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| RESEARCH ARTICLE

Chronic Thromboembolic Pulmonary Hypertension Manifesting as Exertional Limitation: A Clinical Diagnostic Perspective

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| ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but potentially progressive cause of pulmonary hypertension, often presenting with subtle exertional symptoms that delay diagnosis. We report the case of a 34-year-old man with no prior chronic medical conditions who presented with a three-month history of progressive exertional dyspnea and fatigue, accompanied by intermittent lower extremity edema and Raynaud-like color changes in the toes. Physical examination revealed mild ankle edema and subtle digital clubbing, with otherwise unremarkable cardiopulmonary and musculoskeletal findings. Laboratory evaluation showed elevated NT-proBNP, modestly raised D-dimer, and preserved renal and hepatic function. Transthoracic echocardiography revealed right ventricular dilation with preserved systolic function and an estimated pulmonary artery systolic pressure of 62 mmHg. Pulmonary function testing was largely normal, but computed tomography pulmonary angiography demonstrated organized thrombotic material in segmental and subsegmental pulmonary arteries bilaterally. Right heart catheterization confirmed pre-capillary pulmonary hypertension. Further evaluation revealed combined congenital deficiencies of protein S and protein C, explaining the thrombotic predisposition in the absence of prior venous thromboembolic events. The patient was managed with anticoagulation, cautious diuresis, supportive therapy, and initiation of pulmonary vasodilator therapy, with referral to a specialized center for consideration of surgical intervention. This case emphasizes the importance of thorough clinical evaluation, early imaging, and hemodynamic assessment in young adults presenting with unexplained exertional limitation. Recognition of underlying thrombophilic disorders is crucial to guide management, prevent recurrent thrombosis, and preserve right ventricular function, underscoring the value of a multidisciplinary approach in optimizing long-term outcomes in CTEPH.

| KEYWORDS

Shortness of breath, Dyspnea, Chronic thrombo-embolic pulmonary embolism, CTEPH, Protein S\C deficiency, Thrombophilia

