Two Cases of Interstitial Infiltrates with Hyperinflation

Clinical Conference in Pulmonary Disease from the
Ohio State University College of Medicine, Columbus

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CASE PRESENTATIONS

CASE 1

A 34-year-old woman was transferred to The Ohio State University Hospitals for evaluation of recurrent pneumothoraces. She was in good health until approximately one year prior to admission when she developed acute shortness of breath and was found to have left pneumothorax. Her chest roentgenogram also revealed diffuse interstitial infiltrates. Over the next year she had two right pneumothoraces and four left pneumothoraces treated successfully with chest tube drainage. Serial chest roentgenograms revealed a persistent, diffuse interstitial pattern. Her past medical history was unremarkable including no previous cigarette use and a normal menstrual history. At the time of admission, auscultation of the lungs revealed bilateral, diffuse rales and decreased breath sounds over the right hemithorax. There was also a grade 2/6 systolic ejection murmur audible in the cardiac apex. There was no cyanosis, clubbing, or peripheral edema.

An admission chest roentgenogram showed a diffuse bilateral, reticulonodular pattern with hyperinflated lungs, right pneumothorax and a small right pleural effusion (Fig 1). Results of routine laboratory studies were normal. Right thoracentesis revealed a transudative effusion. Arterial blood gas analysis showed a pH of 7.43, PaO₂ of 72 mm Hg, and PaCO₂ of 22 mm Hg. Pulmonary function studies showed an FEV₁/FVC ratio of 47 percent and TLC of 145 percent of predicted. The Dco was 42 percent of predicted. An open lung biopsy was performed for diagnostic purposes.

CASE 2

A 41-year-old woman was admitted to The Ohio State University Hospitals for evaluation of dyspnea on exertion. She was well until five months prior to admission when she noticed dyspnea on climbing one flight of stairs. Her chest roentgenogram taken at a local hospital was reported to show interstitial pneumonia. She denied fever, cough, weight loss or hemoptysis. She had a 20-pack-year history of smoking. Occupational exposures included working with Masonite for one year and fiberglass for three years. She denied any drug ingestion. The remainder of her history, including menstrual history, was unremarkable. Results of the physical examination at the time of admission were entirely normal.

Routine laboratory studies gave normal findings and assays for antinuclear antibodies and rheumatoid factor were negative. Levels of complement were normal. Admission chest

Figure 1. Admission chest roentgenogram of patient 1 demonstrating diffuse interstitial infiltrates, right pneumothorax and right pleural effusion.
Dr. Whitcomb: The open lung biopsies obtained from each patient revealed pathologic changes consistent with chronic fibrosing alveolitis (CFA). These results were surprising since we suspected that both patients had lymphangioleiomyomatosis (LAM). The clinical, roentgenologic and physiologic manifestations of CFA and LAM are quite distinct (Table 1) and, therefore, the two diseases are not usually confused. We will begin our discussion today by contrasting the essential features of these two diseases.

Dr. Schonfeld: Lymphangioleiomyomatosis and chronic fibrosing alveolitis are both considered interstitial lung diseases. The majority of patients with CFA are between the ages of 40 to 70 years when the diagnosis is made and slightly more than half are men. Exertional dyspnea is the presenting complaint of almost all patients. The great majority of patients (85 percent) also have a nonproductive cough, while constitutional symptoms of fatigue, weight loss, and arthralgias are present in only a small percentage.1 In contrast, LAM is a rare disease of women of childbearing age. The majority of patients with this disease also present with progressive dyspnea. Pleural effusion has been observed in 75 percent and spontaneous pneumothorax in 40 percent of reported cases. Hemoptysis, resulting from obstruction and disruption of pulmonary veins, has been observed in 40 percent of reported cases. Spontaneous lymphatic rupture resulting in the develop-

