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Case 12-2003: An 82-Year-Old Man with Dyspnea and Pulmonary Abnormalities

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PRESENTATION OF CASE

An 82-year-old man was admitted to the hospital because of dyspnea and peripheral edema.

The patient had a long history of hypertension, diabetes mellitus, and depression with mild dementia. He had smoked heavily until 30 years before admission and had chronic obstructive pulmonary disease. Fifteen months before the current admission, he was admitted to another hospital because of substernal pain, dyspnea, and sustained ventricular tachycardia. The rhythm did not respond to the administration of adenosine, metoprolol, diltiazem, or lidocaine, but electrical cardioversion restored a normal rhythm. The results of laboratory tests are shown in Table 1.

FIRST ADMISSION

On the third day, the patient was transferred to this hospital. The pulse was 90 beats per minute and the blood pressure 120/50 mm Hg. The jugular venous pressure was normal. The breath sounds were diminished, and there were diffuse wheezes bilaterally. A soft systolic murmur was heard. The abdomen was normal, and there was no peripheral edema. The levels of electrolytes, aspartate aminotransferase, alanine aminotransferase, creatine kinase, and creatine kinase isoenzymes were normal. The results of other laboratory tests are shown in Tables 1 and 2. An electrocardiogram revealed a normal rhythm, a normal PR interval, and left bundle-branch block.

A chest radiograph (Fig. 1) disclosed cardiomegaly, interstitial pulmonary edema, and small bilateral pleural effusions. Healed fractures of the left ribs were present. A cardiac ultrasonographic examination revealed that the left ventricle was dilated and diffusely hypokinetic, with regional variation in contractility and an estimated ejection fraction of 38 percent. The aortic leaflets were thickened, but there was no stenosis or regurgitation. The size and systolic function of the right ventricle were normal, and there was trace mitral regurgitation. Cultures of blood, sputum, and urine were sterile. A technetium-99m sestamibi exercise stress test with adenosine showed a large, fixed, posterobasal defect, without evident ischemia or chest pain. The patient was discharged on the eighth hospital day while taking captopril, diltiazem, amiodarone (initially at a daily dose of 400 mg, which was later reduced to a 200-mg daily dose), furosemide, aspirin, glipizide, and atorvastatin.

Table 1. Blood Chemical Values.*

Variable	Three Days before First Admission	First Admission	Second Admission	Third Admission				
				Day 1	Day 4	Day 5	Day 6	Day 7
Urea nitrogen (mg/dl)		35	27		28	38	49	41
Creatinine (mg/dl)		1.1	0.9		1.3	1.5	1.4	1.1
Glucose (mg/dl)		157	129	137		167		172
Iron (μg/dl)			20					
Iron-binding capacity (μg/dl)			205					
Bilirubin (mg/dl)								
Total		1.0		0.8		1.0		
Conjugated		0.7						
Protein (mg/dl)								
Total		6.0	7.3	6.5	7.2			
Albumin		2.6	2.5	2.2	2.2			
Globulin		3.4	4.8	4.3	5.0			
Lactate dehydrogenase (U/liter)		261						
Troponin I (ng/ml)		5.8						
Sodium (mmol/liter)			140				133	
Potassium (mmol/liter)			3.2				4.1	
Chloride (mmol/liter)			106				98	
Carbon dioxide (mmol/liter)			27.1				34.7	
Alanine aminotransferase (U/liter)			68	100	107	105		
Aspartate aminotransferase (U/liter)				102	82	77		
Creatine kinase (U/liter)	205							
Creatine kinase MB isoenzyme (ng/ml)	5.95							
Creatine kinase index (%)	3.0							

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791. To convert the values for total and conjugated bilirubin to micromoles per liter, multiply by 17.1.

SECOND ADMISSION

Twelve and a half months later, the patient was readmitted to this hospital because of progressive exertional dyspnea of one week's duration, increasing disorientation with visual hallucinations, and a brief episode of substernal pain on the day of admission. The temperature was 36.7°C, the pulse 82 beats per minute, the respiratory rate 28 breaths per minute, and the blood pressure 120/60 mm Hg. The oxygen saturation was 94 percent while the patient was breathing supplemental oxygen. The jugular venous pressure was elevated. A few crackles and expiratory wheezes were heard bilaterally. The heart sounds and the abdomen were normal, and there was peripheral edema (+).

The levels of conjugated and total bilirubin, calcium, phosphorus, aspartate aminotransferase, alkaline phosphatase, creatine kinase, creatine kinase isoenzymes, and troponin I were normal. The results of other laboratory tests are shown in Tables 1 and 2. An electrocardiogram showed a normal rhythm at a rate of 91 beats per minute, a PR interval of 221 msec, a QRS interval of 121 msec, a possible old inferior infarct, and questionable anterolateral ischemia. Chest radiographs showed volume loss in the right upper lobe, interstitial pulmonary edema,

Table 2. Hematologic Laboratory Data.

