A 77-Year-Old Woman With Dyspnea and Raynaud Phenomenon

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A 77-year-old black woman who was a lifelong nonsmoker presented to our office for evaluation of worsening dyspnea over the last year that had severely limited her activities of daily living. Her medical history included type 2 diabetes, hypertension, and pacemaker placement. She reported paroxysmal nocturnal dyspnea and dry cough. She denied fevers, chills, chest pain, hemoptysis, or weight loss. She also reported whitening of her fingers with cold temperatures, suggestive of Raynaud phenomenon (RP). However, this symptom was not apparent on the initial visit, and she did not complain of it at that time.

Physical Examination

Vital signs were as follows: temperature, 37.1°C; BP, 140/80 mm Hg; heart rate, 58 beats/min; respiratory rate, 18 breaths/min; and room air saturation of 95%. The patient appeared comfortable and in no acute respiratory distress. Chest examination showed decreased air entry at the lung bases without wheezing or crackles. Cardiac examination results were as follows: soft, S1; loud, S2. Examination of the extremities showed minimal pedal edema bilaterally. Neck and abdominal examination results were normal. The initial skin examination was unrevealing.

Laboratory Findings

The patient's hemogram results revealed a normocytic anemia with normal WBC and platelet counts. Serum chemistry tests were significant for an elevated BUN level of 34 mg/dL and a creatinine level of 1.5 mg/dL. A pulmonary function test revealed an FVC of 1.4 L (75% predicted), an FEV1 of 1.1 L (72% predicted), and an FEV1/FVC of 76, as well as a total lung capacity of 2.68 L (62% predicted), a residual volume of 1.19 L (65% predicted), and a diffusing capacity of the lung for carbon monoxide of 7.0 mL/kg/min (37% predicted), indicating a mild restrictive ventilatory defect with a significant gas exchange abnormality. On 6-min walk test she walked 144 m, and on cardiopulmonary exercise testing her maximum oxygen consumption was 7.0 mL/kg/min (37% predicted). A ventilation/perfusion scan showed low probability for pulmonary embolism, and duplex ultrasonography of the legs showed no evidence of DVT. A CT scan of the chest revealed dilatation of the main pulmonary artery measuring 3.4 cm, suggestive of pulmonary hypertension (Fig 1). A transthoracic
echocardiographic examination showed an estimated pulmonary artery systolic pressure of 56 mm Hg and an ejection fraction of 70%. Right-sided heart catheterization revealed a pulmonary artery pressure of 52/16 mm Hg, with a mean pulmonary artery pressure (mPAP) of 27 mm Hg, pulmonary capillary wedge pressure of 10 mm Hg, peripheral vascular resistance (PVR) of 217 dynes/s/cm$^5$, and cardiac output by Ficks of 6.25 L/min. Multiple serologic test results were positive: anti-dsDNA, 125 IU/mL (reference range <7 IU/mL); anticentromere antibody, 1:1,280 (reference range <1:40); cardiolipin IgG >100 U/mL (reference range >80 U/mL); and SS-A IgG, 227 U/mL (reference range <100 U/mL).

Figure 1  CT scan of chest revealing dilatation of main pulmonary artery (arrow), measuring 3.4 cm at largest diameter.

What is the diagnosis?

*Diagnosis: Pulmonary arterial hypertension as a complication of sclerosis sine scleroderma*

