CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION AS A CAUSE OF DYSPNEA IN A 78-YEAR OLD MAN WITH HISTORY OF DEEP VENOUS THROMBOSIS AND PERMANENT ATRIAL FIBRILLATION – A CASE REPORT AND REVIEW OF LITERATURE

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Abstract: *Chronic thromboembolic pulmonary hypertension (CTEPH) results from inadequate recanalization of the pulmonary arteries as a consequence of their occlusion by thromboembolic material; it represents a cause of severe pulmonary hypertension, being associated with significant morbidity and mortality. CTEPH 2-year incidence is 0.1–9.1% after an acute pulmonary embolism. Complete diagnostic work-up in patients with CTEPH is important for an optimal management. Transthoracic echocardiography, multidetector CT pulmonary angiography and digital subtraction pulmonary angiography are useful tools for the diagnosis and follow-up of CTEPH. We present a case of a 78 y.o. man with dyspnoea, previous diagnostic of COPD and right heart failure, permanent atrial fibrillation and bilateral deep venous thrombosis in which a well-oriented work-up identified CTEPH as the cause of dyspnoea. Pulmonary endarterectomy is the treatment of choice for CTEPH when thrombi are surgically accessible. In inoperable cases, optimal medical treatment and interventional treatment are considered.*

INTRODUCTION

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC).(1)

Chronic thromboembolic pulmonary hypertension is a pre-capillary pulmonary hypertension, characterized by a mean pulmonary arterial pressure ≥25 mmHg and pulmonary arterial wedge pressure≤15 mmHg in patients with multiple chronic organized occlusive thrombi or emboli in the pulmonary arteries. These hemodynamic data are obtained after at least 3 months of effective anticoagulation after an acute or so-called "subacute" pulmonary embolism.(2) It is included in Group 4 "CTEPH and other pulmonary artery (PA) obstructions" in recent guidelines.(2)

Independent risk factors, such as splenectomy, acute pulmonary embolism, chronic inflammatory states, ventriculo-atrial shunt and intravenous catheters are associated with CTEPH. Increased levels of factor VIII and antiphospholipid antibody syndrome are associated with CTEPH. In situ thrombosis may contribute to disease progression. Additional risk factors have been evaluated in patients with CTEPH including blood groups, lipoprotein (a), diabetes mellitus, myeloproliferative disorders, but these have not been validated in larger series.(3,4,5)

The incidence and prevalence of CTEPH may be significantly underestimated. Lang et al. reported a cumulative incidence of this distinct disease of 0.1–9.1% within the first 2 years after asymptomatic PE event.(6) CTEPH may occur in 5 individuals per million population per year.(7)

Other diseases, such as pulmonary artery sarcoma, tumour cell embolism, parasites (hydatic cyst), foreign body embolism and congenital or acquired pulmonary artery stenosis must be considered in the differential diagnosis of CTEPH.

Prognosis of patients with CTEPH depends on severity of pulmonary hypertension (PH). Patients with a mean pulmonary artery pressure >30 mmHg have a survival rate at 5 years of about 30% and a mPAP ≥50 mmHg is associated with only a 10% survival rate at 5 years.(8)

The treatment of choice for symptomatic patients with CTEPH is pulmonary endarterectomy (PEA).(2,9,10)

Successful PEA usually leads to substantial relief of symptoms and near normalization of right ventricular function.(10,11,12,13) Patients not suitable for PEA or have persistent or recurrent PH after PEA have a poor prognosis. (2) For such type of patients, medical therapy is an important option.(14)

The BENEFIT trial demonstrated that Bosentan (an endothelin receptor antagonist) has a positive therapeutic effect on hemodynamics in CTEPH patients, but no improvement was observed in exercise capacity.(5) Riociguat is the only approved medical therapy for inoperable CTEPH or persistent/recurrent PH after PEA.(2,16)

We present the case of a 78-year-old man who presented with a 5-year history of progressive exertional dyspnea and prior episodes of deep venous thrombosis, who was subsequently diagnosed with CTEPH. A review of the approach to diagnosing and treating this entity is also provided.

