Journal of Clinical Case Reports

Case Report Open Access

A Case Report to Estimate Approximately 5 to 8% of the PE Patients has Inherited Thrombophilia's I

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Abstract

A 42-year-old, previously healthy woman, admitted to our emergency department with first episode of severe dyspnea and chest pain, hemodynamically stable. She has no history of previous cardiovascular or respiratory disease, no history of PE or DVT. She had elevated D-dimers. Urgent echocardiography showed indirect signs of PE, which was confirmed by pulmonary artery CT angiography, which showed massive PE. After two days of heparin infusion she developed hemodynamic instability with cardiogenic shock, treated successfully with fibrinolysis. The thrombophilia profile was done two weeks after stopping therapy with rivaroxaban after six months. Thrombophilia panel came back positive for high levels of homocysteine (67 μmol/L), with other thrombophilia results within normal limits. Pulmonary embolism should be always suspected in younger patients with acute severe dyspnea event without provocable risk factors. High suspicion level and fast diagnosis are lifesaving. In younger patients presenting with unprovoked pulmonary emboli, clinicians should consider inherited prothrombotic factors and homocystinemia as a potential cause. Longer anticoagulation therapy should be considered in these cases with novel oral anticoagulants as recommended safer and superior therapy.

Keywords: Fibrinolysis; Echocardiography; Rivaroxaban; Therapy

Introduction

Pulmonary Embolism (PE) is the third vascular cause of death and one of the most often missed diagnosis. 5% of PE patients present with hemodynamic instability and cardiogenic shock which is related to high intrahospital mortality [1]. An elevated level of homocysteine is a risk factor for arterial and venous thromboembolism [2]. Overweight and obesity individuals have 2-3-fold increased risk for deep vein thrombosis (DVT) and PE [3]. Studies shown potential impact of body fat distribution and the cardiometabolic abnormalities associated with central obesity with the risk of arterial and venous thrombosis [4]. Venous stasis because of obesity, may be of more importance for venous thromboembolism [4]. We present a non-smoker, overweight 42-year woman with unprovoked first episode of acute PE, and Right Ventricle (RV) disfunction complicated with cardiogenic shock, successfully treated with fibrinolysis and six-month therapy with rivaroxaban. She was diagnosed with homocysteinemia with normal vitamin B12 and folate levels.

Case Presentation

We are presenting a 42-year-old, previously healthy woman, admitted to our emergency department with first episode of severe dyspnea and chest pain. She has no history of previous cardiovascular or respiratory disease, no history of PE or DVT. Symptoms started one hour before arrival at our clinic at home, not provoked from any physical effort. She had increased body weight, with BMI 28 kg/m^2, without other CV risk factors. Physical examination showed tachycardia, tachypnea with respiratory rate 16/min, without abnormal pulmonary findings and no heart murmurs. ECG showed sinus tachycardia with HR 130 bpm, RBBB, and S1Q3T3 sign. Blood pressure was 125/90 mmHg. In order to find the causes of patient symptoms urgent echocardiography was performed, with PE as one of the suspected symptoms causes. No signs of DVT was found at the clinical examination. Wells score for PE probability was <4 (PE unlikely). Patient denied any provocable PE risk factor (no history of injury, no surgical treatment, bed rest over 72 h, no cancer history, no history of contraceptives or hormone therapy, no signs of DVT or previous PE/DVT). She also denied recent respiratory infection, or longer flights.

Admission ECG

Echocardiography was performed immediately after emergency department examination in order to evaluate the cause of patient symptoms. Examination showed increased Right Ventricle (RV) size, increased RV to LV ration >1, reduced RV function (TAPSE 15, TDI S' 8), presence of McConnell's sign, severe tricuspid regurgitation with dilated non-collapsible v. cava-21 mm, and signs of pulmonary hypertension (SPAP 54 mmHg). LV function was normal, with left ventricular ejection fraction 65%, and no wall motion abnormalities. There were no thrombus formations ween in the RV cavities or pulmonary artery (Figure 1). Due to clinical picture and echocardiography findings of RV dysfunction, severe tricuspid regurgitation and signs of pulmonary hypertension, patient was admitted to our intensive care unit for suspected PE and anticoagulation treatment was started (Figure 2).

