A 29-year-old man had received a diagnosis of chronic myelogenous leukemia (CML) 6 years before presentation. He had not undergone bone marrow transplantation because of the lack of an adequate donor. He entered an accelerated phase in 1994 and was treated with oral hydroxyurea and 6-mercaptopurine. The patient developed a dry cough and mild fever in December 2000 and was treated for pneumonia in a local hospital. He was sent to the emergency department of our hospital in April 2001 with a 1-month history of fever, chills, and exertional dyspnea. He also had complained of malaise and a dry cough in the preceding 3 months. There was no history of recent travel, and he was taking no drugs other than hydroxyurea and 6-mercaptopurine.

Physical Examination

The patient’s temperature was 38.5°C, BP was 130/80 mm Hg, pulse was 100 beats/min, and respiration was 40 breaths/min. The sclerae were not icteric. The pupils were isocoric with prompt light reflex. The neck was supple without jugular vein distension or lymphadenopathy. Chest auscultation revealed diffuse, coarse crackles bilaterally. There were no heart murmurs. The abdomen was soft and flat without tenderness or rigidity. The liver and spleen were not palpable. No skin rash or wounds were detected.

Laboratory Findings

The initial laboratory studies revealed the following: WBC count, $26.8 \times 10^3$ cells/$\mu$L with 94% neutrophils; platelet count, $778.0 \times 10^3$ cells/$\mu$L; hemoglobin, 9.0 g/dL; and hematocrit, 28%. The prothrombin time and activated partial thromboplastin time were within normal limits. The aspartate aminotransferase level was 32 U/L, total bilirubin level was 0.9 mg/L, BUN level was 12 mg/L, creatinine level was 0.8 mg/L, and lactate dehydrogenase level was 965 U/L. The urinalysis showed no hematuria or pyuria. Arterial blood gas analysis when breathing 100% oxygen via a nonrebreathing mask showed the following: pH, 7.40; $\text{PaO}_2$, 72 mm Hg; $\text{PaCO}_2$, 28 mm Hg; and $\text{HCO}_3^-$ level, 18 mEq/L. The induced sputum was negative for *Pneumocystis carinii* and acid-fast bacilli. Imaging studies, including the chest radiograph taken in the emergency department in April 2001 (Fig 1) and a high-resolution CT (HRCT) scan of the chest taken on the fifth hospital day (Fig 2), are shown.

Hospital Course

An open lung biopsy was performed on the 13th day of the hospital stay. The pathologic findings revealed confluent filling of alveolar spaces with eosinophilic, granular material positive for the periodic acid-Schiff staining which was resistant to diastase. No microorganisms or inflammatory cells could be identified.

What is the most likely cause of the bilateral dense pulmonary infiltrates?

What is the most likely diagnosis?
Figure 1. The chest radiograph shows dense alveolar infiltrates bilaterally in the lower lung field.

Figure 2. The HRCT of the chest reveals reticulation and ground-glass opacities of both lungs.
Diagnosis: Secondary alveolar proteinosis complicating CML

Pulmonary alveolar proteinosis is a rare disease characterized by the deposition of a granular extracellular material composed of protein and lipids within the air spaces. Genetic predisposition, smoking, chemical exposure, and dust have been implicated in the pathogenesis of the disease, but the cause remains unknown. It has been hypothesized that alveolar proteinosis may be a consequence of defective macrophage function. The filling of proteinaceous material within the alveoli is thought to impair intra-alveolar anti-infectious mechanisms and, therefore, to be partially responsible for the occurrence of opportunistic infection.