CASE REPORT

A 78 year-old Caucasian male presented in 2010, and then admitted again in 2011, at a community hospital, with signs of deep venous thrombosis, for which he was admitted and treated consecutively. From his previous medical records, a history of smoking in the past, cardiac, venous disease and

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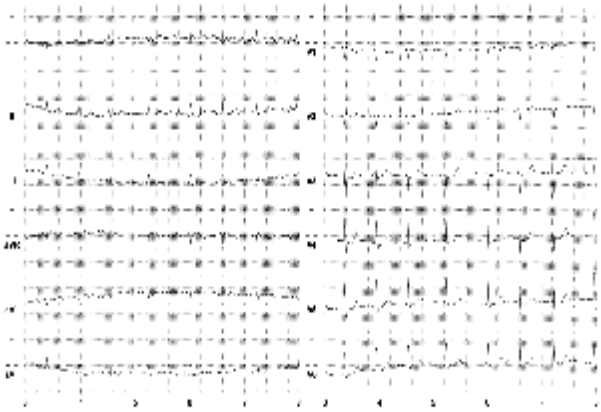
diabetes mellitus were noticed. The patient was diagnosed with chronic obstructive pulmonary disease, congestive heart failure, arterial hypertension, atrial fibrillation, post-thrombotic syndrome and discharged. Medical treatment was started with acenocumarol, carvedilol, furosemide, spironolactone, oxygen and long-acting teophylline, but later anticoagulation was stopped for unclear reasons. In March 2015, he presented to a specialized cardiac and pulmonology university hospital with symptoms of progressive exertional dyspnea, fatigue, easy tiring, heart failure NYHA functional class III.

On admission, the patient was in WHO-FC 3 with resting dyspnea, cyanotic lips and extremities, reddish skin discoloration and moderate edema of the lower limbs. Jugular venous distension and hepatomegaly were also present. Pulmonary physical examination revealed emphysema, bilateral basal rales; on cardiac exam, an accentuated and split second heart sound in the pulmonic area and a systolic tricuspid valve regurgitation murmur were audible. A 100 bpm heart rate and a 68 bpm peripheral pulse were noticed.

Blood tests revealed elevated blood sugar (7.68 mmol/l), a total bilirubin of 1.7 mg/dl and brain natriuretic peptide level at 210 ng/l. Erythrocyte sedimentation rate was 20 mm at 1 hour. Coagulation studies revealed an INR in therapeutic ranges (2.7-3.1). Lupus anticoagulant, antiphospholipid antibodies, antithrombin III, protein S, protein C levels, C-reactive protein, other biochemical values and urinalysis were within normal ranges. Scanning for active cancer, familiar venous thromboembolism was negative.

Rest EKG revealed atrial fibrillation with a 100 bpm heart rate, but no signs of right atrial or ventricular hypertrophy (figure no. 1).

Figure no. 1. Rest EKG recording: atrial fibrillation, heart rate approx. 100 bpm, intermediate axis, no signs of right heart overload



A plain chest X-ray showed a mildly enlarged cardiac contour, mild enlargement of the pulmonary arteries, an inhomogeneous opacity, poorly defined in the basal left inferior lobe and obliteration of the left pleural sinus with a small effusion. A similar inhomogeneous opacity was also described in right pulmonary base.

A transthoracic echocardiography was performed. Right ventricle was enlarged (diastolic diameter 37 mm); enlarged right atrium (22 cm^2), moderate/severe tricuspid regurgitation (grade III/IV), mild pulmonary regurgitation (grade II) and severe pulmonary hypertension (grade III, systolic gradient RV-RA: 50 mmHg, systolic pulmonary artery pressure approx. 62 mmHg) were noticed. Dimensions and systolic function of left ventricle were in normal ranges (LVDD: 50 mm, EF: 50%) (figures no. 2,3).

