

A case of chronic thromboembolic pulmonary hypertension

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially fatal complication of pulmonary embolism (PE). Organized thrombus in the pulmonary artery causes a chronic obstruction, leading to a vascular system remodeling, an increase of pulmonary vascular resistance and a chronic pulmonary hypertension. Epidemiology is mostly unknown due to the difficult diagnostic process that often leads to a late diagnosis: findings of persistent pulmonary hypertension (PH), despite correct treatment of PE, lead to the diagnostic suspect. The first choice treatment is pulmonary endarterectomy (PEA) associated with lifelong anticoagulant therapy with vitamin K antagonist. We present the case of a 53-year-old male affected by dyspnea for months, admitted to a sub-intensive care unit for intermediate low-risk PE; echocardiography showed signs of PH persisting after anticoagulant therapy; after 2 months of specific treatment the diagnosis of CTEPH was confirmed and the patient was successfully treated with PEA.

Case Report

A 53-year-old Italian man presented to the emergency department with worsening dyspnea on exertion for about 18 months, without further symptoms like chest pain or syncope. For those symptoms he recently decided to undergo a pneumological examination including lung function test, that resulted normal.

He had history of recent pneumonia, systemic arterial hypertension treated with ACE inhibitors, depressive anxious syndrome, and one episode of acute

urinary retention associated with benign prostatic hyperplasia chronically treated with alfuzosin.

In the Emergency Department the patient was oriented and presented a Kelly Score 1, he was afebrile, his arterial pressure was 150/95 mmHg, the cardiac rate was 105 beats per minute, SpO₂ was 93% in ambient air with a respiratory rate of 22 breaths per minute. Physical examination showed neither alteration, apart from tachycardia, nor signs of deep or superficial venous thrombosis (DVT, SVT). Previous and family medical history did not include any episodes of thromboembolism nor events that could lead to that disease (traumatic events, surgical procedures, long bed resting). Wells score calculation resulted in an intermediate probability of PE (4.5 pts). A differential diagnosis process for dyspnea was executed: EKG showed sinus rhythm, 100 beats per minute, S1Q3T3 and right ventricular volume overload signs, arterial blood gas analysis resulted in type 1 respiratory failure and respiratory alkalosis, while chest x-ray showed bilateral increased volume of pulmonary hila and vascular structures in the superior pulmonary area (Figure 1). Laboratory tests showed high D-dimer 3740 ng/mL (reference values 0-500 ng/mL), troponin 32 ng/L (reference values <34 ng/L). A computed tomography angiography (CTA) confirmed PE affecting the main branches of the pulmonary arteries and the lobar and segmental branches of the lower lobes (Figure 2).

Once hospitalized in sub-intensive care unit a bedside ultrasound study was immediately performed, showing a negative compression ultrasonography, a left lung focal interstitial syndrome and a right cardiac dilation with tricuspid annular plane systolic excursion

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(TAPSE) of 12 mm (reference values >16 mm), left ventricular D-shape with 55% ejection fraction (reference values 50-70%), and a systolic pulmonary artery pressure (sPAP) of 80 mmHg (reference values 18-25 mmHg).

Prognostic risk stratification resulted in an intermediate low class risk (sPESI 0 with the presence of right ventricular dysfunction) and anticoagulant therapy with weight-adjusted low molecular weight heparin (LMWH) was administered (enoxaparin 8000