Variable	First Admission	Second Admission	Third Admission	
			Day 1	Day 8
Hematocrit (%)	37.2	28.3	32.5	29.0 before transfusion, 33.1 after transfusion
White-cell count (per mm³)	11,500	9600	11,500	10,300
Neutrophils (%)			86	
Platelets (per mm³)	187,000		513,000	
Erythrocyte sedimentation rate (mm/hr)	67			
Mean corpuscular volume (μm^3)	89			
Prothrombin time (sec)			14.6	
Partial-thromboplastin time			Normal	

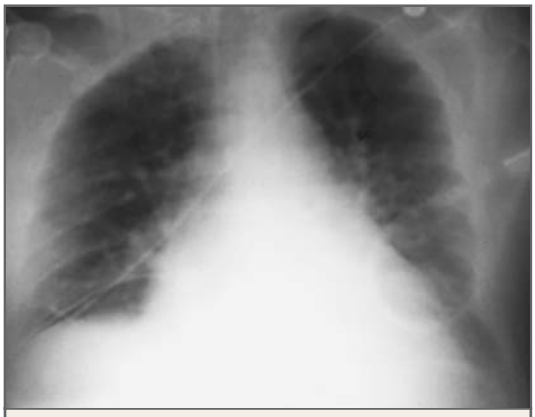

Figure 1. Chest Radiograph Obtained during the First Admission.
There is mild interstitial edema, small bilateral pleural effusions, and cardiomegaly.

bilateral basal atelectasis, and cardiomegaly. Cultures of the blood and urine were sterile, and a test for urinary legionella antigen was negative.

Azithromycin, cefuroxime, and nebulized albuterol and ipratropium were added to the patient's regimen. The axillary temperature rose to 37.3°C during the next 24 hours but was normal thereafter. On the fourth hospital day, another chest radiograph (Fig. 2) revealed coarse, reticular opacities bilaterally, with consolidation and volume loss in the right upper lobe and small pleural effusions. Another cardiac ultrasonographic study, which was limited because the patient was unable to cooperate, again showed a diffusely hypokinetic left ventricle, with an estimated ejection fraction of 28 percent; the size and systolic function of the right ventricle remained normal. A brief course of prednisone was followed by some resolution of the tachypnea and crackles, but the wheezing persisted. On the seventh hospital day, the patient was discharged to a rehabilitation hospital.

Two months later, the patient was discharged from the rehabilitation facility while taking captopril (12.5 mg twice a day), amiodarone (200 mg daily), furosemide, aspirin (daily), atorvastatin, glipizide, nebulized triamcinolone, fluoxetine, and an antacid. Six days later, the progressive exertional dyspnea recurred but was not accompanied by chest pain. The next day, the patient had hypotension and mild congestive heart failure. The dose of furosemide was increased and the dose of captopril reduced, but his condition did not improve. Two days later, a nurse found that the oxygen saturation was 80 percent, and he was readmitted to this hospital.

THIRD ADMISSION

The temperature was 36.6°C, the pulse was 83 beats per minute, and the respiratory rate was 28 breaths per minute. The blood pressure was 125/60 mm Hg. On physical examination, the patient was wheezing. No lymphadenopathy was found. The jugular venous pressure was increased. Fine crackles at both lung bases and a grade 2 systolic murmur were audible. The abdomen was unremarkable. There was peripheral edema (++). Neurologic examination revealed no abnormalities.

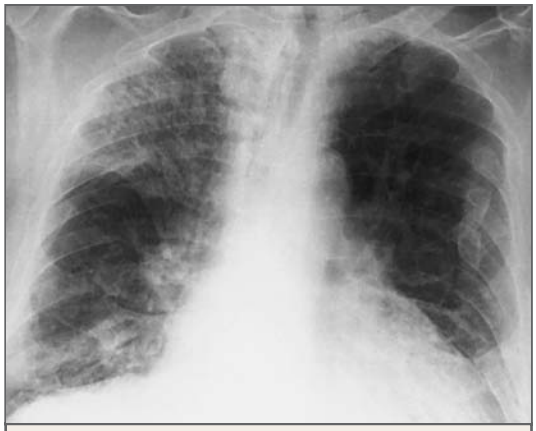

Figure 2. Chest Radiograph Obtained during the Second Admission.

There are bilateral irregular pulmonary opacities, with consolidation and partial volume loss in the right upper lobe.

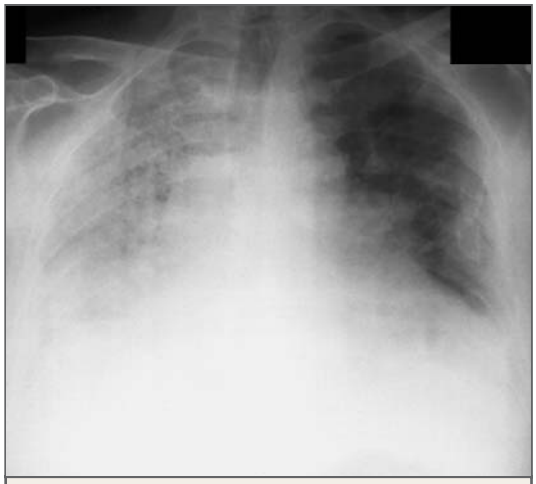

Figure 3. Chest Radiograph Obtained during the Third Admission.

