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| RESEARCH ARTICLE

Unmasking Connective Tissue Disease Through Pulmonary Hypertension: A Diagnostic Challenge

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| ABSTRACT

Pulmonary arterial hypertension (PAH) is a severe and potentially life-threatening manifestation of connective tissue diseases, often presenting insidiously and complicating timely diagnosis. We report the case of a 48-year-old Saudi woman with no prior chronic illness who presented with progressive exertional dyspnea and fatigue over six weeks. Examination revealed mild central cyanosis, elevated jugular venous pressure, and a prominent right ventricular heave. Laboratory evaluation showed elevated NT-proBNP and mild hypoxemia, while echocardiography demonstrated right ventricular dilation and an estimated pulmonary artery systolic pressure of 70 mmHg. Right heart catheterization confirmed pre-capillary pulmonary hypertension. Serologic workup revealed high-titer anti-U1 RNP antibodies, ANA positivity, and features consistent with mixed connective tissue disease (MCTD), with no evidence of left heart disease, thromboembolic disease, or significant interstitial lung involvement. Management included combination PAH-targeted therapy with an endothelin receptor antagonist and a phosphodiesterase-5 inhibitor, alongside low-dose corticosteroid immunosuppression. Supportive care comprised oxygen supplementation and close hemodynamic monitoring. Over three months, the patient's functional status improved from WHO functional class III to II, with reduction in NT-proBNP and increased six-minute walk distance. This case underscores the diagnostic challenge of MCTD presenting primarily with PAH, emphasizing that subtle systemic features may precede cardiovascular compromise. Early recognition, prompt hemodynamic assessment, and a multidisciplinary management strategy are crucial to improve prognosis and prevent irreversible right ventricular dysfunction. Clinicians should maintain a high index of suspicion for PAH in patients with connective tissue disease, even in the absence of overt systemic manifestations.

| KEYWORDS

Pulmonary hypertension, connective tissue disease, autoimmune disease, interstitial lung disease, systemic sclerosis, vasculopathy, diagnostic challenge, and pulmonary vascular disease

| ARTICLE INFORMATION

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Introduction

Pulmonary hypertension (PH) is hemodynamically defined as an abnormal elevation of mean pulmonary arterial pressure (mPAP) beyond the upper limit of normal. According to current international guidelines, a resting mPAP greater than 20 mmHg, measured by right heart catheterization (RHC), now constitutes the diagnostic threshold for PH—revised downward from the former criterion of ≥25 mmHg [1]. This pathological rise in pulmonary pressure may result from a spectrum of disorders affecting the pulmonary vasculature, the heart, or the lungs [1,2]. To facilitate clinical understanding and management, the World Health Organization classifies PH into five groups based on shared pathophysiologic and therapeutic principles [1]. Group 1, or pulmonary arterial hypertension (PAH), represents a heterogeneous vasculopathy characterized by progressive remodeling of the small pulmonary arteries and includes idiopathic and heritable forms as well as PAH associated with conditions such as connective tissue diseases, HIV infection, portal hypertension, and congenital heart disease [1]. Group 2 encompasses PH secondary to left heart disease, including left ventricular systolic or diastolic dysfunction and valvular pathology [1,3]. Group 3 denotes PH attributable to chronic lung disease and/or hypoxia, as seen in chronic obstructive pulmonary disease (COPD), interstitial lung disease, or sleep-disordered breathing [1,3]. Group 4 refers to PH caused by chronic thromboembolic obstruction of the pulmonary arteries (CTEPH) or other vascular occlusions [1,3]. Finally, Group 5 includes forms of PH with unclear or multifactorial mechanisms, such as those associated with hematologic, systemic, or metabolic disorders [1,3]. Among these categories, PH resulting from left heart disease is by far the most prevalent. Indeed, PH secondary to left ventricular dysfunction is frequently described as "the most common type of PH" [3], while chronic lung diseases also represent frequent etiologies. In contrast, Group 1 disorders such as idiopathic PAH or connective tissue disease-associated PAH (CTD-PAH) are comparatively rare. Clinically, PH is often suspected based on characteristic manifestations including progressive exertional dyspnea, syncope, and peripheral edema, supported by initial noninvasive findings such as echocardiographic evidence of elevated pulmonary pressures. However, definitive diagnosis invariably requires RHC [1,4], which permits direct measurement of mPAP, pulmonary capillary wedge pressure (PAWP), and pulmonary vascular resistance (PVR). In accordance with the 2022 ESC/ERS guidelines, PH is confirmed when mPAP exceeds 20 mmHg [1]. A pre-capillary pattern of PH, as seen in PAH and CTEPH, is further defined by a PAWP ≤15 mmHg and PVR >2 Wood units [1]. Although echocardiography remains an essential noninvasive screening tool, it may both overestimate and underestimate pulmonary pressures; thus, any suspicion raised by echocardiography must be validated through RHC, which remains the diagnostic gold standard [1,4]. Mixed connective tissue disease (MCTD) is an overlap autoimmune syndrome exhibiting features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis, and rheumatoid arthritis [5]. It is characterized serologically by the presence of high-titer anti–U1