| ARTICLE INFORMATION

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Introduction

Chronic thromboembolic pulmonary hypertension stands as one of the most intriguing and complex entities within the modern classification of pulmonary vascular disease. It represents a form of pulmonary hypertension in which organized thrombotic material becomes permanently incorporated into the pulmonary arterial circulation and gradually obstructs blood flow, while a secondary small vessel arteriopathy develops in parallel [4,5]. The condition has long been considered an uncommon sequel of acute pulmonary embolism, yet contemporary studies have shown that a substantial proportion of patients do not recall a definite thromboembolic episode, and instead present with gradual changes in breathing capacity that evolve silently over months or even years [11]. This insidious clinical course often leads to delays in recognition, since the early manifestations appear non specific and may be attributed to far more prevalent causes of exercise related breathlessness. The hemodynamic consequences of chronic obstruction begin with persistent mechanical barriers to pulmonary blood flow, but the overall physiology soon becomes more intricate. As the disease advances, the pulmonary circulation undergoes profound structural remodeling that involves both proximal and distal vessels, creating a sustained elevation of pulmonary vascular resistance and a progressive burden on the right side of the heart [4,8]. The combination of unremitting thrombotic remnants and secondary vascular changes distinguishes chronic thromboembolic pulmonary hypertension from the more transient forms of pulmonary hypertension sometimes seen after acute pulmonary embolism, and underscores why the condition requires such careful diagnostic evaluation and timely management. During the past decade, interest has grown in the potential contribution of hereditary thrombophilia to the pathogenesis of chronic thromboembolic pulmonary hypertension. Among the congenital risk factors that have received particular scrutiny are deficiencies of protein S and protein C, two naturally occurring anticoagulants that play a central role in the regulation of coagulation and in the prevention of unwarranted thrombus formation [1,2]. Although these deficiencies are relatively rare in the general population, their clinical significance is well established, as individuals with reduced levels of protein S or protein C exhibit an increased lifetime tendency toward venous thrombosis. Recent systematic evaluations of patients with chronic thromboembolic pulmonary hypertension have revealed that a measurable minority harbor such abnormalities, suggesting that these defects may influence not only the initial thrombotic event but also the persistence of thrombotic material within the pulmonary arterial circulation [1,2]. One of the most comprehensive recent reviews reported that several percent of patients with chronic thromboembolic pulmonary hypertension demonstrate protein S deficiency, while a slightly smaller proportion exhibit protein C deficiency [1]. These figures, although modest, are notable given the overall rarity of these conditions in the general population, and they point toward a possible pathogenic link between inherited impairment of natural anticoagulation and chronic obstruction of pulmonary arteries. A separate investigation that included genetic analysis further supported this concept by demonstrating that abnormalities involving protein S or protein C pathways may contribute to a tendency toward recurrent or inadequately resolved thrombosis, an issue that may be especially relevant within the low pressure environment of the pulmonary circulation where thrombi are cleared less efficiently than in systemic vessels [3]. These observations have broadened the conceptual framework of chronic thromboembolic pulmonary hypertension, which is no longer viewed solely as the passive consequence of a single unresolved embolus but rather as a process shaped by the interaction between thrombus biology, individual predisposition, and the intrinsic features of the pulmonary vascular bed. The clinical presentation of chronic thromboembolic pulmonary hypertension is often subtle. Patients may initially describe a gentle decline in exercise capacity, a sense of reduced stamina during activities that once felt effortless, or an increased awareness of breathlessness when ascending stairs or walking at a brisk pace [9]. Because these symptoms unfold gradually, they are frequently interpreted as benign or attributed to aging, reduced fitness, or common respiratory complaints such as mild airway inflammation. The often normal appearance of resting vital signs and the lack of dramatic symptoms early in the course of the disease contribute further to this misperception. As the disorder progresses, however, the physiologic stresses placed upon the pulmonary circulation and the right side of the heart become more evident. Even modest exertion may provoke marked breathlessness, and some patients begin to experience sensations of chest tightness, lightheadedness, or near fainting. These manifestations reflect the rising pressure within the pulmonary arteries and the increasing difficulty the right side of the heart encounters as it attempts to preserve forward blood flow through a circulation that has become progressively obstructed [11]. By the time these symptoms prompt detailed cardiopulmonary evaluation, many patients already display clear evidence of right sided strain on imaging or invasive hemodynamic assessments. The present case centers on a man in his mid thirties who experienced several months of gradually worsening breathlessness during exertion. At first, the symptoms were subtle and easily dismissed. He noted that he could no longer sustain the level of physical activity he had tolerated previously, and that routine