There is persistent consolidation throughout the lungs, more in the right lung than in the left, and it appears worse than it had on a radiograph obtained 50 days earlier, during the previous admission. A moderate left-sided pleural effusion and a small right-sided pleural effusion are present, and the heart is enlarged.

The urine was positive (+) for protein; the sediment contained 20 to 50 red cells and 50 to 100 white cells per low-power field and numerous bacteria. The levels of urea nitrogen, creatinine, phosphorus, magnesium, electrolytes, alkaline phosphatase, creatine kinase, creatine kinase isoenzymes, and troponin I were normal. Other laboratory values are shown in Tables 1 and 2.

An electrocardiogram revealed a normal rhythm at a rate of 73 beats per minute; the PR interval was 179 msec and the QRS interval 133 msec. A chest radiograph (Fig. 3) showed air-space disease throughout the lungs; it was greater in the right lung than in the left and appeared worse than it had on an examination 50 days earlier, during the previous admission. A moderate left-sided pleural effusion and a small right-sided pleural effusion were present, and the heart was enlarged. Five blood cultures and two urine cultures were sterile, and tests for legionella urinary antigen, influenza A and B, parainfluenza, respiratory syncytial virus, adenovirus, and cytomegalovirus were negative.

The patient's usual medications were continued, and additional agents included nebulized ipratropium and albuterol, minidose heparin, ranitidine, ferrous sulfate, potassium supplements, levofloxacin, and supplemental oxygen. His mental status fluctuated daily, and he had intermittent visual hallucinations. During the first five hospital days, his temperature rose daily to a level as high as 37.9°C, but it was normal on most occasions thereafter. On the second hospital day, the oxygen saturation rose to a level as high as 90 percent while the patient was breathing 28 percent oxygen through a face mask. The patient reported that he did not have dyspnea, but he had tachypnea at rest, with audible wheezing. Another chest radiograph revealed reticular opacities at the left lung base and in diffuse areas in the right lung; the cardiomegaly persisted. Use of a high-flow mask was begun and resulted in improvement. The atorvastatin was discontinued, and spironolactone was added to the regimen.

On the fourth day, the levels of electrolytes and alkaline phosphatase were normal. The results of other laboratory tests are shown in Table 1. Another chest radiograph disclosed reticular and confluent opacities in the right lung and increasing reticular opacities in the left lower lobe. Amiodarone, levofloxacin, and captopril were discontinued, and ceftriaxone, azithromycin, and vancomycin were begun. The partial pressure of oxygen was 90 mm Hg, the partial pressure of carbon dioxide 42 mm Hg, and the pH 7.49. The patient was transferred to an intensive care unit.

On the fifth day, another chest radiograph showed minor improvement in the pulmonary edema. The left mediastinum had an irregular contour, with deviation of the trachea to the right, raising the question of a mass or aneurysm. The furosemide

was discontinued. The oxygen saturation ranged from 91 to 95 percent. The results of other laboratory tests are shown in Table 1.

On the sixth day, the patient became agitated. The oxygen saturation declined to 88 percent while the patient was receiving high-flow oxygen. Laboratory values are shown in Table 1. Tracheal intubation was performed. Computed tomographic (CT) examination of the thorax, performed without the use of contrast material (Fig. 4), disclosed diffuse ground-glass opacities in both lungs, with relative sparing of the left upper lobe, with traction bronchiectasis and honeycombing at the bases. Pleural effusions were present bilaterally. No mass or aneurysm was detected, but cardiomegaly was observed. Insertion of a Swan–Ganz catheter showed that the pulmonary arterial pressure was 49/17 mm Hg and the pulmonary-capillary wedge pressure 12 mm Hg; the cardiac output was 6.1 liters per minute, the stroke volume 67 ml, and the cardiac index 3.0 liters per minute per square meter of body-surface area. Examination of bronchoalveolar-lavage specimens disclosed a very small number of gram-positive cocci in clusters, a few yeasts, and no acid-fast bacilli or *Pneumocystis carinii* microorganisms. A culture of the specimens yielded normal respiratory flora, and a wet preparation was negative for fungi. A fungal culture grew *Torulopsis glabrata;* polymerase-chain-reaction analysis yielded no evidence of *Mycoplasma pneumoniae.*

On the seventh day, another cardiac ultrasonographic study revealed no marked changes. The results of laboratory tests are shown in Table 1. On the eighth day, another chest radiograph revealed partial clearing of the pulmonary opacities. The partial pressure of oxygen was 117 mm Hg, the partial pressure of carbon dioxide 46 mm Hg, and the pH 7.41 while the patient was receiving 40 percent oxygen. Two units of packed red cells were transfused. The results of laboratory tests performed that day are shown in Table 2.

A diagnostic procedure was performed.

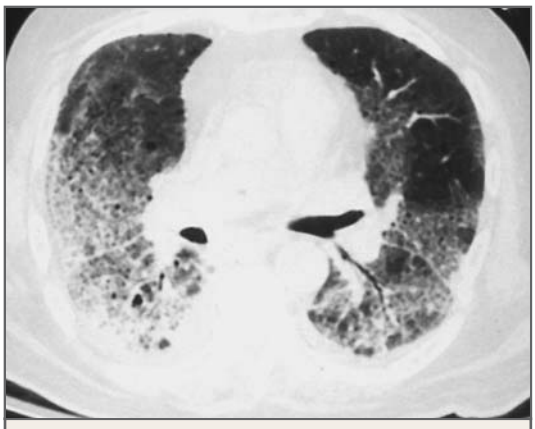

Figure 4. High-Resolution CT Scan of the Thorax Obtained on the Sixth Day of the Third Admission.

