Lung Transplantation for Chemotherapy-induced Pulmonary Fibrosis∗

Jean T. Santamauro, M.D.† Diane E. Stover, M.D. F.C.C.P.
Kathy Jules-Elysee, M.D.; † and Janet R. Maurer, M.D.

A 26-year-old man cured of childhood acute lymphoblastic leukemia underwent a single lung transplant for drug-induced pulmonary toxicity 9 years after the completion of chemotherapy. It is not known whether patients cured of a malignancy who undergo organ transplantation are at increased risk of malignancy as compared to other organ transplant recipients. There was no evidence of recurrent or secondary malignancy in this case. Since single lung transplantation has been effective for idiopathic pulmonary fibrosis, it should be considered for patients cured of a malignancy who develop chemotherapy-induced pulmonary fibrosis.

(Chest 1994; 105:310-12)

Pulmonary toxicity is a well recognized side effect of many chemotherapy drugs.1-3 Pulmonary fibrosis, acute hypersensitivity pneumonitis, and noncardiogenic pulmonary edema are three patterns of toxicity described.1 Chronic pneumonitis with subsequent fibrosis is the most common clinical presentation associated with cytotoxic drugs.1 Delayed pulmonary toxicity presenting as fibrosis, although uncommon, is described and when it does occur it is difficult to treat.2-4 We report one case of pulmonary fibrosis presenting many years after chemotherapy which was treated with single lung transplantation.

CASE REPORT

The patient was a 26-year-old white man with acute lymphoblastic leukemia diagnosed at age 3 years who underwent induction chemotherapy followed by multiple courses of chemotherapy for central nervous system, bone marrow, and testicular relapses. He received almost continuous chemotherapy for 12 years. The chemotherapeutic agents and their total doses are listed in Table 1.

At the age of 13 years, asymptomatic wheezing was heard at the time of physical examination during a course of therapy with vincristine, intrathecal methotrexate, cyclophosphamide, carbustine, and cytostine arabinoside. Although the chest radiograph was normal, pulmonary function studies revealed combined restrictive and obstructive ventilatory defects with a forced vital capacity of 1.6 L (52 percent of predicted) and a FEV₁ of 1.13 L (71 percent of forced vital capacity). The wheezes resolved without therapy but physiologic testing was not repeated. He completed all chemotherapy at age 15 years.

One year after chemotherapy was discontinued, the patient experienced several episodes of pneumonia which were treated with orally administered antibiotics on an outpatient basis. Six and a half years later, he developed dyspnea on exertion. At that time, a chest radiograph revealed extensive bilateral interstitial infiltrates, pleural thickening, and loss of lung volume. The forced vital capacity was 1.02 L (23 percent of predicted) with a diffusing capacity of 28 percent of predicted. Transbronchial biopsies performed...

∗From the Pulmonary Service, Memorial Sloan Kettering Cancer Center, New York (Drs. Santamauro, Stover, and Jules-Elysee); and Toronto General Hospital, Toronto, Canada (Dr. Maurer).
†Presently at North Carolina Baptist Hospital, Winston-Salem, NC.
‡Presently at New York Hospital, New York City.

Reprint requests: Dr. Stover, Pulmonary Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York 10021.
formed during fibroptic bronchoscopy showed severe interstitial fibrosis with atypical alveolar lining cells. Treatment with corticosteroids was begun for a presumed diagnosis of delayed drug-induced pulmonary toxicity.

Initially there was mild clinical improvement; however, progressive and significant dyspnea with minimal exertion ensued despite corticosteroid therapy. Because of the lack of any other effective treatment, the patient was referred for and underwent a left lung transplant at age 24 years. Pathology revealed both pleural and parenchymal fibrosis. Despite a postoperative course complicated by persistent left lower lobe collapse secondary to narrowing of the left bronchial anastomosis and cytomegalovirus pneumonitis, the patient did well clinically for more than 2 years after his transplant. Unfortunately, 2½ years after his transplant the patient developed hemoptysis and hypoxemic respiratory failure and died. Cytomegalovirus, Candida, Aspergillus, and Pseudomonas had all been isolated from his respiratory tract prior to his death. Autopsy showed diffuse alveolar damage with bronchiolitis obliterans and bronchiolitis obliterans with organizing pneumonia bilaterally. In addition, there was a left main bronchus stricture at the anastomosis site which had been previously stented as well as left-sided bronchiectasis with mucus plugging and a suppurative aspergilloma in the right apex.

Based on the autopsy, the cause of death was diagnosed to be multifactorial respiratory failure. Bilateral bronchiolitis obliterans and bronchiolitis obliterans with organizing pneumonia secondary to infection and/or rejection, airway ectasia with mucus plugging, and opportunistic infection with Aspergillus were probably the most important factors leading to the patient's death. Of note, clinically and at autopsy, there was no evidence of recurrent leukemia or secondary neoplasm.

