Protein-C deficiency presenting as Pulmonary embolism and Deep vein thrombosis: A case report

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ABSTRACT

Plasma protein-C is a naturally occurring anticoagulant and its deficiency, either homozygous or heterozygous, predisposes the individual to a state of thrombosis, particularly venous thromboembolism, and manifests as deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), or stroke. Protein C exerts anticoagulatory effects by inactivating factors V and VIII. Hereditary protein C deficiency is inherited as an autosomal dominant disorder. Homozygous individuals usually develop purpura fulminans as newborns; heterozygous protein C-deficient individuals are at increased risk for venous thrombosis and pulmonary embolism. We describe a young patient with protein-C deficiency who experienced recurrent pulmonary embolism as well as deep vein thrombosis due to thrombotic occlusion without underlying major risk factors.

Keywords: *Protein-C deficiency, Pulmonary embolism, Deep vein thrombosis.*

INTRODUCTION

Protein C is a vitamin K-dependent protease - a 62 kD glycoprotein, synthesized in liver, circulates in plasma at low concentrations and serves a critical role in the regulation of thrombin[1]. Protein C becomes activated to form activated protein C (APC) via interactions with thrombin. APC acts to downregulate coagulation by cleaving and inactivating clotting factors V and VIII. A deficiency of protein C disturbs the delicate balance between procoagulant and anticoagulant proteins and engenders a prothrombotic state. The Cardinal manifestation of protein-C deficiency is venous thromboembolism. However, there are few case reports of arterial stroke[2,3] and myocardial infarction[4-9] occurring in young adults with congenital protein-C deficiency; but results of other large studies are inconclusive,[10-14], and the existence of an association between protein-C deficiency and arterial thrombosis remains controversial.

CASE PRESENTATION

Our patient, a 18 year old Bangladeshi male, presented on March 2023 with the complaints of hemoptysis for few episodes, sharp chest pain on the right side, mild shortness of breath along with pain and swelling of the right lower limb.

He gave a past history of hemoptysis associated with left sided chest pain in 2019, when he was admitted in a hospital. Based on HRCT finding of left sided atelectasis and consolidation in addition to other routine investigations, he was diagnosed and treated as a case of left sided pneumonia at that time. Regarding relevant family history, one of his brothers had sudden cardiac death at the age of 17 years.

On examination he had dyspnea, tachycardia, crepitation in the right lung and clinical signs of deep vein thrombosis of right leg. The complete blood count, liver function test and renal function test results were unremarkable except for mildly high Leucocyte count and elevated transaminases. The levels of inflammatory markers were not elevated, and microorganisms were not isolated in the blood, urine, or sputum. The prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT) levels and d-dimer were 15.2 s, 1.30, and 30.1, respectively. His d-dimer level was more than 50,000 µ/L. (Table 1).

Table 1: Result of complete blood count, liver function test and renal function test.

Test	Patient value	Reference range
Complete blood count		
Hemoglobin (gm/dl)	13.5	13.5-17.5
White blood cell	13.48	4-11
(10^9/L)	88.80	40-80
Neutrophil (%)	6.50	20-40
Lymphocyte (%)	200	150-400
Platelet count (10^9/L)	49	0-10
ESR (mm in 1st hour)		
Liver function test		
Bilirubin (mg/dl)	1.4	(0-1)
SGPT(IU/L)	137	<50
SGOT(IU/L)	111	15-45
GGT(IU/L)	145	10-50
Alkaline phosphatase	112	40-115
(IU/L)	7.7	6.5-8.5
Total protein(gm/dl)	3.6	3.5—5
Albumin(gm/dl)	4.1	2-4
Globulin (gm/dl)	0.85	0.5-1.3
Serum creatinine(gm/dl)		

The protein C activity level was significantly lower at 36% (normal range: 70–130%).

Other markers of the coagulation profile showed normal results for homocysteine, antithrombin, protein S, prothrombin gene mutation, factor V Leiden, and antinuclear antibody. (Table 2)

Table 2: Coagulation profile

Test	Patients value	Reference value
PT (seconds)	15.2	9.8-12.1
INR	1.30	
APTT		
ANA (AU/ML)	7.59	<40
Protein S (%)	81	60-140
Homocystein level	12.9	5.5-16.2
Protein C (%)	36	70-130
Thrombophilia mutation panel		
F-II prothrombin mutation		
F-V Leiden Mutation		
F-V 1299 Mutation	Not detected	
F-V Cambridge Mutation		
MTHFR 677 Mutation		
MTHFR 1298 Mutation		
F-XIII Val34Leu Mutation		
B-Fibrinogen 455 G>A Mutation		
PAI-1 4G/5G Mutation		

CT pulmonary angiogram revealed thrombus in right interlobar artery extending inferiorly into the lower lobe artery, lateral basal and posterior basal segmental / subsegmental arteries. Small areas of consolidation and peripheral ground glassing in the right lower lobe. (Fig1)