There are diffuse bilateral ground-glass opacities, with traction bronchiectasis and honeycombing at the lung bases.

DIFFERENTIAL DIAGNOSIS

Dr. Atul Malhotra: May we review the radiologic studies?

Dr. Victorine V. Muse (Radiology): The radiograph obtained during the first admission (Fig. 1) shows bilateral pleural effusions, interstitial edema, and cardiomegaly consistent with the presence of congestive heart failure, which cleared on subsequent radiographic studies. A chest radiograph obtained during the second admission (Fig. 2) shows irregular pulmonary opacities bilaterally, with consolidation and partial volume loss in the right upper lobe. The chest radiograph obtained during the third admission (Fig. 3) shows bilateral consolidation (which had progressed since a previous examination, 50 days earlier), bilateral pleural effusions, and cardiomegaly.

CT scanning was performed without the use of intravenous contrast material after the congestive heart failure had cleared. The high-resolution image (Fig. 4) shows bilateral ground-glass opacities, with traction bronchiectasis and honeycombing at the bases.

Dr. Malhotra: The patient was receiving amiodarone. Was there evidence of increased radiodensity in the pulmonary infiltrates or the hepatic parenchyma?

Dr. Muse: The attenuation of the liver and spleen was normal. There were areas of high attenuation at the lung bases peripherally, within the regions of reticular opacities.

Dr. Malhotra: This patient, who had a history of hypertension, type 2 diabetes, depression with mild dementia, chronic obstructive pulmonary disease, and congestive heart failure due to left ventricular systolic dysfunction, presented with intermittent pulmonary infiltrates and an acute interstitial pulmonary disease superimposed on a chronic pulmonary process. His history is characterized by multi-

ple hospitalizations for apparent exacerbations of congestive heart failure and chronic obstructive pulmonary disease, culminating in respiratory failure that necessitated intubation and mechanical ventilation. I believe that the patient had amiodarone-induced pulmonary toxic effects superimposed on intermittent congestive heart failure and emphysema. An open-lung biopsy would be required to make this diagnosis definitively, and substantial improvement could be anticipated with discontinuation of the amiodarone and initiation of corticosteroid therapy.

I shall discuss the differential diagnosis of the interstitial lung disease as well as its workup and management in a patient with cardiac disease. The causes of interstitial pulmonary infiltrates in such a patient can be classified as either cardiogenic or noncardiogenic (Table 3).[1]

Table 3. Causes of Pulmonary Infiltrates in Patients with Cardiac Disease.

Cardiogenic causes

Disproportionately high left atrial pressure
- Mitral-valve disease
- Atrial fibrillation

High left ventricular end-diastolic pressure
- Diastolic dysfunction (e.g., hypertension, aortic stenosis)
- Systolic dysfunction (e.g., ischemia, cardiomyopathy)

Noncardiogenic causes

Infections
- Mycoplasma
- Legionella
- *Chlamydia psittaci*
- Coxiella
- Viruses
- Fungi
- Pneumocystis

Idiopathic diseases
- Usual interstitial pneumonitis
- Nonspecific interstitial pneumonitis
- Bronchiolitis obliterans organizing pneumonia

Exposures
- Inhalational exposure (asbestosis, silicosis, chronic aspiration, inhalation of hard metal, hypersensitivity pneumonitis)
- Use of medication (amiodarone, bleomycin, penicillamine, nitrofurantoin, carmustine)
- Exposure to radiation
- Smoking (respiratory bronchiolitis with interstitial lung disease, desquamative interstitial pneumonia, Langerhans'-cell histiocytosis)

Cancer
- Lymphangitic adenocarcinomatous metastases
- Lymphoma (with lymphocytic interstitial pneumonitis pattern)

Systemic disease
- Sarcoidosis
- Amyloidosis
- Autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, polymyositis, scleroderma, Sjögren's syndrome)

CAUSES OF INTERSTITIAL PULMONARY INFILTRATES IN ASSOCIATION WITH CARDIAC DISEASE

Cardiogenic

Interstitial pulmonary infiltrates can be associated with a rise in the pulmonary-artery occlusion pressure, caused either by high left ventricular end-diastolic pressure or by a disproportionate elevation in the left atrial pressure due to mitral-valve disease or atrial fibrillation. The absence of the finding of substantial mitral-valve disease on physical and echocardiographic examination and the documentation of normal sinus rhythm make it unlikely that there was disproportionate elevation of the left atrial pressure. An increase in left ventricular end-diastolic pressure may result from systolic or diastolic left-ventricular dysfunction. Because this patient had left ventricular systolic dysfunction due to coronary artery disease, a rise in left ventricular end-diastolic pressure could be due to ischemic dysfunction of the left ventricle; dietary indiscretion, leading to extracellular-fluid volume overload; or failure to take prescribed medications. Acute myocardial ischemia seems unlikely because the patient had not recently had chest pain and because he had normal levels of cardiac enzymes, but the assessment is complicated by the electrocardiographic finding of underlying disease of the conduction system. Dietary indiscretion or failure to take prescribed medications is possible in this case because of the patient's impaired cognitive abilities.