**DISCUSSION**

It is well established that many chemotherapeutic agents can cause pulmonary damage and that combination chemotherapy increases the risk of pulmonary toxicity. Of the many agents that this patient received over prolonged periods of time, carmustine and cyclophosphamide are the drugs most likely to have caused the observed pulmonary effects. Although methotrexate can cause pulmonary toxicity, fibrosis is a distinctly unusual form of pulmonary damage caused by this drug. Methotrexate usually causes acute pulmonary symptoms which occur in close proximity to receiving the drug. Although the mechanism of injury is unknown, it is thought to be due to a hypersensitivity reaction, as suggested by an increase in the number and percentage of T lymphocytes in lavage fluid and a dramatic improvement in response to steroid therapy. On the other hand, cyclophosphamide has been reported to cause pulmonary fibrosis weeks to years after the initial treatment. When used in children, cyclophosphamide can retard lung growth and lead to loss of lung volume during periods of rapid body growth. Carmustine can cause pulmonary fibrosis as late as 17 years after it has been administered. Although the mechanism of carmustine-induced lung injury is unclear, persistent progressive subclinical pneumonitis or stable subclinical disease followed by a period of rapid decline due to an unknown stimulus are two proposed theories.

Therapy for drug-induced pulmonary toxicity is limited. In the setting of acute toxicity, withdrawal of the offending agents may lead to a clinical response. When patients present with drug-induced pulmonary disease many years after treatment, discontinuing the offending agent is not an option. Corticosteroids rarely have been effective and are often instituted in an attempt to alleviate symptoms and disease progression.

Due to improvement in surgical techniques, infection control, and effective medications used for immunosuppression, unilateral lung transplantation is evolving as a viable alternative for patients with a variety of end-stage lung disorders. It was initially successful in patients with severe restrictive disease due to pulmonary fibrosis. More recently, lung transplantation has been performed in patients with terminal lung disease of varying etiologies including COPD and pulmonary vascular disease.

Pulmonary fibrosis induced by chemotherapy is a disease with no known effective treatment. Since single lung transplantation has been successful for end-stage idiopathic pulmonary fibrosis, it also may be effective therapy for chemotherapy-induced pulmonary fibrosis in patients who are considered cured of their underlying malignancy.

The overall risk of secondary cancers following cytotoxic therapy in children treated for various neoplasms is 3 to 20 percent at 20 years. Organ transplant recipients have an increased risk of multiple malignancies as compared with the risk to the general population. It is not known whether patients cured of a primary malignancy who undergo organ transplantation are at any increased risk of malignancy, either secondary or recurrent, as compared with the general organ transplantation population. In this case, however, there was no evidence of malignancy either pre- or post-mortem.

**REFERENCES**

6. Alvarado CS, Boat TF, Newman AJ. Late onset pulmonary fibrosis and chest deformity in two children treated with
Primary antiphospholipid syndrome (PAPS) is a disease manifested by a tendency toward recurrent arterial and venous thrombosis, placental thrombosis, placental thrombosis leading to recurrent fetal loss, thrombocytopenia, and a prolonged activated partial thromboplastin time (PTT) in the absence of other autoimmune diseases in these patients. Because of the hypercoagulable state in this disease, long-term anticoagulation therapy is recommended, although the choice and optimal dose of anticoagulant is not known. Inferior vena cava filter placement has been recommended to prevent recurrent pulmonary emboli in high-risk patients (ie, free-floating or poorly adherent proximal thrombus on venogram, chronic pulmonary hypertension, or marginal respiratory reserve). To our knowledge, the use of an inferior vena cava filter to prevent recurrent pulmonary embolism in patients with PAPS has not been reported. Moreover, perioperative management strategies to prevent postoperative thromboembolism have not been defined. We report a difficult and ultimately fatal case of PAPS in a patient with a previously placed vena cava filter after uncomplicated cholecystectomy despite treatment with heparin and aspirin.

Case Report

A 61-year-old Hispanic woman was diagnosed as having PAPS when she presented with a history of chronic leg ulcer, recurrent spontaneous abortions, pulmonary emboli, extremely high titers of anticardiolipin IgG and IgM, and no other autoimmune diseases. In November 1990, she was admitted to St. Joseph Hospital at the Creighton University Medical Center with recurrent pulmonary emboli that were confirmed by pulmonary angiography. A bird’s nest filter (Cook Inc, Bloomington, Ind.) was placed in the inferior vena cava to prevent further pulmonary emboli. Her clinical condition temporarily stabilized and the platelet count normalized after treatment with low-dose heparin, 5,000 U subcutaneously twice daily, and aspirin, 100 mg/d (Fig 1), and she was discharged from the hospital on this regimen.

She was readmitted to the hospital 7 months later with acute cholecystitis and she underwent cholecystectomy that evening. Following cholecystectomy, she developed progressive thrombocytopenia and required 2 U of packed red blood cells for blood loss.

Platelet Count

Figure 1. The response curves of prothrombin time (PT), partial thromboplastin time (PTT), and platelet count to the treatments of heparin, platelet transfusion, corticosteroid, and aspirin.