Laboratory results

Laboratory results showed increased leucocytes level of 11 × 10^9, Hgb 145, hematocrit values 49%, platelet counts 285.000, glomerular

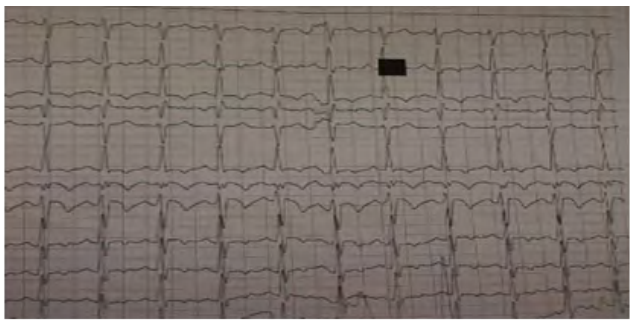

Figure 1: Admission ECG showed sinus tachycardia with 110 bpm, RBBB and S1, Q3, T3 pattern.

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Received January 23, 2020; **Accepted** February 26, 2020; **Published** March 04, 2020

Citation: Mitevska I (2020) A Case Report to Estimate Approximately 5 to 8% of the PE Patients has Inherited Thrombophilia's I. J Clin Case Rep 10: 1321

filtration rate (GFR) 98 ml/min/1.73 m^2. serum electrolytes, renal and liver function tests were within normal range. hs-Troponin I was elevated -182 ng/l. D-dimer levels were 9.835 ng/ml (positive). Hemostasis findings 4 hours after heparin infusion showed good therapy response with prolonged prothrombin time and activated partial thromboplastin time monitoring (56 sec), INR 1.8.

Pulmonary artery CT angiography

PE was confirmed by CT angiography which showed massive pulmonary embolism. The pulmonary trunk was dilated to -33 mm. There was a riding thrombus over the pulmonary trunk, extending to the right and left pulmonary artery with central filling defects. A large partial lumen occluding filling defect was noted in the left main pulmonary artery, which was extending further into the hilar branch, occluding the lumen completely. Another larger non-complete lumen occluding filling defect was noted in the right main pulmonary artery. These filling defects were extending into the segmental and sub-segmental branches of the lateral segment of the right middle and bilateral lower lobe. There was no evidence of mediastinal pathology (Figure 3). Doppler ultrasonography of low extremities showed no signs of DVT.

Clinical risk assessment

Evaluated sPESI score was 2, which indicated elevated 30-day death risk (10.9%). Base on hemodynamic profile, echocardiography findings of RV dysfunction, sPESI score >1 and elevated troponin levels patient was initially assessed as intermediate high risk for early mortality.