The pulmonary-capillary wedge pressure was only 12 mm Hg when measured during the third admission, but this finding must be interpreted cautiously, for several reasons. First, the measurement was made after diuretic therapy, leaving open the possibility that a reading at the time of admission would have been higher. Use of a Swan–Ganz catheter for assessment at the onset of an exacerbation is helpful if it reveals transient elevations in the wedge pressure or the development of V waves suggestive of transient papillary-muscle ischemia leading to mitral regurgitation.[2] Auscultatory findings of an S3 gallop, an increase in the mitral-regurgitation murmur, or both are helpful.

Second, ventilation with positive end-expiratory

pressure leads to decreases in cardiac preload and afterload, which can relieve ischemia[3,4] (Table 4). This patient's cardiac function may have been worse before mechanical ventilation.

Finally, the wedge pressure was measured during positive-pressure ventilation, leading to an overestimation of the actual filling pressure, especially if the lungs are compliant, as in this patient with emphysema. In a setting such as this, it is ideal to record the transmural left ventricular pressure (intracavitary minus cardiac-surface pressure), rather than the intracavitary value referenced to atmospheric pressure, which is the more common measurement. Elevations in pleural pressure (and cardiac surface pressure), such as those that occur with positive end-expiratory pressure, may lead to an increase in left ventricular end-diastolic pressure relative to atmospheric pressure rather than an increase in transmural left ventricular pressure.[5,6] Although the positive end-expiratory pressure applied is not specified, the filling pressure was clearly not elevated, making cardiogenic edema unlikely. Thus, although congestive heart failure was probably present early in the patient's course, it is an unlikely explanation for the substantial residual interstitial infiltrates.

Table 4. Effects of Positive End-Expiratory Pressure in Patients with Congestive Heart Failure.

Reduced preload due to increased vena caval resistance
Reduced left ventricular afterload due to reduced wall stress
Reduced myocardial oxygen consumption due to decreased ventricular size
Increased lung compliance due to reduced extravascular lung fluid
Decreased negative pleural pressure with inspiration
Suppressed catecholamines due to improved cardiac output and oxygenation
Reduced mitral regurgitation

Noncardiogenic

In addition to amiodarone-induced toxic effects, many noncardiogenic factors may have caused this patient's pulmonary infiltrates. Infectious causes of interstitial infiltrates (Table 3) are common. However, the negative results on extensive testing for infectious diseases, the prolonged course of the chronic infiltrates, and the ineffectiveness of the antimicrobial therapies make an infectious cause unlikely. Categories of noninfectious interstitial lung diseases include idiopathic diseases, those associated with inhalational or systemic exposure, and those associated with cancer and systemic diseases. Apart from this patient's history of amiodarone therapy, he had no other relevant exposures. However, two possible explanations for his interstitial pulmonary infiltrates are chronic aspiration due to gastroesophageal reflux and hypersensitivity pneumonitis.

Chronic aspiration is common in elderly patients, particularly those with cognitive impairment or bulbar dysfunction. In this case, a history of reflux or of choking episodes during meals would help support this diagnosis. To diagnose chronic aspiration, a physician may observe the manner in which a patient swallows liquids during a physical examination. If diagnostic uncertainty persists, evaluation by a speech pathologist is a reasonable option.

No aspect of the history in this case suggests exposure to the organic antigens that may trigger hypersensitivity pneumonitis, but that diagnosis is often difficult to make. In many cases, the inciting antigen goes unrecognized. In other cases, the patient minimizes the exposure history (e.g., exposure to birds kept as pets). If the clinical suspicion of this diagnosis is high, a formal evaluation of the patient's home environment and serologic testing for antibodies to agents that can cause hypersensitivity pneumonitis are indicated. The other exposures listed in Table 3 are irrelevant in this case. Likewise, the clinical data do not support the diagnoses of systemic diseases or malignant tumors.

IDIOPATHIC INTERSTITIAL PNEUMONIAS

Idiopathic interstitial pneumonias have recently been reclassified to reflect the better prognoses associated with disorders other than usual interstitial pneumonia. Nonspecific interstitial pneumonia is a recently described entity that previously was often confused with usual interstitial pneumonia. It is characterized by the presence of substantial ground-glass infiltrates on high-resolution CT scans and the presence of chronic inflammatory infiltrates that are temporally uniform (i.e., of similar ages) in histologic specimens.[7] The original report described most cases as idiopathic, although some were related to hypersensitivity antigens and others to collagen vascular diseases. The prognosis in cases of nonspecific interstitial pneumonia (especially those without fibrosis) is substantially better than that in cases of usual interstitial pneumonia.[8,9]

Bronchiolitis obliterans organizing pneumonia occurs either as a reaction to a variety of inciting

agents or as an idiopathic process. It is characterized by fibroplasia within the airways and parenchymal inflammation and typically responds to corticosteroid therapy. Usual interstitial pneumonia is relentlessly progressive and is characterized by patchy interstitial lymphohistiocytic inflammation and foci of active fibroblastic proliferation. The lesions in this disease are temporally nonuniform (i.e., of varying ages in different foci).[10] High-resolution CT scans characteristically show bibasilar, subpleural honeycombing with minimal ground-glass infiltrates. The disease that is recognized by clinicians as idiopathic pulmonary fibrosis usually corresponds to the histologic diagnosis of usual interstitial pneumonitis. Although the older literature contains many reports of cases of usual interstitial pneumonia secondary to a variety of causes, many of these lesions are now believed to be examples of nonspecific interstitial pneumonia. Thus, there are now only a few cases of documented usual interstitial pneumonia associated with either collagen vascular disease or medication.

