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Chronic Thromboembolic Pulmonary Hypertension Mimicking Acute Pulmonary Embolism: A Case Report

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Conflict of interest: None declared

Patient: Female, 68-year-old
Final Diagnosis: Chronic thromboembolic pulmonary hypertension (CTEPH)
Symptoms: Dyspnea
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare disease

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare form of pulmonary hypertension which is often caused by recurrent emboli. The reported prevalence in Latvia is 15.7 cases per million inhabitants. Several risk factors predispose patients to develop chronic thromboembolic pulmonary hypertension, including the presence of chronic myeloproliferative diseases and splenectomy.

Case Report: We present a case of a 68-year-old woman with a variant of chronic myeloproliferative disease, essential thrombocythemia, splenectomy, and chronic thromboembolic pulmonary hypertension, in whom chronic thromboembolic pulmonary hypertension was mimicking acute pulmonary embolism. On admission, the patient had progressive dyspnea, elevated right ventricular systolic pressure (RVSP) 60-70 mmHg, and elevated thrombocytes, C-reactive protein, BNP, and d-dimer levels. These results, as well as the results of thoracic computed tomography angiography with contrast, supported the diagnosis of acute pulmonary embolism. During the sequent follow-up visit after 3 months of effective anticoagulant therapy, the patient had elevated RVSP: 55-60 mmHg. Therefore, right heart catheterization was performed, in which it was found that mPAP was 37 mmHg with PCWP 5 mm Hg and PVR 8.9 Wood units, confirming the CTEPH diagnosis.

Conclusions: Patients who are at high risk of thrombosis need an increased level of monitoring to be properly evaluated. An easy solution to misdiagnosis of CTEPH with an acute pulmonary embolism could be taking scrupulous patient history, which can reveal multiple risk factors of CTEPH development. The subsequent assessment of risk factors can lead to a more appropriate consideration of CTEPH diagnosis vs acute pulmonary embolism.

Keywords: Hypertension, Pulmonary • Pulmonary Embolism • Splenectomy


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Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare form of pulmonary hypertension (PH), with a reported prevalence in Latvia of 15.7 cases per million inhabitants [1]. Despite its low prevalence, CTEPH imposes a large burden both on patients and healthcare systems due to its complex management and high morbidity and mortality rates [2,3]. Although early diagnosis and treatment of CTEPH is crucial for the outcome of patients, CTEPH remains severely underdiagnosed [2,4,5]. It is hypothesized that the reasons for CTEPH underdiagnosis are often vague clinical presentation, the variable association of CTEPH with pulmonary embolism (PE), and discrepancies when interpreting imaging studies [5].

Understanding the developmental processes of CTEPH and determining the risk factors for CTEPH will undoubtedly improve early detection and prophylaxis for patients at risk [6]. Several risk factors predispose patients to develop CTEPH, including the presence of a ventriculoatrial shunt [7], chronic myeloproliferative diseases (CMPD) [8], and splenectomy [7]. The associated risk of CTEPH development for splenectomy patients is reported to be 20 times higher than in the general population [9]. All of the above-mentioned conditions can induce formation of thrombi [10-12], thus accenting the pathophysiology of CTEPH, where failure to resolve the pulmonary thrombus induces remodeling of pulmonary arteries, leading to their occlusion. It is also important to mention that the pathophysiology of CTEPH is multifaceted, involving inflammation, infections, arteriopathies, and venous/capillary diseases as important aspects of CTEPH pathogenesis [13,14].

In the present clinical classification, CTEPH is classified as group 4 pulmonary hypertension, where the diagnosis is established on findings obtained after at least 3 months of effective anticoagulation. Subsequently, CTEPH findings are mean pulmonary arterial pressure ≥ 20 mmHg, pulmonary vascular resistance ≥ 3 Wood units, pulmonary artery wedge pressure ≤ 15 mmHg documented at right heart catheterization, together with at least 1 mismatched segmental perfusion defect determined by ventilation/perfusion scanning, multidetector computed tomography angiography, or pulmonary angiography [15,16].

