutaneous manifestations of chronic GVHD. While the diagnosis of BOS was not made until 47 days after transplantation, the onset of shortness of breath on day 17 suggests that bronchiolitis obliterans had begun by this time.

BOS is a progressive lung disease that is difficult to diagnose promptly due to the non-specific nature of initial symptoms such as exertional dyspnea and fatigue. Progressive BOS diminishes quality of life [11]. Early diagnosis is likely to be essential to achieve optimal outcomes, though this remains to be proven. Spirometry remains the most important tool to screen for BOS, but screening strategies vary by institution, and the large time intervals between routine screening tests may miss rapidly-developing BOS [12]. A 10% decline in FEV1 or 25% decline in FEF 25–75 on two consecutive pulmonary function tests has high sensitivity to diagnose BOS, but also a low positive predictive value due to the low prevalence of BOS [12]. Quantitative CT imaging with parametric response mapping, a technique that quantifies the degree of air trapping by measuring voxel-level attenuation, may help diagnose BOS in unclear cases, but this has not been studied in early BOS [13–15].

Our group and others have shown that early treatment with inhaled corticosteroids may halt the progression of disease [16–19]. Intensive screening strategies such as routine handheld home spirometry are feasible and reproducible in patients receiving HCT and can facilitate early treatment, presumably at a stage when lymphocytic bronchiolitis is present in the airways but subepithelial fibrosis is not extensive [20–22]. While implementation has been limited to date, and the efficacy of early treatment has not been established, this approach is a rational path forward to diagnose and treat BOS early in its course.

The standard treatment to halt the progression of BOS is systemic immunosuppression and treatment with fluticasone, azithromycin, and montelukast (FAM). In fact, montelukast alone has been reported to cause disease stability or improvement in over 90% of patients with an 87% survival rate at two years [23]. Azithromycin is variably used due to a concern for promotion of hematologic relapse [24]. When initial lines of therapy fail, second-line options include ibrutinib, ruxolitinib, and belomudosil, but head-to-head comparative trials are lacking [25–28]. However, belomudosil may have higher response rates for BOS [28]. Extracorporeal photopheresis (ECP) may halt progression, but treatments require multiple sessions per week, and there may be relapse with cessation of therapy [29–31]. Pulmonary rehabilitation is helpful for symptomatic management of dyspnea with minimal risk [32]. If all other therapies have failed, lung transplantation may be offered but is associated with high risks [33].

4. Conclusion

We treated our patient with inhaled and systemic corticosteroids, ECP, and pulmonary rehabilitation. We tapered her steroids to prednisone 5 mg daily and added azithromycin, montelukast, and tiotropium. She had improvement in exertional dyspnea with pulmonary rehabilitation, but her pulmonary function has remained unchanged for fifteen years. However, she has been able to increase her exertional capacity and engage in moderate exercise.

5. Description of case report

We present a case of bronchiolitis obliterans syndrome very soon after hematopoietic cell transplantation. We highlight the importance of considering bronchiolitis obliterans in the differential diagnosis and to start screening early so we may interrupt the progression of disease. We also clarify the timeline of this disease process, provide screening recommendations, and discuss the treatments available obliterans.

Ethics approval and consent

Appropriate written informed consent was obtained for participation and publication of this case report and accompanying images.

Consent for publication

The patient confirmed understanding that the text and any pictures or videos published in the article will be freely available on the internet and may be seen by the public. The pictures, videos and text may also appear on other websites or in print, may be translated into other languages or used for commercial purposes. The patient was sent a copy of the manuscript.

Availability of data and materials

Not applicable.

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CRediT authorship contribution statement

Jacqueline S. Dickey: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Burton F. Dickey:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Amin M. Alousi:** Writing – review & editing. **Richard E. Champlin:** Writing – review & editing. **Ajay Sheshadri:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of competing interest

No conflict.

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List of abbreviations

BO	bronchiolitis obliterans
GVHD	graft-versus-host disease
HCT	hematopoietic stem cell transplantation
BOS	bronchiolitis obliterans syndrome
MUD	matched unrelated donor
FAM	fluticasone, azithromycin, and montelukast
ECP	Extracorporeal photopheresis

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