Table 5. Manifestations of Amiodarone-Induced Pulmonary Toxic Effects.

Diffuse alveolar damage
Bronchiolitis obliterans organizing pneumonia
Bronchospasm
Diffuse alveolar hemorrhage
Hypersensitivity pneumonitis
Congestive heart failure due to myocardial suppression
Pulmonary infiltrates with eosinophilia
Interstitial lung disease

AMIODARONE-INDUCED TOXIC EFFECTS

Toxic Effects

The toxic effects of amiodarone on the lungs are listed in Table 5.[11-14] Amiodarone is an iodinated benzofuranyl used to treat supraventricular and ventricular arrhythmias and nonischemic cardiomyopathy.[15-17] The drug has a half-life of 30 to 90 days, and its active metabolite is desethylamiodarone. The pulmonary toxicity of amiodarone was first recognized in approximately 1980, and subsequent reports suggested a cumulative incidence of 5 to 10 percent.[18-20] The mechanisms underlying the myriad toxic effects of amiodarone on the lungs are complex and may involve both direct toxic effects of free radicals on cells and indirect, inflammatory mechanisms.[21,22] Because this drug can have toxic effects on other organs, including the liver, thyroid, skin, and optic nerves, it may also account for this patient's elevated liver-enzyme levels and visual hallucinations.

Diagnostic Tests

Techniques that are reportedly useful in the diagnosis of amiodarone-induced pulmonary toxic effects include analysis of the cellular composition of bronchoalveolar-lavage specimens and inspection for the presence of radiodense infiltrates on CT scans. However, these abnormalities may be present in patients who have received amiodarone but who do not have pneumonitis.[23] Gallium (or technetium) scanning has a high sensitivity for detecting the toxic effects of amiodarone on the lungs, and thus a positive result may be helpful in ruling out congestive heart failure.[24,25] An investigational technique is measurement of serum levels of KL-6, a mucin-like, high-molecular-weight glycoprotein produced by type 2 pneumocytes; elevated levels may indicate interstitial inflammation.[26]

Three other diagnostic tests deserve comment: measurement of the erythrocyte sedimentation rate, of brain natriuretic peptide, and of the capacity of the lung for diffusing carbon monoxide. The erythrocyte sedimentation rate is commonly elevated in patients with amiodarone-induced pulmonary toxic effects. The classic teaching has been that the erythrocyte sedimentation rate is low in patients with congestive heart failure. However, most patients with congestive heart failure do not have low erythrocyte sedimentation rates,[27,28] and thus the elevated rate (and the elevated levels of globulins) in this case are not useful in distinguishing congestive heart failure from amiodarone-induced pneumonitis.

Serum assay of brain natriuretic peptide was recently approved by the Food and Drug Administration as a sensitive test of left ventricular dysfunction. It may be used as a "point of care" test to assess ventricular function without echocardiographic examination. However, an elevated brain natriuretic peptide value in this case would only have confirmed the well-established presence of left ventricular dysfunction. In contrast, if serial values had been available, a diagnosis of amiodarone-induced pulmonary toxic effects could have been suspected if there was no elevation in the brain natriuretic peptide level in comparison with the patient's base-line values associated with clinical deterioration.[29-31]

The capacity of the lung for diffusing carbon monoxide is another test that may be useful in distinguishing acute congestive heart failure from amiodarone-induced pneumonitis. In this test, the uptake of carbon monoxide while it irreversibly binds hemoglobin is measured as a function of the alveolar surface area, pulmonary vascular supply, and hemoglobin level. In acute congestive heart failure, the diffusing capacity is often elevated because of the hemoglobin present in pink, frothy sputum, which is a typical finding in this condition. In contrast, the diffusing capacity is reduced in most interstitial lung diseases, including amiodarone-induced pneumonitis.[32] Thus, some simple, noninvasive tests would have been useful in this case.

Whether a thoracoscopic lung biopsy is required in this case is debatable. A risk–benefit analysis would arguably favor empirical therapy for amiodarone-induced pneumonitis, but my colleagues and I recently reported a low rate of complications associated with open-lung biopsy, even among patients with the acute respiratory distress syndrome.[33] Therefore, I favor a biopsy as the diagnostic procedure. If examination of the biopsy specimen confirms the diagnosis of amiodarone-induced pneumonitis, I would discontinue the amiodarone and consider the initiation of glucocorticoid therapy. In a patient with left ventricular dysfunction and ventricular tachycardia, an automated implantable defibrillator would control the ventricular arrhythmias.[34] Finally, if Cheyne–Stokes respiration has been diagnosed, nocturnal therapy with continuous positive airway pressure may suppress catecholamines, reduce ectopy, improve the left ventricular ejection fraction, and possibly improve transplant-free survival (Table 5).[35-37]

CLINICAL DIAGNOSIS

Respiratory failure due to amiodarone-induced toxic effects.

