CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 9-2014: A 34-Year-Old Woman with Increasing Dyspnea

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PRESENTATION OF CASE

Dr. Lauren D. Moore (Medicine): A 34-year-old woman was admitted to this hospital because of increasing dyspnea.

The patient had been well until approximately 4 months before admission, when shortness of breath developed. Approximately 3 months before admission, she began to awaken at night with chest tightness associated with fever, coughing, and dyspnea on exertion. She was evaluated in the emergency department at another hospital. A chest radiograph reportedly showed abnormalities in the lower lobe of the left lung, and a diagnosis of community-acquired pneumonia was made; oral antibiotics were administered. Increasing dyspnea and cough developed 2.5 months before admission. A fluticasone–salmeterol combination inhaler and an albuterol inhaler were administered, with minimal improvement. Three weeks before admission, computed tomography (CT) of the chest performed at the other hospital revealed a moderate pericardial effusion, prominent pulmonary arteries, and scarring in the lower lobe of the right lung. A 2-week course of prednisone was administered, with some improvement in cough and energy, with resolution of chest tightness, but with dyspnea, which occurred with minimal activity and increased at night (requiring several pillows to sleep) and occasionally at rest. Other symptoms included early satiety, decreased appetite, hoarseness, and leg swelling. She referred herself to this hospital's Women's Heart Health Program outpatient clinic because of her progressive symptoms and pericardial effusion.

The patient reported cough productive of white mucus, dyspnea on exertion and when lying on her back, dry mouth for 3 months, heartburn and mild dysphagia, intermittent abdominal pain and diarrhea for 3 months, and hair thinning without alopecia. She also had had symmetric pains in her knees, elbows, and metacarpal and proximal interphalangeal joints for approximately 3 years, which were worse in the morning and had recently improved with prednisone therapy. During the previous 14 months, she had an intentional weight loss of more than 45 kg; during the past 4.5 months, she had a weight gain of 10 kg. She had had Raynaud's phenomenon for 1.5 years, eczema since the age of 14 years, and anemia of uncertain cause. On evaluation the previous year, examination of a biopsy specimen of a

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left axillary lymph node had been benign. She had had cellulitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) the previous year and herpes zoster three times in the past. Other daily medications included a multivitamin, vitamin D and iron supplements, and calcium acetate. She had taken phentermine in the past. She was allergic to penicillin, latex, and mushrooms. She was married, had children, and had lived in the midwestern and southern United States and New England. She did not smoke, drink alcohol, or use illicit drugs. Her mother had hyperlipidemia and thyroid disease, her father was deceased, and her children were healthy.

Videos showing transthoracic echocardiograms are available at NEJM.org

On examination, the patient appeared uncomfortable and had a persistent cough while speaking, which worsened when she moved from a chair to the examining table. The blood pressure was 158/120 mm Hg, the pulse 115 beats per minute, and the oxygen saturation 98% while she was breathing ambient air. The height was 171.5 cm, the weight 91.6 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 31. The jugular veins were distended to 10 cm above the right atrium while the patient was lying in a mildly inclined position, and heart sounds were distant, without murmur, rub, or gallop. There was cervical and supraclavicular lymphadenopathy, a swollen left proximal interphalangeal joint, leg edema to the knees, a violaceous macule (1 cm by 1 cm) on the left inner thigh, and no cyanosis or clubbing; the remainder of the examination was normal. An electrocardiogram (ECG) showed sinus rhythm at a rate of 115 beats per minute, right-axis deviation, left atrial enlargement, Q waves in the inferior leads, low voltage, and nonspecific ST-segment changes.

