

# Successful treatment of bleomycin lung

Loren D. Brown, D.O.  
Ronald R. Reimer, M.D.

*Department of Hematology and Medical  
Oncology*

Muzaffar Ahmad, M.D.

*Department of Pulmonary Diseases*

James S. Hewlett, M.D.

*Department of Hematology and Medical  
Oncology*

Bleomycin sulfate is an antitumor antibiotic with clinical activity against Hodgkin's and non-Hodgkin's lymphoma; squamous cell carcinoma of the head and neck, esophagus, cervix, penis, and skin; and carcinoma of the testis.<sup>1</sup>

The major dose-limiting toxicity of bleomycin is pulmonary fibrosis.<sup>1</sup> Factors influencing development of this serious side effect include age, cumulative dose,<sup>1</sup> and prior radiation therapy to the chest.<sup>2</sup> Although pulmonary fibrosis will develop in less than 10% of patients receiving bleomycin,<sup>1, 3</sup> treatment of this complication is generally unsuccessful. Some authors have pointed out that early diagnosis and subsequent withdrawal of the drug may prevent progression to fibrosis,<sup>4, 5</sup> but in most series the irreversible nature of symptomatic bleomycin pulmonary toxicity has been emphasized.<sup>1, 2</sup> Corticosteroid therapy in particular has been disappointing, with only anecdotal mention of responding patients. We have studied two patients with severe bleomycin pulmonary toxicity who recovered after steroid therapy.

## Case reports

**Case 1.** A 52-year-old white man with stage III choriocarcinoma of the testis with involvement of the supraclavicular, mediastinal, and retroperitoneal nodes was treated with cis-platinum, vinblastine sulfate, and bleo-

mycin chemotherapy. He received 360 mg of bleomycin ( $180 \text{ mg/m}^2$ ) for 8 weeks. When the bleomycin was withdrawn, the chest roentgenogram revealed new linear infiltrates in both lung fields. He was asymptomatic and no rales were heard on auscultation. Fourteen weeks later severe dyspnea at rest developed requiring supplemental oxygen therapy. He was afebrile and all cultures were negative.

Open lung biopsy revealed interstitial pneumonitis with fibrosis and focal desquamation. Stain for *Pneumocystis carinii* was negative. Pulmonary function studies were consistent with advanced pulmonary fibrosis, showing a marked restrictive defect with vital capacity (VC) of 1.40 L, forced expiratory volume in one second ( $\text{FEV}_1$ ) of 1.30 L, and  $\text{pO}_2$  of 57 mm Hg.

He was treated with prednisone, 80 mg/day, with gradual improvement during the ensuing 3 months. He now has no dyspnea, even with moderate exertion. Pulmonary function studies have greatly improved with VC of 2.73 L,  $\text{FEV}_1$  of 2.19 L, and  $\text{pO}_2$  of 81 mm Hg. Chest roentgenogram has shown marked clearing (*Fig. 1*).

**Case 2.** A 32-year-old white man with stage III mixed embryonal teratocarcinoma of the testis metastatic to the left lung, perihilar and periaortic nodes received cis-platinum, vinblastine, and bleomycin chemotherapy. Bleomycin was stopped at a dose of  $360 \text{ mg}$  ( $200 \text{ mg/m}^2$ ).

Four weeks after the bleomycin was withdrawn, severe dyspnea and pleuritic chest pain developed. He was afebrile and physical examination revealed a resting tachycardia and bilateral basilar rales. Chest roentgenogram showed diffuse interstitial and alveolar infiltrates in both lung fields compatible with pulmonary fibrosis. Multiple sputum cultures were negative for bacterial, fungal, and acid-fast organisms. Pulmonary function studies showed a severe restrictive defect with VC of 1.39 L and  $\text{FEV}_1$  of 1.20 L. Diffusing capacity for carbon monoxide single breath  $\text{D}_L\text{CO}$  ( $\text{ml CO}/(\text{min torr SPTD})$ ) was 10.2 as compared to 25.7 before treatment. Lung biopsy was not performed.