tasks such as climbing stairs or carrying groceries provoked an unusual sense of breathlessness. Over time, the symptoms became more pronounced, and he began to perceive an almost constant decline in his ability to perform daily activities. Eventually, these concerns prompted further evaluation, which revealed features consistent with chronic thromboembolic pulmonary hypertension. The identification of this disorder in a relatively young adult prompted a thorough investigation for underlying risk factors, including hereditary thrombophilia. This led to the discovery of deficiencies in both protein S and protein C, an uncommon but clinically meaningful combination that has been described in relation to chronic thromboembolic pulmonary hypertension in several recent studies [1,2]. In this individual, the coexistence of these abnormalities offers a compelling explanation for the persistence of thrombotic material within the pulmonary arterial system and provides insight into the biological forces that contributed to the development of long standing pulmonary hypertension. The presence of protein S and protein C deficiency within the setting of chronic thromboembolic pulmonary hypertension raises several important points about the natural history of the disease and the broader context of thrombotic risk. First, it emphasizes that the process leading to chronic pulmonary vascular obstruction is not limited to the acute event of thrombus formation but involves the balance between coagulation, fibrinolysis, and vascular repair. Patients with inherited deficiencies of natural anticoagulants may be less capable of preventing excessive thrombus propagation, and they may also experience impaired clearance of thrombotic material once it has formed [1,2,3]. This provides a logical biological framework for understanding why some individuals progress toward chronic obstruction even in the absence of identifiable episodes of acute pulmonary embolism. Second, the case underscores the importance of maintaining a high index of suspicion for chronic thromboembolic pulmonary hypertension in any patient who presents with unexplained exertional breathlessness, particularly when symptoms evolve slowly. Many individuals with this condition never experience dramatic episodes of chest pain or syncope before diagnosis. Instead, the disorder presents with a constellation of nonspecific complaints that reflect changes in pulmonary vascular resistance rather than overt hemodynamic collapse [11]. For this reason, chronic thromboembolic pulmonary hypertension should be considered even in patients with minimal or absent prior history of thromboembolic events, especially if they display symptoms that appear disproportionate to findings on routine examination. Third, the identification of hereditary thrombophilia in a patient with chronic thromboembolic pulmonary hypertension has important implications for both the management of the disease and the assessment of long term risk. Individuals with protein S or protein C deficiency may be predisposed to further thrombotic complications, and this risk persists throughout life [1,2]. In the context of chronic thromboembolic pulmonary hypertension, failure to recognize this predisposition may result in inadequate long term anticoagulation or insufficient monitoring for recurrent events. Recognizing the underlying thrombophilic state allows clinicians to implement more targeted strategies that address both the acute hemodynamic challenges and the long term predisposition to thrombosis. Beyond the individual case, the literature on chronic thromboembolic pulmonary hypertension continues to expand, with numerous studies exploring the interplay between thrombosis, vascular remodeling, and genetic predisposition. Several reviews have highlighted that the pathophysiologic features of chronic thromboembolic pulmonary hypertension extend beyond persistent mechanical obstruction and involve inflammation, endothelial dysfunction, and maladaptive changes in the microcirculation that resemble the alterations seen in pulmonary arterial hypertension [4,8]. These observations reinforce the idea that chronic thromboembolic pulmonary hypertension is not a static condition but rather a dynamic process that evolves over time, shaped by both thrombotic and non thrombotic mechanisms. Epidemiologic studies have also brought attention to the variability in incidence and risk factors across different populations. Certain investigations have noted that individuals with specific thrombophilic profiles, including protein S or protein C deficiency, may be more susceptible to the persistent obstruction that characterizes chronic thromboembolic pulmonary hypertension [1,2,3]. Other studies have highlighted that antiphospholipid antibodies and related acquired thrombophilic conditions may contribute to a similar pattern of prolonged thrombotic burden within the pulmonary circulation [7]. Together, these findings suggest that chronic thromboembolic pulmonary hypertension may arise from a spectrum of prothrombotic influences, ranging from congenital deficiencies to acquired autoimmune abnormalities. The progressive nature of this condition underscores the importance of prompt recognition and early referral to specialized centers capable of providing comprehensive diagnostic evaluation. Imaging studies such as ventilation perfusion scanning, computed tomography of the pulmonary arteries, and invasive hemodynamic assessment play essential roles in confirming the presence of chronic obstruction and determining the extent of vascular remodeling. In carefully selected patients, surgical removal of organized thrombotic material can offer substantial improvement and, in some cases, near complete resolution of pulmonary hypertension [11]. For patients who are not candidates for surgery, additional therapies including targeted pharmacologic agents and advanced interventional procedures have expanded the range of available options. In summary, chronic thromboembolic pulmonary hypertension represents a clinically significant and multifaceted form of pulmonary vascular disease in which persistent thrombotic obstruction and progressive vascular remodeling converge to produce sustained elevation of pulmonary pressures [4,5,8]. The present case illustrates how this condition can emerge in a relatively young adult who presents with progressively worsening breathlessness during exertion and who is ultimately found to harbor inherited deficiencies of protein S and protein C, two abnormalities that have been increasingly recognized within the chronic thromboembolic pulmonary hypertension population [1,2,3]. The case highlights the importance of considering chronic thromboembolic pulmonary hypertension in patients with unexplained symptoms, the need for thorough assessment of thrombotic risk, and the value of integrating clinical

findings with a nuanced understanding of the complex biological pathways that drive this unique form of pulmonary hypertension.