Dr. Timothy C. Tan: Transthoracic echocardiography was performed. The parasternal long-axis view of the echocardiogram (Fig. 1A) reveals a mild-to-moderate pericardial effusion and thickening of the left ventricular walls, features consistent with concentric left ventricular hypertrophy. Left ventricular function was within the normal range. Color Doppler imaging shows the absence of aortic-valve and mitral-valve disease. The parasternal short-axis view at the base of the heart reveals a dilated pulmonary artery and branches. Color Doppler imaging of the pulmonary valve shows mild regurgitation. M-mode imaging of the pulmonic valve (Fig. 1B) shows systolic notching, also known as the "flying W sign," a feature that suggests pulmonary hypertension. The parasternal short-axis view at the level of the midventricle (Fig. 1C) shows flattening of the ventricular septum, also known as the "D sign," a feature that suggests elevated right ventricular pressures. The apical four-chamber view (Fig. 1D) shows an enlarged right atrium and right ventricle. The right ventricle was hypokinetic. Color Doppler imaging reveals mild tricuspid-valve regurgitation. The right ventricular systolic pressure was estimated to be 91 mm Hg. The echocardiogram also shows no physiological evidence of tamponade and no congenital lesions that may give rise to a left-to-right shunt. (See Videos 1 through 4, available with the full text of this article at NEJM.org.)

Dr. Moore: The patient was transferred from the clinic to the emergency department at this hospital. On examination, the temperature was 37.8°C, the blood pressure 201/147 mm Hg, the pulse 110 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. She was able to speak in complete sentences. The complete blood count showed a red-cell distribution width of 18.1% (reference range, 11.5 to 14.5) and was otherwise normal; the peripheral-blood smear revealed 2+ anisocytosis and hypochromasia; the white-cell differential count, the erythrocyte sedimentation rate, and results of tests of coagulation and liver function were normal, as were the blood levels of electrolytes, calcium, phosphorus, magnesium, thyrotropin, troponin T, iron, iron-binding capacity, ferritin, vitamin B_{12}, and folate; testing for troponin I, rheumatoid factor, and antibodies to the human immunodeficiency virus (HIV) types 1 and 2 was negative. Other test results are shown in Table 1. Urinalysis revealed 2+ blood and trace protein by dipstick and 0 to 2 red cells and few bacteria per high-power field and was otherwise normal; urine pregnancy testing was negative. The patient was admitted to this hospital, and additional imaging studies were performed.

Dr. Amita Sharma: The chest radiograph shows enlargement of the right, left, and main pulmonary arteries (Fig. 2A). A CT scan of the chest and a subsequent pulmonary CT angiogram confirm enlargement of the main pulmonary artery and no evidence of pulmonary emboli. The right ventricle is enlarged; the wall of the right ventricle is thick (5 mm), with flattening of the interventricular septum. The right atrium is di-