Figure no. 2. Transthoracic echocardiography in patient with CTEPH – modified 4 chambers view TR: tricuspid regurgitation, RV: right ventricle, RA: right atrium, LV: left ventricle, LA: left atrium

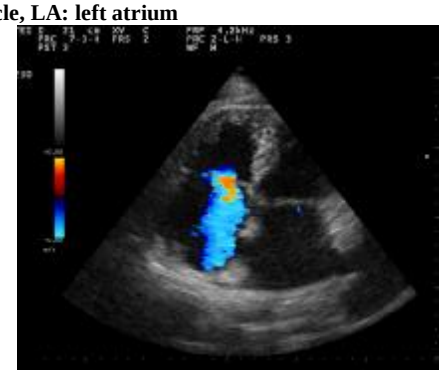
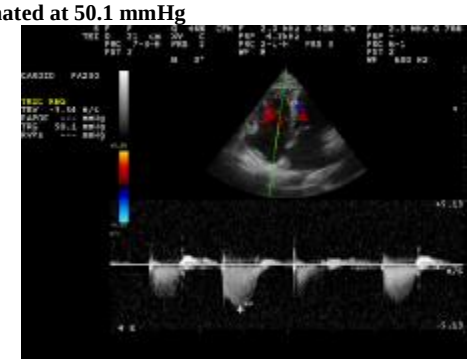


Figure no. 3. Tricuspid regurgitation determined by continuous wave Doppler exam. Peak tricuspid valvular regurgitation velocity was 3.54 m/s and peak pressure was estimated at 50.1 mmHg



No suggestive data for congenital or valvular heart diseases were observed.

Doppler venous examination of lower limb veins showed signs of bilateral post-thrombotic syndrome in the common, superficial and popliteal veins.

6 minute walking distance test (6MWD) confirmed reduced exercise capacity, with a 390 m distance walked; during the test, a significant increase in heart rate was observed (HR before test – 100 bpm and after – 135 bpm).

A CT pulmonary angiography was scheduled and revealed chronic pulmonary thromboembolism in segmental branches of right and left inferior pulmonary arteries, areas of previous pulmonary infarctions. Ventilation/perfusion (V/Q) lung scan was not available.

A right heart catheterization was performed and confirmed the diagnosis of pulmonary arterial hypertension (table no. 1), immediately followed by a coronary angiogram. No significant angiographic signs of coronary artery disease were observed during coronary angiography,

Table no. 1. Hemodynamic data obtained from right heart catheterization

Parameter - units	Value
Mean pulmonary artery pressure (mPAP) - mmHg	31 (57/6)
Pulmonary capillary wedge pressure (PWP) - mmHg	11
Pulmonary vascular resistance (PVR) - HRU (HRUI)	6.48(12.58)
Cardiac index - l/min^2	2.46

Based on the patient's medical history, physical examination findings and the results of imagistic studies the patient was diagnosed with CTEPH. Because pulmonary endarterectomy and interventional procedures (pulmonary

balloon angioplasty – PBA) were completely refused by the patient, a conventional therapy (oral anticoagulation, loop diuretics and aldosterone antagonists, selective beta blockers, oxygen supplementation) was started. Acenocumarol dose was adjusted to maintain INR in a range of 2.5–3. To decrease the pulmonary vascular resistance, treatment with bosentan was initiated with a dose of 62.5 b.i.d. Riociguat was not available at that time. The patient was advised to wear compression stockings. Another clinical follow-up visit was scheduled 4 weeks after hospital discharge for complete non-invasive medical evaluation (including 6MWD, cardiac ultrasound) in order to adjust the therapy (switching to Riociguat).

DISCUSSIONS

CTEPH is a cause of severe pulmonary hypertension. It results from the non-resolution of venous thromboembolism being characterised by the presence of obstructive fibrotic thromboembolic material in the major pulmonary vessels, with concomitant microvascular arteriopathy.(17) Undiagnosed or untreated, it leads to progressive right heart failure and death. Recent data suggest that approximately 0.1 to 9.1% of acute pulmonary embolic events patients would develop CTEPH, but this condition may be underestimated.(2,18,19,20)

Chronic thromboembolic pulmonary hypertension is diagnosed if pulmonary hypertension persists after 3 months of efficient anticoagulation in patients with a previous episode of acute pulmonary embolism.(2,10,21)

The diagnostic criteria determined by right heart catheterization are a mean pulmonary artery pressure ≥25 mmHg, with pulmonary wedge pressure ≤15 mmHg, pulmonary vascular resistance ≥2WU obtained in right heart catheterization and the presence perfusion defects on V/Q scan; or specific signs on multidetector CT pulmonary angiography scan and/or invasive pulmonary angiography.(2) The other causes of PH should be excluded. Our patient met these criteria of CTEPH.