The association of alveolar proteinosis with hematologic disorders, such as leukemia or lymphoma, is well-established, and these forms are considered to be secondary alveolar proteinosis. The incidence of secondary alveolar proteinosis in patients with respiratory symptoms was estimated to be 5.3% among all patients with hematologic malignancies and to be 10% in patients with myeloid disorders. The clinical manifestations of secondary alveolar proteinosis are nonspecific. Dyspnea is most prominent, while nonproductive cough, fatigue, and low-grade fever also may occur. Laboratory investigation may only reveal an elevated serum lactate dehydrogenase level. Typical radiographic findings are bilateral, diffuse, perihilar, ill-defined dense infiltrates, which are usually worse in the lower lung zone. The most common HRCT findings are widespread ground-glass opacity and smooth septal thickening in abnormal areas, and superimposition of these two findings (the so-called “crazy paving” appearance) is characteristic of this disease. A patchy or geographic distribution of consolidation is also a common finding in these patients. The thickened interlobular septa were shown on open lung biopsy to reflect septal inflammation. Septal thickening also can represent interstitial accumulation of material that is positive with periodic acid-Schiff staining. It should be emphasized that septal thickening in patients with alveolar proteinosis is usually visible only in regions of ground-glass opacity.

Pulmonary infections appear to develop with increased frequency in patients with both primary and secondary alveolar proteinosis. Nocardia asteroides and Mycobacterium tuberculosis are the most frequent pathogens reported. Mycobacterium avium-intracellulare (MAI) was isolated from 42% of 19 patients with alveolar proteinosis. Disseminated Mycobacterium abscessus infection without cutaneous manifestations, as in the present case, is extremely rare. To our knowledge, no association of M abscessus infection with alveolar proteinosis has been reported in the literature.

Secondary alveolar proteinosis is potentially reversible without undergoing whole-lung lavage if the underlying disease can be controlled. The prognosis of secondary alveolar proteinosis appears to be related to the prognosis of underlying hematologic malignancy and the curability of any associated infection. Resolution of alveolar proteinosis after successful bone marrow transplantation has been described in three patients with acute myelogenous leukemia and in one patient with acute lymphoid leukemia. Spontaneous recovery from respiratory failure caused by secondary alveolar proteinosis in a patient with leukemia has been reported after neutropenia resolved.

Course and Treatment

IV cefotaxime and erythromycin were administered initially. Trimethoprim-sulfamethoxazole could not be used because of drug allergy. Profound hypoxemia, respiratory distress, and hypotension (ie, BP, 80/40 mm Hg) occurred 2 days later, and the patient was intubated and transferred to the ICUs.

The report of blood culture on the seventh day of hospitalization showed M abscessus. Antibiotics were therefore changed to imipenem, amikacin, and oral clarithromycin. Cultures of bone marrow and BAL fluid also grew the same pathogen.

The whole-lung lavage could not be performed due to severe hypoxemia and difficulties inserting the double-lumen catheter. IV medroxyprogesterone was administered, but the patient’s arterial oxygenation and high ventilatory demand did not improve. Follow-up blood cultures on the 21st and 28th days of the hospital stay did not reveal M abscessus. Cytosine arabinoside at a dose of 20 mg/d was administered from the 35th to the 48th day of the hospital stay as a salvage treatment for CML. The patient’s arterial oxygenation and chest radiograph findings gradually improved. He was weaned from mechanical ventilation on the 53rd day of his hospital stay.

Clinical Pearls

1. Alveolar proteinosis should be considered in the differential diagnosis of patients with hematologic malignancies who present with chronic cough, exertional dyspnea, and diffuse alveolar lung infiltrates.
2. Secondary alveolar proteinosis is a possible cause of respiratory failure in patients with hematologic malignancies, especially in myeloid diseases.

3. The most common HRCT findings in patients with alveolar proteinosis are widespread ground-glass opacity and smooth septal thickening in abnormal areas, and the superimposition of these two findings (the so-called crazy paving appearance) is characteristic of this disease.

4. Secondary alveolar proteinosis is potentially reversible without whole-lung lavage, if the underlying disease can be controlled.

5. Pulmonary infections appear to develop with increased frequency in patients with both primary and secondary alveolar proteinosis.

Suggested Readings