CTEPH management involves 3 approaches – surgical, medical, and interventional – used in various combinations. Currently the treatment of choice is pulmonary endarterectomy (PEA) [17]. This procedure is complicated; therefore, it is provided by expert centers only. It has been found that for the majority of patients after PEA, the quality of life and life expectancy increase, yet patients who do not undergo PEA face a poor prognosis. Supportive medical treatment consists of diuretics, stimulator of soluble guanylate cyclase: Riociguat, synthetic analog of prostacyclin: Treprostinil, lifelong anticoagulation therapy, and

Table 1. Laboratory blood test results.

	At admission	3 months later
RBC $\times 10^{12}/l$	2.97	3.45
HGB (g/l)	114	119
PLT $\times 10^9/l$	547	421
CRP (mg/l)	63	<4.00
D-dimer (mg/l)	7.78	0.45
BNP (pg/ml)	1881	234

RBC – red blood cells, HGB – hemoglobin, PLT – platelet count, CRP – C-reactive peptide, BNP – brain natriuretic peptide.

oxygen therapy in cases of heart failure or hypoxemia. The interventional approach offers balloon pulmonary angioplasty (BPA) [16,18]. A recent meta-analysis has shown evidence of the benefits of BPA with improvements in both hemodynamic parameters and functional capacity [19]. Although BPA is not a broadly used method [20], it is gaining worldwide attention and showing favorable outcomes for patients [21,22]. The BPA procedure has led to a noticeable improvement in hemodynamics, life expectancy, and quality of life for CTEPH patients. In addition, BPA provides a variety of positive effects after the procedure, such as improved renal function and a reduction of serum high-sensitivity troponin T, suggesting that BPA reduces the severity of continuing myocardial damage [22].

Thus, in this case report we aimed to raise awareness of CTEPH underdiagnosis and the undoubted improvement in early CTEPH diagnosis due to the determination of risk factors.

Case Report

A 68-year-old woman was admitted to the emergency room of Pauls Stradiņš Clinical University Hospital (PSCUH) due to progressive dyspnea on exertion for the last 2 weeks (NYHA functional class III). Vital parameters were within normal limits: blood pressure 126/87 mmHg, heart rate 80 bpm, respiratory rate 16 breaths/minute, SpO₂ on 95% (room air). The electrocardiogram showed sinus rhythm 79 beats/minute, right axis deviation, right ventricular hypertrophy, and right atrial enlargement. Transthoracic echocardiography revealed an enlarged right atrium and ventricle with increased right ventricular systolic pressure (RVSP) 60-70 mmHg. Laboratory results showed slightly elevated thrombocyte and C-reactive protein levels, as well as high BNP and d-dimer levels (Table 1). Having scrutinized these results, a presumptive diagnosis of pulmonary embolism was made.

Therefore, a thoracic computed tomography angiography (CTA) with contrast was performed, which revealed acute bilateral

