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CASE REPORT

An Uncommon Severe Case of Pulmonary Hypertension - From Genetic Testing to Benefits of Home Anticoagulation Monitoring

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A 62 year-old caucasian male was admitted in our pulmonary hypertension expert center with initial diagnosis of pulmonary veno-occlusive disease for validation and specific treatment approach. Routine examinations revealed no apparent cause of pulmonary hypertension. Patient was referred for a thorax contrast enhanced multi-slice computed tomography which revealed extensive bilateral thrombi in pulmonary lower lobe arteries, pleading for chronic post embolic lesions. A right heart catheterization and pulmonary angiography confirmed the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH). Following the local regulations, the patient underwent thrombophilia screening including molecular genetic testing, with positive findings for heterozygous for VCORK1 -1639G>A gene single nucleotide polymorphism, PAI-1 4G/5G and factor II G20210A gene. With heterozygous genetic profile of 3 mutations he has a genetic predisposition for developing a thrombophilic disease which could be involved in the etiology of CTEPH. Familial screening was extended to descendants; the unique son was tested with positive results for the same three genes. Supportive pulmonary hypertension drug therapy was initiated together with patient self-monitoring management of oral anticoagulation therapy. For optimal control of targeted anticoagulation due to a very high risk of thrombotic state the patient used a point-of-care device (CoaguChek®XS System, Roche Diagnostics) for coagulation self-monitoring.

Keywords: CTEPH, thrombophilia, gene polymorphism, heredity, anticoagulation self-monitoring management

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Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct group (CTEPH and other pulmonary artery obstructions – WHO Group 4) among entities included in the large etiology of pulmonary hypertension, as they are defined in recent guidelines [1].

The diagnosis of CTEPH can be established after at least 3 months of anticoagulation therapy in patients with a mean pulmonary arterial pressure ≥25 mmHg and pulmonary arterial wedge pressure≤15 mmHg associated with at least one segmental perfusion defect in V/Q lung scan and chronic organized occlusive thrombi in the pulmonary arteries revealed on CT pulmonary angiography [1].

Multiple conditions are associated with CTEPH: splenectomy, ventriculoatrial shunt, infected pace-maker, chronic inflammatory bowel disease, myeloproliferative disorders, antiphospholipid antibody syndrome, increased levels of factor VIII, malignancy, chronic venous ulcers, thyroid hormone replacement, non-O blood group [2,3,4,5].

Prevalence and incidence CTEPH in real-life are unknown, it may occur in 5 individuals per million population per year [6] or up to 9.1% within the first 2 years after an acute episode of pulmonary embolism [7].

In well-selected cases pulmonary endarterectomy (PEA) is the treatment of choice, reducing pulmonary pressure and improving right ventricular function by removing chronic intravascular scar [1,8,9,10].

In patients with no indication for surgery or with persistent/recurrent pulmonary hypertension after PEA, medical therapy [1,11] or interventional procedures (percutaneous balloon angioplasty - PBA) are beneficial [12].

We describe a 62 year-old man heterozygous for VKORC1 G-1639A, PAI-1 4G/5G and factor II G20210A single nucleotide gene polymorphisms, and bilateral CTEPH after a unique thoracic pain episode with no hint for a thrombotic event. This case illustrates the importance of an extensive diagnosis in a PH/CTEPH expert centre and the severe clinical outcomes of the undiagnosed thrombophilic defects.

Case report

A white male aged 62, former smoker, was admitted in a county hospital in December 2014 with symptoms of coronary artery disease with a right bundle branch-block (RBB) on 12-leads rest ECG with no suggestive laboratory findings for an acute coronary syndrome; no other medical history of risk factors for cardiovascular disease were noticed. Due to concomitant symptoms and presence of RBB patient underwent TTE and native CT pulmonary angiography with results suggestive for pulmonary hyper-

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tension. Coronary angiogram was negative for atherosclerotic CAD.

Patient discharged diagnosis was severe pulmonary veno-occlusive disease (POVD group 1' WHO), congestive heart failure NYHA functional class III, chronic kidney disease stage II. Medical treatment was started. On discharge no oral anticoagulation regimen was started, at that moment there was no specific recommendation for anticoagulation therapy in PVOD patients following 2009 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.

Due to persistence of resting dyspnoea and signs of right heart failure, in March 2016 the patient was admitted to PH/CTEPH expert centre for reassessment and specific supportive therapy.