Table 1—Comparison of CFA and LAM

<table>
<thead>
<tr>
<th>Clinical</th>
<th>CFA</th>
<th>LAM</th>
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<tbody>
<tr>
<td>Sex</td>
<td>Male:Female — 1.1:1</td>
<td>Exclusively female</td>
</tr>
<tr>
<td>Age</td>
<td>40-70 predominantly</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Symptoms/Signs</td>
<td>Progressive dyspnea</td>
<td>Progressive dyspnea</td>
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<tr>
<td></td>
<td>Non-productive cough</td>
<td>Pneumothorax</td>
</tr>
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<td></td>
<td>Constitutional symptoms</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td></td>
<td>Fatigue, weight loss, arthralgias</td>
<td>Pleural effusion/chylothorax</td>
</tr>
<tr>
<td>Pathologic</td>
<td>Alveolar wall inflammation and fibrosis</td>
<td>Atypical smooth muscle along lymphatics</td>
</tr>
<tr>
<td></td>
<td>Peribronchiolar inflammation and fibrosis</td>
<td>Peribronchiolar smooth muscle infiltration</td>
</tr>
<tr>
<td>Roentgenologic</td>
<td>Small lungs</td>
<td>Large lungs</td>
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<tr>
<td></td>
<td>Basilar predominance</td>
<td>Diffuse involvement</td>
</tr>
<tr>
<td></td>
<td>Reticular, reticulonodular, or ground-glass infiltrates</td>
<td>Reticular infiltrates</td>
</tr>
<tr>
<td></td>
<td>Honeycombing pattern at end-stage</td>
<td>Pneumothorax/pleural effusion</td>
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<tr>
<td></td>
<td></td>
<td>Honeycombing pattern at end-stage</td>
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<tr>
<td>Physiologic</td>
<td>Restrictive pattern</td>
<td>Obstructive pattern</td>
</tr>
<tr>
<td></td>
<td>Hypoxemia</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td></td>
<td>Dco ↓</td>
<td>Dco ↓</td>
</tr>
<tr>
<td>Treatment</td>
<td>Corticosteroids</td>
<td>Castration</td>
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<tr>
<td></td>
<td></td>
<td>Medroxyprogesterone</td>
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ment of chylothorax or chylous ascites is a common complication.\textsuperscript{2,4}

The differences in the roentgenologic and physiologic manifestations of these two diseases can be attributed to the distinct pathology of each disease. CFA is characterized by varying degrees of inflammation and fibrosis in the alveolar wall (Fig 3). Inflammatory infiltrates include neutrophils, eosinophils, and mononuclear cells. Large cuboidal-shaped type 2 pneumocytes may also be observed lining the alveolar air space. Increased amounts of smooth muscle are usually found in the interstitial space. Peribronchiolar inflammation and fibrosis may also be present, but usually is less prominent than the alveolar component.\textsuperscript{1}

LAM is characterized pathologically by focal proliferation of atypical smooth muscle along pulmonary lymphatic channels (Fig 4). The aberrant muscle masses may also extend into the adjacent walls of some bronchioles and venules. In addition to smooth muscle hyperplasia, emphysematous lesions closely resembling honeycombing, but recently characterized as proximal and irregular emphysema, are distributed throughout the lung. These lesions are often located near the pleural surface and are thought to be caused by direct compression of small airways by abnormal muscle masses resulting in air flow obstruction and distal hyperinflation.\textsuperscript{2,3}

The roentgenographic manifestations of both diseases are quite varied. The majority of patients with CFA have small-appearing lungs roentgenographically with bilateral reticular, reticulonodular, or ground glass pulmonary infiltrates located predominantly in the lower lung fields. Less commonly, localized linear, nodular, or ill-defined densities may be seen.\textsuperscript{1,5} In at least 10 percent of the patients, the chest roentgenogram will be normal when the patient first presents.\textsuperscript{6} If the disease progresses, honeycombing and coarse linear infiltrates may develop. Pneumothoraces are uncommon and pleural effusions are rarely seen.\textsuperscript{1}

Early in the course of LAM, the roentgenogram may also be normal despite the fact that small muscle masses and emphysematous lesions are present pathologically.\textsuperscript{4} During this stage of the disease, the only roentgenographic abnormalities may be a pneumothorax or pleural effusion. As the
disease progresses, diffuse parenchymal infiltrates become apparent. Characteristically, the pattern consists of tiny, irregular nodules distributed uniformly throughout the lungs. These nodular lesions are thought to represent the small masses of hyperplastic smooth muscle seen histologically. Linear infiltrates, usually of a fine reticular nature, may also be observed. A coarse, reticular pattern may be observed in some patients and is thought to represent lymphatic engorgement and interstitial edema caused by obstruction of lymphatic channels. The parenchymal infiltrates may be due to localized edema or hemorrhage and, therefore, are evanescent in nature. A pattern suggesting honeycombing may also be observed and, in contrast to CFA and other fibrosing lung diseases, is distributed more diffusely throughout the lung and is not associated with severe distortion of the lung parenchyma. An important point in the roentgenologic diagnosis of this disease is that, in spite of the presence of interstitial infiltrates, the lungs appear large. Serial roentgenograms may demonstrate progressive enlargement of the lungs with persistence and progression of the parenchymal infiltrates.2,3,8