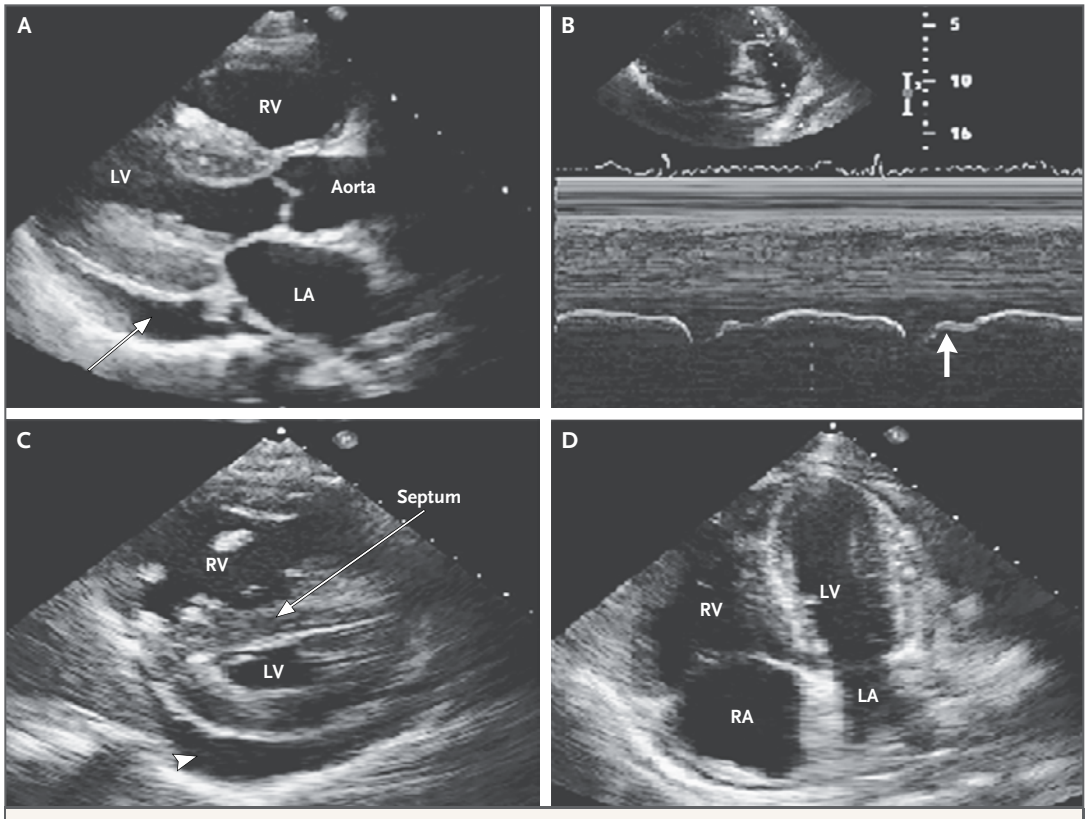

Figure 1. Echocardiographic Imaging.

The parasternal long-axis view shows a mild-to-moderate pericardial effusion (Panel A, arrow) and thickened left ventricular (LV) walls, features suggestive of left ventricular hypertrophy. An M-mode tracing of the posterior pulmonary valve leaflet in the parasternal short-axis view at the base of the heart (Panel B) shows systolic notching (arrow), known as the "flying W sign," which indicates pulmonary hypertension. In the parasternal short-axis view at the midventricular level (Panel C), interventricular septal flattening (arrow) during systole, known as the "D sign," is a finding consistent with increased pressure in the right ventricle (RV); pericardial effusion is also evident (arrowhead). The apical four-chamber view (Panel D) shows an enlarged right atrium (RA) and right ventricle relative to the left heart chambers. LA denotes left atrium.

Table 1. Laboratory Data.

Variable	Reference Range, Adults*	On Admission, This Hospital
C-reactive protein (mg/liter)	<8.0, negative for inflammation	14.0
C3 (mg/dl)	86–184	45
C4 (mg/dl)	16–38	5
N-terminal pro–B-type natriuretic peptide (pg/ml)	0–450 (age <50 yr)	2509
Antinuclear antibody	Negative at 1:40 and 1:60 dilution	Positive at >1:5120 dilution, speckled nuclear pattern
Anti–cyclic citrullinated peptide IgG antibodies (U)	0–19, negative	6
Anti–double-stranded DNA antibodies	Negative at 1:10 dilution	Negative at 1:10 dilution

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

lated, and there is reflux of intravenous contrast material into the inferior vena cava and hepatic veins. A small pericardial effusion is present. There is bilateral axillary lymphadenopathy but no mediastinal or hilar lymphadenopathy. The lungs are clear, with no evidence of interstitial lung disease or emphysema. The airways appear normal (Fig. 2B, 2C, and 2D). A ventilation–perfusion lung scan was normal.

Dr. Moore: During the patient's first 3 days in the hospital, metoprolol, hydrochlorothiazide, and furosemide were administered; systolic blood pressures decreased to between 120 mm Hg and 140 mm Hg. On the third hospital day, diagnostic right heart catheterization was performed.

Dr. Richard N. Channick: The right heart catheterization revealed severe pulmonary hypertension, with elevated right atrial pressure and markedly reduced cardiac output and mixed venous oxygen saturation, features indicating right ventricular failure (Table 2). The pulmonary-capillary wedge pressure was normal, making left heart disease unlikely.

Dr. Moore: Diagnostic test results were received.

