

Experience of chronic thromboembolic pulmonary hypertension (CTEPH) in two cases with scleroderma and immunopathogenesis overview: Case report

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The authors stated that the written consent was obtained from the patient presented with images in the study.

Conflict of Interest

No conflict of interest was declared by the authors.

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Abstract

Systemic Sclerosis (SSc) is a multi-systemic connective tissue disease of unknown etiology. Although many pathological processes play a role in the basis of pulmonary hypertension (PHT) that develops secondary to SSc, vasculopathy has an important place. Chronic thromboembolic hypertension (CTEPH) is in the group 4 PHT class. CTEPH distinguishes it from other causes of PHT by having both surgical and medical treatment options. CTEPH is a pathology that develops chronically and can be overlooked due to its nonspecific symptoms. Early diagnosis and treatment can reduce morbidity and mortality. The physiopathology of vasculopathy secondary to CTEPH and vasculopathy of SSc made us suspect that similar processes operate in both diseases. The processes that cause and follow endothelial damage are similar in both diseases. If this pathophysiological mechanism can be clarified, possible new treatment options can be discovered. We diagnosed CTEPH with the examinations we performed in two of our patients with SSc and interstitial lung disease, both of which developed PHT. We aimed to discuss the immunopathogenesis with two case reports.

Keywords: Scleroderma, Pulmonary Hypertension, CTEPH

Introduction

Systemic sclerosis (SSc) is a chronic and multisystemic disease of unknown etiology and is characterized by fibrosis that develops because of connective tissue accumulation in the circulatory system, musculoskeletal system, gastrointestinal system, heart, lungs, and kidneys, especially the skin [1]. Multiple hypotheses might explain the complex pathogenesis of SSc. In individuals with suitable genetic background, vasculopathy starts with the contribution of various triggering factors, and at the end of the process of immune activation and oxidative stress, SSc occurs with increased fibroblastic activation. Vasculopathy has an essential role in the development of pulmonary hypertension. The immunological process in the formation of vasculopathy is not fully understood and is thought to develop due to multiple mechanisms.

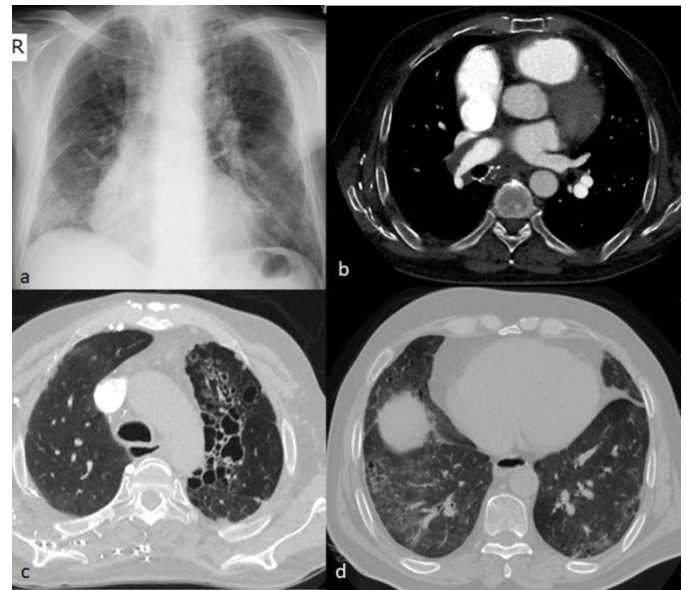
Chronic thromboembolic pulmonary hypertension (CTEPH) causes significant morbidity and mortality. The differential diagnosis of thromboembolic involvement in the pulmonary arteries is of great importance because of the definitive treatment potential with pulmonary endarterectomy (PEA) [2, 3]. Condliffe et al.'s [4] study showed that one and 3-year survival rates of patients with inoperable CTEPH were 82% and 70%, respectively. Although the pathophysiological process underlying CTEPH has not been fully elucidated, it is possible that immunological mechanisms play a significant role in the development of scleroderma vasculopathy, and trigger the development of CTEPH. In these two case reports, we aimed to discuss our experience after diagnosing CTEPH in the follow-up of two patients with interstitial lung disease, who were diagnosed with SSc in our center, and discuss whether a pathophysiological relationship between the two diseases exists. In addition, we discussed the importance of the CTEPH diagnosis, which can be reversed with treatment among PHTs, for SSc patients.