Diagnosis of PH is important to identify the etiology, in order to ensure a correct inclusion in classification and an optimal management. In cases admitted to the hospital with dyspnea and suspicion of pulmonary hypertension, CTEPH must be considered as a differential diagnosis.

In our patient, dyspnea was previous categorized secondary to a history of smoking and heart failure (patient with arterial hypertension, atrial fibrillation). But as we presented, dyspnea was a nonspecific sign, therefore a correct diagnosis of dyspnea requires a full diagnostic work-up.

An algorithm of successive noninvasive and invasive diagnostic techniques is fundamental to confirm the diagnosis, to define the etiology and degree of pulmonary hypertension, and to establish operability of CTEPH.(22)

Echocardiography is a useful noninvasive tool in these situations; at baseline and in regular check-ups of the patient, it estimates pulmonary artery pressure, tricuspid regurgitation, atrial and ventricular dimensions and function. Fisher et al. reported a poor correlation between estimated pulmonary artery pressure by transthoracic echocardiography and that measured directly by right heart catheterization.(23)

Planar ventilation/perfusion (V/Q) lung scan is the main imaging modality in order to differentiate CTEPH from other causes of pulmonary hypertension; it carries a 96-97% sensitivity and a 90-95% specificity for the diagnosis.(2,24)

Multidetector CT pulmonary angiography is widely used for diagnosis of CTEPH. It can identify eccentric thromboembolic material especially in the main and lobar pulmonary arteries and represents an accurate and reliable non-invasive imagistic technique compared to conventional digital subtraction angiography in the diagnostic algorithm.(25)

Direct assessment of pulmonary hemodynamics using right heart catheterization is an essential diagnostic tool. Long-term predictors of prognosis are pulmonary vascular resistances values preoperative and in immediate postoperative status.(26)

Selective pulmonary angiography remains the gold standard; using the anterior–posterior and lateral projections it establishes the diagnosis and assesses the operability.(27)

Patients with CTEPH should be evaluated in referral centers. About 50% of cases are considered to be inoperable.

Optimal medical therapy consists of long life anticoagulation and diuretics, but anticoagulation alone is associated with long term high morbidity and mortality.(2) In hypoxemic patients or with heart failure oxygen administration should be considered.

Bosentan (an endothelin receptor antagonist) demonstrated a positive effect in hemodynamics without improvement of exercise capacity.(15) In CTEPH inoperable patients bosentan significantly improves symptoms, pulmonary vascular resistance, plasma BNP concentration, and time to clinical worsening.(28)

In well-defined groups of CTEPH patients (distal disease, contraindications to PEA, a persistent or recurrent pulmonary hypertension after PEA), specific PAH therapy with Riociguat (oral soluble guanylate cyclase stimulator) is recommended by actual guidelines.(2)

The primary therapy form of CTEPH in patients with proximal pulmonary lesions is pulmonary thromboendarterectomy. A successful PEA leads to functional improvement and decrease signs of right ventricular dysfunction; long term survival of CTEPH patients after PEA is better compared to medical treatment.

In patients with inoperable CTEPH, a refined balloon pulmonary angioplasty can be considered as a therapeutic approach, with a low mortality rate.(29)

CONCLUSIONS

The differential diagnosis of dyspnea in patients with post-thrombotic syndrome must be done carefully. When a CTEPH is suspected, a complete work-up algorithm must be performed. Evaluation of patients must be made by an experienced team. When patients are considered surgically inaccessible for pulmonary thromboendarterectomy, they should be medically treated and/or considered for refined balloon pulmonary angioplasty.

Conflicts of interests:

Mr. Ioan Țilea has received honoraria for speaking from Pfizer, Bayer Schering. All other authors declare that they have no conflict of interest that could interfere with this case report.

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