DIFFERENTIAL DIAGNOSIS

Dr. Kai Saukkonen: At the time of the patient's admission to this hospital, she had marked systemic hypertension, severe pulmonary hyper-

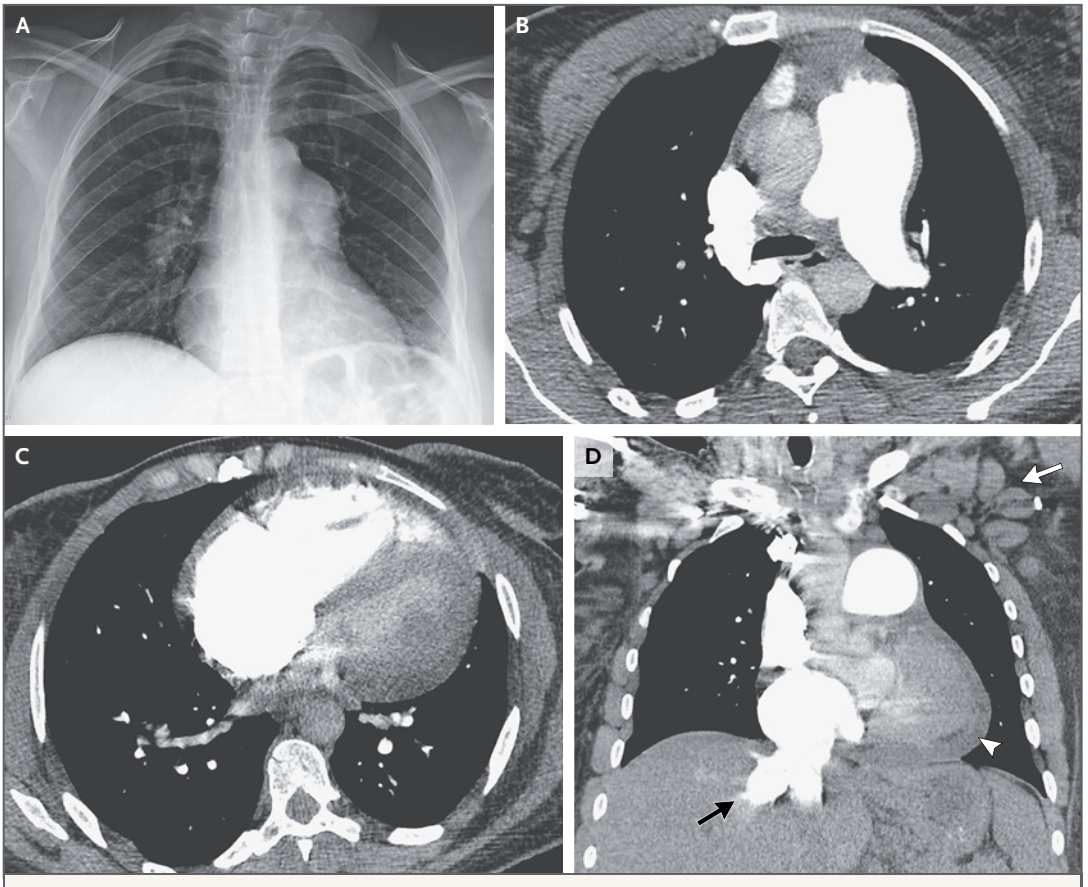

Figure 2. Thoracic Imaging.

A chest radiograph (Panel A) shows enlargement of the main pulmonary artery and of the right and left pulmonary arteries. There is peripheral pruning of the pulmonary vessels, with enlargement of the right atrium. An axial image from a pulmonary CT angiogram (CTA) confirms enlargement of the main pulmonary artery, which measures 3.8 cm just proximal to its bifurcation (Panel B). In another axial image from the CTA, hypertrophy of the right ventricular wall, flattening of the interventricular septum, and right atrial enlargement (Panel C) are seen. A coronal image from the CTA (Panel D) shows reflux of contrast material into the inferior vena cava and hepatic veins (black arrow), with a small pericardial effusion (arrowhead); multiple enlarged left axillary lymph nodes are present (white arrow). There is no mediastinal or hilar lymphadenopathy.

