Pulmonary Toxicity Recurring after a Six Week Course of Busulfan Therapy and after Subsequent Therapy with Uracil Mustard

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A growing number of drugs, including a number of alkylating agents, have been implicated as the cause of pulmonary diseases. A patient with chronic myelogenous leukemia presented with typical cytology, biopsy, and roentgenologic findings of lung toxicity after only six weeks of therapy with busulfan. There was subsequent clearing. A similar roentgenologic change also occurred after administration of uracil mustard. This has not been reported previously.

A number of drugs have been implicated in connection with pulmonary injury, including a growing list of cancer chemotherapeutic agents.1 This report describes a patient who developed pulmonary toxicity after a relatively short period of therapy with busulfan, and a similar pulmonary problem developed later during therapy with uracil mustard.

CASE REPORT

A 52-year-old retired iron mine worker was admitted on October 8, 1975, for increasing abdominal girth and shortness of breath. On evaluation he was found to have Philadelphia chromosome-positive chronic myelogenous leukemia and left sided empyema, secondary to Enterobacter cloacae and Enterococcus. Treatment with cephalothin, gentamicin and chest tube drainage resulted in complete resolution of the empyema. Busulfan was then begun in doses ranging from 2 to 6 mg per day on October 28, 1975, with a decrease in leukocyte count from 342,000 to 81,000.

Six weeks after starting therapy with busulfan, the patient noted the onset of bilateral pleuritic chest pain associated with nonproductive cough and dyspnea. There was no fever, chills, night sweats or hemoptysis.

On physical examination at presentation, the patient was acutely ill and in moderate respiratory distress. His temperature was 99.8°F (37.6°C); pulse rate was 85/min and regular. There were diffuse bilateral rales with scattered rhonchi. A systolic ejection murmur and atrial gallop rhythm were unchanged. There was no ventricular gallop. The jugular venous pressure was normal. The liver was 15 cm in span and was not tender. The spleen remained enlarged to the iliac crest. Two plus ankle edema was present.

Laboratory data included a white blood cell count of 15,400, with all myeloid precursors, platelet count of 1,600,000 and hematocrit 26 percent. The Po2 was 61, with a Pco2 of 36, and a pH of 7.35 mm Hg. A chest roentgenogram (Fig 1) showed diffuse interstitial and alveolar infiltrates. Fungal serology tests and cold agglutinin titers were negative. Sputum smears and cultures for acid-fast bacteria were negative. Sputum cytologic examination showed large atypical cells (Fig 2) compatible with a busulfan-induced lesion.

Treatment with digoxin and diuretics (which produced a ten-pound weight loss) did not result in improvement. A transbronchial biopsy showed findings consistent with a drug-induced pulmonary lesion with desquamated alveolar histiocytes, lining cells with enlarged nuclei and revealed no evidence of fungi, acid-fast bacteria or Pneumocystis.

Administration of busulfan was discontinued after nine weeks of treatment. There was gradual clinical improvement and a chest film in February, 1976, revealed marked improvement.

Chemotherapy was reinstituted with melphalan from January 3 to May 12, 1976, at 2 mg per day. Due to poor control...
of the platelet count, therapy was changed on May 12 to uracil mustard in doses of 2 to 4 mg per day. This was continued until August 4, 1978.

The patient returned to the clinic on July 21, complaining of dyspnea and a nonproductive cough of several weeks’ duration. Digoxin and diuretics again were administered, without success. On admission examination two weeks later, the patient was acutely ill. His pulse rate was regular (100 per minute), temperature was 100.2°F. (37.8°C). Diffuse bilateral rales were present. There were no signs of cardiac decompensation.

The chest roentgenogram showed a diffuse interstitial infiltrate. The hematocrit was 19.4 percent and the white blood cell count was 1,100. Treatment with diuretics and digitalis continued, resulting in a ten-pound weight loss, but no improvement occurred. A second transbronchial biopsy showed inflammatory changes of chronic fibrosing alveolitis; no organisms or inclusions were seen on special staining.

Therapy with uracil mustard was stopped and prednisone was instituted with rapid tapering over three weeks. The patient had marked symptomatic improvement and the x-ray film showed partial clearing, but a chronic infiltrate remained.

Subsequently, the patient was admitted for the last time in December, 1976, for an accelerated phase of his chronic myelogenous leukemia and worsening pulmonary function; he expired. At autopsy, the lungs showed cellular atypia of bronchiolar and alveolar lining cells, chronic interstitial fibrosis and mild inflammation, with no organisms or viral inclusions seen (Fig 3).

**DISCUSSION**

Busulfan and other alkylating agents produce lung changes similar to those produced by radiation, consisting of proliferation and nuclear abnormalities of the type 2 alveolar lining cells, as well as interstitial and alveolar fibrosis. Since the original report of busulfan lung appeared, a number of confirming reports have appeared. In all reported cases, the duration of drug therapy ranged between nine months and seven years. This patient is remarkable, therefore, because of the short course of therapy (six weeks) before he developed the clinical syndrome of busulfan lung. It is also notable that he developed a similar pulmonary process with administration of uracil mustard, which is chemically unrelated, but which is similar to cyclophosphamide, another alkylating agent which has been associated with pulmonary disease.

Cytologic changes have been reported in busulfan lung toxicity. This patient did have characteristic cyto logic findings, and biopsy and autopsy evidence consistent with this lesion. His clinical condition became markedly better after busulfan therapy was stopped during the first episode, and improved to a lesser extent after stopping therapy with uracil mustard later. To prove cause and effect, a rechallenge might have been helpful, but was not done because of the risk. The chest film showed complete clearing after busulfan therapy was stopped, but there was only partial clearing after the cessation of uracil mustard therapy, which suggests that there may be more residual after successive acute episodes. The pathologic findings on biopsy and autopsy excluded the two main differential diagnoses: leukemic infiltration or opportunistic infection.

Busulfan and uracil mustard have not been absolutely proved to have caused this patient’s difficulties, but the temporal relationships between the drugs and the pulmonary lesion are highly suggestive. It is possible that the pulmonary changes induced by use of busulfan made him more susceptible to toxicity from uracil mustard. The life-threatening consequences of progressive, irreversible lung disease are such that any possibly nos communist agent should be removed before ascribing the cause to an idiopathic category. Physicians should be aware that pulmonary injury may result from short periods of therapy with busulfan or uracil mustard.

**REFERENCES**