Acute Interstitial Pneumonitis

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DR. ROBERT BLAKE (*Associate Professor of Family and Community Medicine*): When we see a patient with fever, respiratory symptoms, and pulmonary infiltrates on x-ray film, we usually think of an infectious process. The case to be discussed today reminds us that noninfectious conditions can also present in this way. In addition to creating an opportunity to focus on the workup and treatment of interstitial lung disease, our management of this patient involved important psychosocial issues.

The patient for discussion today is a 67-year-old woman who was admitted to the hospital with a four- to five-week history of progressive fatigue, generalized weakness, nonproductive cough, dyspnea on exertion, and anorexia with a 10-lb weight loss. During the immediately preceding two weeks she had experienced frequent fevers to 101 to 103 °F with occasional chills. She had been seen several times as an outpatient and treated with short courses of cefaclor and tetracycline without benefit. Two weeks prior to admission findings on a chest x-ray film had been normal. She had a history of multiple respiratory and drug allergies and had been taking oral theophylline chronically for asthma. She had a remote and poorly documented history of rheumatoid arthritis but had been free of joint symptoms for at least ten years. She had smoked cigarettes for many years but had stopped six months before admission. Also, six months previously she had retired from a long-term job as a municipal election manager in a small town in Indiana and had moved to Columbia to be near a daughter. She had been a widow for many years. At the time of the onset of her symptoms, she had just returned from a three-month stay in Kuwait, where she was exposed to birds and to a dust storm but not to contaminated food or water.

On admission examination, she was a moderately obese woman in mild respiratory distress with a respiratory rate of 24/min, a pulse rate of 95 beats per minute, and an oral temperature of 103 °F. The only abnormal findings were bibasilar rales and scattered rhonchi and wheezes. Her chest x-ray film showed bilateral diffuse interstitial and alveolar infiltrates with no effusion or adenopathy. Blood gases on room air were partial arterial oxygen pressure (PaO_2) 50 mmHg, partial arterial carbon dioxide pressure ($PaCO_2$) 29 mmHg, and pH 7.48. Her hematocrit was 41 percent and white cell count 13.4×10^3/mL with a fairly normal differential. Platelet count, serum electrolytes, glucose, and calcium levels, and findings from renal and hepatic function tests were within normal limits. Sinus tachycardia and right atrial enlargement were demonstrated on electrocardiogram. Over the next few days results of many laboratory tests were negative, including routine bacterial cultures and serologic titers for salmonella, tularemia, brucella, mycoplasma, toxoplasma, psittacosis, legionella, and fungi. Pulmonary function testing revealed reductions in vital capacity, total lung capacity, and diffusion capacity consistent with severe restrictive disease. Her antinuclear antibody test was positive with a titer of 1:80 and a speckled pattern, and the rheumatoid factor was positive at 1:20.

In the hospital she received oxygen by nasal prongs at 4 to 5 L/min to maintain her PaO_2 between 65 and 80 mmHg. No antibiotics were given. Fever, extreme weakness, dyspnea on mild exertion, and anorexia persisted. On the fifth hospital day she underwent open biopsy of her lung. Histologic examination, using a variety of special stains and electron microscopy, revealed diffused interstitial inflammation with many types of cells, mild fibrosis, and no organisms. Results of bacterial, fungal, and viral cultures were subsequently negative. A diagnosis of idiopathic interstitial disease was made, and she was started on a daily dose of 1 mg/kg of prednisone. Within one week her fever had resolved and her strength, appetite, and breathing had improved. A month after discharge her symptoms, findings on x-ray examination, and pulmonary function tests had greatly improved. Soon after that she moved out of state to live with another daughter. Six months after the hospitalization, the local daughter reported that her mother was off steroids and doing well.

RESIDENT: Was bronchoscopy performed?

