Curiosity CRESTed: Uncovering a PAH's Etiology

Caitlyn Phillips, OMS-III[1], Jacob Wood, MD, MS[2], Jennifer Mundell MD[1]

[1]Marian University Tom and Julie Wood College of Osteopathic Medicine, Indianapolis, IN

[2]Ascension St. Vincent Indianapolis, Department of Internal Medicine, Indianapolis, IN

Abstract

Pulmonary arterial hypertension (PAH) is a progressive condition that may occur idiopathically or in association with connective tissue diseases such as limited cutaneous systemic sclerosis (lcSSc). We present a case of late onset lcSSc identified during evaluation of presumed idiopathic PAH in a 75-year-old patient with longstanding Raynaud's phenomenon. This case highlights missed opportunities for earlier diagnosis and screening. Patients with lcSSc, particularly those with declining DLCO (diffusing capacity of the lungs for carbon monoxide), abnormal FVC/DLCO ratios (FCV = forced vital capacity), elevated NT-proBNP, and positive autoantibodies, are at increased risk for PAH. Screening for lcSSc in older patients with idiopathic arterial hypertension, and for PAH in lcSSc, may enable earlier intervention and improve clinical outcomes.

Keywords: Pulmonary arterial hypertension, Limited cutaneous systemic sclerosis, systemic sclerosis

Background

Pulmonary arterial hypertension (PAH) is a progressive, life-threatening vascular disease characterized by elevated pulmonary vascular resistance and progressive right ventricular failure.[1] While idiopathic PAH is a well-characterized clinical entity, PAH arising secondary to concurrent autoimmune connective tissue diseases carries a significantly higher prevalence and mortality rate.[2-4] Among these underlying conditions, limited cutaneous systemic sclerosis (lcSSc), commonly associated with the "CREST" constellation of symptoms: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias. LcSSc demonstrates the strongest association with the development of PAH.[1]

Importantly, systemic sclerosis-associated PAH (SSc-PAH) carries a notably worse prognosis than idiopathic PAH, a disparity primarily driven by an aggressive underlying pulmonary arterial vasculopathy and a compromised right ventricular capacity to compensate for elevated afterload.[5] Given this accelerated risk, early detection of systemic sclerosis paired with routine, systematic screening for PAH is vital. Initiating targeted interventions at an earlier clinical stage is demonstrably linked to improved long-term survival.[1,6] Recognizing early constitutional or microvascular symptoms, such as progressive exertional dyspnea, Raynaud's phenomenon, and telangiectasias, remains a critical hurdle. These signs are frequently underrecognized or misattributed during the initial stages of the disease.[6]

Current clinical guidelines advocate for routine annual screening using transthoracic echocardiography (TTE) in all patients diagnosed with lcSSc to detect early signs of pulmonary vascular disease.[7] In clinical practice, however, the insidious onset of symptoms and variable initial diagnostic markers frequently complicate early detection, leading to missed opportunities for

timely therapeutic intervention. We present a case of late onset lcSSc identified via evaluation of presumed idiopathic PAH, while highlighting missed opportunities for early diagnosis and potential impact of new therapies.

Case presentation

A 75-year-old female with pulmonary arterial hypertension (PAH), Raynaud's phenomenon, hypothyroidism, dyslipidemia, and essential hypertension was admitted when a basic metabolic panel prior to a pre-planned right heart catheterization showed a serum potassium of 7.8 mmol/L and acute kidney injury. She had recently begun oral potassium supplementation prescribed by her primary care physician.

Prior to her visit, her PAH had been controlled with furosemide, sildenafil, and selexipag (Uptravi). She had no history of smoking, coronary artery disease, or other identifiable secondary causes of PAH and no prior documented autoimmune workup.

Investigation

On presentation in the emergency department, the patient appeared visibly anxious with increased work in breathing at 20 breaths per minute. She was afebrile, and in normal sinus rhythm, with intermittent episodes of tachycardia at 110 bpm and a blood pressure averaging 120/50. She required home use of 5-6 L of supplemental oxygen via nasal cannula and was saturating 92% on 4 L nasal cannula in the emergency department. Cardiovascular examination revealed a blowing systolic murmur best heard at the left upper sternal border. Pulmonary examination was unremarkable aside from increased work of breathing and tachypnea. Trace pitting edema was present in the lower extremities, although right heart catheterization suggested overall low volume status. Her skin was warm and dry without rash or any active digital discoloration suggestive of her known Raynaud's phenomenon.