Treatment and complication

Due to high probability of PE base of echocardiography findings

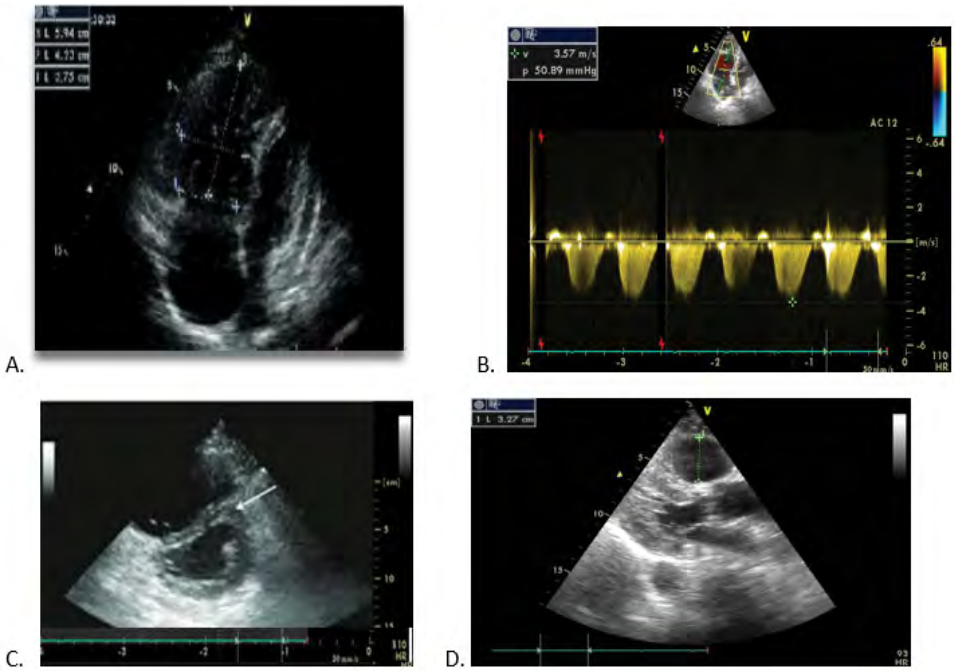

Figure 2: A: Apical 4 chamber view showing increased right heart cavities with RV:LV ratio >1; B: Color Doppler showing severe tricuspid regurgitation; C: Short axis view showing D shaped left ventricle; D. Parasternal long axis view shoving increased right ventricular outflow track dimension.

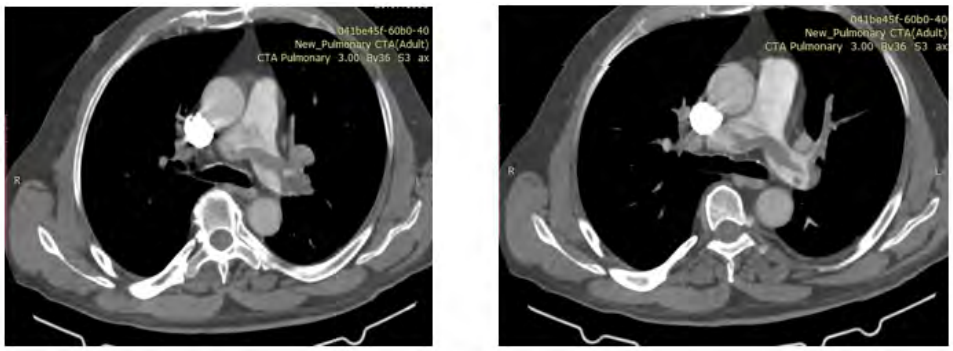

Figure 3: CT angiography of pulmonary artery showing a large partial-lumen occluding filling defect in the left main pulmonary artery, extending further into the hilar branch, occluding the lumen completely. Another larger non-complete lumen occluding filling defect was noted in the right main pulmonary artery.

intravenous heparin therapy was started (7.500 IE iv bolus, with continued infusion of 30.000 IE/24 h). The patient tolerated the treatment well, dyspnea significantly diminished, heart rate reduced to 80-90 bpm after three hours, respiratory rate 11/min, O_2 saturation 90% with oxygen mask. Two days after admission and receiving Heparin infusion patient developed again severe dyspnea, with low blood pressure (85/55 mmHg), tachycardia with HR 142 bmp, cold and wet periphery, 0_2 at room temperature 81%, Gas analyses showed respiratory acidosis with pH 7.32, increased pCO_2 53 kPa, HCO_3 25 mEq/L, lactate 2.1. Due to shock development, patient was given rescue fibrinolysis with Actilisae 100 mg in two hours. Patient hemodynamically stabilized after first hour of actilisae infusion, with BP normalization to 110/70 mmHg, HR 100 bpm, 2.89% on room air. Gas analyses normalized after 4 hours. Patient received heparin infusion for three days after fibrinolysis and continued management with rivaroxaban with recommended doses of 15 mg 2 × 1 for 21 days than 20 mg 1 × 1 for further six months due to episode of unprovoked PE. Patient was discharged after 10 days clinically stable, without dyspnea, and decreased hs-Troponin values to 45 ng/l. Control echocardiography before discharge showed normalization of RV function, reduction of tricuspid regurgitation and no PAH.

Follow up

Patient come on first control after one month. She was asymptomatic, clinically stable and physically active. She did not report side effects from rivaroxaban therapy. D-dimer values normalized (325 mg/l). Second control was performed after three months, and patient was clinically stable with no echocardiographic signs of right ventricular disfunction or pulmonary hypertension. The thrombophilia profile was done two weeks after stopping therapy with rivaroxaban after six months (factor V Leiden mutation, prothrombin gene mutation, protein C, protein S and AT III activity or deficiency, anti-beta 2 glycoprotein, anticardiolipin antibodies, and serum homocysteine levels). Thrombophilia panel came back positive for high levels of homocysteine (67 μmol/L), with other thrombophilia results within normal limits. Vitamin B12, folate, and vitamin B6 levels were normal.