Table 2. Right Heart Catheterization.

Variable	Normal Range	This Patient
Right atrial pressure (mm Hg)	1–6	18
Pulmonary-artery pressure (mm Hg)	15–25/4–12 (mean, <25)	74/33 (mean, 52)
Pulmonary-capillary wedge pressure (mm Hg)	4–12	5
Mixed venous oxygen saturation (%)		32
Cardiac output (liters/min)	4–6	2.93
Pulmonary vascular resistance (dyn · sec · cm^{-5})	<240	1283

tension with right-sided heart failure, a pericardial effusion, and numerous symptoms that at first appear to be unrelated but on further consideration point us toward the most likely diagnosis.

SYMPTOMS

Many of the patient's symptoms were nonspecific, but when they are evaluated in conjunction with the elevated levels of inflammatory markers, a positive antinuclear antibody (ANA) assay, and hypocomplementemia, they suggest a collagen vascular disease. For 3 years, in the mornings, she had symmetric pains in the knees, elbows, and metacarpal and proximal interphalangeal joints that responded to treatment with glucocorticoids; she also had Raynaud's phenomenon for 1.5 years. In the 3 months before presentation, she had dry mouth and abdominal pain, with intermittent diarrhea. Other findings included hair thinning, eczema, anemia, and benign axillary lymphadenopathy, all of which have been associated with connective-tissue diseases. Does the most impressive finding in this case, severe pulmonary hypertension, fit with a rheumatologic diagnosis?

PULMONARY HYPERTENSION

Pulmonary hypertension may be asymptomatic or may be manifested as dyspnea, chest discomfort, exertional syncope, leg swelling, or even abdominal discomfort related to hepatic congestion from right-sided heart failure. Pulmonary hypertension most likely accounted for many of this patient's symptoms.

Once pulmonary hypertension is suspected, echocardiography is the initial diagnostic test. Right heart catheterization is confirmatory, yields more precise pressure measurements, and can help guide therapy. Since there are many causes of pulmonary hypertension, defining the underlying cause is critical for choosing the most effective disease-specific therapy.

The causes of pulmonary hypertension are classified into five groups that are based on the underlying disorder.[1] Group 1 is the pulmonary arterial hypertension group, which contains many broad categories of disease, such as idiopathic pulmonary arterial hypertension, inherited pulmonary arterial hypertension, and pulmonary arterial hypertension that is associated with any of a variety of entities (e.g., drugs and toxins, HIV infection, and connective-tissue diseases). We have no relevant family history to support a heritable cause of pulmonary hypertension in this patient. However, since she had taken phentermine in the past, it is worth considering drug exposure as a possible cause. Phentermine gained notoriety in the 1990s because of the development of pulmonary hypertension and cardiac valvular abnormalities in patients who took this medication in combination with fenfluramine. Fenfluramine appears to have been the culprit agent in those patients, although at least one case report showed that phentermine alone was associated with pulmonary hypertension.[2] We are not told that this patient took fenfluramine or any other drug associated with pulmonary hypertension in addition to phentermine, so it is unlikely that drugs caused the pulmonary hypertension. We are told that HIV testing was negative; therefore, we can rule out HIV infection. Further consideration should be given to pulmonary arterial hypertension associated with connective-tissue diseases.

Group 2 includes pulmonary hypertension due to left-sided heart disease. Since the patient had no systolic or diastolic left heart disease or left-sided valvular disease on echocardiography, and the pulmonary-capillary wedge pressure was normal according to right heart catheterization, left heart disease is unlikely.

The disorders included in group 3 (pulmonary hypertension attributed to lung disease with or without hypoxemia) can be ruled out, since the patient had no evidence of any underlying lung diseases. Similarly, the disorders in group 4 (pulmonary hypertension due to chronic thromboembolic disease) can be ruled out by the lack of perfusion defects on the ventilation–perfusion lung scan. Finally, none of the group 5 disorders (pulmonary hypertension due to hematologic, systemic, metabolic, or other disorders) are supported by the patient's presentation.