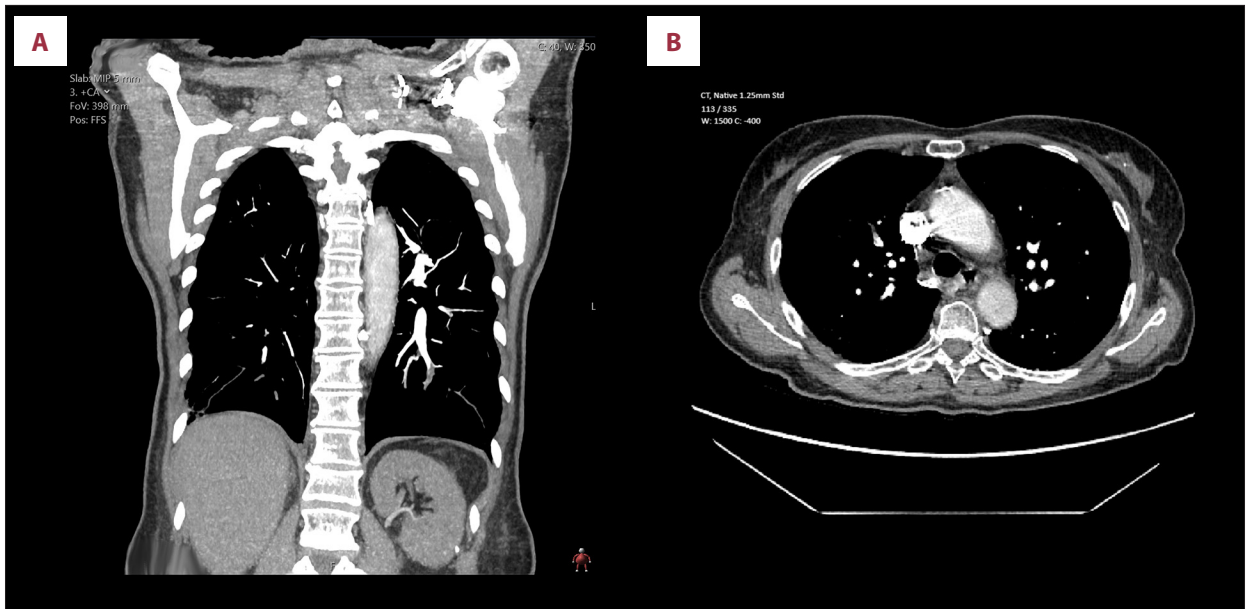


Figure 1. Coronal (A) and axial (B) thoracic computed tomography angiography slices on admission. PACS system Sectra Workstation IDS7 Version 21.2.

pulmonary embolism in lobar, segmental, and subsegmental branches, consolidation of the right upper lobe, dilatation of the right ventricle, right atrium, and main pulmonary arteries, with signs of pulmonary hypertension and chronic bilateral thromboemboli, with subpleural interstitial fibrosis due to recent pulmonary infarction (Figure 1).

Low-risk (PESI score, class II) acute PE was diagnosed, and an immediate anticoagulant therapy was initiated with peroral anticoagulant therapy: Rivaroxaban 15 mg twice a day.

The medical history revealed that the patient was diagnosed with a variant of CMPD, essential thrombocythemia (ET), and underwent a splenectomy 21 years ago. The patient had been treated with INF-alpha therapy in combination with hydroxycarbamide, and for the last 8 years the patient has been treated with hydroxycarbamide.

The patient denied any previous problems of chest pain or thrombotic events, although during physical activities, dyspnea was present. Performing an ultrasound of the lower extremities, chronic deep vein thrombosis in the v. gastrocnemius caput mediale dextra was revealed.

Additionally, the patient received: Spironolactone 12.5 mg once a day OD, Torasemide 5 mg twice a week PO, Ivabradine 5 mg twice a day to decrease the risk of tachycardia, Telmisartan 40 mg OD, and NSAID therapy for chronic back pain. The patient was discharged after 11 days with 6-minute walk distance (6 MWD) of 380 m (New York Heart Association [NYHA] functional class II) on the day of discharge.

Table 2. Right heart catheterization results.

Parameter	
PASP (mmHg)	67
PADP (mmHg)	17
mPAP (mmHg)	37
PCWP (mmHg)	5
CO (l/min)	3.59
CI (l/min/m ²)	2.28
PVR (Wood units)	8.9

PASP – pulmonary arterial systolic pressure; PADP – pulmonary arterial diastolic pressure; mPAP – mean pulmonary artery pressure; PCWP – pulmonary capillary wedge pressure; CO – cardiac output; CI – cardiac index; PVR – pulmonary vascular resistance.

During the subsequent follow-up visit after 3 months, a transthoracic echocardiography revealed elevated RVSP of 55-60 mmHg. Having reconsidered the patient's risk factors, the diagnosis of CTEPH was favored over acute PE. Therefore, right heart catheterization (RHC) was performed. During this procedure, it was found that mPAP was 37 mmHg with PCWP 5 mmHg and PVR 8.9 Wood units (Table 2); thus, the CTEPH diagnosis was confirmed. Repeated thoracic CTA showed almost total disappearance of thrombotic masses from lobar, segmental, and subsegmental branches, with some thromboemboli still present in subsegmental and smaller branches of both lungs (Figure 2). The right heart dilatation was less pronounced, but dilatation of main pulmonary arteries remained.

