Bronchiolitis Obliterans Complicating Bone Marrow Transplantation

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A 19-year-old woman with extensive, persistent chronic graft versus host disease (GVHD), following an HLA-identical bone marrow graft for acute leukemia, developed rapidly progressive airflow obstruction 140 days post-transplantation (PT) and presented clinically with persistent cough, inspiratory rhales, bronchospasm and exertional dyspnea. Pulmonary function tests (PFT) showed rapidly evolving severe airflow obstruction and hypoxemia without restrictive ventilatory defect. Open lung biopsy on the 204th day PT confirmed focal bronchiolitis obliterans. On the 381st day PT, she remained clinically stable. Chest x-ray film showed mild overinflation, but was otherwise unremarkable. PFTs continued to show very severe airflow obstruction without restrictive ventilatory defect. The etiology of the obliterative bronchiolitis might be explained on the basis of a direct immunologic reaction mediated by GVHD or possibly a joint viral-GVHD interaction. Awareness and further detailed documentation and analysis of this unusual respiratory syndrome associated with marrow transplant recipients may help clarify the role of GVHD in the development of lung disease in recipients of marrow grafts.

Most patients undergoing allogeneic bone marrow transplantation (BMT) for severe aplastic anemia or leukemia develop some degree of acute or chronic graft versus host disease (GVHD). The acute disease is restricted to skin, liver and gut involvement and 90 percent survive this complication. The syndrome of chronic GVHD subsequently affects about a third of long-term surviving allogeneic marrow transplant recipients. The protean manifestations of chronic GVHD include skin, liver, gastrointestinal, ophthalmic and neurologic disease. The primary pulmonary pathologic lesions described in transplant patients who develop acute respiratory syndromes concomitant with GVHD have generally been attributed to pneumonias caused by bacteria, fungi and cytomegalovirus, idiopathic pneumonia or interstitial pneumonitis, and rarely lymphocytic bronchitis and lymphoplasmacytic infiltrate of the trachea and large bronchi. The respiratory system is not a generally recognized target organ for acute GVHD of the lung and, furthermore, severe obstructive airways disease and obliterative bronchiolitis have been rarely reported as respiratory complications of BMT.

In this report we present a marrow transplant recipient with persistent chronic-on-acute GVHD who concomitantly developed the clinical, physiologic and pathologic features of rapidly progressing severe bronchiolitis obliterans. Awareness of this unusual syndrome may be the first step in clarifying the role, if any, of GVHD complicated by infection in mediating the primary pathologic lung lesion.

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Case Report

The patient, a 19-year-old woman with acute myeloblastic leukemia in remission, received an HLA-identical marrow graft from her sister on 8 May 1982. She had previously smoked 20 cigarettes per day for four years, but her pretransplant chest radiograph and pulmonary function tests were normal, aside from a mild restrictive defect as indicated by reduced TLC, RV and slightly reduced flow rates (Fig I). As preparation for transplantation, the patient received cyclophosphamide 60 mg/kg on each of two successive days followed by fractionated total body irradiation as 1,260 rads in seven fractions, twice daily. She received a bone marrow infusion several hours after completing the last irradiation dose. On the first day post-transplant (PT), methotrexate 15 mg/m² was given as prophylaxis against acute GVHD. This was followed by methotrexate 10 mg/m² intravenously intermittently during the next 21 days, but was stopped because of persisting pancytopenia and poor marrow engraftment.

On day 33 PT, a skin rash developed; biopsy was compatible with acute GVHD and methylprednisolone 2 mg/kg per day commenced. By day 40 PT, profuse diarrhea had developed and the liver-related enzyme levels were significantly elevated. Both rectal and liver biopsies performed on day 56 PT confirmed acute GVHD. Between days 60-100 PT, liver enzyme levels continued to be abnormal; bilirubin rose to 30 mg/dL (normal to 1.3 mg/dL), SGOT rose to 300-400 IU/L (normal 19-38 IU/L) and alkaline phosphatase rose to 600-800 IU/L (normal 45-1,251 U/L). Methylprednisolone was continued. However, because of deteriorating liver function, azathioprine 1 mg/kg per day was first administered on day 144 PT and prednisone given as 20 mg on alternate days. Subsequently liver function test results showed improvement, but chronic GVHD of the skin and mucus membranes persisted.

On day 100 PT, dry bilateral basilar crepitations and intermittent rhonchi were heard on chest examination. The patient experienced frequent episodes of nonproductive cough associated with bronchospasm. By day 140 PT she was persistently symptomatic with a nonproductive cough, exertional dyspnea and wheezing. The chest radiograph results remained normal. Pulmonary function studies on day 190 PT showed severe airway obstruction with no hypoxemia—a marked deterioration from the pre-transplant studies (Fig I). Trials of bronchodilator therapy with beta-agonists, theophylline and ipratropium, as well as corticosteroids, were unsuccessful in reversing her obstruction. Open lung biopsy was performed on day 204 PT.

The overall lung architecture was normal; there was no interstitial inflammation or fibrosis. Most of the airways were normal, but some small bronchioles showed acute and chronic inflammatory cells in the walls and organizing granulation tissue plugs in the lumen (Fig 2), characteristic of bronchiolitis obliterans. Additionally, there were recently formed thrombi in a number of small arterial branches. Simultaneous endobronchial biopsies were unremarkable. No viral inclusion bodies were seen and results of all cultures were negative.