Case Presentation

Patient's history and Physical Examination

This case concerns a thirty-four-year-old man with no previously diagnosed chronic medical conditions who presented to the outpatient clinic with a three-month history of progressive shortness of breath and exertional limitation. Initially, he noticed breathlessness only during prolonged walking or ascending stairs, but over the preceding four weeks, he reported that even routine daily activities, such as climbing a single flight of stairs or carrying light objects, elicited marked dyspnea. He also described a sensation of early fatigue that limited his capacity to maintain normal work and recreational activities. The patient denied chest pain, syncope, palpitations, hemoptysis, fever, chills, night sweats, or unintentional weight loss. There was no history of wheezing, cough, or respiratory infections preceding the onset of symptoms. He reported intermittent mild swelling in his lower extremities, which initially resolved by morning but had become more persistent, particularly in the evenings. He also described occasional sensations of cold and color changes in his toes during exposure to low temperatures, reminiscent of Raynaud-like phenomena. The patient's past medical history was remarkable only for minor childhood illnesses, with no history of venous thromboembolism, major surgery, immobilization, or long-term medication use. He denied smoking, alcohol consumption, or illicit drug use. The family history was significant for a father who experienced recurrent venous thrombosis in his forties and a maternal aunt with an unspecified clotting disorder. There were no known autoimmune, cardiovascular, or pulmonary diseases in close relatives. The patient was employed in an office setting and reported no recent travel or prolonged immobilization. He denied any occupational exposure to chemicals, dust, or other respiratory irritants. Upon presentation, he appeared alert but mildly anxious due to the progressive nature of his symptoms and was observed sitting upright to ease breathing. His vital signs were: temperature 36.7°C, pulse rate 102 beats per minute, blood pressure 128/80 mmHg, respiratory rate 21 breaths per minute, and oxygen saturation 94 percent on room air. His body mass index was 24 kg per square meter. Cardiovascular examination revealed normal heart sounds without murmurs, rubs, or gallops, and jugular venous pressure was not elevated. Pulmonary auscultation revealed clear lung fields bilaterally with normal breath sounds and no adventitious sounds. Peripheral examination demonstrated minimal non-pitting edema over both ankles and feet, more pronounced toward the end of the day, with no evidence of skin changes suggestive of chronic venous insufficiency. Abdominal examination was unremarkable, with no tenderness, organomegaly, or ascites. Skin assessment revealed subtle bluish discoloration of the distal toes on exposure to cold and mild digital clubbing, but no rashes, telangiectasias, or sclerotic changes were noted. Capillary refill time was within normal limits, and there was no cyanosis of the lips or extremities. Musculoskeletal examination revealed normal joint alignment, full range of motion, and no swelling or tenderness in the major joints. Neurological examination was grossly normal, with intact cranial nerves, normal muscle tone and strength, and preserved sensory function throughout. Laboratory evaluation at presentation demonstrated normal complete blood count, renal and hepatic profiles, and electrolytes. D-dimer levels were modestly elevated, prompting further imaging. Echocardiography revealed elevated pulmonary artery pressures with mild right ventricular dilation but preserved right ventricular function. Computed tomography pulmonary angiography demonstrated evidence of chronic organized thrombotic material within the segmental and subsegmental pulmonary arteries bilaterally, consistent with chronic thromboembolic pulmonary hypertension. Subsequent workup for thrombophilia revealed combined deficiencies of protein S and protein C, confirming a congenital predisposition to thrombosis. The patient denied any prior history of venous thromboembolic events, suggesting that the development of pulmonary hypertension was the first clinical manifestation of his thrombophilic state. The discovery of hereditary anticoagulant deficiencies provided a plausible explanation for the persistence of thrombotic material in the pulmonary circulation and the progressive nature of his exertional limitation. The patient was subsequently referred to a specialized pulmonary hypertension center for comprehensive assessment and management, including consideration of surgical intervention and long term anticoagulation therapy. Throughout the evaluation, he remained hemodynamically stable and did not require supplemental oxygen at rest, although he experienced significant desaturation during exertion. The case highlights the importance of careful clinical assessment in younger patients presenting with unexplained exertional dyspnea, the need to consider inherited thrombophilia as an underlying cause, and the value of early imaging and hemodynamic evaluation in establishing the diagnosis of chronic thromboembolic pulmonary hypertension. The patient was educated regarding the nature of his condition, the implications of protein S and protein C deficiency, and the necessity of long term follow up to monitor right ventricular function, pulmonary pressures, and overall exercise tolerance. Lifestyle modifications and avoidance of additional thrombotic risk factors were discussed, and the patient was counseled regarding the signs and symptoms of recurrent venous thromboembolism. His presentation underscores the subtle onset of chronic thromboembolic pulmonary hypertension, the variable clinical trajectory, and the critical role of comprehensive evaluation in establishing the diagnosis in patients who may otherwise appear healthy and active.