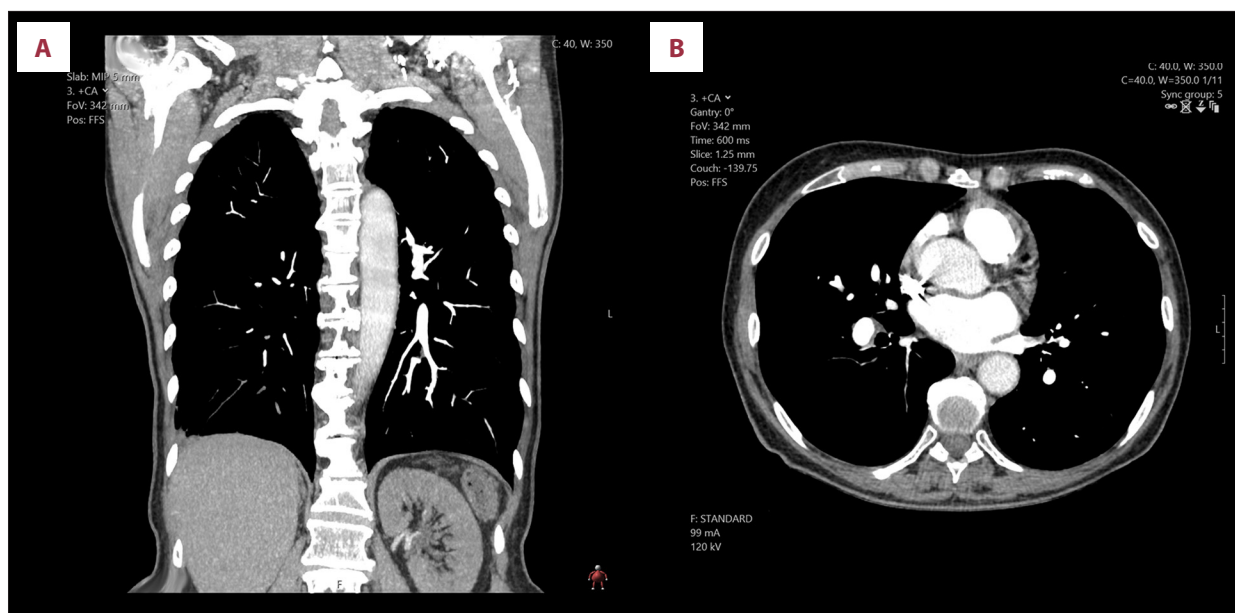


Figure 2. Coronal (A) and axial (B) thoracic computed tomography angiography slices after 3 months of effective anticoagulant therapy. PACS system Sectra Workstation IDS7 Version 21.2.

The laboratory results showed notable changes in D-dimer and BNP levels (Table 1).

The further treatment options can include PEA and BPA, which will be decided by a panel of CTEPH medical experts.

Discussion

The patient was diagnosed with ET 21 years ago, which is a disease associated with vascular complications such as arterial thrombosis in 30-40% of patients and venous thrombosis in 5% of patients [23]. Two years later, due to ischemic infarction and organized thrombi within the spleen, the patient underwent splenectomy and has been regularly treated with cytoreductive agent hydroxycarbamide ever since. Although hydroxyurea significantly reduces the risk of thromboembolic events, the residual incidence of thrombosis in hydroxyurea-treated ET patients is still high (9%) [24]. We have no information for our patient on recent episodes of thrombosis or any other syndromes related to underlying disease over the 20-year time span.

Splenectomy is associated with a higher risk for venous thromboembolism, thereby contributing to CTEPH development [25,26]. Lang et al found that thrombi of CTEPH patients who had undergone previous splenectomy had significant enrichment of anionic phospholipids, which may represent a key mechanism underlying the persistence of venous thrombi, and demonstrates the link between splenectomy and vascular remodeling of thrombosis as it occurs in CTEPH [27]. It

has also been found that in post-splenectomy patients, plasminogen activator inhibitor-1, fibrinogen and d-dimer levels are elevated, thus shifting the coagulation equilibrium toward thrombosis [28].

During the patient examination in the Cardiology ward, an ultrasound of the lower extremities was performed, revealing chronic deep vein thrombosis in the v. gastrocnemius caput mediale dextra. Chronic deep vein thrombosis is also considered a risk factor for CTEPH development.

Analyzing the captured scene from computed tomography angiography of the chest, both acute bilateral pulmonary embolism and chronic bilateral thromboemboli with subpleural interstitial fibrosis were found. However, chest CTA is an essential component for CTEPH diagnosis, according to Lang et al, and the diagnosis of CTEPH cannot be made solely on the basis of a chest CTA, due to CTEPH patients being referred late, after previous misdiagnoses that were based on “negative” CT scans [26].