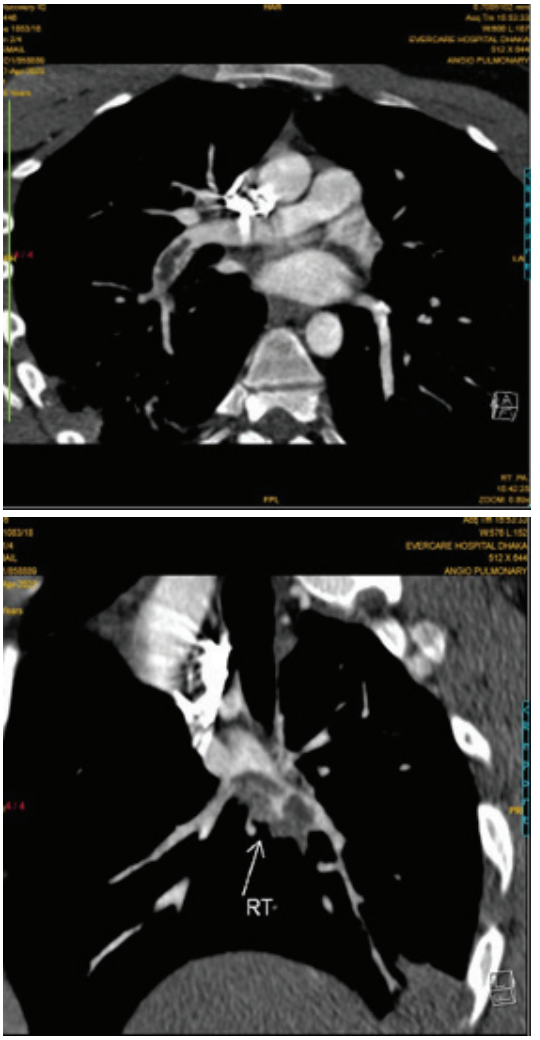

Figure 1: CT pulmonary angiogram coronal & axial section showing thrombus in right interlobar artery extending inferiorly into the lower lobe artery, lateral basal and posterior basal segmental / subsegmental arteries.

Duplex study of right lower limb vessels showed the external iliac vein, common femoral, superficial femoral, popliteal, tibial veins and proximal venous plexus of calf are incompressible and distended with mixed echogenic thrombus and absence of flow within the veins. ECG and Echocardiography findings were within normal limit except for tachycardia.

He was managed with IV unfractionated heparin followed by low molecular weight heparin and warfarin. He was discharged with warfarin with regular monitoring of PT and INR. On follow up after 2 months, he was symptom free and his INR was maintained within 2-3.

DISCUSSION

The prevalence of inherited protein C deficiency is approximately 0.2 to 0.5 percent in the general population and 2 to 5 percent in individuals with venous thromboembolism (VTE)[15]. Most patients with inherited protein C deficiency are heterozygous caused by a variety of mutation in PROC gene located on chromosome 2 (2q13-14)[16-17]. Homozygous or compound heterozygous protein C deficiency is a rare, life-threatening disorder characterized by very low protein C activity and causing purpura fulminans in the neonatal period whereas heterozygous cases are more common presenting mainly with venous thromboembolism like pulmonary embolism, deep vein thrombosis, rarely dural venous sinus thrombosis, less commonly arterial thrombosis like stroke and myocardial infarction. In our particular case, the patient is of young age with no risk factor for thrombotic event. However, having a family history of unexplained sudden death of his brother at young age with clinical presentation of recurrent hemoptysis, radiological evidence of pulmonary embolism with DVT on the same time necessitated further evaluation for thrombophilia. The mainstay of treatment of Protein C deficiency is prevention of thromboembolic events with anticoagulants such as heparin, warfarin, DOAC (Direct-acting oral anticoagulants like rivaroxaban, apixaban, dabigatran, edoxaban etc). Protein C concentrate is usually reserved for the treatment of severe form of protein c deficiency like neonatal purpura fulminans and unavailable in most countries. Counselling of the patients regarding the probable outcomes and risk factors that can aggravate the condition can help with medication compliance and reduction in recurrence rate.

CONCLUSION

Although, several case studies showed relation between unexplained VTE with inherited thrombophilia, the overall incidence and prevalence of such inherited coagulopathies are rare. As such, high degree of clinical suspicion is needed to diagnose and evaluate these cases promptly. Reporting this case was our attempt to increase consciousness towards early recognition and treatment of thromboembolic diseases to prevent life threatening complications and vital organs damages. As of now, there is no clinical data about incidence and prevalence of Protein C deficiency in Bangladesh. Hence, we would encourage to carry out systematic survey of literature to estimate the prevalence and incidence of such thromboembolic conditions in this region.

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