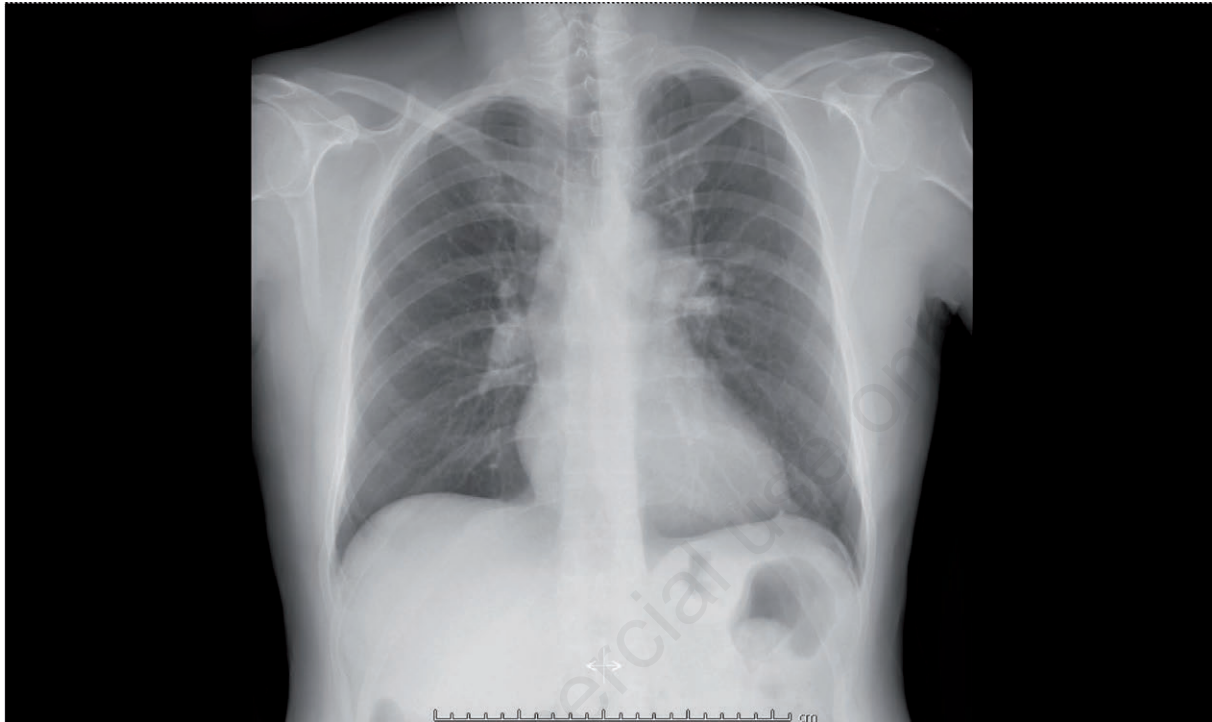


Figure 1. Chest radiography: dilation of pulmonary artery, right heart dilation.

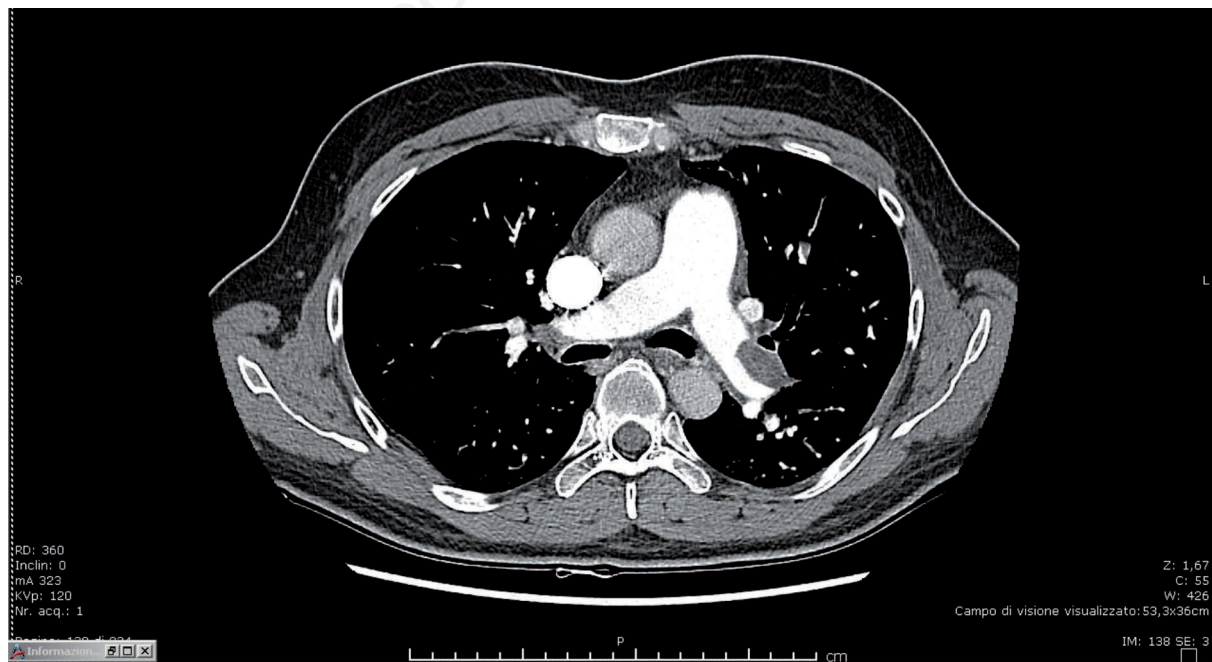


Figure 2. Computed tomographic scan: thrombus inside left main pulmonary artery.

IU twice daily for a 75 kg weight patient). During the hospital stay, possible causes of PE were researched: total body CT scan, tumor markers and thrombophilia screening resulted all negative.

We discharged the patient with no symptoms, indication to continue anticoagulant therapy with LMWH, and with a diagnostic-therapeutic program for pulmonary hypertension: right heart catheterization (RCH) and pulmonary angiography as suggested by the cardiology specialist.

The RCH was executed few days after discharge, showing a mean pulmonary arterial pressure (mPAP) of 47 mmHg (reference values 12-16 mmHg) and a pulmonary capillary wedge pressure (PCWP) of 9 mmHg (reference values 6-12 mmHg), meaning a severe pre-capillary PH and a severe reduction of cardiac performance. A pulmonary angiography was executed as well, revealing a thromboembolic involvement of all pulmonary principal arterial branches: cardiology specialist suspended LMWH and administered dabigatran 150 mg twice daily and macitentan 10 mg daily.