Investigations and diagnostic reasoning:

Initial investigations were directed at identifying the underlying cause of the patient's progressive exertional limitation and evaluating for possible pulmonary vascular and cardiac pathology. A twelve-lead electrocardiogram demonstrated sinus tachycardia with a rate of 104 beats per minute, right-axis deviation, and incomplete right bundle branch block, suggestive of right ventricular strain. Routine laboratory studies revealed a hemoglobin concentration of 14.1 grams per deciliter, a platelet count of 210×10^9 per liter, and a white blood cell count of 7.9×10^9 per liter, all within normal limits. Renal function, including serum creatinine and blood urea nitrogen, was normal, as were liver enzymes including aspartate aminotransferase and alanine aminotransferase. Coagulation studies showed a normal prothrombin time and activated partial thromboplastin time, but further thrombophilia screening revealed deficiencies in both protein S and protein C, confirming a congenital predisposition to thrombosis. D-dimer levels were modestly elevated at 1.2 milligrams per liter, raising suspicion for ongoing thrombotic activity. Arterial blood gas analysis on room air revealed a mild hypoxemia with partial pressure of oxygen at 70 millimeters of mercury, partial pressure of carbon dioxide at 34 millimeters of mercury, and a pH of 7.45, reflecting early pulmonary vascular compromise with compensatory respiratory alkalosis. Cardiac biomarkers were notable for an elevated N-terminal pro-B-type natriuretic peptide at 620 picograms per milliliter, consistent with right ventricular strain. Transthoracic echocardiography demonstrated right ventricular dilation with preserved systolic function, estimated pulmonary artery systolic pressure of 62 millimeters of mercury, and flattening of the interventricular septum, indicative of significant pulmonary hypertension. Left ventricular size and systolic function were normal, with no evidence of valvular disease, intracardiac thrombus, or pericardial effusion. Pulmonary function testing revealed normal spirometry but a mildly reduced diffusing capacity of carbon monoxide at 55 percent of predicted, suggestive of impaired gas exchange without overt restrictive or obstructive lung disease. High-resolution computed tomography of the chest revealed subtle subsegmental perfusion defects without evidence of parenchymal lung disease, consolidation, or honeycombing. Computed tomography pulmonary angiography confirmed the presence of organized thrombotic material within segmental and subsegmental pulmonary arteries bilaterally, consistent with chronic thromboembolic pulmonary hypertension. Ventilation-perfusion scanning further demonstrated multiple segmental perfusion mismatches, corroborating the diagnosis of chronic thromboembolic obstruction. No evidence of acute pulmonary embolism was noted. Right heart catheterization was performed to obtain definitive hemodynamic measurements and confirmed pre-capillary pulmonary hypertension, with a mean pulmonary arterial pressure of 32 millimeters of mercury, pulmonary capillary wedge pressure of 12 millimeters of mercury, and pulmonary vascular resistance elevated at 5.2 Wood units. Cardiac output and index were preserved, indicating compensatory adaptation of the right ventricle. Laboratory evaluation for autoimmune and inflammatory markers, including antinuclear antibody, anti-dsDNA, and rheumatoid factor, was negative, ruling out connective tissue or systemic inflammatory disease as contributing factors. Blood cultures and inflammatory markers including C-reactive protein and erythrocyte sedimentation rate were within normal limits, reducing the likelihood of infection or vasculitis. The combined assessment of laboratory, imaging, and hemodynamic studies established the diagnosis of chronic thromboembolic pulmonary hypertension in the setting of congenital protein S and protein C deficiency. The diagnostic reasoning considered the progressive exertional dyspnea, subtle peripheral edema, and impaired exercise tolerance in a young adult with no prior thrombotic events, supported by echocardiographic evidence of right ventricular strain and confirmatory imaging of chronic thromboembolic obstruction. Differential diagnoses such as pulmonary arterial hypertension from idiopathic or connective tissue disease, left heart disease, and parenchymal lung disorders were systematically excluded through normal left ventricular function, absence of valvular pathology, preserved pulmonary function, and negative autoimmune and inflammatory panels. The laboratory and imaging findings collectively highlighted a pathophysiologic process in which congenital thrombophilia predisposed the patient to chronic intrapulmonary vascular obstruction, leading to progressive right ventricular strain and exertional limitation. The patient's presentation underscored the importance of integrating clinical, laboratory, and imaging data to establish the diagnosis of chronic thromboembolic pulmonary hypertension in the context of an underlying hereditary prothrombotic state, guiding the subsequent management strategy that included anticoagulation and referral for specialized evaluation for potential surgical or interventional therapy.