The disorders included in groups 2 through 5 are unlikely to explain the underlying cause of this patient's pulmonary hypertension. Therefore, we are left with pulmonary arterial hypertension associated with connective-tissue diseases (a category in group 1).

CONNECTIVE-TISSUE DISEASES

In this patient with severe pulmonary hypertension and numerous symptoms suggestive of a rheumatologic disease, which connective-tissue disease is most likely?

Systemic lupus erythematosus is a chronic inflammatory disease that can affect multiple organ systems. The cause is unknown, although autoantibodies (especially ANA and anti–double-stranded DNA [dsDNA], anti-Smith [Sm], and antiphospholipid antibodies) are associated with this disease. Women are affected more often than men, and the incidence is greatest in the third and fourth decades of life. Pulmonary hypertension is an uncommon complication of lupus and may be more common in patients with Raynaud's phenomenon and serous effusions.[3]

This patient meets the clinical and immunologic criteria for lupus.[4] However, the negative test for anti-dsDNA antibodies makes this diagnosis less likely, since between 66% and 95% of patients with lupus have a positive test for anti-dsDNA antibodies.[5]

Scleroderma involves collagen deposition in the skin of patients in their fourth through sixth decades of life, more often women than men. When internal organs are also involved, the disease is termed systemic sclerosis, which is further divided into limited cutaneous and diffuse cutaneous systemic sclerosis. The skin changes may progress from early pruritus to edema to sclerodactyly. Other common associations include Raynaud's phenomenon, pulmonary hypertension, esophageal involvement, and interstitial lung disease. Scleroderma renal crisis, which may be precipitated by the use of glucocorticoids, develops in a small percentage of patients and, if present, might explain this patient's apparently new systemic hypertension. Pulmonary hypertension is much more common in scleroderma than in lupus, with or without interstitial lung disease. Several autoantibodies are associated with scleroderma, especially ANA and antitopoisomerase I (anti–Scl-70), anticentromere, anti–RNA polymerase III, and anti–β_2-glycoprotein I antibodies.

Although Raynaud's phenomenon, pulmonary hypertension, and hypertension are suggestive of scleroderma in this case, the absence of typical skin findings makes this diagnosis unlikely.

Mixed connective-tissue disease is an overlap syndrome, with features of lupus, scleroderma, and polymyositis.[6] It is much more common in women than in men, is typically diagnosed in the second or third decade of life, and is associated with substantial morbidity and mortality. Treatment is given according to the disease that the patient's disease most closely resembles (lupus, scleroderma, or polymyositis). Although there is some controversy in the literature about whether mixed connective-tissue disease should be thought of as a disease or as a constellation of findings, its classification as a disease is useful in understanding this patient's condition. Patients with mixed connective-tissue disease may ultimately meet criteria for lupus or scleroderma.[7] Testing for the anti–U1-ribonucleoprotein (RNP) antibody (an extractable nuclear antigen antibody) is positive in patients with mixed connective-tissue disease.

Arthralgias, arthritis (with swollen hands), Raynaud's phenomenon, and pulmonary hypertension are particularly prominent features of mixed connective-tissue disease. Pulmonary hypertension may be relatively rapid in onset and is often the cause of death. Some other possible manifestations of mixed connective-tissue disease are pericarditis and interstitial lung disease. This patient did not have myositis or myalgias to suggest polymyositis, but these manifestations frequently develop over time in patients with mixed connective-tissue disease.

This patient had had joint symptoms for several years, which preceded accelerating respira-

tory, gastrointestinal, and other somatic problems. The joint symptoms responded to treatment with glucocorticoids. Possible serositis developed in the form of a pericardial effusion, accompanied by severe systemic and pulmonary hypertension. She had a very high titer of ANA, low levels of complement, and a negative test for anti-dsDNA antibodies. In sum, she had features of both scleroderma and lupus, but because neither diagnosis fits her condition well and because of the prominence of pulmonary hypertension, arthralgias with swelling, and Raynaud's phenomenon, the most likely diagnosis is mixed connective-tissue disease. I believe the test result that was received was a positive anti–U1-RNP antibody test.

