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Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism? A Case Report and Discussion

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Abstract

Keywords

- chronic thromboembolic pulmonary hypertension
- multidisciplinary team discussion
- thyroidectomy

Introduction

Chronic thromboembolic pulmonary disease (CTEPD) is characterized by chronic obstruction of major pulmonary arteries with organized thrombi that appear as rings, simple or complex webs, and as subtotal or total vascular occlusions. CTEPD has been established as the overarching term to define cases of chronic pulmonary thrombosis with pulmonary hypertension (CTEPH) and without pulmonary hypertension. Today, the condition is believed to be a sequela of acute pulmonary embolism (PE). Early diagnosis is hampered by a paucity of typical symptoms until the afterload of the right ventricle (RV) is increased and signs of RV dysfunction are leading to clinical congestion and other signs of heart

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A 61-year-old male presented with New York Heart Association class II breathlessness. Three years earlier, he had presented with a swollen leg, had received a diagnosis of deep vein thrombosis on ultrasound and of low-risk acute pulmonary embolism, and had been discharged on a direct oral anticoagulant after 8 hours. The patient also had a history of thyroidectomy and was on levothyroxine substitution. The case illustrates a patient with acute pulmonary embolism who developed chronic thrombotic pulmonary vascular lesions within 3 years after acute pulmonary embolism in the presence of typical risk factors.

failure. While the delay from first symptoms to diagnosis is about 14 months,¹ and has not been shortened over the years, it has been recognized that significant numbers of cases are hidden in the population of severe acute PE, and that imaging of acute PE may help the early diagnosis of CTEPD.² Whether CTEPH cases that are identified in acute PE cohorts are pre-existent or have developed longitudinally from classical acute PE that occurred prior to the acute PE episode is not known. It will be difficult to demonstrate "primary CTEPD" versus "CTEPD evolving from acute PE" in a clinical study setting because of the general lack of symptoms of pulmonary vascular disease. We are describing a clinical case that illustrates well the transition of acute to chronic PE speaking in favor of a linear relationship of the

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Year	Year of acute PE	3 years after the acute PE	Current status	
Symptoms	Swelling of the left leg	New-onset exertional dyspnea		
Diagnostic tests	Clinical DVT, confirmed by ultrasound			
	TTE: normal	TTE: normal		
	V/Q: not done, because CTPA was done	V/Q: multiple small bilateral mismatched defects		
	CTPA: saddle thrombus in the main pulmonary artery	 CTPA: no central clot, but 1. Intravascular webs 2. Complete arterial occlusion of segmental and subsegmental PA branches 3. Small pulmonary infarctions⁷ 		
		Invasive PAG: major vessel chronic thromboembolic disease, with complex webs as the predominant lesion type		
Treatments	Anticoagulation with DOAC	Continuous anticoagulation with full-dose DOAC	Anticoagulation with VKA	
		Presentation to the MDT	Patient accepted in BPA program, and undergoing BPA	

Table	1 Clinica	I CTEPD case:	key clinica	events/dia	agnostic tests	/therapies
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Abbreviations: BPA, balloon pulmonary angioplasty; CTEPD, chronic thromboembolic pulmonary disease; CTPA, computed tomography pulmonary angiography; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; MDT, multidisciplinary team; PA, pulmonary artery; PAG, pulmonary angiography; TTE, transthoracic echocardiography; V/Q, ventilation perfusion lung scintigram; VKA, vitamin K antagonist.

two conditions, rather than suggesting a separate vascular CTEPD entity (\sim Table 1).³

Past Medical History

Clinical Presentation

A 61-year-old male presented with New York Heart Association (NYHA) class II breathlessness. Symptoms had evolved slowly over the previous 6 months, mainly on exertion, and were unexpected and unexplained as the patient was a non-smoker.

Patient medications on presentation were apixaban 5 mg 1-0-1, levothyroxine sodium $100 \,\mu g$ 1-0-0, and nebivolol 5 mg $\frac{1}{2}$ -0-0.

Three years earlier, the patient had presented with a swollen left leg, which had been diagnosed as deep vein thrombosis on ultrasound. Although he had had no dyspnea, and a cardiac troponin of 15 ng/L (normal 0–14 ng/L), computed tomography pulmonary angiography (CTPA) had been performed showing central PE (**-Fig. 1A**) extending from the pulmonary artery (PA) main stem to segmental compartments bilaterally. Because of a low-risk PE status with normal right ventricular (RV) function, the patient had been discharged on a direct oral anticoagulant after 8 hours.



Fig. 1 Computed tomography pulmonary angiography (CTPA) cross-sectional view at the level of the main pulmonary artery bifurcation. (A) Acute PE in 2020. (B) Follow-up CTPA in 2022 showing complete clearance of the central thrombus. There is a web lesion on this section as a sign for chronic disease (white arrow).



Fig. 2 Native pulmonary angiogram of the case example of chronic thromboembolic pulmonary disease without pulmonary hypertension, with typical major vessel pulmonary artery lesions. (A) Right lung in the AP projection; (B) right lung in a 60-degree LAO projection; (C)left lung in the AP projection; and (D) left lung in a 60-degree LAO projection. AP, anterior-posterior view; LAO, left anterior oblique; RAO, right anterior oblique. White arrows point to vascular lesions.

