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CME CREDIT HOURS

Nonresolving alveolar infiltrates in a 43-year-old woman

A 43-year-old woman presents with a 1-year history of intermittent nonproductive cough. During this year, she received multiple courses of antibiotics for recurrent pneumonia. Initial chest radiographs during this time showed bilateral infiltrates. There was subjective improvement in response to antibiotics; however, follow-up chest radiographs between episodes were not obtained.

Three months before presentation her symptoms worsened, and she began experiencing low-grade fever, and dyspnea on climbing one half flight of stairs. At that time, her oxygen saturation was noted to be 81% on room air at rest, and supplemental oxygen was prescribed. The patient quit smoking 3 months before presentation; she had smoked one pack of cigarettes per day for 13 years. No environmental exposures were identified. An earlier echocardiogram was normal. The patient has no risk factors for human immunodeficiency virus (HIV) infection, and is immunocompetent. She has not experienced hemoptysis.

Physical examination reveals bilateral rales but no other abnormalities. Cardiac examination reveals no S_3 gallop, clubbing, edema, or jugular venous distension. Pulmonary function tests show decreased diffusion capacity. The complete blood count is normal; the lactate dehydrogenase level is 479 U/L (normal range 200–380). The chest roentgenogram and computed tomographic (CT) scan are shown in **FIGURES 1 and 2**.

A DIAGNOSIS OF EXCLUSION

Which of these processes most likely accounts for these radiographic findings?

- ☐ Pulmonary edema
- ☐ Alveolar hemorrhage
- ☐ Pulmonary alveolar proteinosis
- ☐ Bacterial infection
- ☐ Bronchoalveolar cell carcinoma

The chest roentgenogram shows a diffuse alveolar filling process, but it is not clear what fills the alveoli: water, blood, inflammatory cells, bacteria, lipids, or cancer cells.

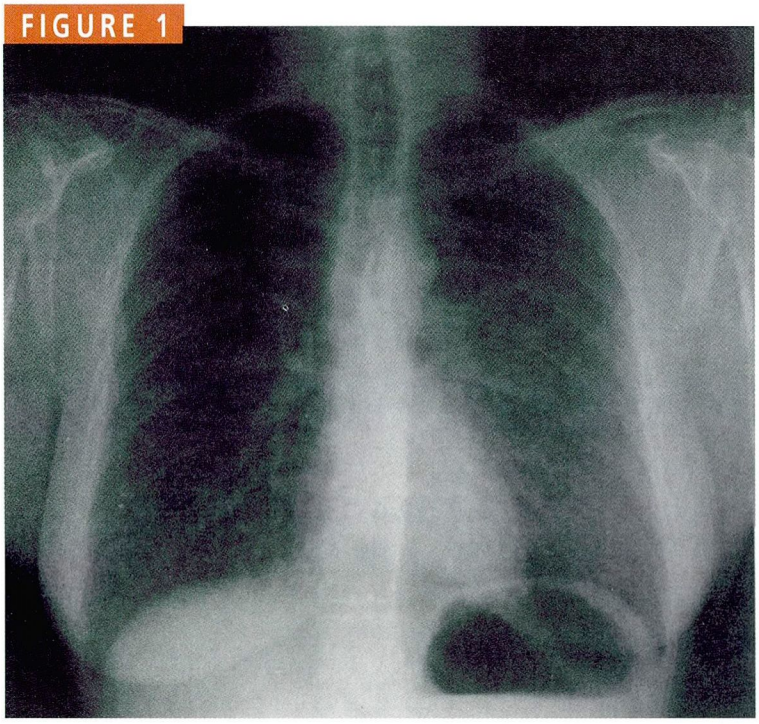
Pulmonary edema is highly unlikely in this patient, given her age, normal physical examination, and normal echocardiogram. Further, absent on chest roentgenogram are signs of left ventricular dysfunction such as cardiomegaly, pleural effusions, or Kerley B lines.

The lack of sputum production, the chronicity of the disease, and the lack of response to multiple courses of antibiotics argue against a bacterial infection.