A basic metabolic panel as well as a N-terminal pro–B-type natriuretic peptide (NT-proBNP) was obtained (Table 1). The patient had no history of immunologic serum evaluation, so one was initiated. Testing revealed a positive anti-centromere B (>9.0 antibody index units) and antinuclear antibodies (ANA), with negative anti-Scl-70, anti-RNA polymerase III, anti-Th/To, anti-cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor. In the context of her PAH and Raynaud's phenomenon, these findings supported a diagnosis of limited cutaneous systemic sclerosis (lcSSc). Additional testing for viral hepatitis, including hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM antibody, and hepatitis C antibody were negative. Anti–Sjögren's-syndrome–related antigen A (SSA/Ro), anti–Sjögren's-syndrome–related antigen B (SSB/La) antibodies, and anti–histidyl–transfer RNA synthetase (anti–Jo-1) antibodies all returned negative.

Chest imaging was also performed. X-ray demonstrated increased pulmonary vascular markings and peribronchial cuffing consistent with the patient's known pulmonary arterial hypertension diagnosis (Figure 1). A nuclear medicine ventilation-perfusion scan of the lungs was performed and showed normal ventilation and perfusion without evidence of mismatch and thus, no evidence for thromboembolic disease.

Table 1. Baseline serum biochemistry and cardiac biomarkers obtained at admission of the patient.

	Patient Value	Reference Range
Sodium	121 mmol/L	136-146 mmol/L
Potassium	7.8 mmol/L	3.5-5.0 mmol/L
Chloride	94 mmol/L	95-105 mmol/L
Creatinine	2.2 mg/dL	0.6-1.2 mg/dL
Calcium	10.3 mg/dL	8.4-10.2 mg/dL
NT-proBNP	625 pg/mL	< 125 pg/mL

Results are notable for critical electrolyte abnormalities (severe hyperkalemia and hyponatremia), acute renal insufficiency, and elevated NT-proBNP consistent with right ventricular strain.

Treatment

Due to her acute abnormalities including hyperkalemia and acute kidney injury, likely secondary to recent initiation of oral potassium supplementation in the setting of chronic diuretic use, she was treated with standard hyperkalemia management including intravenous calcium gluconate for cardiac membrane stabilization, insulin with dextrose, and loop diuretics. Due to persistent hyperkalemia and worsening renal function following these treatments, she ultimately required one session of hemodialysis, after which her potassium levels normalized and renal function improved.

Given her known diagnosis of PAH, her chronic pulmonary vasodilator therapy with sildenafil and selexipag was continued, while diuretic therapy was adjusted in the setting of her acute kidney injury.

Outcome

Following correction of her electrolyte abnormalities, the patient's serum potassium normalized, and renal function improved toward baseline without further need for renal replacement therapy. Potassium supplementation was discontinued, and her diuretic regimen was adjusted. She remained hemodynamically stable throughout hospitalization without escalation of her baseline oxygen requirement. Her PAH therapies were continued without modification during admission.

With her serologic workup returning strongly positive for anti-centromere B, Raynaud's Phenomenon, and history of PAH, and her subsequent new diagnosis of lcSSc allowed her to schedule with a rheumatologist in a timely manner to optimize her treatment plan.

Discussion

This case exemplifies the importance of recognizing early clinical features of systemic sclerosis in patients with idiopathic PAH. Connective tissue disease associated PAH accounts for a significant portion of PAH, with systemic sclerosis representing the most common underlying etiology in the United States. Currently, 10-15% of patients with SSc develop PAH, which has become the leading cause of morbidity and mortality.[2] When untreated, patients who have SSc and develop PAH, have a median survival rate of less than 3 years. Outcomes in patients with SSc and PAH are significantly worse than those who exclusively have idiopathic PAH. This is likely due to various pathophysiological mechanisms including diffuse vasculopathy, intimal fibrosis, and impaired right ventricular adaptation.[9,10]

Raynaud's phenomenon, telangiectasias, and dyspnea are early clinical features of systemic sclerosis (SSc) and serve as strong predictors of future PAH development.[6] Additional risk factors for PAH development are highly prevalent in patients with lcSSc. Specifically, those demonstrating a progressive decline in DLco, an elevated FVC/DLco ratio, increased N-terminal pro-brain natriuretic peptide (NT-proBNP), and positivity for ANA including anti-centromere antibodies are at a substantially heightened risk.[7,11] Screening algorithms, such as the evidence-based DETECT model, systematically incorporate these clinical, laboratory, and electrocardiographic variables to identify patients who are at an elevated risk of asymptomatic PAH. Those identified at increased risk are subject to earlier diagnosis through a sequential evaluation spanning transthoracic echocardiography and definitive right heart catheterization.[11]