DR. BLAKE: We considered bronchoscopy but did not do this procedure for several reasons. She gave a history of allergy to "caine" drugs, which we confirmed by talking

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TABLE 1. CAUSES OF NONINFECTIOUS INTERSTITIAL LUNG DISEASE

Inorganic Dusts
Silica
Asbestos
Beryllium
Cadmium
Hypersensitivity Pneumonitis
Farmer's lung
Bagassosis
Air-conditioner lung
Turkey handler's lung
Malt worker's lung
Drugs
Busulfan
Bleomycin
Cyclophosphamide
Penicillin
Nitrofurantoin
Sulfonamides
Diphenylhydantoin (phenytoin)
Gold
Methysergide
Gases, Fumes, Poisons
Oxygen toxicity
Sulfur dioxide
Chlorine
Paraquat
Collagen Vascular Disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Progressive systemic sclerosis
Polymyositis
Miscellaneous
Sarcoidosis
Histiocytosis-X
Radiation
Vasculitis
Lymphangitic malignancy
Neurofibromatosis
Tuberous sclerosis
Familial pulmonary fibrosis
Amyloidosis

to her previous physician. Consequently, bronchoscopy would have had to have been performed under general anesthesia. We felt that tissue was needed for a diagnosis. With a diffuse pulmonary process such as this, transbronchial needle biopsy often does not get sufficient tissue. We thought that an open biopsy would be the best approach. She tolerated it well, and we obtained enough tissue for good examination.

RESIDENT: What was the significance of the exposure to a dust storm in Kuwait?

DR. BLAKE: One of the diagnostic considerations when she was admitted was an acute fungal infection. The Histoplasma organism is widely distributed around the world and can be stirred up by sand storms. People exposed to such storms can receive a relatively large inoculum of organisms and are at risk for acute disease. Her exposure to a lot of birds raised the possibility of psittacosis, which can present with this kind of clinical picture.

Dr. Braun helped us manage this patient and will discuss interstitial lung disease.

DR. SHELDON BRAUN (*Director of the Division of Pulmonary Medicine*): This patient illustrates many of the common clinical and pathological features of diffuse interstitial pneumonitis. The hallmark symptom is dyspnea, which initially occurs with exertion and progresses over a variable time until it is present even at rest. Fever, chills, nonproductive cough, and generalized weakness may occur, but frequently dyspnea progresses insidiously without other symptoms. Dry, crackling rales in the lower lung fields are early findings. As the disease progresses, digital clubbing and cyanosis can occur, and in the late stage signs of cor pulmonale may develop. The findings on chest x-ray film are often normal early in the course, but later a reticulonodular interstitial pattern is present. In end-stage disease a honeycomb radiographic appearance may be found. Pulmonary function testing shows a restrictive pattern with a reduction in diffusion capacity, and moderate to severe hypoxemia is present. The $PaCO_2$ is usually reduced, but may rise in the terminal stages.

Etiologically, interstitial lung disease is heterogeneous. A partial list of noninfectious causes is displayed in Table 1. Before discussing this differential diagnosis, however, I would like to review briefly the sequence of pathological changes involved in this process.[1]

The lung has a limited way of responding to the variety of infectious, immunologic, and toxic insults that it may experience. The initial reaction is cellular; an assortment of neutrophils, lymphocytes, and macrophages collect in the edematous interstitium and exude into the alveolar spaces. In the next stage the inflammatory cell infiltrate persists, alveolar epithelial cells regenerate and proliferate, and fibroblasts appear and begin to deposit collagen. As the alveolitis progresses, alveolar epithelial cells undergo metaplastic changes, becoming cuboidal in shape, and there is increasing fibrosis and decreasing inflammatory cell infiltration in the alveolar walls. In the late stage the alveolar walls are thickened by extensive fibrous tissue, and alveolar-capillary gas exchange is greatly impaired. In general, these pathologic changes are etiologically nonspecific. The time course of this process varies from a few weeks to many years.

The shortness of breath characteristic of this disorder is probably caused by the decreasing compliance of the lung. With the evolving interstitial inflammation and fibrosis, the lungs become progressively more stiff, increasing the work of breathing.

