

## Progressive Bronchiectasis as a Manifestation of Chronic Graft Versus Host Disease Following Bone Marrow Transplantation

Tej D. Phatak, Pierre D. Maldjian

We describe a case of progressive bronchiectasis resulting in cystic bronchiectasis with regions of mucoid impaction as a manifestation of chronic graft versus host disease as a late complication of allogeneic bone marrow transplantation.

### Introduction

Allogeneic bone marrow transplantation (BMT) is performed as part of treatment for serious hematologic and immunologic diseases. Severe pulmonary disease in the context of chronic graft-versus-host disease (GVHD) is a late complication, occurring at least 100 days after BMT following recovery of function of the immune system [1]. Pulmonary manifestations of chronic GVHD usually involve airflow obstruction secondary to bronchiolitis obliterans, occurring in about 10% of patients following BMT [2]. While prior reports have described mild bronchiectasis in patients with chronic GVHD following BMT [3, 4], we describe a case of severe cystic bronchiectasis with illustration of progression of the disorder.

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Abbreviations: BMT, bone marrow transplantation; BAL, bronchoalveolar lavage; CT, computed tomography; GVHD, graft-versus-host disease; PDGF, platelet-derived growth factor.

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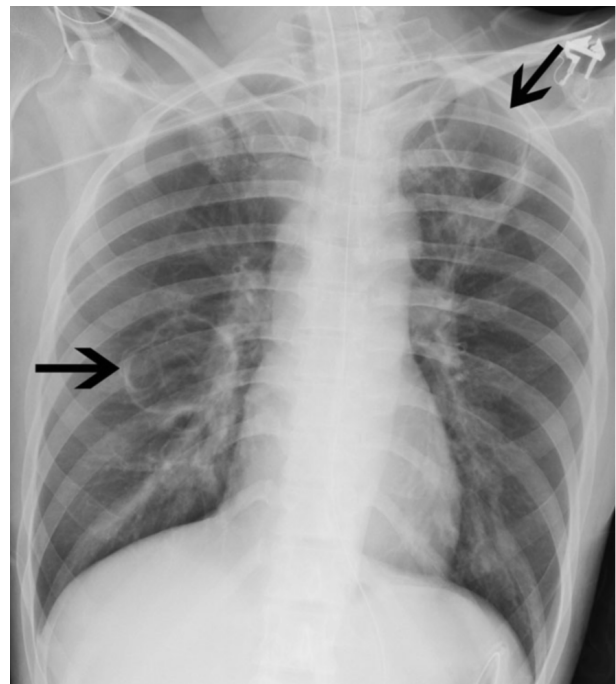


Figure 1A. Bronchiectasis in a 29 year-old woman with chronic graft versus host disease following bone marrow transplantation. Chest x-ray shows hyperinflation and peribronchial thickening. Large bilateral pneumatoceles (arrows) are also present.

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### Case Report

A 29 year-old woman presented with acute respiratory distress. Her past medical history was significant for acute myelogenous leukemia which was in remission after treatment with an allogeneic BMT three years prior to this admission. The patient was in respiratory failure on presentation, with an arterial pH of 7.13, PCO<sub>2</sub> of 59 mm Hg, and PO<sub>2</sub> of 400 mm Hg on 100% FiO<sub>2</sub>. She required intubation and mechanical ventilation for respiratory support. Central line placement was also performed for vascular access but this was complicated by pneumothorax which required evacuation by a chest tube. The chest radiograph on admission showed hyperinflation, peribronchial thickening and bilateral pneumatoceles (figure 1a). After stabilization of her respiratory status, a chest computed tomography (CT) scan was obtained to evaluate her pulmonary disease.

The chest CT (figures 1b-d) demonstrated bronchiectasis in the right middle and both lower lobes with regions of cystic bronchiectasis at the lung bases and mucoid impaction in the left lower lobe.