Alveolar hemorrhage is not likely; although not all patients with alveolar hemorrhage present with hemoptysis, this patient's nonproductive cough and normal hematocrit argue against an alveolar hemorrhagic syndrome such as Wegener's granulomatosis or Goodpasture's syndrome.

Bronchoalveolar cell carcinoma is a possibility. Proliferating neoplastic cells lining the small airways and airspaces in bronchoalveolar

FIGURE 1



Chest roentgenogram, anterior-posterior view.

cell carcinoma can produce a radiographic pattern resembling pneumonia and can be isolated to one area of the chest or be multicentric. The disease is typically indolent and chronic, consistent with this case. However, the "bat-wing" distribution seen here would be an unusual radiographic manifestation of bronchoalveolar cell carcinoma.

The remaining possibility is that the alveoli are filled with lipid or lipoprotein, possibly due to lipid aspiration or pulmonary alveolar proteinosis. The bat-wing pattern of infiltrates in this patient's roentgenogram suggests pulmonary alveolar proteinosis.

WHICH DIAGNOSTIC STUDY TO PERFORM?

■ What would be the most appropriate diagnostic study to perform next?

- ☐ Mediastinoscopy
- ☐ Bronchoscopy
- ☐ Open lung biopsy
- ☐ Ventilation-perfusion (V/Q) scanning

The most appropriate next diagnostic study would be bronchoscopy, which allows one to sample alveolar epithelial lining, fluid, and small pieces of the lung parenchyma. This test would distinguish between cancer, infection, and other diseases.

If bronchoscopy does not establish a diagnosis, then open lung biopsy would be required. Given the patient's radiographic findings, we can expect a V/Q scan to be abnormal, and its results would have little impact on management decisions, especially as this patient has a low prior probability of pulmonary embolism.

With no evidence of mediastinal abnormality (ie, lymphadenopathy), a mediastinoscopy would not be indicated.

Bronchoalveolar lavage and transbronchial biopsy were performed. The lavage effluent had a milky appearance, and proteinaceous material settled to form a layer at the bottom of a saline solution. On laboratory analysis of this material, the periodic acid-Schiff (PAS) test yielded a positive result. Transbronchial biopsy established the diagnosis of pulmonary alveolar (lipo)proteinosis, with PAS-positive material filling the alveolar spaces.

PULMONARY ALVEOLAR PROTEINOSIS

■ Which of the following statements about the natural history of pulmonary alveolar proteinosis are true?

- ☐ Patients may improve without therapy
- ☐ Steroids have been shown to improve outcome
- ☐ Pulmonary alveolar proteinosis may be complicated by superinfection with *Nocardia*
- ☐ All of the above

In pulmonary alveolar proteinosis, first described by Rosen in 1958,[1] a lipid-rich insoluble proteinaceous material similar to surfactant accumulates in the alveoli and bronchioles. Two processes or a combination of both may account for this accumulation: overproduction of surfactant by type II pneumocytes or decreased reabsorption by alveolar macrophages.[2]

Evidence that alveolar macrophage dysfunction is a cause of pulmonary alveolar proteinosis comes from studies of mice that lack either granulocyte macrophage colony-stimulating factor (GM-CSF) or one of its receptor components.[3] These mice develop a lung process similar to pulmonary alveolar proteinosis, presumably because their alveolar macrophages lack GM-CSF-mediated activity.

Pulmonary alveolar proteinosis is termed "secondary" when it occurs in association with other conditions such as hematologic malignancies (eg, leukemia), infections (eg, *Pneumocystis carinii* pneumonia), or exposure to certain dusts including silica and aluminum. The term "primary" applies when there is no known exposure or associated disease.[4]