Influenza A Bangkok hemagglutination inhibition titters rose from 1:40 on day 184 PT to 1:320 16 days later, suggesting recent viral infection. Clinical (symptomatic) deterioration in the patient occurred at least 40 days before the first titer was drawn.

The patient's clinical status remained stable through day 300 PT. Chronic GVHD of the skin and oral mucosa persisted and the patient continued to receive azathioprine 50 mg daily and 20 mg of prednisone on alternate days. At day 381 PT she appeared chronically ill, mildly cusionoid, emaciated and dyspneic at rest, weighing only 37.5 kg. Skin examination showed the changes of chronic GVHD. Oral examination showed severe atrophy and erythema of the buccal mucosa. There was no resting whole saliva or parotid flow. Ophthalmologic examination confirmed evidence of keratoconjunctivitis sicca. Oral (lip) biopsy showed chronic mucositis and sialadenitis (grade II) of GVHD. No raes were heard on chest examination. Results of the remainder of her examination were normal. The alkaline phosphatase was 153 IU/L (normal to 120); SGOT was 153 IU/L (normal to 40); and total bilirubin was 1.8 mg/dL; direct 0.7 mg/dL.
FIGURE 1. Serial pulmonary function studies before and after bone marrow transplantation. There is an increase in residual volume (RV) and a fall in forced vital capacity (FVC), forced volume in 1 second (FEV₁) and maximum mid expiratory flow rate at day 184 PT which is sustained over time. Gas transfer (Dco₅) fell in concert with the flow rates and there was a mild reduction in Pco₂ with a mild elevation in Po₂.

The spectrum of bronchiolitis obliterans has recently been reviewed.¹³ This condition is characterized by the presence of granulation tissue plugs within the lumens of small airways or destruction of the small airways. The causes are many and include toxic fumes,¹⁴ viral infections,¹⁵ rheumatoid arthritis¹⁶ and possibly penicillamine.¹⁷ Recently, a relationship with bone marrow transplantation has been described.¹⁸,¹⁹

Bronchiolitis obliterans is characterized clinically by rapid onset of shortness of breath and nonproductive cough with inspiratory rales heard on auscultation, and with relatively normal chest film findings. Lung function tests show normal total lung capacity but an elevated residual volume. Airflow obstruction which does not respond to bronchodilators is usually present. The carbon monoxide diffusing capacity, adjusted for alveolar volume, is usually normal.²⁰,²¹

The relationship of this syndrome to GVHD remains to be clarified. Link et al¹ describe two patients, a 12-year-old boy and a 26-year-old woman, who developed bronchiolitis obliterans eight months and four months, respectively, after marrow transplantation. In each instance, dyspnea, nonproductive cough, scattered rhonchi on auscultation and over-distention of the lungs were the presenting symptoms. Both patients were hypoxic and treated with corticosteroids, bronchodilators and intermittent positive pressure respiration. They both developed pneumothorax and died of overwhelming infection. Roca et al² report a 22-year-old male, a nonsmoker with no previous pulmonary disease, who developed pulmonary disease associated with cough, fever, and mucopurulent sputum nine months PT. No pathogenic organisms were found. Ralph et al²³ described four bone marrow transplant patients with extensive GVHD, in whom cough and exertional dyspnea were the main presenting symptoms. The patients were all nonsmokers. One had an associated esophageal web while a second had esophageal reflux with an endobronchial biopsy showing acute bronchitis. One patient had H influenza and S aureus revealed by shielded bronchial catheter studies and experienced some improvement on

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Figure 2. Light micrograph of small bronchiole demonstrating characteristic mural inflammation and organizing granulation tissue plug in lumen (elastic stain x 160).
aminophylline and antibiotics. The fourth patient had associated cytomegalovirus. All patients had an elevation in their residual volume, a decrease in FEV1, and a decrease in diffusing capacity. The pathologic findings included widespread obliteration of small airways, peribronchial and mural infiltration by plasma cells and neutrophils, and bronchial necrosis. Intraluminal polyps were not present and there was no evidence of emphysema.26

Chronic graft versus host disease may be associated with disorders of immune regulation and local impairment of host defense mechanisms.27,28 The sicca syndrome in these patients is associated with low salivary IgA levels29 and mucosal abnormalities. It is possible that both of these defects in GVHD may have a role in the production of this complication.23

In children, adenovirus infection can occasionally lead to oblitative bronchiolitis.12,30 All of the patients described by Ralph et al30 had either airway infection or irritation from recurrent aspiration of gastric esophageal contents. Our patient had evidence of a recent infection with influenza A.

While neither bacterial nor viral infections are typically associated with the clinicopathologic syndrome of bronchiolitis obliterans in adults, it is possible that the immunologic abnormality occurring with GVHD renders such patients increasingly susceptible to this sequela. The signs and symptoms of bronchiolitis seemed to be present before the elevated titer to influenza A. It is unlikely, therefore, that influenza A was the precise etiology of the bronchiolitis but, along with the GVHD, may have further modified the pathophysiologic process.

The prognosis of this condition appears to be variable. The patients with bronchiolitis associated with connective tissue disease and interstitial pneumonia may do well.31 This does not appear to be the case in patients with GVHD. Three of the eight cases post-marrow transplant reported in the literature have died. Of those who have survived, the airway obstruction has not been reversed, despite therapy with large amounts of corticosteroids.

In summary, the precise etiology of the bronchiolitis obliterans in these patients is obscure. It may be related to the GVHD or to a combination of GVHD and a recent viral or bacterial bronchial infection.

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