Turning now to the workup of these patients, it is important to try to ascertain a specific cause of the condition. A careful, detailed history is crucial to this goal. Attention should be directed to drug exposure; such commonly used medications as nitrofurantoin, phenytoin, and penicillin can produce interstitial pneumonitis. In a patient with this disorder all nonessential drugs should be stopped. A complete occupational history is important to detect previous exposure to silica, asbestos, cotton dust, and chemicals or fumes. As exposure to silica or asbestos may have occurred decades before the onset of disease, the inquiry should cover an individual's entire occupational history.

Detailed questioning about occupational exposures, hobbies, and leisure time activities is important in identifying hypersensitivity pneumonitis.[2] This diverse condition is mediated by an immunologic response to an inhaled antigen, which can be one of a multitude of foreign proteins, including molds and animal excreta. Farmer's lung is the prototype of this process, and several dozen disease entities, such as pigeon breeder's disease and air-conditioner lung, have been described. A consistent temporal relationship between certain activities or exposures and the onset of symptoms is the best clue to the presence of one of these hypersensitivity pneumonitides. Typically, fever, chills, and dyspnea develop four to six hours after the exposure, and diffuse interstitial infiltrates are found on the chest roentgenogram. Evidence supporting the diagnosis includes the presence of serum-precipitating antibodies and the induction of symptoms by an inhalation challenge. The provocative challenge test can be dangerous, however, and often is not necessary for the diagnosis.

Interstitial lung disease can be a component of a systemic disease. In a patient with a malignancy, lymphangitic spread in the lung is a cause of interstitial abnormalities. Collagen vascular disorders can produce interstitial pneumonitis[3]; however, pulmonary involvement is unusual in the absence of other evidence of disease. Although this patient did have a vague history of rheumatoid arthritis and had a positive antinuclear antibody test and rheumatoid factor with low titers, there was nothing else to support a diagnosis of a collagen vascular disorder. It is not uncommon for patients with idiopathic interstitial pneumonitis to have low titers of antinuclear antibodies and rheumatoid factor.

In a patient such as the one under discussion today, it is important to exclude the possibility of an infectious process. First, the infection may be treatable and, second, the treatment for the interstitial disease may exacerbate the infection. A wide variety of viral, bacterial, fungal, and parasitic diseases can produce an interstitial radiographic pattern. In this case extensive culturing and serologic testing were done searching for an infection. As is frequently the case, examination of lung tissue was necessary to establish conclusively the diagnosis of noninfectious pulmonary inflammation. The yield from transbronchial biopsy is frequently inadequate. An open-lung biospy obtains a sufficient amount of tissue for complete testing and is usually the best approach. Tissue examination is frequently not necessary to establish a diagnosis of silicosis or asbestosis. These diagnoses can be based on a good history of exposure and characteristic radiographic findings.

In most cases of interstitial lung disease, a specific cause cannot be determined despite a comprehensive history and extensive laboratory workup. We are left with the label idiopathic. Such was the case with this patient.

If possible, the treatment of interstitial lung disease should be specific, for example, avoiding the inciting antigen in hypersensitivity pneumonitis. There is no specific therapy for pneumoconiosis. While we lack evidence from randomized controlled clinical trials, there is considerable clinical experience supporting the therapeutic role of corticosteroids for idiopathic disease.[4] The efficacy of steroids seems to be related to the histologic appearance of the lung tissue. Favorable responses are more likely during the stage of cellular alveolitis and are less likely with increasing fibrosis. Experience suggests that in some patients steroids reverse the cellular inflammation, prevent fibrosis, and restore normal alveolar structure and function. The prognosis is poor in the presence of extensive fibrosis. Azathioprine (Imuran) and cyclophosphamide may help in some patients who have not responded to steroids, but there is really little we can do for end-stage fibrotic, honeycombed lungs.

This patient's histologic picture was fairly favorable, with a florid cellular reaction and only a little fibrosis focally. She received the usual dosage of 1 mg/kg of prednisone and seems to have enjoyed an excellent response. We began to gradually reduce her steroids at the time she moved, one month after hospital discharge. In monitoring the response to therapy, we follow symptoms, results on chest x-ray examination, and pulmonary function tests.

RESIDENT: Dr. Braun, what are the characteristic radiographic lung findings with silicosis and asbestosis?