**Discussion**

Pulmonary arterial hypertension (PAH) almost always appears late in cases of sclerosis sine scleroderma (ssSSc), a rare variant of the connective tissue disease systemic sclerosis (SSc), with multiorgan involvement in the absence of skin manifestations. Scleroderma refers to the presence of hardened, thickened skin that is a characteristic feature of SSc. The degree of skin involvement defines the classification of the sclerosis into limited or diffuse cutaneous conditions. Approximately 10% of patients with SSc do not have obvious skin manifestations. The rare form of ssSSc is characterized by the absence of skin thickening, but involves multiple organ systems, as seen in SSc. Without the distinctive skin thickening, ssSSc becomes a challenge to diagnose, which could delay the diagnosis until years after injury to the internal organs has occurred. Other possible findings in ssSSc are calcinosis, RP, esophageal dysfunction, and telangiectasias. Pulmonary involvement in ssSSc includes interstitial lung disease (ILD) and pulmonary hypertension. According to a systemic review of all published cases of ssSSc, pulmonary involvement was reported in 66% of cases, second to GI involvement (80%) but greater than cardiac involvement (25%). We are aware of only one published case of PAH as the initial presenting feature of ssSSc; that patient displayed symptoms of RP and dyspnea and had positive serologic test results for nucleolar-staining antinuclear antibody and antifibrillarin. Variable serologic test results have been reported in ssSSc, most commonly for anticentromere, as seen in our case, but also including antitopoisomerase, anti-RNA polymerase III, and anti-Th/To ribonucleoprotein. In general, antitopoisomerase antinuclear antibody, anti-RNA, and antifibrillarin are associated with diffuse cutaneous SSc. Anticentromere is usually associated with limited cutaneous SSc.

A difficulty in diagnosing PAH early is the absence of symptoms in the patient as a consequence of the right ventricle increasing its output to compensate for the developing PVR. When pulmonary hypertension is diagnosed using echocardiography, confirmation and evaluation of a vasodilator response should be determined using right-sided heart catheterization. Common etiologic characteristics associated with pulmonary hypertension need to be excluded using several diagnostic studies: a CT scan of the chest to evaluate for ILD, a CT pulmonary angiogram or ventilation/perfusion scan to evaluate for chronic thromboembolic disease, and polysomnography for sleep apnea. Pulmonary hypertension secondary to scleroderma portends a poor prognosis.
Physicians should be aware of PAH as a presenting feature of ssSSc. This will help to avoid misclassifying PAH associated with ssSSc as idiopathic pulmonary arterial hypertension (IPAH), which will affect prognostication. The response to therapy is worse in scleroderma-related PAH compared with IPAH, with three-year survival in people with scleroderma-related PAH of 48.9%, compared with 83.6% in people with IPAH. A 6-year longitudinal study reported that the risk of death increases by 11% for every 10 mm Hg increase in mPAP at diagnosis; however, outcomes were improved in patients who received earlier treatment. It is imperative that we monitor patients with ssSSc by using annual echocardiography to diagnose PAH earlier and improve patient outcome. Other organ involvements that can occur over time include ILD, esophageal dysmotility, pericardial disease, and peripheral vascular disease. The prevalence of RP may be higher than reported because mild signs can be missed. The patient's main complaint was dyspnea, not her skin manifestation.

Clinical Course

The patient was initially treated with bosentan and later treated with amlodipine, furosemide, and spironolactone. After 1 year of treatment with bosentan, a repeat right-side heart catheterization showed a pulmonary artery pressure of 47/17 mm Hg with an mPAP of 30 mm Hg and a pulmonary capillary wedge pressure of 15 mm Hg, PVR of 209 dynes/s/cm$^5$, and cardiac output by Ficks of 5.74 L/min. On repeat 6-min walk test she walked 194 m, and on cardiopulmonary exercise testing her maximum oxygen consumption was 6.6 mL/kg/min. Clinically, her symptoms improved on this regimen, and she moved from New York Heart Association class 4 to class 3. On follow-up visits, she continues to be in class 3.

Clinical Pearls

1. ssSSc is a condition where there is internal organ involvement in the absence of skin involvement.
2. PAH can be the first presentation of ssSSc.
3. Pulmonary hypertension associated with ssSSc can be problematic diagnostically and has a worse prognosis than IPAH.
4. Patients with pulmonary hypertension should be screened for collagen vascular diseases, especially scleroderma, as the underlying cause, even in the absence of skin manifestations.

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SUGGESTED READINGS:

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