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CASE REPORT

BEGINNER

CLINICAL CASE

Chronic Thromboembolic Pulmonary Hypertension Secondary to Thrombophilia and Incidentally Diagnosed Atrial Septal Defect

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ABSTRACT

A 46-year-old man developed chronic thromboembolic pulmonary hypertension and atrial fibrillation after acute pulmonary embolism. He was found incidentally to have an isolated secundum atrial septal defect, as well as a homozygous mutation for the plasminogen activator inhibitor-1 gene. He was successfully treated with pulmonary endarterectomy and atrial septal defect repair. He has continued to do well on a regimen of dabigatran. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:658–61) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 46-year-old, nonsmoking, previously healthy man apparently presented to the emergency department with dyspnea and pre-syncope. Examination findings at that time were as follows: blood pressure: 90/60 mm Hg, heart rate: 110 beats/min, respiratory rate: 28 breaths/min, temperature: 37°C, normal oxygen saturation as measured by pulse oximetry on room air, a grade 3 of 6 holosystolic murmur at the left lower sternal edge, and lower extremity edema. He was hospitalized and treated for acute pulmonary embolism (PE). After discharge, he had continued to have exertional dyspnea, which prompted him to come to our clinic. He denied any additional cardiac or obstructive sleep apnea syndrome symptoms. On examination, he had an irregularly irregular heart rate, a loud P_2, and a grade 3 of 6 holosystolic murmur at the left lower sternal edge. No other findings of heart failure (HF) were noted.

LEARNING OBJECTIVES

- An extensive and methodic diagnostic work-up, including RHC and multimodality imaging, is crucial for reaching a correct diagnosis of PH.
- Several groups or subtypes may contribute to the development of PH in an individual patient. Therefore, it is important to have multidisciplinary discussions for the diagnosis and management of a complex case of PH.
- This case illustrates that dabigatran may be safe and effective in thromboembolism associated with PAI-1 mutation.

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PAST MEDICAL HISTORY

He had no significant medical history of heart disease and venous thromboembolism (VTE). His family history was negative for known thrombophilia, VTE, or miscarriages.

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DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute dyspnea included acute coronary syndromes, acute exacerbation of asthma or chronic obstructive pulmonary disease, acute pneumonia or bronchitis, acute PE, pneumothorax, and HF. High-probability findings on the echocardiogram prompted investigation for pulmonary hypertension (PH).

INVESTIGATIONS

His initial computed tomography angiogram demonstrated acute PE. When he presented to our clinic after several months, his echocardiographic findings showed a high probability of PH and his transesophageal echocardiogram demonstrated an atrial septal defect (ASD) measuring 15 × 16 mm. The right-sided chambers were severely dilated: right ventricular (RV) diameter at the base was 54 mm, and RA area was 32 cm^2 (**Figure 1**, Video 1). RV systolic function was normal, with tricuspid annular excursion (TAPSE) of 1.7 cm and pulsed Doppler peak annular velocity of 12 cm/s. His pulmonary function test results and diffusing capacity of lung for carbon monoxide were normal. His ventilation-perfusion scan showed a high probability of chronic thromboembolic pulmonary hypertension (CTEPH). The abdominal ultrasound scan was normal. The duplex ultrasound scans of the lower extremities were negative. The results of serological tests for rheumatological diseases and human immunodeficiency virus infection were negative. He walked 500 m without desaturation on a 6-min hall walk. He underwent both right-sided heart catheterization (RHC) and left-sided heart catheterization, which demonstrated precapillary PH (systolic blood pressure: 120/63 to 94 mm Hg; heart rate: 95 beats/min and regular; pulmonary arterial pressure [PAP]: 50/28 to 37 mm Hg; pulmonary capillary wedge pressure: 9 mm Hg; left ventricular end-diastolic pressure: 10 mm Hg; right atrial [RA] pressure: 10 mm Hg; pulmonary vascular resistance [PVR]: 4.5 Woods units; cardiac index: 3.7 l/min/m^2, mixed venous saturation: 70%; and pulmonary-to-systemic flow ratio:1.6) and normal coronary arteries. Pulmonary angiography demonstrated bilateral lesions consistent with CTEPH. Genetic testing revealed a homozygous mutation for the plasminogen activator inhibitor (PAI)-1 (5G>4G) gene.