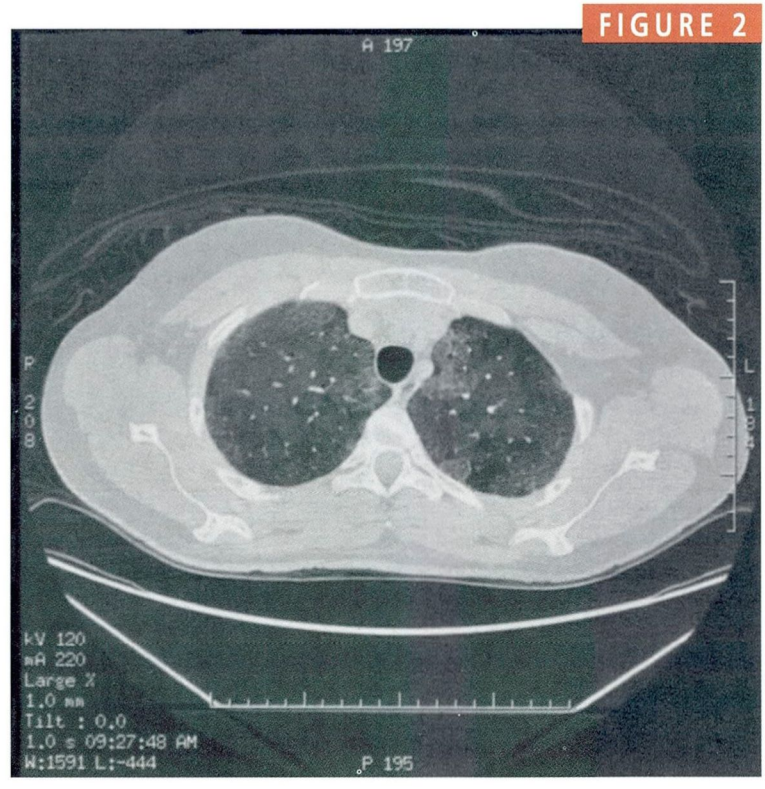
Signs and symptoms of pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis most commonly develops in adults 20 to 50 years of age, and is twice as common in men as women. Dyspnea is the most common presenting symptom[2]; other symptoms include cough, fever, chest pain, and weight loss. Some patients have no symptoms in spite of prominent chest radiographic abnormalities. Rales and clubbing may be present, but often there are no physical signs. The complete blood count is usually normal, but occasional eosinophilia may occur. The LDH level is often elevated,[5] but this test is neither sensitive nor specific for this disease. Pulmonary function tests may reveal a restrictive defect, but a decreased diffusing capacity for carbon monoxide is more common.

The chest radiograph usually shows a relatively symmetric bilateral alveolar filling process. Infiltrates are most prominent in the perihilar region, and there is a relative sparing of the costophrenic angles, a pattern dubbed the bat-wing pattern.[2] There have also been reports of asymmetric, patchy, alveolar-interstitial infiltrates or diffuse reticulonodular opacities. Pleural involvement and lymphadenopathy are rare. Chest CT scans often show a ground-glass alveolar filling process, which may be patchy or diffuse. A pattern of consolidation that is sharply demarcated from normal lung has been called a "geographic pattern" of infiltrates.[6] Ill-defined nodules and thickened interlobular septa may also be seen, but air bronchograms (ie, chest radiographic findings indicating lung consolidation surround the bronchus) are rare .

In up to 90% of cases, flexible fiber-optic bronchoscopy can establish the diagnosis. The fluid obtained by bronchoalveolar lavage is often thick, milky, and PAS-positive and settles into a layer on the bottom of a container of normal saline. Microscopic evaluation of this fluid shows a paucity of macrophages,[2] and acellular eosinophilic bodies. Histologic studies show alveoli flooded with a PAS-positive material that is biochemically similar to surfactant.[2] The alveolar architecture is usually preserved (**FIGURE 3**), but septal thickening may occur.