Management course

Management of this patient centered on stabilizing cardiopulmonary function, reducing right ventricular strain, and addressing the underlying chronic thromboembolic process in the context of congenital protein S and protein C deficiency. Upon admission, she was placed in a monitored unit with continuous cardiac and oxygen saturation monitoring. Supplemental oxygen via nasal cannula was administered to maintain oxygen saturation above ninety-three percent. Intravenous access was secured for laboratory monitoring and potential pharmacologic interventions. Given evidence of right ventricular dilation and elevated pulmonary pressures, careful fluid management was instituted, aiming to reduce right ventricular preload while avoiding hypoperfusion. Diuretic therapy was initiated with intravenous furosemide, titrated according to clinical response and urine output, to alleviate peripheral edema and facilitate right heart unloading. Simultaneously, anticoagulation therapy was commenced using weight-adjusted low-molecular-weight heparin transitioning to a vitamin K antagonist with close monitoring

of international normalized ratio, reflecting the patient's prothrombotic state due to protein S and C deficiency and the risk of recurrent thrombosis. Echocardiographic and hemodynamic parameters were closely monitored to assess the response of right ventricular size, function, and pulmonary pressures. After confirming the diagnosis of chronic thromboembolic pulmonary hypertension through computed tomography pulmonary angiography and right heart catheterization, a multidisciplinary team involving pulmonology, cardiology, and hematology evaluated the patient for potential surgical or interventional therapy. Pulmonary endarterectomy was considered the definitive treatment for surgically accessible lesions; however, the extent and distribution of thromboembolic material indicated the need for individualized risk-benefit assessment. For patients with distal or inaccessible lesions, medical therapy with pulmonary vasodilators was initiated to reduce pulmonary vascular resistance and improve functional capacity. In this case, oral phosphodiesterase-5 inhibitor therapy was started at standard dosing, with careful monitoring of blood pressure, oxygenation, and right heart function. Adjunctive supportive care included gradual mobilization and supervised physiotherapy to improve exercise tolerance and maintain muscle strength, recognizing the need to avoid excessive strain on a compromised right ventricle. Serial laboratory assessments, including N-terminal pro-B-type natriuretic peptide, were used to track right heart stress and guide titration of therapy. The patient's clinical response was closely observed, with particular attention to dyspnea, peripheral edema, and functional capacity. Education on the recognition of early symptoms of right heart decompensation, adherence to anticoagulation, and avoidance of factors predisposing to venous thromboembolism was provided, given her underlying thrombophilic disorder. Nutritional counseling and maintenance of an optimal fluid and salt balance were emphasized to support cardiac function. Arrhythmia surveillance was conducted due to intermittent sinus tachycardia noted on initial assessment, and electrocardiograms were repeated periodically to detect potential conduction disturbances related to right ventricular strain. Discharge planning involved coordination for outpatient follow-up with specialized pulmonary hypertension clinics, including repeat echocardiography, exercise testing, and ongoing hematology assessment for anticoagulation management and monitoring of protein S and C activity. The patient was counseled on lifestyle modifications, including avoidance of prolonged immobilization, and the importance of timely evaluation if new symptoms arose. A long-term plan for serial imaging, functional assessment, and laboratory monitoring was established, with consideration for escalation to targeted therapies such as endothelin receptor antagonists or prostacyclin analogs if progressive right heart dysfunction occurred despite optimal anticoagulation and supportive measures. Over the initial hospitalization, the patient demonstrated gradual improvement in dyspnea and reduction of ankle edema, and she was discharged in a clinically stable condition with detailed instructions regarding medication adherence, monitoring for recurrent thromboembolic events, and engagement with the multidisciplinary care team. The management approach combined immediate stabilization, long-term anticoagulation, functional support, and careful planning for definitive intervention, reflecting the complex interplay between congenital thrombophilia and chronic thromboembolic pulmonary hypertension while prioritizing preservation of right ventricular function and prevention of further thrombotic complications.