MANAGEMENT

He was admitted to the coronary care unit with acute PE on his first presentation. After stabilization with anticoagulant therapy, he was discharged on warfarin. When he presented to our clinic, the decision was made to perform pulmonary endarterectomy (PEA) and close his ASD after discussion with the multidisciplinary team. He underwent bilateral PEA, a patch repair for the ASD, and a maze procedure for atrial fibrillation (AF) (**Figure 2**).

DISCUSSION

The diagnosis of CTEPH after acute PE is made with RHC after an effective anticoagulation regimen for at least 3 months. PEA is the first-line treatment in eligible patients. An individual's operability is determined by an expert team (1,2). Closure of an isolated secundum ASD should be considered when a concomitant surgical procedure is being performed (3). Because our patient was in a gray area because of his elevated PVR, a fenestrated closure may have worked better than closing the ASD completely. However, there was not any concern at all perioperatively.

Thrombophilias are inherited and acquired hypercoagulable states that increase the risk of VTE (4). Causes of inherited thrombophilia include antithrombin deficiency, deficiencies of proteins C and S, and factor V Leiden mutation (5). PAI mutation is very rare (6). Arterial thrombosis associated with thrombophilias occurs even more rarely. Specific enzymes are involved in the removal of blood clots from the circulation and the turnover of extracellular matrix proteins. One of the most important enzymes in this setting is plasmin. The main role of plasmin is to degrade fibrin, which makes up the structural basis of a blood clot. Plasmin exists in its inactive form as plasminogen; the activation of plasminogen is mediated by serine enzymes known as tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). The proteolytic activity of t-PA and u-PA is, in turn, regulated by specific protease inhibitors, PAI-1 and PAI-2 (7). Mutations in

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ASD = atrial septal defect

CTEPH = chronic thromboembolic pulmonary hypertension

DOAC = direct oral anticoagulant agent

HF = heart failure

PAI = plasminogen activator inhibitor

PAP = pulmonary arterial pressure

PE = pulmonary embolism

PEA = pulmonary endarterectomy

PH = pulmonary hypertension

PVR = pulmonary vascular resistance

RA = right atrial

RHC = right-sided heart catheterization

RV = right ventricular

TAPSE = tricuspid annular excursion

t-PA = tissue-type plasminogen activator

u-PA = urokinase-type plasminogen activator

VTE = venous thromboembolism

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FIGURE 1 Severely Dilated Right-sided Heart Chambers

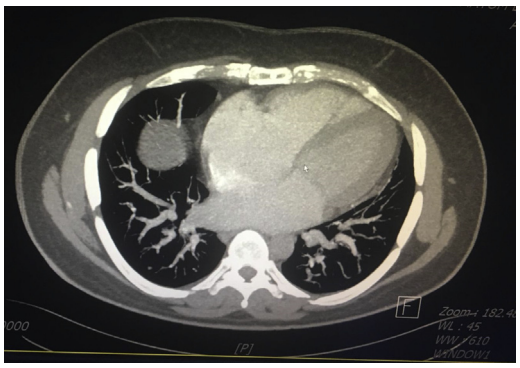
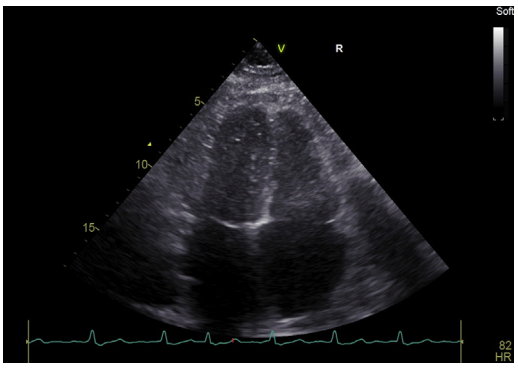
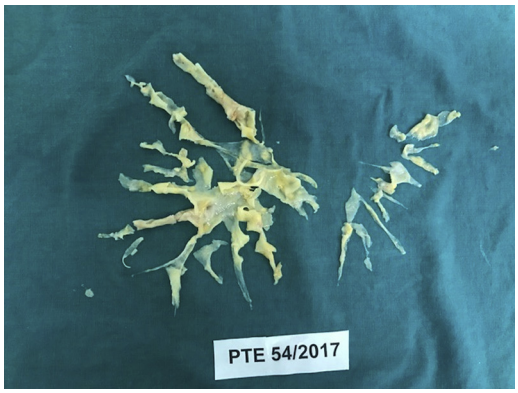