This patient demonstrated a long history of Raynaud's phenomenon represents a missed opportunity for earlier diagnosis and screening with pulmonary function testing, echocardiography, and additional biomarkers, to identify PAH earlier. Early identification has become paramount as new treatments become available. SSc-PAH management is continuing to evolve as new pathophysiological mechanisms and antibodies are being identified. Current first line therapy includes endothelin receptor antagonists and phosphodiesterase type 5 inhibitors, and higher risk patients are escalated to include prostacyclin analogs with concurrent treatment.

Novel agents, such as sotatercept, an activin signaling inhibitor which targets pulmonary vascular remodeling, has shown improved outcomes in patients with PAH.[8] These evolving therapies

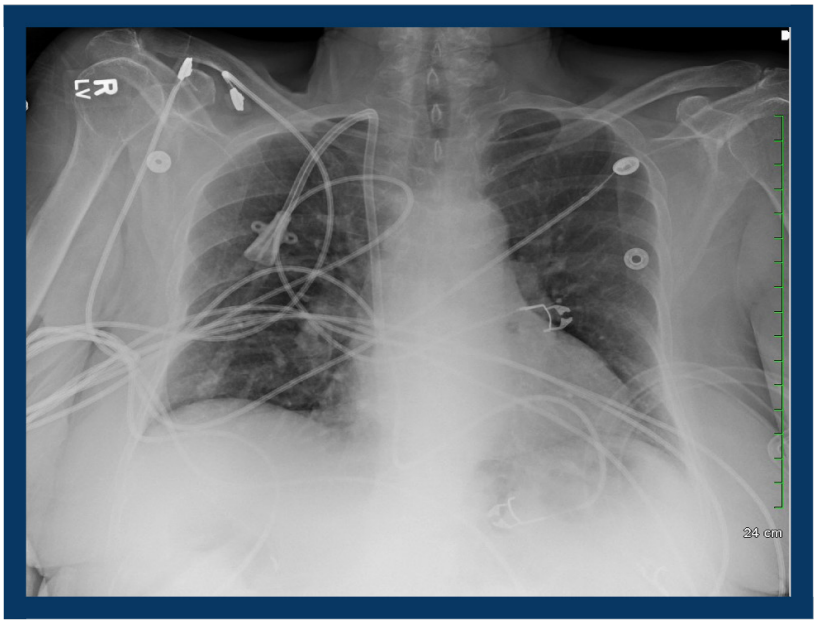

Figure 1: Chest X-ray demonstrating increased pulmonary vascular markings and peribronchial cuffing.

and identification of disease-specific antibodies shows the importance of early diagnosis, as earlier therapy and intervention improves patient outcomes.

Conclusion

This case demonstrates the importance of recognizing early manifestations of SSc, particularly Raynaud's phenomenon and telangiectasias, to initiate early screening and detection of both scleroderma and PAH. Allowing for early intervention and timely identification of connective tissue disease in patients with PAH, has shown improved clinical outcomes. Increased awareness among primary care providers is critical for improving early diagnosis rate and treatment.

Conflict of Interest: The authors declare no conflicts of interest.

Funding Statement: This research received no external funding.

References

1. Haque A, et al. Eur Respir Rev. 2021;30(161):210053.
2. Grygiel-Górniak B, et al. J Clin Med. 2025;14(13):4742.
3. Brown ZR, Nikpour M. Eur J Rheumatol. 2020;7(Suppl 3):187-192.
4. Thoreau B, Mouthon L. Autoimmun Rev. 2024;23(4):103506.
5. Kolstad KD, et al. Chest. 2018;154(4):862-871.
6. Weatherald J, et al. Eur Respir Rev. 2019;28(153):190023.
7. Humbert M, et al. Eur Heart J. 2022;43(38):3618-3731.
8. Humbert M, et al. N Engl J Med. 2025;392(20):1987-2000.
9. Attanasio U, et al. Int J Mol Sci. 2020;21(12):4430.
10. Tedford RJ, et al. Circ Heart Fail. 2013;6(5):953-963.
11. Coghlan JG, et al. Ann Rheum Dis. 2014;73(7):1340-1349.