Discussion

This case illustrates the multifaceted challenges posed by chronic thromboembolic pulmonary hypertension in the context of congenital protein S and protein C deficiency, highlighting the importance of early recognition, accurate diagnosis, and individualized management. Chronic thromboembolic pulmonary hypertension is a rare but potentially life-threatening condition characterized by persistent obstruction of pulmonary arteries by organized thrombi, leading to progressive pulmonary vascular remodeling, elevated pulmonary arterial pressures, and ultimately right ventricular dysfunction [4,9]. Although the majority of pulmonary emboli resolve spontaneously with appropriate anticoagulation, a subset of patients develops persistent obstruction, culminating in chronic thromboembolic disease. Epidemiological studies estimate that approximately 2–4% of patients following acute pulmonary embolism progress to CTEPH, although the precise incidence may be underrecognized due to subtle early symptoms and nonspecific presentations [12,13]. In patients with congenital thrombophilia, including deficiencies of protein C and protein S, the risk of recurrent venous thromboembolism is significantly elevated, although the contribution of these inherited deficiencies to the pathogenesis of CTEPH remains complex and somewhat inconsistent across studies [1,2,15,16]. In systematic reviews, protein C and protein S deficiencies are detected in approximately 5–10% of patients with confirmed CTEPH, though other studies suggest prevalence similar to that of the general population, underscoring the multifactorial nature of disease development [1,16]. Clinically, the patient's progressive exertional dyspnea, fatigue, and peripheral edema reflect the hemodynamic consequences of elevated pulmonary vascular resistance and early right ventricular strain. Subtle clinical cues such as mild ankle swelling, tachycardia, and reduced exercise tolerance often precede overt right heart failure, and their recognition is crucial for timely diagnosis [4,5]. Physical examination may reveal signs including elevated jugular venous pressure, accentuated pulmonary component of the second heart sound, and peripheral edema, though these findings are frequently mild or intermittent in early disease [4,11]. In this patient, the presence of exertional dyspnea with minimal activity and mild peripheral edema indicated progressive pre-capillary pulmonary hypertension, prompting further diagnostic evaluation. The diagnostic approach in CTEPH integrates clinical suspicion with imaging and hemodynamic assessment. Echocardiography provides initial noninvasive evidence of right ventricular dilation, impaired systolic function, and estimated pulmonary artery pressures, serving as a useful screening tool [4,10]. In this patient, echocardiography demonstrated right ventricular enlargement with preserved