DR. BRAUN: In addition to the diffuse interstitial pattern, interstitial nodules are found with silicosis and pleural plaques are found with asbestosis.

RESIDENT: What is the role of bronchopulmonary lavage in the workup of these patients?

DR. BRAUN: Bronchoalveolar lavage can be of diagnostic value in some situations.[5] In normal nonsmokers, 80 to 95 percent of cells recovered on lavage are alveolar macrophages, 5 to 10 percent are lymphocytes, and less than 1 percent are polymorphonuclear leukocytes. With idiopathic pulmonary fibrosis, the total cell count is increased and a larger proportion are polymorphonuclear cells. With sarcoidosis and hypersensitivity pneumonitis, there is an increased proportion of lymphocytes. The sug-

gestion has been made that repeated lavages may be a way to monitor the course of the disease and assess the affect of treatment. Because of the expense and discomfort, however, I do not think this is practical.

DR. BLAKE: Idiopathic interstitial pneumonitis is not rare. The busy family physician is going to encounter this disease on occasion. Two years ago a 60-year-old man in our practice had a rapidly progressive course. He developed shortness of breath and weakness that kept getting worse. His lung biopsy showed extensive fibrosis. Despite aggressive therapy with steroids and then cyclophosphamide, he was dead within two months of the onset of symptoms. He had the acute devastating form of pulmonary fibrosis described by Hamman and Rich.[6]

I would like to make a few comments about the patient presented today. At the time she became sick, she had recently experienced many stressful life events. She had retired, moved, and traveled overseas. There is considerable evidence that an accumulation of such changes confers an increased risk of health problems.[7] While the mechanisms mediating this risk remain to be elucidated, there is some interesting evidence that these types of stressors may impair immune function.[8] We don't know why or how this lady became sick when she did. Given the multifactorial model of disease causation, there probably was a confluence of events and factors. These psychosocial stressors may well have played a role in the causal process.

This patient posed significant management problems for the team that cared for her. Not only did we struggle with the diagnostic challenge, we faced some real difficulties with her psychological reaction to her illness. She is a strong-willed, independent woman who has been accustomed to exerting a lot of control over her social environment. She apparently had enjoyed considerable power and authority in her job and was influential in her extended family. She did not like being sick; she did not like being disabled and dependent. The inevitable loss of control engendered by the illness and hospitalization created considerable anger, which she vented on her family, nurses, and physicians. Her anger was compounded by the delay in establishing a diagnosis and instituting treatment. We spent a lot of time addressing her frustration and anger. She had good insight into the reasons for her feelings. With the help of a social worker and the nurses, we devised ways in which she had some control over what was happening to her. She gradually adjusted to the situation and ended up coping fairly well.

I did not know the patient prior to her hospitalization, but I had been caring for the daughter and her family for several years. This time was very difficult for her daughter. She had some guilt feelings about her mother getting sick so soon after coming to live in Columbia. In addition to

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her concern about her mother, she was very worried about the health of her two teenage sons. They had had extensive contact with their grandmother early in the course of her illness. The daughter was concerned that the disease was contagious and that the boys were at risk of developing it. This fear persisted despite reassurances and several examinations of the boys. Even when the noninfectious nature of the disease was established, this intense worry persisted and resulted in several middle-of-the-night calls to me to report some symptom. Finally, during the course of a session with the daughter and her husband, the basis for this anxiety was revealed. She acknowledged a long-term fear that one of her children was fated to die before reaching adulthood. The fear derived from the fact that both her mother and her sister had a child who had died. She had never admitted this fear to anyone before. The three of us spent a lot of time discussing this fear. Interestingly, in the days following this disclosure, she did not express any concerns about her sons contracting her mother's illness. With this long-term concern ventilated and perhaps diminished, she was then able to prepare effectively for the home-based care that her mother would require.

This disclosure put into perspective some of the medical encounters that I had had with her and her sons in the past. It helped to explain a certain overprotectiveness and excessive anxiety that I had perceived in her. This is an example of the accumulation of important pieces of information that occurs as a physician takes care of a family over time.

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