He was treated with prednisone, 30 mg/

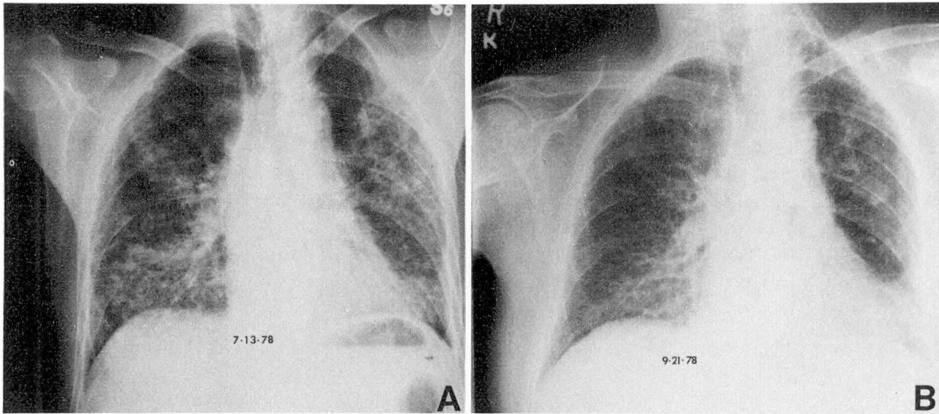
day. In the following 5 months he showed gradual improvement with resolution of symptoms and improved pulmonary functions: VC, 2.48 L;  $\text{FEV}_1$ , 2.21 L; and  $\text{D}_L\text{CO}$ , 16.5. Chest roentgenogram has shown complete clearing of both lung fields (*Fig. 2*).

## Comment

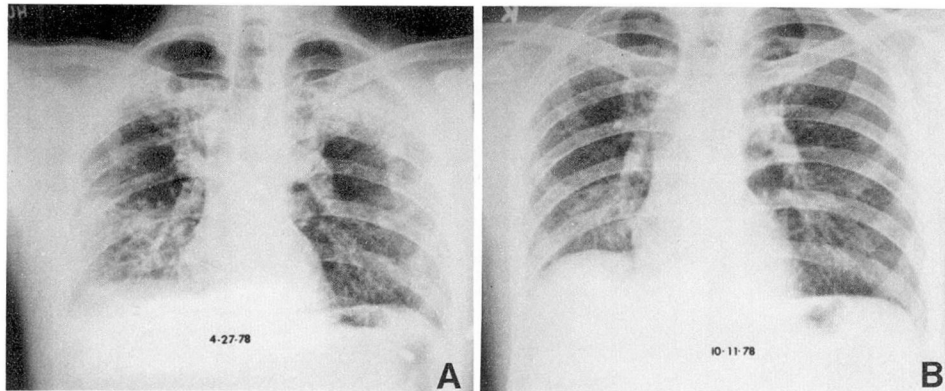
Bleomycin pulmonary fibrosis was first reported by Ichikawa et al.<sup>6</sup> Subsequent clinical studies have shown that most patients have the classic picture of interstitial fibrosis, usually similar pathologically to other types of drug-induced fibrosis.<sup>7</sup>

Previous reports of bleomycin lung toxicity have documented its severe nature. Among patients treated with bleomycin to the maximum recommended dose (400 mg), pulmonary dysfunction will develop in up to 10% of patients and 1% to 2% will die of pulmonary fibrosis. With higher doses of bleomycin ( $>500 \text{ mg}$ ), the mortality rate increases from 3% to 5%.<sup>2</sup> In a review of bleomycin pulmonary fibrosis by Sostman et al.,<sup>3</sup> corticosteroids were not considered to be of benefit. Samuels et al.<sup>8</sup> emphasized the dismal prognosis in patients with the advanced presentation of dyspnea and hypoxemia at rest. Although successful treatment with steroids has been reported,<sup>1, 2, 4</sup> most responses have been in patients with minimal evidence of pulmonary toxicity or in patients who have received a relatively low cumulative dose of bleomycin. In addition, some of these patients may have had bleomycin hypersensitivity pneumonitis, which responds well to steroids.<sup>9</sup> Neither of the patients we treated had peripheral blood eosinophilia or other stigmata of hypersensitivity pneumonitis.

In our experience, advanced bleomycin pulmonary fibrosis has not been uniformly fatal. Although the responses after steroid therapy in these two pa-



**Fig. 1.** A, Posteroanterior chest roentgenograms showing bilateral interstitial infiltrates at start of treatment. B, Marked clearing after therapy.



**Fig. 2.** A, Posteroanterior chest roentgenograms showing bilateral interstitial and alveolar infiltrates at start of treatment. B, Complete clearing after therapy.

tients are gratifying, early recognition and prevention of pulmonary toxicity are essential.

Patients receiving bleomycin should be monitored carefully for the development of pulmonary symptoms. Regular measurement of the lung diffusion capacity and forced vital capacity appear to be the most sensitive studies for detecting early interstitial disease.<sup>10</sup> Differentiation from bleomycin hypersensitivity pneumonitis and other causes of pulmonary infiltrates may provide valuable therapeutic and prognostic information. Finally, prompt withdrawal of bleomy-

cin and early treatment with steroids may prevent progression to an otherwise fatal process.

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