The key to successful management of CTEPH is early diagnosis; however, the diagnosis of CTEPH is impeded by the poor awareness of CTEPH and the unclear knowledge of the CTEPH connection with an acute PE. It is considered that CTEPH is a severe complication of an acute PE due to inability to resolve thrombotic vascular obstruction; however, in most cases the diagnosis of an acute PE was not well documented and the first symptoms that were linked to acute PE might have been the first manifestations of CTEPH [29].

Table 3. Risk factors of CTEPH development [8,33-35].

Risk factors of CTEPH development
<ul style="list-style-type: none">• Splenectomy• Ventriculoatrial shunt and/or infected pacemakers• Hypothyroidism/ongoing thyroid replacement therapy• Chronic venous ulcers• Elevated VIII factor• Elevated Von Willebrand factor• Abnormalities in fibrinogen structure• Non-O blood group• Chronic inflammatory diseases<ul style="list-style-type: none">• Osteomyelitis• Inflammatory bowel disease• Lupus anticoagulant/Antiphospholipid antibodies• History of malignancy• Chronic myeloproliferative diseases• Deep vein thrombosis• Recurrent venous thromboembolism• Female gender• Chronic obstructive pulmonary disease• Heart failure• Atrial fibrillation

To resolve the problem of misdiagnosis of CTEPH with an acute PE, we suggest taking scrupulous, prospective patient history from patients with an acute PE. Multiple risk factors of CTEPH development have been discovered and scrupulous patient history can reveal these risk factors. This indicates that certain patients are in need of a more in-depth clinical examination considering the CTEPH diagnosis and a more serious patient follow-up plan for early diagnosis of potential thrombotic events. The discovered risk factors for CTEPH development are listed in **Table 3**.

Currently, the imaging method of choice for the confirmation of CTEPH diagnosis in pulmonary hypertension patients is a ventilation/perfusion (V/Q) lung scan [30], which is considered superior to a CT pulmonary angiogram due to V/Q lung scan's higher sensitivity compared with CT pulmonary angiogram [30-32]. Poor optimization of acquisition and post-processing parameters in CT pulmonary angiogram are considered a pivotal point of misdiagnosis [31]. As the V/Q lung scan is not available yet in Latvia, the conformation of CTEPH diagnosis must be done by means of CT pulmonary angiogram.

Our patient was diagnosed with multiple risk factors for CTEPH development, severely increasing the risk for CTEPH development: female gender with a reported odds ratio 1.44 [33], chronic deep vein thrombosis with a reported odds ratio 2.46 [33], splenectomy with a reported odds ratio 22.09 [34],

and chronic myeloproliferative disease [8]. Risk factors contributing to the pathophysiology of CTEPH development must be taken seriously and patients with these factors should follow a strict follow-up plan.

We presented a very complicated case of a patient with CMPD, including splenectomy and CTEPH. Because CTEPH can mimic an acute PE, it is hard to know when the first episode of thrombosis occurred.

Conclusions

CTEPH is a rare disease and an early diagnosis is important, as a late diagnosis is associated with high mortality rates. Our case shows that pulmonary thrombosis in patients can develop asymptotically or with no evidence of a detected thrombotic event; however, that does not exclude the possibility of CTEPH. Patients with CMPD are prone to a high risk of thrombosis, thereby these patients are in need of an increased level of monitoring to be properly evaluated. CTEPH is impeded by the poor awareness of CTEPH and the unclear knowledge of the CTEPH connection with an acute PE. To find a proper solution of the problem of the misdiagnosis of CTEPH with an acute PE, it is essential to carefully elicit the patient's history, as it can reveal multiple risk factors for CTEPH development. The subsequent assessment of risk factors can lead to a more appropriate consideration of CTEPH diagnosis vs PE. If there are significant risk factors in the patient history, it is crucial to perform transthoracic echocardiography after 3 months of effective anticoagulant therapy. If the signs of pulmonary hypertension are still present, right heart catheterization and digital subtraction angiography should be performed to further evaluate treatment options. For proper evaluation and diagnosis of CTEPH, all of the clinical, laboratory, and radiological data of the patients has to be analyzed critically and as a whole. These are the prerequisites for such patients to receive adequate and proper treatment.

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Declaration of Figures Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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