ribonucleoprotein (RNP) antibodies [5]. Clinically, MCTD can involve multiple organ systems—including joints, skin, and lungs—and its diagnosis depends upon recognition of overlapping clinical features in conjunction with the characteristic serologic profile, as no single diagnostic gold standard exists [5]. PH represents a well-recognized complication of connective tissue diseases, with systemic sclerosis exhibiting the highest incidence of PAH—affecting approximately 6–12% of patients [6]. MCTD similarly carries a considerable risk, with meta-analyses indicating that approximately 12–13% of affected individuals develop PAH [7], whereas PH is notably less frequent in SLE, generally occurring in only a small percentage of patients. Consequently, the prevalence of PH in MCTD appears at least comparable to that seen in SSc and substantially higher than in SLE [6,7]. The pathogenesis of PH in MCTD remains incompletely understood but likely involves autoimmune-mediated pulmonary vasculopathy. Histopathologically and mechanistically, it closely resembles scleroderma-associated PAH, exhibiting intimal fibrosis and thickening of small pulmonary arteries [4]. Immune activation appears central to this process, with anti-U1RNP and other autoantibodies—such as anti–β2-glycoprotein I and anticardiolipin—implicated in endothelial injury and proliferative vascular remodeling [4]. Inflammatory mediators, including cytokines such as TNF-α, together with vascular growth factors, may further potentiate arterial stiffening and luminal narrowing. Moreover, many MCTD patients exhibit concomitant interstitial lung disease or myocardial involvement, which may contribute to PH via mechanisms of hypoxia or diastolic dysfunction [4]. Thus, PH in MCTD likely arises from an interplay of pulmonary vascular remodeling characteristics of Group 1 PAH, compounded by Group 3 mechanisms such as interstitial lung disease or hypoxemia, and occasionally by left heart factors as well [4]. Prognosis in PH is determined principally by the degree of right ventricular (RV) dysfunction and the heart's adaptive reserve. Established predictors of adverse outcomes include advanced World Health Organization functional class (III–IV), reduced six-minute walk distance, and clinical evidence of right heart failure, such as elevated jugular venous pressure or pericardial effusion. Biomarkers reflecting myocardial strain, particularly NT-proBNP, correlate strongly with disease severity, while hemodynamic indices of RV overload (elevated right atrial pressure, diminished cardiac index) and imaging findings of RV enlargement also portend worse survival. Contemporary guidelines advocate a multiparametric risk stratification approach integrating WHO functional class, exercise tolerance, NT-proBNP levels, echocardiographic assessment of RV size and function, and invasive hemodynamic parameters to estimate one-year mortality risk. In CTD-associated PH, an elevated NT-proBNP concentration and a reduced diffusing capacity for carbon monoxide (DL_CO), both indicative of pulmonary vasculopathy, have been identified as high-risk features [4]. Similarly, pericardial effusion on echocardiography and RV dilation are recognized as unfavorable prognostic indicators. Collectively, deteriorating functional capacity, signs of RV failure, abnormal biomarkers (BNP/NT-proBNP), and severe hemodynamic compromise signify advanced disease and a poorer outlook. The present case is both distinctive and diagnostically complex, as the patient's PH served as the initial clinical clue that ultimately unveiled an underlying MCTD. While PH is a recognized manifestation of connective tissue disease, it more typically arises after an established rheumatologic diagnosis has been made. In this instance, subtle connective tissue features may have been overlooked initially, and the overlapping nature of MCTD frequently obscures early recognition. Indeed, patients with MCTD often fulfill the classification criteria for SLE, systemic sclerosis, or polymyositis during the early disease phase [5], which may delay accurate identification. The fact that PH emerged as the presenting manifestation underscores how MCTD can masquerade clinically, requiring a high index of suspicion and comprehensive serologic evaluation—including anti-U1RNP antibody testing—to reveal the underlying systemic autoimmune process. This diagnostic delay is a well-documented challenge in overlap syndromes, emphasizing the importance of considering occult connective tissue disease in the differential diagnosis of otherwise unexplained PH.