The patient also had prior CT scans for evaluation of episodes of respiratory distress. Review of these studies demonstrated a pattern of progressive bronchiectasis. The lung bases were normal on a CT scan from one year prior to BMT (four years prior to the current admission). Even 15 months after BMT, the lung parenchyma was normal on CT (figure 2a). Mild bronchiectasis without any cystic disease was demonstrated in the lower lobes 19

months after BMT (figure 2b). A CT scan obtained about two and a half years after BMT showed worsening of the bronchiectasis (figure 2c). Progression of airway disease culminated in cystic bronchiectasis with mucoid impaction as seen on the most recent study.

Over the 2 years prior to this admission, the patient had 4 bronchoalveolar lavage (BAL) cultures each approximately 6 months apart and several sputum cultures. Of these, 1 simultaneous sputum and BAL culture was positive for

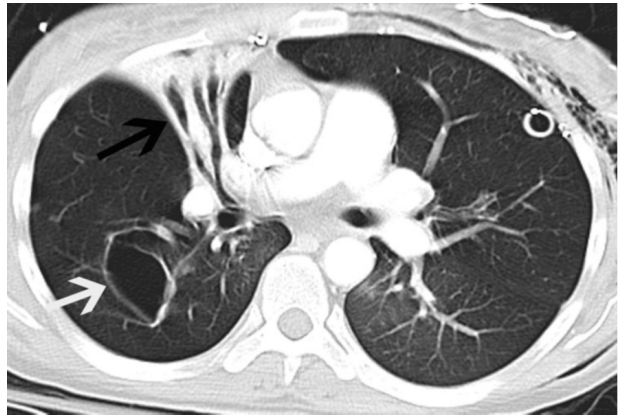


Figure 1B. CT scan at the level of the right middle lobe bronchus shows atelectasis of the right middle lobe with bronchiectasis (black arrow). A large pneumatocele (white arrow) is present in the right lower lobe. A left-sided chest tube and subcutaneous air in the left chest wall are also visible.



Figure 1C. CT scan through the lower lobes shows cystic bronchiectasis in the right lower lobe containing an air-fluid level (arrowhead).



Figure 1D. CT image at the lung bases demonstrates mucoid impaction of dilated bronchi in the left lower lobe (arrowheads).

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Figure 2A. Progression of bronchiectasis in a young woman with chronic graft versus host disease following bone marrow transplantation. CT image through the lower lobes obtained 28 mths prior to current admission shows normal lung parenchyma.

Staphylococcus aureus and 1 BAL culture was positive for *Pseudomonas aeruginosa*. She was treated for both of these infections and had no other positive culture results, including testing for acid-fast bacilli. Prior to the BMT the patient had no history of asthma or other conditions that would predispose her to pulmonary infections. A skin biopsy performed two and a half years prior to the current admission showed mild dermal and perivascular infiltration with lymphocytes in a pattern consistent with chronic GVHD. By increasing the patient's susceptibility to pulmonary infections, the chronic GVHD was presumed to be the underlying disorder responsible for the progressive bronchiectasis. The patient was unable to be weaned from the ventilator and required a tracheostomy, after which she was discharged to a long term acute care facility.

### Discussion

Approximately 40-60% of patients undergoing BMT develop pulmonary disease resulting in 10-40% mortality [5]. While acute infection is the most common pulmonary complication soon after BMT, chronic lung disease is common, particularly in the setting of chronic GVHD. Manifestations of chronic GVHD typically occur at least 100 days after BMT following recovery of immunologic function [1]. In patients with chronic GVHD, airway damage often occurs with a diffuse inflammatory process

involving bronchioles and larger bronchi. This can result in bronchiolitis obliterans or post-transplant obstructive lung disease, occurring in about 11% of patients after BMT [6]. Post-transplant bronchiolitis obliterans is characterized by dyspnea, progressive nonreversible airflow obstruction on pulmonary function tests and high mortality [1]. Other pulmonary manifestations of chronic GVHD include diffuse bronchiolitis obliterans with organizing pneumonia, alveolar damage, diffuse alveolar hemorrhage, lymphocytic interstitial pneumonitis, and lymphocytic bronchitis [3].