left ventricular function, consistent with pre-capillary pulmonary hypertension. Definitive diagnosis requires confirmation via right heart catheterization, which allows direct measurement of mean pulmonary arterial pressure, pulmonary vascular resistance, and pulmonary capillary wedge pressure, thereby distinguishing pre-capillary from post-capillary causes of pulmonary hypertension [4,10]. Pulmonary imaging, particularly computed tomography pulmonary angiography or ventilation-perfusion scanning, identifies organized thrombi and evaluates the distribution and accessibility of lesions for potential surgical intervention [4,11]. In this patient, imaging revealed chronic thromboembolic obstruction predominantly affecting segmental and subsegmental branches, consistent with distal CTEPH and limiting surgical options to pulmonary endarterectomy. Pulmonary function tests may demonstrate mild restrictive defects and reduced diffusion capacity, reflecting early parenchymal changes secondary to chronic vascular obstruction [4,11]. From a pathophysiological perspective, CTEPH represents the convergence of persistent thromboembolic obstruction, abnormal thrombus resolution, and secondary pulmonary vascular remodeling. Histopathological studies show that organized thrombi integrate with the vascular intima and are accompanied by medial hypertrophy, intimal fibrosis, and microvascular remodeling in non-obstructed areas, leading to elevated pulmonary vascular resistance disproportionate to the mechanical obstruction [4,8,9]. Hemodynamic compromise increases right ventricular afterload, initially producing compensatory hypertrophy and eventual dilation as right heart contractile function decompensates [4,10]. In patients with congenital thrombophilia, the propensity for recurrent thrombotic events amplifies these processes, though not all carriers of protein C or S deficiency develop CTEPH, highlighting the interplay of additional risk factors including antiphospholipid antibodies, splenectomy, chronic inflammation, and unresolved acute pulmonary embolism [2,6,7,15]. Laboratory markers, such as elevated N-terminal pro-B-type natriuretic peptide, provide clinically useful surrogates of right heart strain and correlate with functional limitation and prognosis [9,11]. In this case, NT-proBNP was elevated, reflecting early right ventricular compromise, while routine hematologic and biochemical tests excluded concomitant organ dysfunction. Serological workup for thrombophilia confirmed protein S and protein C deficiencies, explaining her susceptibility to thrombotic events and guiding the initiation of long-term anticoagulation. Exclusion of other contributing conditions, including antiphospholipid syndrome and paraneoplastic thrombophilia, was important to tailor therapy [7]. Management of CTEPH requires a dual approach addressing both the mechanical obstruction and secondary pulmonary vascular remodeling. Pulmonary endarterectomy remains the treatment of choice for surgically accessible lesions, providing potential cure with significant hemodynamic and symptomatic improvement [4,11]. Surgical outcomes are favorable in experienced centers, with perioperative mortality below 5% and five-year survival exceeding 80%, although distal lesions or comorbidities may preclude surgery [1,4]. In this patient, the distal distribution of thrombi limited the utility of endarterectomy, necessitating medical therapy with anticoagulation and pulmonary vasodilators. Lifelong anticoagulation is essential in patients with congenital thrombophilia to prevent recurrent thrombosis and further pulmonary vascular compromise [1,2,15]. Targeted pulmonary vasodilator therapy, such as phosphodiesterase-5 inhibitors, improves pulmonary hemodynamics and exercise capacity, particularly in patients with inoperable disease or residual pulmonary hypertension post-surgery [4,9]. Supportive measures, including judicious diuretic therapy, oxygen supplementation, graded rehabilitation, and close monitoring of fluid balance, help optimize right ventricular preload and functional status [4,11]. Multidisciplinary collaboration among pulmonology, cardiology, hematology, and rehabilitation specialists is critical for individualized treatment planning and long-term follow-up [4,9]. Prognosis in CTEPH depends on the extent of thromboembolic obstruction, right ventricular function, comorbidities, and timely initiation of therapy. In historical cohorts, inoperable CTEPH is associated with a median survival of 3–5 years if untreated, emphasizing the importance of early recognition and comprehensive management [4,12]. Clinical vigilance for subtle symptoms such as progressive exertional dyspnea, fatigue, and peripheral edema is essential, as early intervention can prevent irreversible right heart failure and improve long-term outcomes. Serial assessment using echocardiography, NT-proBNP, and functional exercise testing allows ongoing risk stratification and therapy adjustment [9,11]. This case reinforces key teaching points: congenital thrombophilia may predispose to CTEPH even in the absence of prior overt thrombotic episodes; subtle clinical findings often precede significant cardiopulmonary compromise; early hemodynamic assessment and imaging are essential to confirm diagnosis; and combined surgical, pharmacologic, and supportive strategies optimize outcomes [1,4,9]. In conclusion, this patient's presentation exemplifies the complex interplay between congenital thrombophilia and chronic thromboembolic pulmonary hypertension. Clinical cues such as progressive dyspnea, peripheral edema, and exercise intolerance, when integrated with imaging, echocardiography, and hemodynamic assessment, provide a robust framework for diagnosis. Management requires lifelong anticoagulation, judicious use of pulmonary vasodilators, supportive care, and consideration of surgical intervention where feasible. Awareness of subtle systemic features, understanding the pathophysiological mechanisms, and employing a multidisciplinary approach are essential for optimizing functional status, preventing complications, and improving survival in patients with CTEPH [1,2,4,9,11,15].

Conclusion

Progressive exertional dyspnea, fatigue, or subtle signs of right heart strain in patients with a history of thromboembolic events or congenital thrombophilia should prompt early evaluation for chronic thromboembolic pulmonary hypertension. Noninvasive tools such as echocardiography provide initial assessment of right ventricular function and pulmonary pressures, but definitive diagnosis requires right heart catheterization to quantify hemodynamics and distinguish pre-capillary pulmonary hypertension.

Imaging modalities, including ventilation-perfusion scanning or CT pulmonary angiography, are critical to identify organized thrombi and guide therapeutic decisions. Lifelong anticoagulation is essential in patients with protein C or protein S deficiency to prevent recurrence, while targeted pulmonary vasodilators improve exercise capacity and right ventricular function in inoperable cases. Multidisciplinary follow-up—integrating pulmonology, cardiology, hematology, and rehabilitation—is key to optimizing functional outcomes, detecting complications, and tailoring therapy. Clinicians must maintain high vigilance, as early recognition and individualized management decisively influence morbidity, survival, and quality of life [1,2,4,7,9,11].

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