DR. ATUL MALHOTRA'S DIAGNOSIS

Amiodarone-induced pneumonitis.

PATHOLOGICAL DISCUSSION

Dr. Eugene J. Mark: The diagnostic procedure was a thoracoscopic biopsy of the lung. On histopathological examination, there was a cellular infiltrate that diffusely filled the alveoli and interstitium (Fig. 5A) — findings typical of interstitial pneumonitis. Branching tufts of fibrous tissue filled the respiratory bronchioles (Fig. 5B), indicating the presence of bronchiolitis obliterans. Vacuolated histiocytes filled some alveoli (Fig. 5C); this common and nonspecific finding may be seen distal to bronchiolar obstruction. It generally reflects the presence of cellular detritus that, when ingested by macrophages, results in lipid vacuoles in the cytoplasm of the intraalveolar histiocytes. In this case, however, the interstitial infiltrate also contained many vacuolated histiocytes in addition to lymphocytes, and many enlarged pneumocytes had voluminous, vacuolated cytoplasm that protruded into the alveolar lumina (Fig. 5D). These findings are consistent with the presence of amiodarone-induced pneumonitis.[38-41]

Ultrastructural examination showed that macrophages, alveolar pneumocytes, bronchiolar epithelial cells, and endothelial cells were packed with membrane-bound lamellar bodies approximately 1 μm in diameter. The lamellae were closely packed in concentric or parallel arrays (Fig. 5E). These bodies develop after the administration of amiodarone and account for the vacuolization of the cytoplasm seen on light-microscopical examination. The lipid particles are birefringent on microscopical examination of unstained frozen sections with polarized light.[42] The bodies have an ultrastructural appearance similar to that of surfactant, but surfactant is restricted to pneumocytes. Similar bodies may be seen after the administration of some drugs used to treat depression or to lower cholesterol.

Amiodarone-induced lung disease must be distinguished from the effects of amiodarone in the lung. Vacuolated histiocytes without associated fibrin, inflammation, or fibrosis are found in many patients who are receiving amiodarone on a continual basis and who do not have respiratory compromise. Vacuolated cells, including histiocytes and parenchymal cells, may also be seen in the liver, thyroid, skin, and other organs, with or without signs or symptoms. The diagnosis of amiodarone-induced pneumonitis can be made when, in addition to the presence of vacuolated cells, there are changes indicative of damage to the tissue, such as an interstitial lymphocytic infiltrate or fibrosis that widens the interstitium and alters the normal alveolar architecture.

A few patients with amiodarone-induced lung disease have the acute respiratory distress syndrome clinically and diffuse alveolar damage pathologically, particularly in association with angiography