Given the insufficient response to the pharmacological therapy, the patient was rehospitalized in a specialized center (Policlinico Sant'Orsola-Malpighi of Bologna) for new evaluation with trans-thoracic

echocardiography, lung function tests, RHC, pulmonary angiography and coronary angiography: all these tests showed an impaired cardiac index (NYHA III class) and for these reasons sildenafil was added to the existing therapy.

After 2 months of correctly administered therapy symptoms persisted: this led to the definitive diagnosis of CTEPH. The patient was treated with PEA (Figure 3) during extracorporeal circulation, deep hypothermia and selective cerebral anterior perfusion. Subsequent ultrasound study showed a major reduction of right ventricular pressure and of indirect signs of PH (sPAP of 25 mmHg), an improvement of right ventricular function (TAPSE 16 mm). The patient was finally discharged with indication of anticoagulant therapy with Warfarin adjusted to international normalized ratio (INR) range of 2-3 indefinitely.

Discussion

CTEPH is a complication of PE: it may develop as a consequence of misdiagnosed and untreated PE, but also after a correctly treated PE.¹ Overall incidence is unknown since many bias interfere with a correct statistical calculation (*e.g.* misdiagnosed and asympto-



Figure 3. Surgical finding.

matic CTEPH); an estimate shows 1 to 5% of surviving PE patients with average age of 63 and no sex differences in prevalence.²

Etiology is unclear, but many risk factors have been identified in the genesis of CTEPH: history of PE or DVT, ventriculoatrial shunt, implantable cardioverter defibrillator or pacemaker infection, splenectomized patient, coagulation pathologies (e.g. high blood levels of factor VIII or antiphospholipid antibody syndrome), non-O blood type, hormone-treated hypothyroidism, malignancy, myeloproliferative disease, chronic osteomyelitis, and benign prostatic hyperplasia.

Patients with CTEPH can present various pathologic findings leading to the diagnosis: arterial thrombosis of the main pulmonary artery, ultrasound signs of PH (e.g. right ventricular dysfunction), CT angiography showing signs of chronic thromboembolism.

CTEPH usually results from a fibrotic evolution of thrombus inside pulmonary artery with a mechanical obstruction causing an incremental blood flow in the remaining healthy arterial vessels, this leads to a microvascular remodeling and progressive increase of pulmonary vascular resistance.

Clinical presentation includes worsening dyspnea and asthenia, until the severe PH and right ventricular dysfunction bring more severe symptoms: chest pain, syncope, abdominal pain (caused by hepatic congestion).

Imaging is not defining for the diagnosis: plain chest radiography can show dilation of pulmonary artery and, with the increase of PH, right heart dilation, CT scan results can be suggestive of PH showing a main pulmonary artery/ascending aorta ratio >1 .³

Average timing for diagnosis is about 2 year after CTEPH insurgence. In the presence of clinical suspicion, the first imaging test should be pulmonary scintigraphy that is more sensible compared to CT angiography, followed by RHC and a pulmonary angiography. Diagnostic criteria are the coexistence of PH with RHC showing $mPAP \geq 25$ mmHg and $PCWP \leq 15$ mmHg and of pulmonary arterial thromboembolic occlusion (established or alleged cause of PH).⁴

Primary differential diagnosis is with post-PE syndrome, a frequent occurrence in patient with treated PE, characterized by persistence of PE symptoms and limitations that cannot be explained by organic anomalies.⁵ Other possible differential diagnoses are cardiologic, pulmonary and hematologic causes of chronic dyspnea.

Surgery is the only definitive therapy: Pulmonary Endarterectomy (PEA) can be executed after considering the surgical accessibility of the thrombi, the presence of hemodynamic and/or ventilator impairment and the impact of patients comorbidities on the risk assessment for surgery.⁶ Balloon Pulmonary An-

gioplasty (BPA) represents another therapeutic option, while the only medical treatment approved is riociguat (stimulator of soluble guanylate cyclase); both BPA and riociguat are intended for patients with inoperable CTEPH or with persisting PH after PEA.

3-year survival after PEA is about 89% while it decreases to 70% in patients with inoperable CTEPH.⁷

Lifelong anticoagulant therapy with VKAs is recommended in all patients, there are no literature data about DOACs efficiency. Diagnostic and treatment procedures should be an exclusive of expert centers.

Conclusions

CTEPH is often a misdiagnosed complication of PE. It has good prognosis if managed by specialized centers and if surgically attackable, while the 3-year survival ratio drops if the patient cannot undergo surgery. Clinical suspicion should arouse when treating a patient with dyspnea and history of PE or with signs of PH not diagnosed before.

Given the low overall incidence among the general population and the severity of CTEPH, it is recommended to leave the management to specialized and expert centers.

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