Discussion

We present a case of successful treatment of intermediate high-risk PE patient complicated by cardiogenic shock. Although it was a clear case of massive PE, initially the underlying etiology was unknown, without provocable risk factors. The final discharge diagnosis of unprovoked VTE was made. However further thrombophilia panel testing after discontinuation of rivaroxaban six months therapy showed increased blood homocysteine levels. Our patient has increased body weight, which is a risk for PE. High clinical suspicion is very important for diagnosis of acute PE in young patients, especially in the absence of history suggestive of DVT, since this condition is not uncommon in this population and potentially fatal [5]. Homocystinuria is a rare cause of acute pulmonary embolism, which increase a risk of repetitive PE episodes [6]. Any young patient presenting with unprovoked PE should have thrombophilia and homocysteine level evaluated, and have close monitoring for PE, as early recognition of the problem can prevent this serious disease. The normal blood levels of homocysteine range from 5-15 μmol/L [7]. Individuals with severe homocysteinemia have homocysteine concentrations in the range of 50 to 500 ftmol/L [8]. The classification of homocysteinemia is as follows:

- Moderate risk, 15 to 30 μmol/L
- Intermediate risk, 30 to 100 μmol/L
- Severe risk, >100 μmol/L [8]

Our patient had abnormally high homocysteine levels with normal vitamin B12 and folate levels and no abnormalities of other thrombophilia tests. It is necessary to monitor a patient with homocysteinemia carefully due to the high risk of recurrence of thromboembolic events. Homocysteine is a sulfhydryl amino acid formed by the demethylation of dietary methionine [8]. Homocysteine levels in the blood are usually elevated in patients with folate deficiency because folate is required for the remethylation of homocysteine to methionine. A case-control study by Falcon et al. found that homocysteinemia was a risk factor for thrombosis in people younger than 40 years [9]. Vitamins B6 and B9 or B12 supplements, while they lower homocysteine level, do not change the risk of heart disease, stroke, or death [10].

Obesity has been consistently reported as a moderate risk factor for venous thrombosis. According to the literature and the MEGA study, the relative risk of venous thrombosis associated with obesity was higher in women than in men [11]. Weight gain is associated with increased risk for cardiovascular disease, diabetes and hypertension, but also with increased risk of VTE, particularly among obese individuals. The prothrombotic changes in individuals with obesity may contribute to the VTE risk. Several studies have shown that chronic inflammation, assessed by CRP, is associated with obesity. inflammation stimulates synthesis of factors involved in the coagulation cascade [12,13]. Plasma levels of PAI-1, CRP and factor VIII are elevated in obesity, and high levels of these factors have been associated with increased VTE risk in several studies particularly in women [14].

Patients with PE and cardiogenic shock have intrahospital mortality rate between 30-60%. Rescue fibrinolysis is lifesaving treatment in hemodynamically unstable patients [15,16]. It also saves the life of our patient, who has favorable clinical and one-year outcome. Latest European Society of Cardiology PE guidelines indicates at least three-month anticoagulation therapy for patients with unprovoked PE. After we have received the homocystinemia results we decided to follow up the patient yearly and more closely due to increased risk for repeat PE.

Conclusion

We described a successful treatment of massive PE complicated by cardiogenic shock in relatively young overweight women with additionally diagnosed homocystinemia. Pulmonary embolism should be always suspected in younger patients with acute severe dyspnea event without provocable risk factors. High suspicion level and fast diagnosis are lifesaving. In younger patients presenting with unprovoked pulmonary emboli, clinicians should consider inherited prothrombotic factors as a potential cause. Although a rare cause, homocystinemia is one of the inherited risk factors for PE. A thrombophilia screen allows better management of the patients. Rescue fibrinolysis is lifesaving treatment in intermediate risk PE patients with hemodynamic deterioration.

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