Dyspnea, Cough, and Interstitial Lung Disease in a 32-Year-Old Smoker*

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A 32-year-old woman was referred because of progressive fatigue, dyspnea on exertion, and nonproductive cough of 1 year's duration. She had a 10-pack/y history of cigarette smoking, but denied a prior history of cardiopulmonary disease.

Physical Examination


Laboratory Findings

WBC: 8,500/µl with normal differential; hematocrit, 42 percent. Blood chemistry: normal. Serology: negative for antinuclear antibodies and rheumatoid factor. Pulmonary function: total lung capacity, 77 percent of predicted; FEV₁/FVC 78 percent of predicted, DCO, 26 percent of predicted. Radiology: chest radiograph (Fig 1) showed mid- and lower-zone cysts. Fiberoptic bronchoscopy with transbronchial biopsy: nondiagnostic.

What is the most likely diagnosis?

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Figure 1. Posteroanterior chest radiograph shows mid- and lower-zone cystic opacities with sparing of costophrenic angles.

Figure 2. High-resolution CT scan of chest shows marked profusion of cystic shadows (thin arrow) with few nodules (thick arrow) typical of advanced disease.
Dyspnea, Cough, and ILD (Wade, King)

Diagnosis: Pulmonary histiocytosis X (eosinophilic granuloma of the lung)

The constellation of dyspnea, cough, finger clubbing, reduced Dco, and radiographic findings of mid- and upper-zone nodular opacities and cysts in a young cigarette smoker are highly suggestive of pulmonary histiocytosis X.

Pulmonary histiocytosis X is a Langerhans cell granulomatous interstitial lung disease of unknown etiology occurring almost exclusively in smokers, usually between the ages of 20 and 40 years. Patients typically present with nonproductive cough and dyspnea on exertion. Weight loss, fever, and fatigue are other manifestations. Chest pain is common and results from either granulomatous rib lesions or pneumothorax, which occurs in 25 percent of patients. Occasionally, patients present with diabetes insipidus as a result of hypothalamic involvement. A surprising number of patients (approximately 25 percent) are asymptomatic despite extensive radiographic evidence of disease.

The physical examination is often normal even in symptomatic patients. Inspiratory crackles occur in a minority of cases. Digital clubbing, as seen in the present case, is rare and usually a late manifestation of the disease. Laboratory findings are nonspecific. Notably, peripheral eosinophilia is not a feature of pulmonary histiocytosis X. Pulmonary function tests reveal obstructive, restrictive, or mixed patterns, and reductions in Dco are seen in most symptomatic patients. In progressive or late-stage disease, air trapping and hyperinflation occur as the granulomatous inflammation is replaced by cysts and bullae; these changes do not correlate with the degree of smoking.

A diagnosis of pulmonary histiocytosis X should be suspected in a smoker whose chest radiograph shows mid- and upper-zone nodular opacities and cysts, normal or increased lung volume, and sparing of the costophrenic angles. Unfortunately, this characteristic combination of findings is often not present. The chest radiograph in the present case demonstrated mid- and lower-zone cystic opacities with sparing of the costophrenic angles (Fig 1). High-resolution computed tomography (HRCT) of the chest is very helpful in suggesting the diagnosis of pulmonary histiocytosis X. This patient showed marked profusion of cystic shadows with few nodules typical of advanced disease (Fig 2). The chest HRCT findings of upper lobe micronodules and cysts (often bizarrely shaped) are virtually pathognomonic of pulmonary histiocytosis X. Serial chest HRCT scans may demonstrate a sequence of progression from a predominance of nodular opacities to cavitating nodules, thick-walled cysts, confluent cysts, and honeycombing. The literature suggests a high spontaneous remission rate of pulmonary histiocytosis X marked by a regression of nodules on chest radiograph. However, chest HRCT frequently demonstrates extensive cystic changes in these cases. Therefore, true regression of disease probably occurs less frequently than previously thought.

Tissue examination remains the definitive diagnostic test. Although transbronchial biopsy specimens may occasionally be sufficient, open-lung biopsy is often required. In the lung, granulomatous inflammation of the alveolar septa, terminal airways, and perivascular interstitium forms stellate nodules composed of clusters of Langerhans cells, eosinophils, plasma cells, and occasional multinucleated giant cells. Langerhans cells have distinctive features under light microscopy; however, the electron microscopic demonstration of small, rodlike, intracytoplasmic inclusions called X bodies or Birbeck granules is pathognomonic. Unfortunately, electron microscopy is time consuming and expensive and requires fresh or frozen tissue. In addition, sampling errors are a potential problem of any ultrastructural analysis.

Tissue immunostaining for S-100 protein distinguishes Langerhans cells from other histiocytes and is a useful adjunct in difficult cases. It can be performed on routinely fixed tissue and is less expensive than electron microscopy. Occasionally, Langerhans cells are found in other interstitial lung diseases (especially idiopathic pulmonary fibrosis). In pulmonary histiocytosis X, Langerhans cells are characteristically found in clusters and significantly outnumber those seen in other lung diseases. Absolute quantitative guidelines for diagnosis of pulmonary histiocytosis X have not been established.

Langerhans' cells also express CD1 antigen (OKT6), and recent data suggest that the finding of more than 5 percent CD1-positive cells in bronchoalveolar lavage fluid reliably identifies patients with pulmonary histiocytosis X. Fewer numbers of CD1-positive Langerhans cells can be recovered from bronchoalveolar lavage fluid of patients with other interstitial lung diseases. Immunoperoxidase staining for CD1-positive Langerhans cells requires fresh bronchoalveolar lavage fluid. This method has the potential of becoming a rapid, relatively noninvasive diagnostic tool. Quantitative criteria for diagnosis have not been conclusively established. In cases of progressive disease with extensive fibrosis, the number of Langerhans cells present in either tissue specimens or bronchoalveolar lavage fluid decreases dramatically. Diagnosis at this stage can be difficult regardless of the laboratory methods used.

The clinical course is unpredictable. A large percentage of patients experience stable, persistent disease, but many have a progressive course. Extremes of age, constitutional symptoms, significant radiographic abnormalities at presentation, reduced Dco, and continued cigarette smoking are associated with a poor
outcome. Corticosteroids may be helpful in symptomatic cases, but there is a paucity of data to support their role.

The present case was diagnosed by open-lung biopsy. The patient was treated with corticosteroids; however, she continues to smoke and has experienced a progressive worsening in respiratory symptoms. Repeat pulmonary function tests 2 years after presentation revealed minimal obstruction with hyperinflation and significant air trapping. The chest radiographic findings remain unchanged.

CLINICAL PEARLS

1. Interstitial lung disease in the setting of hyperinflation and/or obstructive physiology suggests a limited number of possibilities: pulmonary histiocytosis X, lymphangioleiomyomatosis; stage III sarcoidosis; chronic hypersensitivity pneumonitis; any interstitial lung disease associated with emphysema; cystic fibrosis; and tuberous sclerosis.

2. The presence of cysts and nodules on HRCT in a young smoker is virtually pathognomonic for pulmonary histiocytosis X.

3. The presence of numerous Langerhans cells in transbronchial biopsy specimens and bronchoalveolar lavage fluid as determined by S-100 immunostaining or CD1 positivity may preclude the need for open-lung biopsy.

4. Interstitial lung diseases associated with cigarette smoking include pulmonary histiocytosis X, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonitis.

SUGGESTED READING

Auerswald U, Barth J, Magnussen H. Value of CD-1 positive cells in bronchoalveolar lavage fluid for the diagnosis of pulmonary histiocytosis X. Lung 1991; 169:305-09