FIGURE 3 Biatrial Dilatation and Moderately Dilated Right Ventricle



the PAI-1 gene are associated with elevated plasma levels of PAI-1, with an increased risk of thrombosis. Many patients with thrombophilia receive anticoagulant therapy for primary or secondary prevention of VTE. Direct oral anticoagulant agents (DOACs) are recommended in preference to vitamin K antagonists for the acute phase treatment of PE, yet there is no specific guidance for use of these drugs in patients with inherited thrombophilia (8). Although case reports and a post hoc analysis of clinical trials have indicated positive results of DOACs in patients with inherited thrombophilia and VTE, substantial evidence supporting widespread use is lacking (5). Dabigatran has been approved for the treatment of acute deep vein thrombosis and PE, as well as for the secondary prevention of recurrent VTE. The use of DOACs in CTEPH is not well established. Little is known about the potential effects of thrombophilic factors on clinical outcomes in patients with acute VTE who are treated with dabigatran. In the RE-COVER (Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism) and RE-COVER II trials (Phase III Study Testing Efficacy and Safety of Oral Dabigatran Etexilate vs Warfarin for 6 m Treatment for Acute Symptomatic Venous Thromboembolism), 34% of patients were tested for thrombophilia, and 23% of these patients tested positive (9,10). The overall proportion of patients in the pooled analysis with known thrombophilia was 8%. In RE-MEDY (Re-medy is Secondary Prevention of Venous Thrombo Embolism [VTE]; NCT00329238), 48% of patients were tested for thrombophilia, and 38% of these patients tested positive (11). The overall proportion of patients with known thrombophilia was 18%. The overall proportion of patients with known antiphospholipid syndrome in the pooled RE-COVER and RE-COVER II and RE-MEDY analysis was 2.2%. The presence of thrombophilia did not significantly affect the efficacy or safety of dabigatran in preventing recurrent VTE. In patients with antiphospholipid antibody syndrome, it is mandatory to continue oral anticoagulant treatment with a vitamin K antagonist indefinitely.

FIGURE 2 Calcification and Organized Level IV Thromboembolic Material Removed During Surgery



PTE = pulmonary thromboendarterectomy.

FOLLOW-UP

He was discharged on anticoagulant and antiarrhythmic therapies after an uneventful postoperative course. He was switched from warfarin to dabigatran for labile international normalized ratios, and antiarrhythmic agents were discontinued for AF recurrences during follow-up. A repeat RHC demonstrated complete normalization of PAP and PVR

10 months after the surgery. He has continued to do well on a dabigatran regimen for the last 2 years. His echocardiogram at 2-year follow-up demonstrated interval improvement in RV size (41 mm at the base), RA area (18 cm^2), and RV systolic function (TAPSE: 2.4 cm) (**Figure 3**, Video 2).

CONCLUSIONS

We reported the case of a man with thrombophilia who presented with CTEPH, AF, and the incidental finding of an isolated secundum ASD. He underwent a successful PEA and a patch repair for his ASD, and he had an uneventful 2-year follow-up on dabigatran. Dabigatran could be a safe and an effective alternative to warfarin in CTEPH associated with PAI-1 homozygous mutation.

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KEY WORDS dabigatran, plasminogen activator inhibitor-1 (PAI-1) mutation, pulmonary endarterectomy

APPENDIX For supplemental videos, please see the online version of this paper.