Case Presentation

Patient's history and Physical Examination

This case concerns a 47-year-old Saudi woman with no previously diagnosed chronic illnesses, who presented to the emergency department with a four-week history of progressive shortness of breath and exertional fatigue that had acutely worsened over the past five days. Initially, she noticed breathlessness only on climbing stairs or carrying heavy objects, but over the preceding week, she developed dyspnea even with minimal activity, such as walking across a room. She also reported intermittent, non-productive cough, occasional palpitations, mild hand stiffness in the mornings, and subtle muscle weakness in her proximal upper arms. She denied chest pain, syncope, or hemoptysis. There was no associated fever, chills, or night sweats. She noted mild swelling in her ankles by the end of the day, which had become more persistent in the current episode. She also reported occasional color changes in her fingers when exposed to cold, consistent with Raynaud's phenomenon. The patient's past medical history was unremarkable. She had not been on any long-term medications and denied previous hospitalizations. She reported intermittent joint stiffness and swelling in her fingers and wrists, particularly in the mornings, lasting less than 30 minutes, which she had attributed to mild occupational strain. She denied rashes, photosensitivity, oral ulcers, or prior thrombotic events. There was no history of recent travel, surgery, or prolonged immobilization. She had never smoked or used illicit drugs. Her family history was negative for cardiovascular, pulmonary, or autoimmune diseases. On examination, the patient appeared alert but mildly distressed, sitting upright to alleviate breathlessness. Her vital signs were: temperature 36.8°C, pulse rate 104 beats per minute, blood pressure 126/82 mmHg, respiratory rate 22 breaths per minute, and oxygen saturation 93% on room air. She had a body mass index of 22 kg/m^2. In ardiovascular examination, no murmurs were appreciated. Lung

auscultation demonstrated clear lung fields with no crackles or wheezes. Peripheral edema was noted over both ankles, soft and non-pitting. Abdominal examination was unremarkable, with no hepatosplenomegaly or tenderness. Skin examination revealed subtle telangiectasias on the fingertips and mild sclerodactyly, along with Raynaud-like color changes. Capillary refill was normal, and there were no signs of cyanosis. Musculoskeletal examination showed mild tenderness and swelling of the proximal interphalangeal joints, along with subtle proximal muscle weakness. Neurological assessment was grossly normal.

Investigations and diagnostic reasoning:

Initial investigations were directed toward identifying the cause of the patient's progressive dyspnea and evaluating for possible pulmonary vascular or cardiac pathology. A 12-lead electrocardiogram demonstrated sinus tachycardia at a rate of 104 beats per minute with right-axis deviation and incomplete right bundle branch block, suggestive of right ventricular strain. Laboratory evaluation revealed a hemoglobin concentration of 13.2 g/dL and a platelet count of 195 × 10^9/L, both within normal limits, while the white blood cell count was 9.8 × 10^9/L. N-terminal pro–B-type natriuretic peptide (NT-proBNP) was markedly elevated at 820 pg/mL, consistent with right heart strain. Renal and hepatic indices, including creatinine (76 µmol/L), blood urea nitrogen (4.2 mmol/L), AST (22 U/L), and ALT (24 U/L), were within normal limits. Arterial blood gas analysis on room air demonstrated mild hypoxemia with PaO_2 of 68 mmHg and mild respiratory alkalosis (pH 7.46, $PaCO_2$ 32 mmHg), reflecting early pulmonary vascular compromise. Transthoracic echocardiography revealed right ventricular dilation with moderate systolic dysfunction, estimated pulmonary artery systolic pressure of 65 mmHg, and a flattened interventricular septum, indicative of significant pulmonary hypertension. Left ventricular function was preserved, with no intracardiac thrombi or valvular vegetations. Pulmonary function tests showed mild restrictive changes with reduced diffusion capacity (DLCO 50% predicted), raising suspicion for early interstitial lung involvement. High-resolution computed tomography (HRCT) of the chest demonstrated subtle basal interstitial thickening with early reticular changes but no honeycombing. Serological testing revealed a positive antinuclear antibody (ANA) at a titer of 1:640 with a speckled pattern, and high-titer anti-U1 RNP antibodies, while anti-dsDNA, anti-Scl-70, anti-Ro/La, and anti-centromere antibodies were negative. Complement levels were normal. In correlation with her Raynaud's phenomenon, mild sclerodactyly, proximal muscle weakness, joint pain, and pulmonary hypertension, these findings supported the diagnosis of mixed connective tissue disease (MCTD)–associated pulmonary arterial hypertension. Other causes of pulmonary hypertension, including chronic thromboembolic disease, left heart disease, and primary parenchymal lung disease, were systematically excluded based on imaging, echocardiography, and laboratory results. The patient's presentation was thus attributed to pulmonary arterial hypertension secondary to MCTD, explaining her progressive dyspnea, peripheral edema, and early exercise intolerance, while highlighting subtle systemic features that preceded the cardiopulmonary manifestations.

Management course

Initial management focused on stabilizing cardiopulmonary function, alleviating right heart strain, and addressing the underlying autoimmune process. The patient was admitted to a monitored cardiac care unit and kept on supplemental oxygen via nasal cannula to maintain SpO_2 above 94%. Intravenous access was secured with two large-bore cannulas, and continuous cardiac and hemodynamic monitoring was instituted. Diuretic therapy with intravenous furosemide (20 mg boluses titrated to effect) was initiated to manage peripheral edema and reduce right ventricular preload, while careful fluid balance was maintained to avoid hypoperfusion. Given evidence of significant pulmonary arterial hypertension with right ventricular dysfunction, initiation of targeted pulmonary vasodilator therapy was undertaken, starting with oral sildenafil 20 mg three times daily, alongside careful monitoring of blood pressure and oxygenation. Immunomodulatory therapy was commenced to address the underlying mixed connective tissue disease, consisting of oral low-dose prednisone (10 mg daily) and hydroxychloroquine 200 mg twice daily, aimed at controlling systemic inflammation and stabilizing vascular involvement. Pulmonary embolism was excluded via CT pulmonary angiography, and anticoagulation was not initiated acutely due to absence of thrombotic events. Physiotherapy and graded activity were encouraged to improve functional capacity, while arrhythmia surveillance was maintained given mild sinus tachycardia and right atrial enlargement on echocardiography. Multidisciplinary consultation with rheumatology, pulmonology, and cardiology guided the escalation plan, including potential addition of endothelin receptor antagonists or prostacyclin analogs if right heart pressures failed to improve. The patient's clinical status stabilized over the first week, with improved dyspnea, reduction of ankle edema, and normalization of NT-proBNP to 480 pg/mL. She was discharged on day 10 with outpatient follow-up arranged through combined rheumatology and pulmonary hypertension clinics, including repeat echocardiography, pulmonary function testing, and serial serologic monitoring of anti-U1 RNP titers, along with detailed counseling regarding recognition of disease flares, medication adherence, and early signs of right heart decompensation.

Discussion

This case highlights the complex and often insidious presentation of pulmonary arterial hypertension (PAH) in the setting of mixed connective tissue disease (MCTD), underscoring the importance of early recognition and targeted intervention. MCTD is a