Case presentation

Case 1

A 55-year-old male patient with a diagnosis of SSc for two years presented with complaints of wheezing, shortness of breath, and cough. Previously, this patient was followed up with findings of skin involvement, sclerodactylitis, Raynaud's phenomenon, interstitial lung disease (non-specific interstitial pneumonia (NSIP)) (Figure 1), the positivity of antinuclear antibody (granular pattern), and anticentromere autoantibody. He had no diseases other than scleroderma. Previous immunosuppressive treatments were cyclophosphamide 1000 mg/month intravenously (IV) for one year, azathioprine 150 mg/day for eight months, and mycophenolate mofetil 1500 mg/day for one year. He was using mycophenolate mofetil and methylprednisolone at the time of admission. On physical examination, there were Velcro crackles in the bilateral lower zones. Oxygen saturation measured from the fingertip was 88%. In the blood analysis performed after the patient was hospitalized, C-reactive protein (CRP) was 15 mg/L and erythrocyte sedimentation rate (ESR) was 15 mm/h. The carbon monoxide diffusion capacity (DLCO) value was 64%, the forced expiratory volume per second (FEV1) value was 86%, and the forced vital capacity (FVC) value was 87%. The FEV1/FVC ratio was %81. Pulmonary artery pressure (PAP) was 110 mmHg in echocardiography, and the mean PAP value was 43 mmHg in right heart catheterization. Computed tomography (CT) showed ground-glass density areas increasing towards the basal in both lungs, traction bronchiectasis, interlobular and interseptal thickening, and reticular density areas that tend to merge were consistent with the interstitial lung disease (NSIP) pattern. Pulmonary angiographic CT revealed thromboembolism that started before the lobar arterial branching of both pulmonary arteries and continued to the lower lobe branches on the left and right, all of which were consistent with CTEPH (Figure 1). The homocysteine, protein C, protein S, and antithrombin III levels in the patient's thrombophilia panel were normal. The patient had been on enoxaparin therapy for more than three months before being diagnosed with CTEPH, after which his treatment was re-planned.

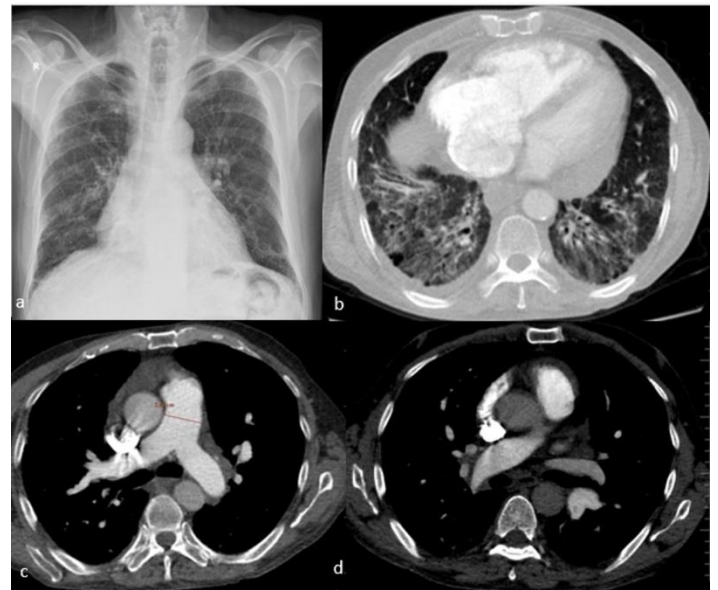
Figure 1: Plain radiography of a 55-year-old male patient (a) shows interstitial reticular opacities in the lower zones of both lungs, parenchymal cystic changes in the left upper zone, an increase in the cardiothoracic index and a prominence in the pulmonary conus. In the mediastinal window section of pulmonary CT angiography (b), filling defect causing wall thickening in the right descending pulmonary artery, collateral arterial structures in the mediastinum and enlargement in the right heart cavities are observed. In the section passing through the upper lobe of the lung window (c), cystic bronchiectasis in the left upper lobe (a) and the section passing through the lower lobe basal (d) thin reticular densities joining each other, traction bronchiectasis, NSIP pattern of interstitial involvement are observed. It is seen that the esophageal lumen is accompanied by air-containing enlargement.