Dr. Eric S. Rosenberg (Pathology): Dr. Moore, what was your impression when you initially evaluated this patient?

Dr. Moore: We knew from our examination, imaging, the echocardiogram, and the right heart catheterization that she had severe pulmonary hypertension and lymphadenopathy. Given her long history of eczema, anemia, and joint pain, we thought an underlying rheumatologic condition was most likely. However, the presence of lymphadenopathy raised some concern for lymphoma, sarcoidosis, tuberculosis, and HIV infection, although skin testing for tuberculosis and HIV-antibody testing were negative. Ultimately, we thought that a lymph-node biopsy might provide useful diagnostic information.

CLINICAL DIAGNOSIS

Pulmonary arterial hypertension caused by a rheumatologic disorder.

DR. KAI SAUKKONEN'S DIAGNOSIS

Pulmonary hypertension caused by mixed connective-tissue disease.

PATHOLOGICAL DISCUSSION

Dr. Lawrence R. Zukerberg: A lymph-node biopsy was performed, and the specimen showed a reactive lymph node with intact nodal architecture (Fig. 3A). Two types of lymphoid hyperplasia were seen, follicular hyperplasia and paracortical hyperplasia, as well as sinus histiocytosis with occasional pigmented histiocytes and a plasmacytosis involving the interfollicular and medullary areas. The plasmacytosis was more evident after immunostaining for CD138 (Fig. 3B) and was a mixture of plasma cells producing kappa and lambda light chains, IgG, IgM, and IgA. IgG4 plasma cells were present but did not predominate. Plasma cells also were present in the germinal centers. No evidence of cancer, granulomas, or viral inclusions was found.

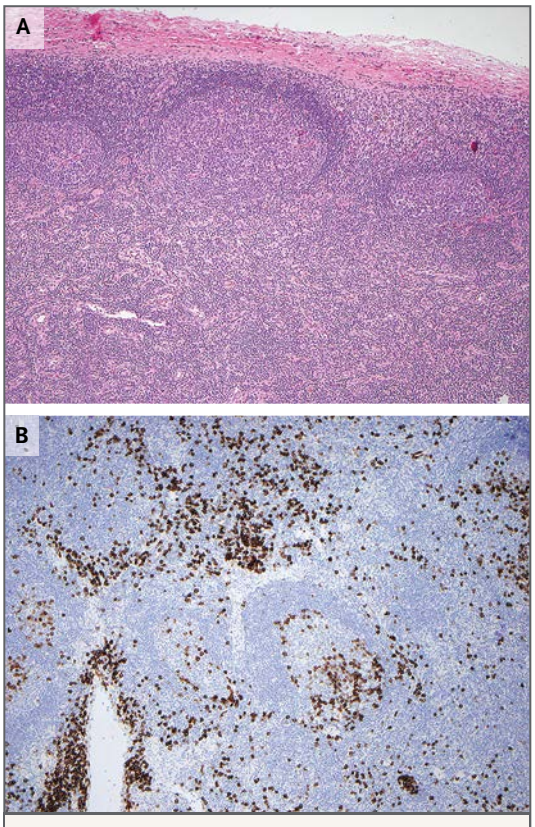

Figure 3. Biopsy Specimen of the Lymph Node.
Examination of a biopsy specimen of an axillary lymph node showed follicular and interfollicular lymphoid hyperplasia, features consistent with a reactive lymph node with intact nodal architecture (Panel A, hematoxylin and eosin). The specimen was notable for an increased number of CD138-positive plasma cells seen after immunostaining for CD138 (Panel B).