The patient had had a previous thyroidectomy, multiple lipoma and Schwannoma surgeries, and a hearing loss, presumably due to intracranial vestibular Schwannoma.

Investigations

Dyspnea workup was performed. Electrocardiogram showed sinus rhythm, 72 beats per minute, atrioventricular delay 190 milliseconds, normal axis deviation, and normal chest wall leads. Transthoracic echocardiography showed normal left and RV function, normal valves, trivial tricuspid regurgitation. Ventilation perfusion lung scan demonstrated multiple small bilateral mismatched defects. CTPA showed normally sized pulmonary arteries, no central clot, but chronic thrombotic occlusion of segmental and subsegmental PA branches (**~ Fig. 1B**, arrow). Old small subpleural infarcts appeared in the right upper and middle lobes.

Despite the absence of intermediate or high echocardiographic probability of pulmonary hypertension, and in the absence of pulmonary comorbidity,⁴ invasive right and left cardiac catheterizations were performed via a radial and brachial approach. There was normal mean PA pressure of 20 mm Hg, PA wedge pressure of 7 mm Hg, and a cardiac index of 2.7 L/min/m², resulting in a pulmonary vascular resistance of 1.9 Wood units. Invasive PA angiography (**Fig. 2**) illustrated major vessel chronic thromboembolic disease, with complex webs as the predominant lesion type, throughout both lower lobes. Coronary angiography was normal.

At this time, the CTPA on the original acute PE presentation 3 years earlier was re-reviewed to look for signs of CTEPD.⁴ Acute CTPA showed a saddle thrombus in the main PA (**-Fig. 1A**), extending to the lobar and segmental pulmonary arteries on both sides. There were no webs and bands at this time, no insight into segments with fresh clot, and there was no mosaic perfusion pattern. However, the RV to left ventricle (RV:LV) ratio was 1.5:1 suggesting a large RV at the time of the acute PE.

Management (Medical/Interventions)

Patient had an inconspicuous laboratory and thrombophilia screen. The data were presented to the multidisciplinary team. Because of class II breathlessness attributable to CTEPD without pulmonary hypertension, the patient was offered pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA), and sent home on life-long oral anticoagulation.

Patient Perspective and Discussion

Since the acute PE 3 years earlier, the patient had been asymptomatic. However, 6 months ago he noticed that he slowly became dyspneic when walking uphill, with no dyspnea when walking on ground level. After the diagnostic investigation the multidisciplinary team recommended PEA as the initial treatment. However, the patient decided to step back and decide over the summer whether he wanted to accept PEA, BPA, or remain on anticoagulation only.

CTEPD presenting as acute PE appears to be not so rare after all.⁵ Imaging characteristics of acute and chronic PE have been classified,⁶ and introduced into machine learning algorithms to facilitate CTEPH diagnosis based on CT images.^{7,8} Traditional thinking is that chronic thrombus develops from acute fresh PE. Studies have been designed to longitudinally observe the development of fibrous lesions from red thrombus.^{9,10} Recent evidence is suggesting that CTEPH is rare on these grounds, with a cumulative incidence of only 2.3% within 2 years after the acute symptomatic event as observed under optimal conditions in a prospective setting in expert tertiary centers with the ability to diagnose CTEPD.¹⁰

Conclusions

CTEPD is a pulmonary vascular disease that evolves after PE due to a systemic inflammatory milieu, ^{11,12} favoring in

situ thrombosis.^{13,14} In the present patient, the established risk factor for CTEPH is the previous thyroidectomy followed by levothyroxine substitution over many years. There exists a U-shaped correlation between thyroid hormone levels and the risk of cardiovascular disease.¹⁵ A study analyzing ¹⁸F-FDG uptake in the carotids, aortic arch, ascending, descending, and abdominal aorta suggests that supression of thyroid-hormone stimulating hormone is aggravating arterial inflammation.¹⁶ This evidence supports the epidemiological link between hypothyroidism, thyroid hormone substitution, and CTEPH.^{17,18} It is still unclear how long it takes in an individual case from acute fresh red clot to organize and cause pulmonary hypertension, but clinical observations have suggested a short period of 129 days¹⁰ or 6 months for that to occur.¹⁹ In the current case, pulmonary hypertension had not yet developed, presumably because of the residual open vessels allowing for normal resting pressures. In cases that are less clear, cardiopulmonary exercise testing may be needed to prove the symptomatic relevance of pulmonary vascular obstructions.⁴ Recognizing CTEPH earlier is an unmet need,²⁰ and best addressed if the condition is followed up in cases of large central thrombus and the presence of CTEPH risk factors.

In summary, this case should serve as an example that acute PE may become CTEPH and in this case more precisely CTEPD without PH. We cannot exclude that CTEPH was preexisting and what we saw was "acute-on-chronic PE." However, what is more likely is that CTEPH developed on the basis of acute PE.

Disclosures

I.M.L. has relationships with drug companies including AOP-Health, Actelion-Janssen, MSD, Pulnovo, United Therapeutics, Medtronic, Neutrolis, and Sanofi. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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