Case 2

A 60-year-old male patient was followed for ten years with sclerodactylitis, Raynaud's phenomenon, skin findings, NSIP and ANA (granular pattern), and anti-centromere autoantibody positivity. Previous immunosuppressive treatments were IV cyclophosphamide 1000 mg /month for one year, azathioprine 100 mg/day (stopped immediately due to side effects), and 1000 mg rituximab on days 0 and 15 and 6 months for one year. He was using cyclophosphamide and rituximab combination therapy at admission. In routine blood tests, CRP was 8 mg/L and ESR: 12 mm/h. DLCO value was 86%, FEV1 value was 84%, FVC value was 72%, and FEV1/FVC ratio was 72%. The PAP value measured on echocardiography was 85 mmHg. Right heart catheterization of the patient could not be performed. In CT, the pulmonary trunk increased by 39 mm, and its ratio to ascendant aorta diameter was less than 1. Also, the pulmonary artery diameter was enlarged at the segmental level, and the findings were compatible with pulmonary hypertension. Right heart chambers were enlarged. An appearance compatible with cystic bronchiectasis was detected, being more common in the upper lobe apical posterior segment and lower lobe superior segment of the left lung. Besides, increasing reticular density towards the lower lobe and traction bronchiectasis were observed in both lungs, the subpleural areas were relatively unaffected, which was considered the NSIP pattern. In the patient's CT pulmonary angiogram, the diameter of the pulmonary trunk was measured as 39 mm, where it is widest, and it had increased. An increase was observed in pulmonary artery diameters at both main pulmonary artery and segmentary levels, which was considered a sign of pulmonary hypertension. An appearance compatible with thin vein-like thromboembolism was detected in the upper lobe anterior segment on the right, at the level of the lower lobe branching level and the lower lobe posterobasal segment branch, and in the lower lobe posterobasal segment branch on the left, all of which were compatible with CTEPH (Figure 2). Homocysteine, protein C, protein S, and antithrombin III levels were normal in the patient's thrombophilia panel evaluation. The patient had been on enoxaparin therapy for more than three months before being diagnosed with CTEPH. The patient was diagnosed with CTEPH, and his treatment was re-planned.

Figure 2: On plain radiography (a) of a 60-year-old male patient, interstitial reticular opacities in the lower zones of both lungs and an increase in cardiothoracic index are seen. Interstitial involvement of systemic sclerosis in the form of NSIP pattern in the form of continuing thin reticulations, traction bronchiectasis and bronchiectasis, ground glass densities are observed in the lung window section (b) passing through the lower lobe basales of CT angiography. An enlargement is noticed in the right heart chambers. In sections of the mediastinal window (c), enlarged pulmonary trunk pericardial effusion and air-containing enlargement in the esophageal lumen are seen. In the lower section (d), a thin web-like linear filling defect in the lumen of the left descending pulmonary artery is noticeable.



Discussion

Vasculopathy has an important role in the development of interstitial lung disease and pulmonary hypertension in SSc. It develops with the contribution of both the humoral and the cellular immune system. Antibodies developed by B lymphocytes, one of the most critical parts of the humoral immune system, against Type IV collagen and laminin, an important element of the subendothelial basement membrane in the vascular wall, are related to the severity of interstitial lung disease [5]. In cellular mediated immunity, T lymphocytes exposed to Type I collagen are activated to produce interleukin-2 (IL-2), and studies have shown that the level of IL-2 and IL-2 receptors in the blood correlate with the severity of the disease [6]. The increased level of IL-2 is thought to directly induce endothelial damage by converting natural killer (NK) cells into lymphokine-activated killer (LAK) cells [7]. As a result, humoral and/or cellular immunity triggered by various reasons causes endothelial damage. In SSc, vasculopathy has the potential to affect arterioles with a diameter of 150-500 μ m, and intimal proliferation is observed with mononuclear cell infiltration due to the cytokines and adhesion molecules released in this region. The cause of the pathologies that develop in these regions is the development of vascular restructuring at the end of the process leading to endothelial activation, mononuclear cell infiltration, the intimal proliferation of arterioles, capillary necrosis, and occlusion of blood vessels [8]. This pathological process occurs in organs such as muscle, lung, heart, kidney, and this process is called vasculopathy. Endothelial cell apoptosis plays a central role in the vasculopathy in SSc. It results from multiple pathophysiological processes involving environmental factors, infectious agents, reperfusion injury, autoantibodies, and cytotoxic T lymphocytes. Endothelial apoptosis can be induced for reasons such as the induction of EAM by infectious agents such as human cytomegalovirus (hCMV) with TGF- β

stimulation through TNF- α , IL-1, and IL-6, which causes EAM upregulation by autoantibodies, T lymphocytes exposed to collagen in the region stimulating IL-2 [9-12]. Another pathophysiological process is reperfusion injury. In the formation of mononuclear cell infiltration, events such as capillary necrosis, triggering of endothelial cell damage by oxygen radicals due to reperfusion after occlusion, upregulation of TNF- α , IL-1, IL-6, and IL-8, and increase in EAMs occur. IL-8 can also trigger in situ thrombotic events by platelet activation.

