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Life threatening lung toxicity induced by low doses of bleomycin in a patient with Hodgkin's disease

Sir,

Bleomycin is a polypeptide antibiotic isolated from *Streptomyces verticillus*. Its activity against a variety of tumors, particularly squamous cell carcinoma of various origins, lymphomas and germ cell tumors has been demonstrated for over 20 years.¹ Possible toxicities include dermatitis, mucositis, alopecia, fever, as well as pulmonary toxicity (PT). Approximately 1% to 2% of patients develop fatal PT, and an additional 5% to 10% develop non fatal PT.²⁻⁴ Several risk factors have been described, such as cumulative dose, the presence of renal impairment, prior pulmonary function abnormalities, adjunctive thoracic radiotherapy, high dose oxygen therapy, and age above 70.^{1,4} Total dose is clearly a risk factor. The incidence of fatal PT increases with a total dose higher than 400 U.^{1,4,5} In contrast, sporadic cases have been reported of bleomycin PT with total doses lower than 100 U.⁶ The pathogenesis of bleomycin PT remains unknown.

We report the case of a patient who developed severe bleomycin induced PT after a very low dose of bleomycin. The patient, a 63-year old man, was treated with COPP/ABV hybrid regimen for stage 1A (left axillary lymph nodes) Hodgkin's disease, nodular sclerosis. His past medical history included esophageal replacement by a colon transposition after a caustic esophageal burn, and he smoked half a pack of cigarettes a day. The patient denied any history of allergy. Seven days after the second cycle of COPP/ABV with a cumulative dose of 34 U of bleomycin he required hospital admission because of fever, breathlessness and a dry cough. Physical examination revealed a temperature of 37.8°C, a respiratory rate of 20 breaths per minute and crepitations at both lung bases. The WBC count was 3,200 cells/mL with 1,920 neutrophils. The hemoglobin value was 10.4 gr/dL, and the platelet count was 248,000 cells/mL. With the patient breathing air, the arterial blood gas determination showed a PaO₂ of 49 mmHg, PaCO₂ of 34 mmHg, pH of 7.48 and a saturation level of 87%. Electrolyte levels, liver tests, and coagulation studies were within normal limits. The admission chest radiograph demonstrated bilateral basal diffuse interstitial infiltrates. CT scan of the chest revealed a decrease in the size of the axillary lymph nodes. Bronchoscopy was negative for infection. The patient started treatment with empiric antibiotics for presumed infection and inspired oxy-

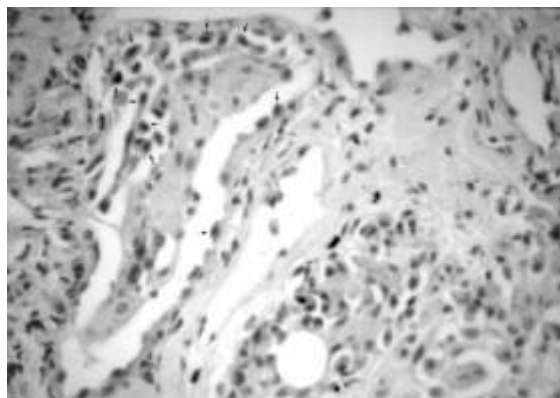


Figure 1. Light microscopy of lung biopsy showing alveolar spaces and atypical pneumocytes with large and hyperchromatic nucleus (arrows).

gen concentrations of 35-40%. Despite this treatment, his respiratory function deteriorated rapidly and he was transferred to the intensive care unit for intubation and ventilation. Chest radiography showed extensive alveolar and interstitial shadowing of both lungs. After admission to the intensive care unit, pulmonary function continued to deteriorate throughout this time. A transbronchial biopsy was done and the biopsy specimen showed a large number of atypical pneumocytes (type II cells) with big and hyperchromatic nucleus. No eosinophilic infiltration was observed (Figure 1). Antibiotic therapy was stopped, and prednisone 1 mg/kg/day was started. There was a marked improvement in his pulmonary function and chest radiographs revealed gradual clearing over a 7-day period. One month after starting corticosteroid therapy chest radiography showed almost complete resolution of the infiltrates. The corticosteroids were completely withdrawn after the clear chest radiograph. Three cycles of COPP regimen have been administered, and the patient is now free of disease and asymptomatic.