Blood tests revealed a total bilirubin of 3.3 mg/dl, GGT: 91 u/l, eGFR: 41 ml/min/1.73 m^2 (MDRD formula) and O (zero) blood type, positive Rh group.

Specific blood tests and imagistic studies for associated medical conditions of PH were negative for congenital and/or left heart disease, deep venous thrombosis, thyroid disorders, lung disease and/or hypoxia, malignancy, portal hypertension, connective tissue disease, antiphospholipid antibody syndrome, inflammatory bowel disease, HIV, drugs, toxins and radiation induced PVOD.

Rest ECG showed sinus rhythm with a 75 bpm heart rate and right bundle branch block associated with left posterior fascicular block (figure 1).

Transthoracic echocardiography pointed out enlarged right heart cavities, moderate/severe tricuspid regurgitation, mild pulmonary regurgitation and enlargement of pulmonary artery (figure 2, 3).

Contrast enhanced computed pulmonary tomography revealed dilated main pulmonary artery branches (left 26 mm, right 27 mm) and extensive adherent pulmonary thrombi in bilateral inferior lobar pulmonary arteries, suggestive for chronic post embolic lesions.

Ventilation/perfusion (V/Q) lung scan was not available.

Echocardiographic and right heart catheterization characteristics are summarized in Table I

The 6MWD test confirmed reduced exercise capacity, with 77% of predicted distance, decrease in peripheral O_2 saturation from 92% to 87% at the end of test with Borg scale dyspnoea 2.

A final diagnosis of CTEPH was established by CT pulmonary angiogram, right heart catheterization and pulmonary angiography. At this point POVD was infirmed.

Due to no potential causes suggestive for CTEPH, a thrombophilic status related to a gene mutation or to gene polymorphism was suspected.

Fresh whole blood samples collected on EDTA were used for isolation of genomic DNA. Genotyping of the investigated polymorphisms was performed by using the Polymerase Chain Reaction - Restriction Fragment Length Polymorphism (PCR-RFLP) method.

Absence of gene mutation for factor V G1691A (Leiden), factor V H1299R (R2), factor XIII V34L has been determined. Extended genetic tests were performed for the patient and his unique direct male descendant. Both cases were heterozygous for the VKORC1 G1639A gene single nucleotide polymorphism, PAI-1 4G/5G, factor II G20210A gene and the clinical final judgement was that a genetic predisposition for developing a thrombophilic disease can be considered.