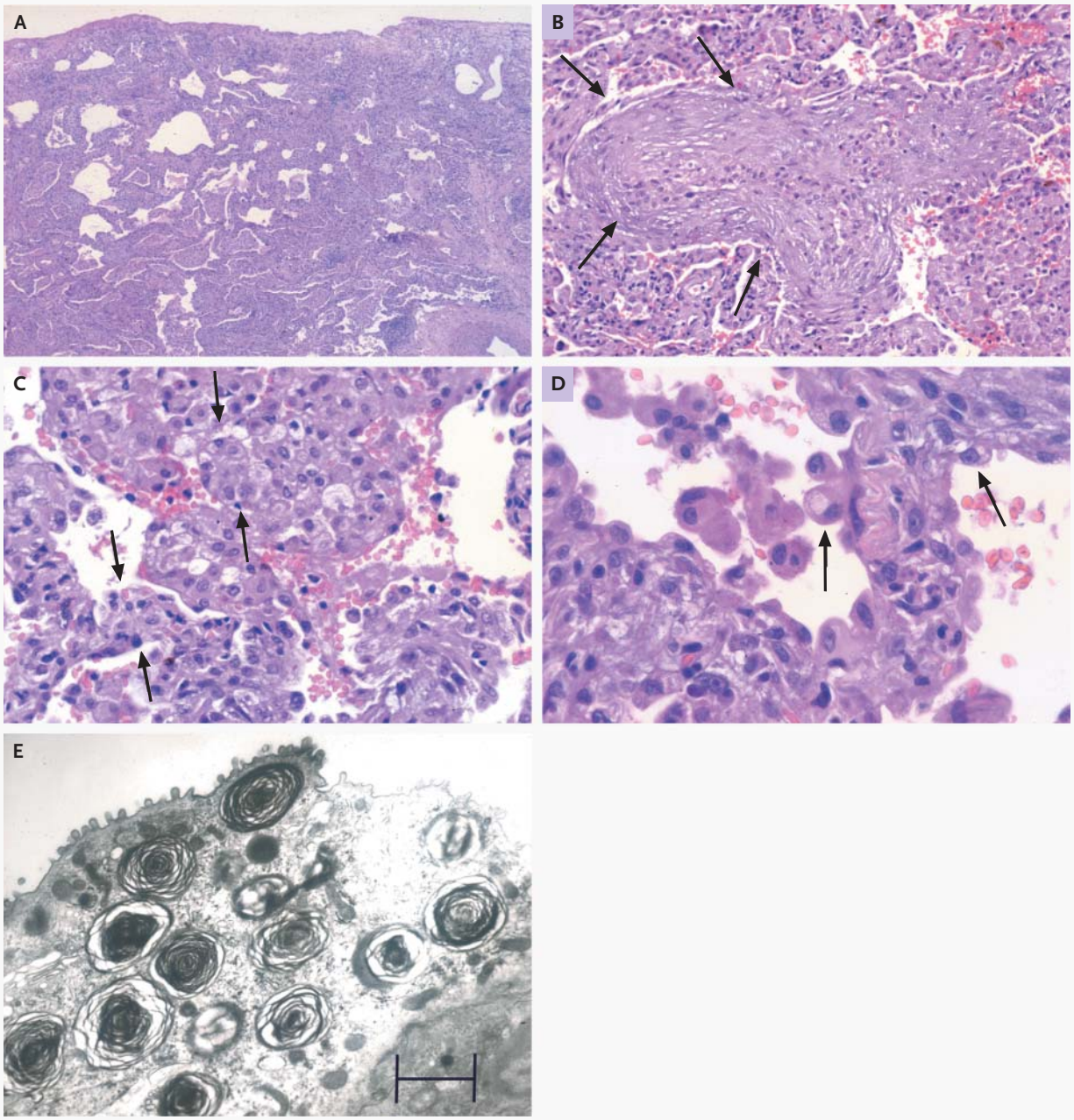

Figure 5. Biopsy Specimen of the Lung (Hematoxylin and Eosin).

There is a cellular infiltrate in the alveoli and widening of the interstitium (Panel A, ×72). Bronchiolitis obliterans (Panel B, ×125), with a branching tuft of myxoid fibrous tissue (arrows) filling a respiratory bronchiole, is evident. Vacuolated histiocytes (Panel C, ×250) are present in an alveolus (between arrows at right) and in the interstitium (between arrows at left). There is vacuolization of the cytoplasm of pneumocytes (arrows, Panel D, ×500), a finding characteristic of an amiodarone-induced effect. An electron micrograph of the lung-biopsy specimen (Panel E, ×8500) shows whorled, lamellar, membranous inclusions in an alveolar pneumocyte — another finding indicative of an amiodarone-induced effect. The bar represents 1.175 μm.

or cardiac surgery.[43,44] Most of the patients have a chronic disease, as in this case. Chronic forms of amiodarone-induced lung disease include bronchiolitis with organizing pneumonia, interstitial pneumonitis, interstitial fibrosis, and a combination of these conditions. The clinical course is difficult to predict. To establish the diagnosis, it is important to correlate the timing and dosage of amiodarone relative to the occurrence of lung disease and to rule out other potential causes of lung disease. The condition often improves after the diagnosis has been made and amiodarone discontinued. If interstitial pneumonitis with respiratory failure progresses after the drug has been discontinued, it may be that the patient has concomitant usual interstitial pneumonitis, which is a common disease.

Dr. Robert Brown (Pulmonary Medicine): How homogeneous are the pathological features, and can one rely on a biopsy specimen to represent the entire lung?

Dr. Mark: The pathological features tend to be homogeneous, and thus the biopsy specimen can be considered representative. The problem for the pathologist is that of determining whether the amiodarone present in the lung is causing the clinical disease.

Dr. Charles A. Hales (Pulmonary Medicine): In a study reported from this hospital in 1983,[45] interstitial pneumonitis developed in 4 of 80 patients receiving amiodarone. Although one of those four patients had a small pleural effusion, recent experience has confirmed that pleural effusions are not a feature of amiodarone-induced pulmonary toxic effects. I believe the pleural effusions in the case under discussion were a result of the patient's cardiac disease and not of his pulmonary disease.

Dr. Ishir Bhan (Medicine): I saw the patient in the hospital soon after his stay in the medical intensive care unit. At that time, he was receiving high doses of prednisone, and use of a nonrebreathing mask was required to maintain the oxygen saturation in the range of 90 percent. With the continued administration of prednisone, his condition rapidly improved, and within a few weeks, he no longer needed supplemental oxygen. The dose of prednisone was tapered, and the drug eventually discontinued.

Dr. Mark: What therapy replaced the amiodarone?

Dr. Bhan: Metoprolol tartrate was substituted for the amiodarone before the patient's discharge from the intensive care unit. His arrhythmia did not recur.

ANATOMICAL DIAGNOSIS

Amiodarone-induced lung disease with bronchiolitis obliterans organizing pneumonia and interstitial pneumonitis.

ADDENDUM

The patient was discharged after a seven-week hospitalization that was complicated by corticosteroid-induced psychosis, *Clostridium difficile*–associated colitis, and insulin-requiring hyperglycemia. All these problems resolved. He was well 15 months after discharge, without arrhythmia or respiratory failure.

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