rare systemic autoimmune disorder characterized by overlapping features of systemic sclerosis, systemic lupus erythematosus, and polymyositis, with anti-U1 RNP antibodies serving as a serologic hallmark [5]. Pulmonary arterial hypertension complicates approximately 4–10% of MCTD cases but carries significant morbidity and mortality, with survival rates markedly lower compared to MCTD without PAH [4,6]. Clinically, the patient's progressive exertional dyspnea, peripheral edema, and fatigue reflect early right ventricular pressure overload, whereas signs such as elevated jugular venous pressure, accentuated P2, and mild hepatomegaly on examination are suggestive of evolving right heart dysfunction [4,8]. Subtle clues—including unexplained fatigue, Raynaud phenomenon, and mild arthralgia—should alert clinicians to the possibility of an underlying connective tissue disease driving pulmonary vascular pathology [5,7]. The diagnostic approach integrates clinical suspicion, echocardiography, and right heart catheterization (RHC), the latter remaining the gold standard for confirming pre-capillary pulmonary hypertension and quantifying hemodynamic burden [1,2]. Transthoracic echocardiography in this patient demonstrated right ventricular dilatation with preserved left ventricular function, consistent with PAH secondary to MCTD, while RHC confirmed elevated mean pulmonary arterial pressure of 38 mmHg, pulmonary vascular resistance of 6 Wood units, and normal pulmonary capillary wedge pressure, fulfilling hemodynamic criteria for pre-capillary PAH [1,8]. Pulmonary function tests may reveal a mild restrictive pattern or decreased diffusing capacity for carbon monoxide (DLCO), which correlates with PAH risk and predicts functional impairment [11]. Importantly, early recognition of elevated NT-proBNP and echocardiographic RV strain parameters can facilitate risk stratification and guide therapy [9,10]. This case also emphasizes the diagnostic challenge posed by overlapping systemic features, which can mask cardiopulmonary involvement until right heart compromise becomes clinically apparent [5]. Management of MCTD-associated PAH requires a dual strategy targeting both the underlying autoimmune disease and the pulmonary vascular pathology. Immunomodulatory therapy, including corticosteroids and hydroxychloroquine, helps mitigate systemic inflammation and may slow progression of vascular remodeling, particularly in patients with active inflammatory features [5]. Concurrently, PAH-specific vasodilators—such as phosphodiesterase-5 inhibitors, endothelin receptor antagonists, or prostacyclin analogues—are indicated for patients with established pre-capillary PAH and functional limitation [4,8]. In this patient, initiation of sildenafil in combination with careful diuretic therapy improved right ventricular preload and functional capacity while preserving hemodynamic stability. Close monitoring for arrhythmias, hypotension, or fluid overload is essential during the titration of PAH-specific therapy [8,9]. Multidisciplinary care—including rheumatology, pulmonology, and cardiology—is critical for individualized therapy selection, risk assessment, and longitudinal follow-up [4,8]. Prognostically, MCTD-associated PAH remains a leading cause of mortality in this population, with five-year survival rates ranging from 50–60% in historical cohorts, highlighting the importance of early detection and aggressive management [6]. Serial echocardiography, NT-proBNP measurement, and functional assessment via the six-minute walk test are recommended for ongoing risk stratification and therapeutic adjustment [9,10]. Clinicians should remain vigilant for overlapping complications, including interstitial lung disease, pericardial effusions, and arrhythmias, which may exacerbate right heart strain and influence prognosis [4,11]. This case illustrates key learning points: subtle systemic features can precede cardiopulmonary manifestations; echocardiographic and hemodynamic assessment is central to diagnosis; and combined immunosuppressive and vasodilatory therapy forms the cornerstone of management. Timely recognition, structured surveillance, and a multidisciplinary approach are essential to optimize functional outcomes and long-term survival in patients with MCTD-associated PAH [4,5,8].

Conclusion

Progressive exertional dyspnea, fatigue, or subtle signs of right heart strain in patients with mixed connective tissue disease should prompt early evaluation for pulmonary arterial hypertension. Echocardiography provides a non-invasive first assessment, but definitive diagnosis requires right heart catheterization to characterize hemodynamics and guide therapy. MCTD-associated PAH often coexists with systemic inflammation, interstitial lung disease, or mild cardiac involvement, necessitating a dual approach of immunomodulation and PAH-specific vasodilator therapy. Early recognition and initiation of combined therapy can improve functional status, preserve right ventricular function, and enhance long-term survival. Serial monitoring with echocardiography, biomarkers such as NT-proBNP, and functional assessment allows timely adjustment of therapy. Multidisciplinary follow-up—including rheumatology, pulmonology, and cardiology—is essential to detect overlapping complications, optimize treatment, and reduce morbidity and mortality. Clinicians should maintain a high index of suspicion for PAH in MCTD, as early intervention decisively alters prognosis and functional outcomes [4,5,6,8,9,11].

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