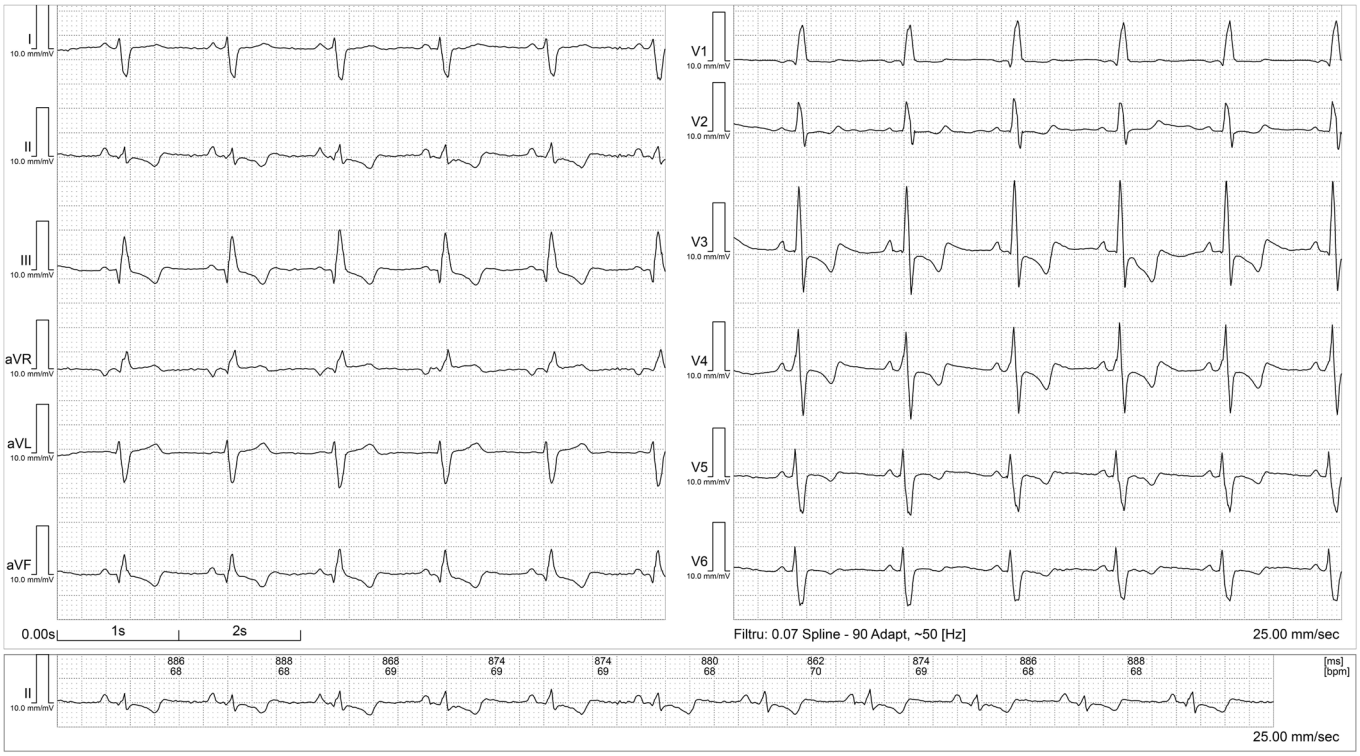


Fig. 1. Rest EKG –Sinus rhythm, right bundle branch block and left posterior fascicular block (RBBB+LPFB)

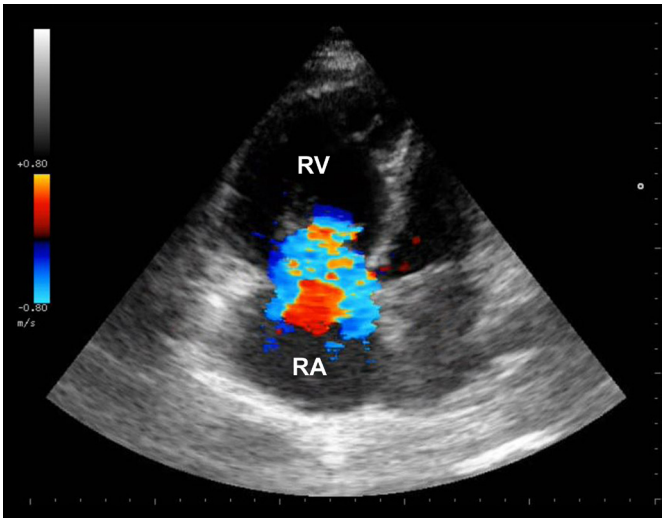
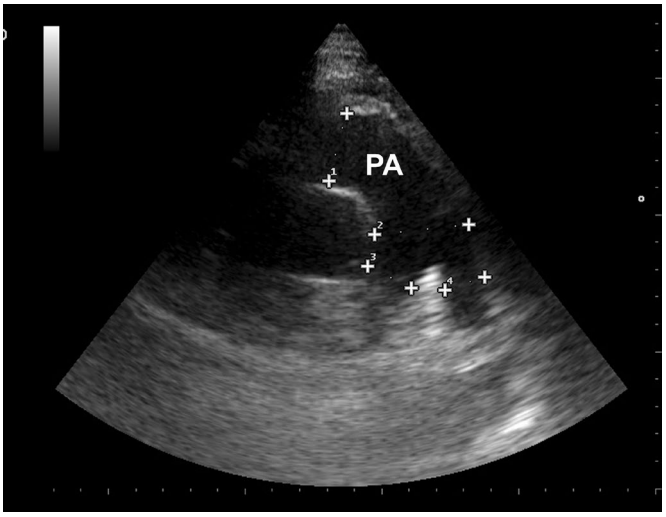


Fig. 2. Transthoracic examination. Moderate/severe tricuspid regurgitation, enlarged right ventricle (RV: 54.8 mm) and right atrium (RA: 57.2 mm)



Fig, 3. Transthoracic examination. Enlarged main pulmonary artery and it's branches.

Surgical procedure (PEA) was refused by the patient, so a conventional therapy (oral anticoagulation, loop diuretics and aldosterone antagonists, oxygen supplementation) was started. Using a point-of-care device (CoaguCheck® Roche Diagnostics, USA) the anticoagulation regimen with Acenocumarol was regularly adjusted to maintain the INR in therapeutic range. Specific therapy to decrease the pulmonary vascular resistance with endothelin receptor antagonist - Bosentan was initiated with a dose of 125 mg b.i.d. Guanylate cyclase stimulator (Riociguat – class I level of evidence B, ESC 2015 guidelines indication) was not available at that time. Subsequent clinical follow-up visit was scheduled 4 weeks after hospital discharge for complete non-invasive medical evaluation in order to assess clinical and haemodynamic status and to adjust the therapy.