Endothelin-1 (ET-1), which is a potent vasoconstrictor, is also released after endothelial damage. It causes proliferation, especially in pulmonary arterial smooth muscle cells, and by decreasing the level of nitric oxide (NO) released from the endothelium, it prevents vasodilation and becomes vulnerable to radical oxygen damage, contributing to endothelial dysfunction. In the chronic process, ET-1 triggers vascular restructuring [13-15]. As a result, dysfunction develops in endothelial cells exposed to cytokines, mononuclear cells, and autoantibodies, remodeling occurs in the vascular endothelium, and the process leading to pulmonary hypertension is triggered. Similarly, this pathophysiological process is also experienced in CTEPH patients. The diagnosis of CTEPH is based on the presence of at least one segmental perfusion defect on scintigraphy with or without a prior episode of pulmonary thromboembolism, or a mean pulmonary arterial pressure (PAP) ≥ 25 mmHg with intraluminal filling defects on computed tomography (CT) and pulmonary capillary wedge pressure < 15 mmHg [16]. To be diagnosed with CTEPH, patients must use anticoagulant therapy for at least three months, and their findings must be continuous [17]. It has been shown that a significant portion of patients diagnosed with CTEPH have not been diagnosed with PTE before [18, 19].

The pathophysiology of CTEPH is a combination of incomplete thrombus resolution, abnormal coagulation, inflammation, oxidative stress, defective fibrinolysis, and endothelial dysfunction. According to the Jamieson classification, CTEPH patients have organized incomplete thromboembolism in Type-1 and Type-2. Vascular intimal thickening is present in Type-3 and Type-4, and chronic inflammation has been shown in most patients [20-22]. Histological studies of resected PEA material showed that lymphocytes, macrophages, and neutrophils were present with chronic thrombus [23]. Studies have shown that fibrinogen and cytokines are very important in the pathophysiology of CTEPH. In retrospective studies, fibrinogen plasma levels were significantly higher in CTEPH patients than in the control group [24]. TNF- α , IL-1 β , IL-6, and IL-8 levels are high in patients with CTEPH [25-27]. In particular, IL-6 and IL-8 levels are useful in predicting the disease's prognosis in the long term after PEA [27]. It was also observed that TNF- α levels significantly decreased in the first 24 hours after PEA [28]. In another study, IL-6 level correlates with hemodynamic parameters and exercise capacity in patients with CTEPH [29].

C-reactive protein (CRP) is a well-known biomarker for inflammation, and it is one of the first inflammation markers identified in CTEPH. CRP triggers vascular remodeling and in situ thrombosis. Larger et al. [30] showed that CRP decreases gradually in CTEPH patients in the first 12 months after PEA,

which correlates with the reduction of mononuclear phagocytic cell migration to that area. As we previously described in the pathogenesis of SSc vasculopathy, ET-1 acts with a similar mechanism in the development of CTEPH. The resulting endothelial damage releases ET-1 and contributes to the proliferation and restructuring of vascular smooth muscles. Studies have shown that pre-PEA ET-1 level correlates with disease severity.

All these inflammatory markers suggest that the pathophysiology of CTEPH has some similarities with the development of SSc vasculopathy. In both cases, the main process appears to be chronic inflammation and consequent endothelial dysfunction, increased adhesion molecules, mononuclear phagocytic cell migration, and the restructuring of the vascular structure. No deep vein thrombosis was detected in the lower extremity Doppler USG performed in both of our patients. There were no findings suggestive of acute pulmonary embolism in the patients. This suggested a chronic process. In addition, when the blood values measured during the follow-up of both patients were analyzed retrospectively, CRP values were consistently high. In the light of these data, we think that chronic inflammation triggered pulmonary endothelial damage and remodeling in these two cases with SSc. This complex inflammatory process may have caused in situ thromboembolism in the damaged endothelium by activating the platelets and triggering the development of CTEPH. Moreover, thickening and vasoconstriction of the vascular wall may have contributed to the development of CTEPH, a type of PAH. Detection of thromboembolism and absence of DVT by pulmonary angiographic CT performed due to the slowly and insidiously developing symptoms in these two cases, and the high inflammatory markers support our thought. New studies are needed to prove these thoughts.

Conclusion

The possibility of CTEPH should be considered in cases such as increased effort dyspnea, decreased exercise capacity, and increased oxygen demand in SSc patients with pulmonary arterial hypertension (PAH) and/or interstitial lung disease. Early diagnosis of CTEPH contributes to reducing morbidity and mortality, as shown by Condliffe et al. Development of PTH should be carefully investigated in SSc patients with interstitial lung disease. CTEPH is in the group 4 class of PHTs and differs in terms of surgical and medical treatment, and morbidity and mortality can be reduced with treatment.

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