This patient had an unusual life threatening bleomycin PT after a very low cumulative dose (34U). Only three cases of severe PT induced by bleomycin at doses lower than 40U have been reported.⁷⁻⁹ Moreover, our patient had none of the well established risk factors for fatal bleomycin induced PT. The exclusion of infection and the pathology results all pointed to a diagnosis of acute or subacute bleomycin-induced interstitial pneumonitis. In addition, a rapid response was observed to prednisone treatment. The low cumulative dose, the absence of risk factors and the prompt corticosteroid response suggest a hypersensitivity response. Sporadic cases of bleomycin hypersensitivity pneumonitis have been reported.¹⁰ Although radiologic and functional pulmonary changes were similar to the usual bleomycin interstitial pneumonitis, lung biopsies showed a pattern of hypersensitivity reaction. Biopsy specimens from the reported cases of hypersensitivity pneumonitis all showed similar characteris-

tics: a patchy eosinophilic infiltrate affecting the distal air spaces and absence of hyperplastic pneumocytes (type II) with bizarre shapes usually noted in cases of bleomycin-induced interstitial pneumonitis.¹⁰ The pathologic changes described in our patient are different from those described for bleomycin hypersensitivity pneumonitis and appear to be a classic bleomycin interstitial pneumonitis.¹¹ This case illustrates that life threatening bleomycin PT, although unusual, can occur with very low doses of bleomycin. The case also illustrates that prompt recognition is essential since some patients have a favorable response to corticosteroid therapy. Further studies are needed for a better understanding of the mechanisms involved in the development of PT induced by bleomycin.

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Intrauterine anemia due to parvovirus B19: successful treatment with intravenous immunoglobulins

Sir,

Fetal hydrops is a frequent complication of B19 infection during pregnancy.¹⁻³

We report the case of an infant who, after intrauterine B19 infection, developed hydrops, and, subsequently, severe chronic anemia which responded to intravenous immunoglobulins (IVIGs).

A 2,330 g male was born by Cesarean section at 35 weeks gestation after ultrasonography had shown fetal hydrops, pericardial effusion and ventricular hypertrophy. At 22 weeks, the patient's brother had developed erythema infectiosum. At birth, generalized edema and hepatosplenomegaly were present, and rales were heard over the entire chest.

Hb was 49 g/L, platelets $42 \times 10^9/L$, reticulocytes $16.8 \times 10^9/L$. The peripheral blood smear showed severe anisopoikilocytosis, giant platelets, myelocytes and metamyelocytes. In the bone marrow, the erythroid precursors were vacuolated, and dyserythropoiesis, with *dog-ear* projections, was evident in the proerythroblasts¹ (Figure 1). B19 infection was suspected, and confirmed, a few days later, by B19 DNA detected in the infant's bone marrow and placenta by PCR.⁴ Serum IgG and IgM for B19 were negative. The patient's mother and brother had B19 specific serum IgG but no specific B19 IgM. Indirect Coombs' test was negative.

The infant required mechanical ventilation for four days, and two platelet transfusions because of platelet count $<20 \times 10^9/L$. Twelve units of packed erythrocytes were needed to keep the Hb level above 60 g/L. In accordance with previous literature reports,^{5,6} at the age of 10 months IVIGs (1 g/kg every three weeks) were started and continued for 8 months (Figure 2). PCR for B19 was still positive in the bone marrow at 1 and 12 months of age. At age

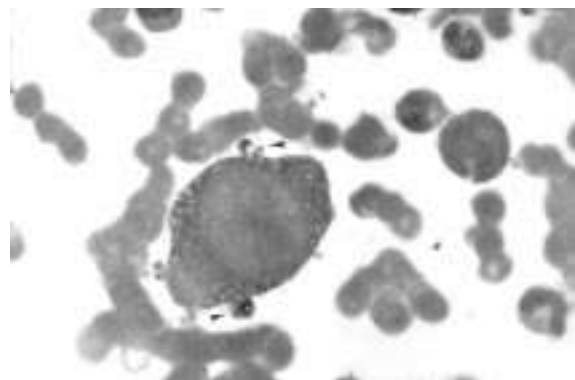


Figure 1. Bone marrow aspirate with giant vacuolated proerythroblasts. The arrows indicate the *dog-ear* projections of the cytoplasmic membrane.