Physiologically, gas exchange is markedly abnormal in both diseases. Hypoxemia and a markedly reduced diffusing capacity are observed in most patients.1,2 CFA characteristically causes a pure restrictive ventilatory defect with a low total lung capacity (TLC) and normal flow rates.1,5,7 The distinguishing feature of LAM is that the total lung capacity is increased and marked air flow obstruction is usually present. These physiologic abnormalities are felt to be caused by extensive peribronchial smooth muscle hyperplasia resulting in the narrowing of airway lumens and the development of emphysematous lesions observed pathologically.2,4

**Dr. Whitcomb:** To summarize, CFA and LAM have distinct clinical, roentgenologic, and physiologic manifestations and should rarely be confused. In fact, it has been stated in the literature that the combination of air flow obstruction and severe gas exchange abnormalities, large lungs, and interstitial infiltrates occurring in a woman of childbearing age is virtually diagnostic of LAM.5,9 Our two cases clearly emphasize that the clinical diagnosis alone is inadequate and that tissue diagnosis must be obtained to substantiate this diagnosis. Due to the heterogeneous involvement of CFA and LAM, open lung biopsy is more reliable for diagnostic purposes than transbronchial biopsy which may be associated with sampling error.12 This is particularly important since the approach to therapy of the two diseases is so different. Before discussing therapy, however, Dr. Dixon will tell us why our two patients may have had such impressive air flow obstruction that they mimicked patients with LAM.

**Dr. Dixon:** Involvement of small airways in CFA has been a subject of interest to a number of investigators in recent years. Physiologic evidence of increased resistance to air flow in small airways was first demonstrated by Ostrow and Cherniack.10 Although these changes are not universally found in this disease, 70 percent of the patients in one study had physiologic evidence of small airways involvement.1 Subsequently, Fulmer et al11 demonstrated a morphologic correlation with the physiologic changes of small airways disease. In their study, the degree of peribronchial inflammation and fibrosis correlated in a semi-quantitative way with the physiologic abnormalities. In other forms of interstitial lung disease, it has been shown that progressive small airways obstruction may result in an obstructive, rather than a pure restrictive ventilatory pattern by pulmonary function testing. This has been documented best in sarcoidosis and extrinsic allergic alveolitis.12,18 In addition, McCarthy et al14 have reported two patients with CFA who subsequently developed severe chronic obstructive pulmonary disease. Thus, it seems clear that peribronchial inflammation and fibrosis may produce extensive small airway narrowing with evidence of air flow obstruction and hyperinflation in some patients with CFA and other interstitial lung diseases. In both of our patients, pathologic studies showed considerable peribronchial inflammation and fibrosis, although this was not quantitated in any manner. Our cases are exceptional since the degree of airflow obstruction observed in our patients was more severe than that observed in previously reported cases.12 Obviously, it is possible that our patients had some form of primary airway disease that had gone unrecognized. Although patient 2 was a heavy smoker, airway obstruction to the degree observed in this patient is generally not seen in patients with chronic bronchitis at this early age.15 Since pathologic material was obtained from both patients, we have no evidence of another disease that would explain the air flow obstruction.

**Dr. Whitcomb:** As mentioned previously, the therapeutic approach to these two diseases is quite different. Administration of corticosteroids is the standard therapy for CFA.5 Since the majority of patients fail to respond to corticosteroids, regimens containing various immunosuppressive agents have been employed. To date, there is no convincing evidence that these drugs are effective in the treatment of the disease.1,16

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There have been several exciting observations made recently in patients with LAM suggesting a novel approach to the treatment of this disease. McCarty et al. recently reported a patient treated with medroxyprogesterone who had symptomatic, roentgenologic, and physiologic improvement over a three-year period. Of great interest is the fact that the investigators were able to demonstrate progesterin binding receptors in lung tissue obtained from this patient and not in normal lung tissue. There have also been reports of improvement or stabilization of status in LAM following oophorectomy. The inconsistent improvement following hormonal manipulation raises the possibility that response may be limited only to those patients who have hormone receptors in their lungs.

Following open lung biopsy, both patients were treated with corticosteroids. Dr. Dixon, can you give us a follow-up on these patients?

Dr. Dixon: Despite administration of corticosteroids, patient 1 had progressive disease. She was actually referred to our institution quite late in the course of her disease after having been treated by her private physician. Within a month of referral to us, she died of progressive respiratory failure. Unfortunately, no post-mortem examination was performed. We did obtain the slides of her open lung biopsy and, because of the high index of suspicion that she had LAM, asked Dr. Charles Carrington to review them for us. Dr. Carrington concurred with the interpretation of our pathologist.

Patient 2 has now been followed-up for 18 months. She was initially treated with high-dose corticosteroids which were gradually tapered over a six-month period. She had a very dramatic response to therapy. The residual volume and total lung capacity decreased, the vital capacity increased and the diffusing capacity was unchanged. She remains symptomatic with minimal exertion.

REFERENCES