Though less common, bronchiectasis is increasingly being identified in patients with chronic GVHD after BMT [3, 4, 6, 7], suggesting that chronic GVHD is an important factor in progressive airway disease. The case presented here is unusual as gradual progression of bronchiectasis is captured on CT and the degree of bronchiectasis, with cystic dilatation of the airways and mucoid impaction, is more severe than previously described.

Formation of bronchiectasis in the setting of chronic GVHD may be multifactorial in etiology. One hypothesis is that host bronchial epithelial cells are attacked and damaged by donor T lymphocytes and cytokines [8]. This theory is supported by recent research demonstrating that both T-cell depletion and antithymocyte globulin reduce post-BMT pulmonary disease [9,10]. The role for immunomodulators in lung injury is further implicated by research demonstrating the presence of stimulatory autoantibodies to platelet-derived growth factor (PDGF) in patients with extensive GVHD [11]. Another speculation is that cytotoxic drugs and radiation treatments used in the conditioning regimens for BMT may result in injury to the pulmonary mucociliary clearance mechanism. Cellular and humoral immune deficiency characteristic of chronic GVHD results in increased susceptibility to infection and colonization of damaged airways with microbial pathogens such as *Pseudomonas aeruginosa*. Subsequently, a host-mediated inflammatory response to the persistent microbial stimulus may produce progressive airway damage [12]. We believe that the latter mechanism explains the findings in the case presented here as progressive bronchiectasis is usually a sequela of recurrent pulmonary infection. Pneumatocele formation, as in this case, can also result from repeated pulmonary infections and air trapping [13].

### Conclusion

In summary, progressive bronchiectasis can develop gradually in patients with chronic GVHD after BMT. This is partly due to increased susceptibility to chronic or recur-

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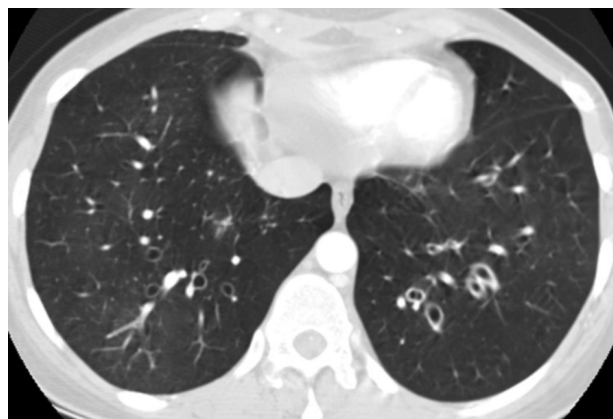


Figure 2B. CT image through the lower lobes obtained 2 yrs prior to current admission shows mild bilateral lower lobe bronchiectasis.

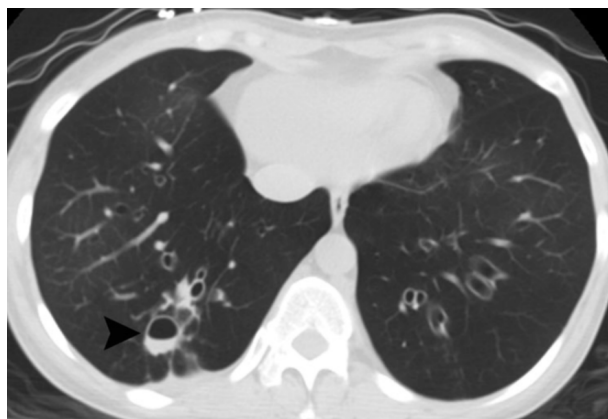


Figure 2C. CT image obtained 7 months prior to current admission shows progression of bronchiectasis with cystic bronchiectasis in the right lower lobe (arrowhead).

rent pulmonary infections. One should consider chronic GVHD as an underlying disease if bronchiectasis occurs in a patient with a history of BMT. Furthermore, CT scan should be considered for evaluation of respiratory symptoms in a patient with a remote history of BMT since the pulmonary complications of chronic GVHD may not be apparent on the chest radiograph.

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