FIGURE 2



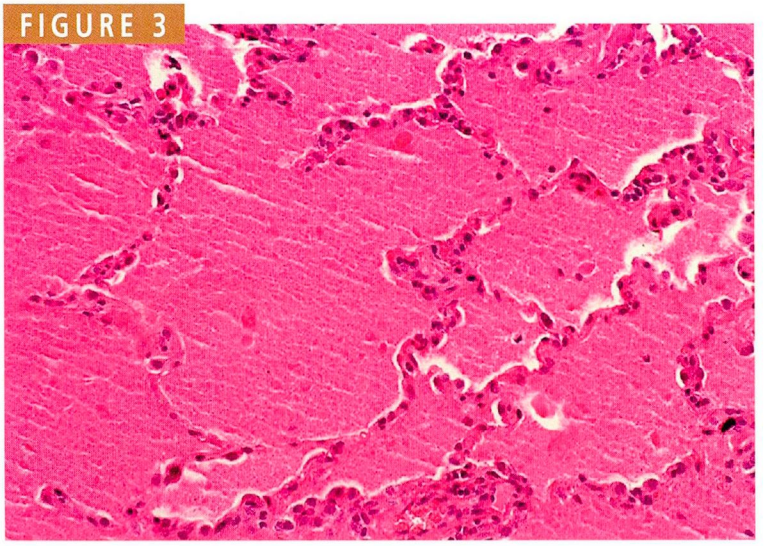
Computed tomographic scan of the chest.

Pulmonary alveolar proteinosis may remit spontaneously

Because this disease is uncommon and available series are small (ie, < 90 patients) and of short duration, its natural history is poorly understood.

In 1965, Larson and Gardinier[7] described six patients with pulmonary alveolar proteinosis. In two, dyspnea began insidiously and the disease progressed slowly until the patient died, either of hypoxemia or superinfection; another two had dyspnea but no progression of the disease, and the remaining two patients improved. The patients who improved appear to have done so spontaneously, because no therapy available at that time was effective. In a recent study by Asamoto et al,[5] 16 of 17

FIGURE 3



Photomicrograph of lung tissue from a patient with pulmonary alveolar proteinosis (hematoxylin-eosin stain, x 200).

patients for whom lavage was not deemed necessary had symptoms that spontaneously resolved.

Superinfection occasionally complicates pulmonary alveolar proteinosis; organisms include bacteria, viruses, *Aspergillus*, *mycobacteria*, *Pneumocystis carinii*, and *Nocardia asteroides*.[4]

MANAGING PULMONARY ALVEOLAR PROTEINOSIS

■ Appropriate management for this patient would include which of the following?

- ☐ Intravenous corticosteroids
- ☐ Cytotoxic agents
- ☐ Aerosolized trypsin
- ☐ Whole-lung lavage with normal saline

Over the years, many medications for pulmonary alveolar proteinosis have been tried, including corticosteroids, iodide, aerosolized trypsin, and bronchodilators. However, none of these has been shown to be effective.

The only treatment shown to alleviate symptoms and increase oxygen saturation in pulmonary alveolar proteinosis is bilateral whole lung lavage. The procedure is performed in the operating room with the patient under general anesthesia and intubated with a dual-lumen endotracheal tube, which isolates the lavaged lung from the ventilated lung. One lung is filled with normal saline and drained after a few minutes. This process is repeated until the effluent is clear. Chest physiotherapy as externally applied chest percussion is usually performed during the lavage to improve clearance. At the end of the procedure the lavaged lung is reinflated and the endotracheal tube is removed. The procedure may be repeated on the contralateral lung within 1 or 2 days. In the past, the lavage fluid consisted of saline with acetylcysteine and heparin, but saline by itself has been found equally effective.[4]

After lavage, patients usually experience rapid improvement in their symptoms and oxygen saturation. Improvement in radiographic findings often lags behind clinical improvement.

There is no consensus about the indications for whole-lung lavage. Most clinicians rely on a combination of symptoms and physiologic findings, such as dyspnea on exertion and worsening hypoxemia with exercise,[2] to decide when to proceed with lavage. Many patients require repeat lavage, but one patient, followed for 20 years, did not require repeat lavage over a 13-year interval.[4] Since whole-lung lavage was introduced in 1972, several studies have shown that only about 10% to 20% of cases are refractory to treatment.[2,5] In one study, which followed 51 patients for up to 23 years after lavage, pneumothorax occurred four times, and no patients died of pulmonary alveolar proteinosis.[5] However, the paucity of long-term follow-up after lavage, and the disease's propensity for resolving spontaneously, precludes a clear picture of its long-term benefits.

Our patient underwent whole-lung lavage on consecutive days, after which her symptoms quickly resolved and her oxygen saturation improved markedly. She was discharged without supplemental oxygen on the day after lavage was completed. ■

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