

LETTERS TO THE EDITOR

Infection Caused by *Streptococcus pneumoniae*: Cause or Consequence of Alveolar Proteinosis?

To the Editor: Pulmonary alveolar proteinosis (PAP) is a rare disease of unknown origin first described in 1958. It develops as a consequence of abnormal accumulation of surfactant phospholipids in the alveolar space due to defective clearance by macrophages. Patients with PAP are at greater risk of infection, mainly by *Nocardia* species, mycobacteria, and *Pneumocystis jiroveci*. We report a case of PAP with concurrent infection by *Streptococcus pneumoniae* in which treatment of the infection and use of corticosteroids were sufficient to resolve the clinical picture.

Our patient was a 47-year-old male civil servant, a current smoker (20 pack-years) who had an active lifestyle and no surgical or medical history of note. The patient was transferred to the emergency room for syncope. He reported that in the last 3 days he had had a cough with greenish sputum, pleuritic pain in the right hemithorax, poor temperature regulation unverified by thermometer, sweating, and malaise. Tachycardia, oxygen saturation (SaO₂) of 92%, and temperature of 38°C were observed upon physical examination. The following was noted from the analysis: white cell count, 16 410 000/mL with 85% neutrophils; creatinine, 1.5 mg/dL; total bilirubin, 1.8 mg/dL; γ -glutamyl transpeptidase, 90 U/L; ferritin, 952 ng/mL; and C-reactive protein, 20.6 mg/dL. Baseline blood gases analyzed on admission showed the following values: pH, 7.48; PaCO₂, 26 mm Hg; PaO₂, 71 mm Hg; HCO₃⁻, 19.4 mmol/L; and SaO₂, 95%. Chest x-ray revealed diffuse alveolointerstitial infiltrates in both lung fields. A test for specific *Legionella* species antigen in urine was negative, and *S pneumoniae* grew on 2 blood cultures. High

resolution computed tomography (HRCT) of the chest showed numerous areas of ground-glass attenuation in both lung fields. These mainly involved the left upper lobe. Both costophrenic angles and the peripheral regions of the lung fields were relatively clear posteriorly. Some of the lesions had well-defined margins. In several locations thickening of the interlobular septa and ground-glass opacities were observed (Figure). The following values were obtained from respiratory function tests: forced vital capacity (FVC), 4780 mL (100%); forced expiratory volume in 1 second (FEV₁), 3360 mL (90%); FEV₁/FVC, 73.3%; residual volume (RV), 1590 mL (75%); total lung capacity (TLC), 6210 mL (89%); RV/TLC, 79%; and carbon monoxide diffusing capacity, 7.30 mmol/min/kPa (70%). Fiberoptic bronchoscopy showed an edematous and friable mucosa in both bronchial trees. Cytologies of the bronchial aspirate and bronchoalveolar lavage (BAL) fluid were negative for malignancy and the BAL smear showed the following differential cell count: 73% macrophages, 20% lymphocytes, and 7% polymorphonuclear cells. Transbronchial biopsy material showed a pulmonary parenchyma with foamy alveolar macrophages and intraalveolar deposits of an amorphous material which had a positive periodic acid-Schiff reaction (Figure). During admission, treatment commenced with oxygen therapy and levofloxacin and led to a partial improvement in the patient's condition with the occasional presentation of fever. Given the lack of radiologic improvement, treatment with deflazacort (60 mg/d) and omeprazole was prescribed. The fever then completely disappeared and the patient improved significantly and was discharged. During outpatient follow-up visits clinical and radiologic improvement continued and the dosage of corticosteroids could gradually be reduced and finally withdrawn. A chest x-ray a year after admission was normal.

Three clinical forms of PAP have been described: congenital, secondary, and idiopathic or primary. The secondary form of PAP has been related to hematologic diseases (leukemia, myeloma, and some lymphomas); exposure to toxic fumes, inorganic dust, and drugs (busulfan, chlorambucil); and infections (*Nocardia* species, mycobacteria, and *P jiroveci*). The idiopathic, or primary, form of PAP, accounts for 90% of the cases. Mean age at the time of diagnosis is 39 (range, 20 to 50 years) and more patients are males. Most patients with PAP have progressive

dyspnea of insidious onset and cough. The presence of hemoptysis or chest pain is rare. Bilateral interstitial infiltrates with a poorly defined micronodular pattern—often with predominance in the perihilar region—can be observed on chest x-ray. This finding is indicative of pulmonary edema. No other radiographic signs, such as those of left heart failure, are noted. HRCT shows diffuse and patchy ground-glass opacities associated with a superimposed linear pattern corresponding to thickening of the interlobular and intralobular septa. Centrally or peripherally distributed, this pattern is known as crazy-paving. Although highly indicative of PAP, crazy-paving can also be observed in other conditions, such as infection by *P jiroveci*, neoplastic disease (bronchioloalveolar carcinoma), idiopathic diseases (sarcoidosis, nonspecific interstitial pneumonia), diseases caused by inhalation, pulmonary hemorrhage, and respiratory distress.¹ In general restrictive ventilatory defects as well as disproportionate and marked reduction in carbon monoxide diffusing capacity are usually observed during lung function tests. An opalescent, viscous and milky-looking material, together with foamy alveolar macrophages, an increased number of lymphocytes, and a small number of other inflammatory cells can be found in the BAL fluid.² A transbronchial or open lung biopsy is the definitive diagnostic test for PAP, although in many cases this is unnecessary.³

Patients with PAP have a greater risk of developing infection by respiratory pathogens.⁴ The presentation was acute in our patient, *S pneumoniae* grew on blood culture, and there was good response to antibiotic and corticosteroid treatment. This led us to ask whether the infection was the cause of PAP rather than its consequence as has been described in a subgroup of patients with secondary proteinosis. Although we have found no other reports of a favorable response of proteinosis to corticosteroids, the anti-inflammatory action of these drugs added to the effect of the antibiotic itself was probably a determining factor in our patient's outcome. Although some primary

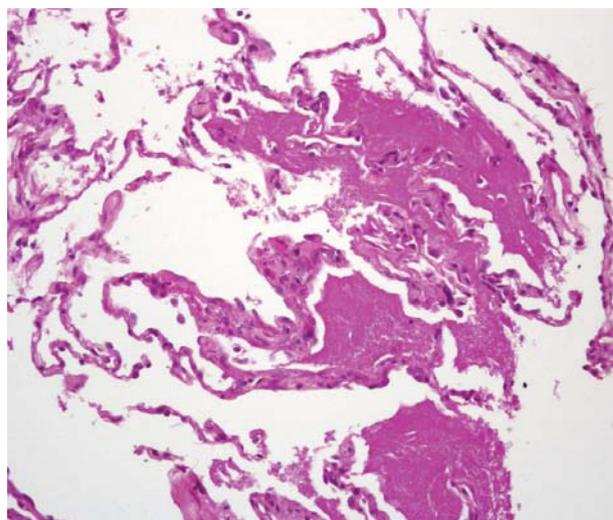


Figure. Chest computed tomography scan that shows the typical ground-glass pattern with alveolar opacities and a patchy and diffuse distribution of linear septal thickening. The lower part shows details of the transbronchial biopsy where it can be seen that the alveolar spaces are filled with an eosinophilic and acellular material that had a positive periodic acid-Schiff reaction (3 washes, 20 minutes each).

forms of PAP go into remission spontaneously, favorable results have been described with granulocytic and microcytic colony stimulating factor.⁵ Despite progress made in treatment, total pulmonary lavage⁶ is still the treatment of choice with a rate of recurrence—albeit transient—of 80%.⁴

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