The causes of reactive lymphoid hyperplasia are numerous and include both viral and bacterial infections, autoimmune disorders (e.g., rheumatoid arthritis, lupus, and mixed connective-tissue disease), drugs, and iatrogenic causes. Lymphadenopathy in autoimmune disease is common, and biopsy is frequently performed to

rule out cancer and granulomatous disorders.[8,9] Common histologic features include follicular and paracortical hyperplasia and a plasmacytosis in the medullary area. Some cases of lupus also show foci of necrosis with nuclear debris, which can also be seen in cases of mixed connective-tissue disease.[10]

Dr. Mandakolathur R. Murali: A panel of autoantibodies to define the nature of the systemic inflammatory connective tissue was ordered. This patient had a very high ANA titer (>1:5120) with a nuclear speckled pattern. The speckled pattern is seen with antibodies directed to nuclear constituents, such as the small nuclear RNPs (snRNPs), RNA-binding and DNA-binding proteins, helicase, and topoisomerase. The diffuse or homogeneous pattern is a feature of antibodies directed against dsDNA, histones, or deoxyribonucleoprotein. A negative test for anti-dsDNA antibodies and an absence of a homogeneous pattern suggests that the specificity of the autoantibody in this patient is to snRNPs and not to a DNA–histone complex.

During the process of DNA transcription, introns are removed or spliced from precursor RNA or heterogeneous nuclear RNA (hnRNA) by a complex of five small nuclear RNAs (snRNAs) and other protein subunits that make up the spliceosome.[11] The snRNAs that make up the major spliceosome are U1, U2, U4, U5, and U6, and they participate in several RNA–RNA and RNA–protein interactions. The RNA component of the snRNP is rich in uridine. The proteins complexed to the uridine-rich RNA are the epitopes that define the individuality of the extractable nuclear antigens and the specificity of these antibodies.

This patient had an equivocal antibody titer to anti-Smith and a negative test for anti-dsDNA antibodies, making systemic lupus erythematosus unlikely. However, this patient had a high titer of anti–U1-RNP antibody. The presence of this antibody is a prerequisite for the diagnosis of mixed connective-tissue disease. Mixed connective-tissue disease is defined by the presence of serologic and clinical features[12]; these features have been incorporated into criteria used in making the diagnosis.[13,14] This case fulfills both the serologic and the clinical requirements for mixed connective-tissue disease.

Dr. Channick: This patient had severe pulmonary arterial hypertension requiring rapid institution of disease-specific therapy. Because she had severe shortness of breath and functional impairment, as well as rapid progression of symptoms, a pericardial effusion, and hemodynamic measurements indicating severe pulmonary hypertension with right ventricular failure, she was considered to be in a poor prognostic category. Continuous intravenous epoprostenol is generally considered the treatment of choice for such a patient, and the administration of this agent was begun.

Dr. Moore: Within a few days after the initiation of epoprostenol, the patient reported symptomatic improvement. A pump for its continuous infusion was placed, and after she learned how to manage the pump, she was discharged from the hospital. At the time of discharge, she was receiving intravenous epoprostenol, oral bosentan, and sildenafil. She was eventually weaned off the epoprostenol and now is receiving inhaled treprostinil, bosentan, and sildenafil. Since discharge, she has undergone several right heart catheterizations that showed a marked improvement in mean pulmonary-artery pressure; the most recent measurement was 29 mm Hg. A repeat echocardiogram also showed a normal pulmonary artery and right ventricle. She is also being treated with hydroxychloroquine and prednisone for mixed connective-tissue disease and is doing very well.

A Physician: What was the cause of her hypertension?

Dr. Channick: We never identified the cause of the hypertension. It is unusual in cases of mixed connective-tissue disease, and in pulmonary hypertension generally, to have this magnitude of systemic hypertension. Usually, relative hypotension is seen because of low cardiac output.

ANATOMICAL DIAGNOSIS

Systemic inflammatory rheumatic disease identified as U1-ribonucleoprotein–associated mixed connective-tissue disease.

This case was presented at the Medical Case Conference.

Dr. Channick reports receiving consulting fees and grant support from Actelion Pharmaceuticals, Bayer, and United Therapeutics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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