Table 1. Echocardiographic and right heart catheterization data

Echocardiography	
LVEDD (mm)	45
IVS diastole (mm)	9
LAD (mm)	35
RVD (mm)	46
RA (mm)	57
LVEF (%)	55
TAPSE (mm)	29
LV diastolic function	Abnormal relaxation
RV/RA pressure gradient (mmHg)	100
IVC diameter (mm)	23, inspiratory collapse <50%
PA pressure (mmHg)	120
Main PA diameter (mm)	35
Pericardial effusion (mm)	NO
Pleural effusion	NO
Right heart catheterization	
Mean pulmonary artery pressure (mPAP) - mmHg	53 (89/36)
Pulmonary capillary wedge pressure (PWP) - mmHg	11
Pulmonary vascular resistance (PVR) - HRU (HRUI)	6.24 (12.67)
O2 saturation pulmonary artery	54%
O2 saturation aorta	86%

Discussions

Even if previously was thought that CTEPH is a rare cause of PH, in expert centers precise imaging techniques and specific laboratory testing refines the cause of diagnosed cases of CTEPH as pulmonary embolism in 0,1-9% cases [1].

In the absence of planar V/Q lung scan, modern CT pulmonary angiography can be an accurate method for the detection of CTEPH as it is suggested in recent works (96.1% sensitivity, 95.2% specificity and 95% accuracy) [12,13,14].

Although no specific genetic mutation have been linked to the development of CTEPH due to increased risk on genetic alteration, in cases with unclear etiology patients should be genetically screened for thrombophilic disorders after excluding the antiphospholipid and anticardiolipin antibody, lupus anticoagulant etiology.

The genetic predisposing factor is an important component in the mechanism of CTEPH patients. Li et al (2014) in a meta-analyse of 10 clinical case-control studies (7329 patients with cardiovascular disease and 7951 healthy controls) demonstrated that VKORC1 rs2359612 and rs9923231 polymorphisms correlate with high risks of cardiovascular and cerebrovascular diseases [15].

A meta-analyse performed by Wang J et al (2014) which included 34 studies with 3561 cases and 5693 controls suggested that PAI-1 4G/5G polymorphism is a risk factor venous thromboembolism [16].

Treatment algorithm of CTEPH brings to the forefront the recommendation of life long anticoagulation for all patients. (class IC recommendation) [1].

Beyond specific therapy with sGC stimulators in patients with CTEPH, anticoagulation and INR maintaining in therapeutic range plays a pivotal role for long term management and preventing recurrent thrombotic events in cases linked to thrombophilic disorders [17].

Conclusions

In CTEPH cases without clear etiology of the thrombotic event, a hypercoagulable state must be suspected. Extensive genetic testing should be conducted.

Descendants screening for heterozygous state susceptible for thrombotic events helps at-risk individuals for correct evaluation performed in a timely manner.

The clinician can offer a patient – centered approach to self-manage of their disease for INR monitoring that is associated with health and quality of life benefits.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

6MWD	6 minutes walking distance
CI	Cardiac index
CO	Cardiac output
CT	Computed tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
IVC	Inferior vena cava
LA	Left atrium
LPFB	Left posterior fascicular block
LV	Left ventricle
LVEDD	Left ventricle end-diastolic diameter
LVPW	Left ventricle posterior wall
PAI-1	Plasminogen activator inhibitor-1
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RA	Right atrium
RV	Right ventricle
TAPSE	Tricuspid annular plane systolic excursion
VKORC-1	Vitamin K epOxide Reductase Complex subunit
V/Q scan	Ventilation/Perfusion Scan
PEA	Pulmonary endarterectomy
PBA	Percutaneous balloon angioplasty
RBBB	Right bundle branch block
EKG	Electrocardiogram
TTE	Trans thoracic echocardiography
CT	Computed tomography
CAD	Coronary artery disease
POVD	Pulmonary veno-occlusive disease
WHO	World Health Organisation
NYHA	New York Heart Association
PH	Pulmonary hypertension
MDRD	Modification of Diet in Renal Disease
EDTA	Ethylenediaminetetraacetic acid
DNA	Deoxyribonucleic acid
PCR-RFLP	Polymerase Chain Reaction - Restriction Fragment Length Polymorphism

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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