

Case Study

Pulmonary Thromboembolism from Familial Protein S Deficiency

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ABSTRACT

Hereditary thrombophilias are a group of inherited conditions that predispose to thrombosis. Most of the inherited thrombotic disorders are associated with venous thromboembolism. Pulmonary embolism represents a major cause of morbidity and mortality. Chronic thromboembolic disease is a 'great masquerade' and often mistakenly diagnosed as coronary artery disease, asthma, pneumonia and psychogenic dyspnoea. Recurrent pulmonary embolism with pulmonary hypertension can be missed if awareness of the condition is not created. The consequences of a missed diagnosis can be deadly. We present a case of familial protein S defects leading to recurrent pulmonary thromboembolism.

Keywords: Venous thrombosis, pulmonary thromboembolism, pulmonary hypertension, protein S deficiency

INTRODUCTION

The worldwide annual incidence of venous thrombosis is estimated at 1 in 1000 individuals and associated pulmonary embolism represents a major cause of morbidity and mortality.^[1] Thrombophilia may be an inherited or acquired condition, with the former identified in approximately 25-30% of patients with thromboembolic disease.^[1]

The hereditary thrombophilias are a group of inherited conditions that predispose to thrombosis.^[2] Most of the inherited thrombotic disorders are associated with venous thromboembolism rather than arterial thrombosis.^[3] Heritable deficiencies of the endogenous anticoagulants protein C, protein S and antithrombin have been recognised for some years, but their prevalence even among patients with familial thrombosis is low.^[2]

This case report illustrates a young man with protein S deficiency who presented to the clinic with acute chronic pulmonary embolism, leading to secondary pulmonary hypertension.

THE CASE

Mr LKT, a 41 year old Chinese gentleman, working as a painter, presented to the casualty department complaining of intermittent slight pulling chest pain of 5 minutes duration associated with exertional dyspnoea and shortness of breath for the past 1 month. It was associated with a syncopal attack and palpitations. The pain was relieved by rest and aggravated by exercise. He had similar symptoms of shortness of breath, a year ago, which was relieved spontaneously after visiting a general practitioner. He is a smoker and a social drinker. He works as a painter in a private company. No significant and relevant family history.

On clinical examination, he was generally comfortable and was not in respiratory distress. Blood pressure (BP) was 133/82 mm Hg and he was tachycardic at 109 rate/min, regular rhythm. The jugular venous pressure (JVP) was not raised.

Respiratory examination revealed normal lung field with no added sounds. On cardiovascular examination, there was a loud P2 at pulmonary area. Other systems were unremarkable.

The electrocardiogram showed sinus tachycardia, S1, QIII, TIII with T inversion at V1-V3 with right bundle branch block. Arterial blood gas at room air showed the patient was hypoxaemia with pO_2 57 kPa (kiloPascal) and SpO_2 at 92% with pCO_2 24 kPa. Chest X-ray revealed prominent hilar marking of pulmonary artery. The echocardiogram showed a dilated and thickened wall of right ventricle and atrium. The left chambers and septum were not dilated or thickened. Ventilation/perfusion scan showed multiple wedge-shaped segmental perfusion defect with normal ventilation. Full lung function test performed showed spirometry/diffusion capacities were within normal limit. A provisional diagnosis of subacute pulmonary thromboembolism with secondary pulmonary hypertension was made.

Further investigations were then performed and showed high total cholesterol and low density lipoprotein (LDL) levels. Thrombophilic screening was performed and showed a moderately low protein S level of 15% (60-124 %) with normal levels of protein C 83% (50-136 %) and anti-thrombin III 130% (75-125%). Factor V Leiden mutation was equivocal. Family screening of thrombophilia was done due to the recurrent nature of presumed chronic thromboembolic disease. The thrombophilic family screening showed his two elder brothers had severely low protein S levels of less than 5% and 8% respectively. Anti-thrombin III and protein C levels were within normal limits. Factor V Leiden study was equivocal.

His final diagnosis was of hereditary protein S deficiency leading to subacute pulmonary thromboembolism with secondary pulmonary hypertension and hypercholesterolemia.

He was anti-coagulated accordingly, to keep the international normalised ratio (INR) at 2-3 and it was planned for as life-long treatment. He was also started on a cholesterol lowering agent, Lovastatin® 40mg nocte with addition of Ciprofibrate® 100 mg nocte. Counseling on life style modification involving diet and exercise was also recommended.

During follow up, no other episodes of pulmonary embolism was experienced. He was only hospitalised once due to high INR of more than 5.5 with bleeding symptoms, and was treated with infusion of 2 units of fresh frozen plasma. Currently, he is on warfarin treatment 5.5 mg nocte with his latest INR being 2.35.

DISCUSSION

The signs and symptoms of pulmonary embolism are varied and non specific. A reasonable clinical suspicion is required to avoid missing the diagnosis of pulmonary embolism. In our case, no clinical features of deep vein thrombosis were elucidated and neither was it found on investigations done. It is most likely that the thrombi are small and dislodged over a period of time in which the patient reported similar symptoms a year ago and this current symptom has been going on for a month.

Chronic thromboembolic disease is a 'great masquerade' and often mistakenly diagnosed as coronary artery disease, asthma, pneumonia, and psychogenic dyspnoea, which was also presumably experienced by this patient a year ago.

Prevalence of thrombophilia varies among different populations of patients, being lowest in unselected patient populations with deep vein thrombosis (DVT) and highest in specialised centres where patients are referred for suspected familial thrombophilia.^[4] Prevalence of protein C deficiency is 1:200 and 1: 500 among the general population in the West, but its figure is much lower in the Asian context.^[4]

Patient heterozygous for a deficiency of anti-thrombin, protein C or protein S and heterozygous carriers of Factor V Leiden mutation usually present with venous thrombosis of lower limb or pulmonary embolism^[4] as seen in our case. These familial thrombophilias are not shown to have an increased risk of arterial thrombosis.^[4] A study has reported that familial deficiency of protein C and protein S with co-segregation with factor V Leiden mutation will increase the risk of thrombosis in a patient^[5] which presumably occurred in our patient. Unfortunately, no DNA analysis was performed. Protein S deficiency prevalence in the general population is 0.3% whilst in venous thromboembolism population is 3%.^[4]

Protein S deficiencies are inherited as an autosomal dominant pattern.^[5] Protein C and protein S are Vitamin K dependent co-factors whose levels may drop after initiation of warfarin, leading to transient hypercoagulation. Liver disease and disseminated intravascular coagulation can lead to decreased activity of protein C (PC) and protein S (PS). A decrease in protein S can also be seen in pregnancy, oral contraceptive (OCP) use and nephrotic syndrome. Circulating protein S is partly bound to C4b-binding protein and only free protein S can act as a co-factor for protein C, a natural anticoagulant.^[6] Two types of protein S deficiencies are commonly observed in patients with unexplained thrombosis, and they are characterised by having both low total protein S levels and a low free protein S level (type I) or by having only a low free protein S level (type IIa).^[6] Patients heterozygous for a protein C or protein S gene abnormality may develop recurrent thromboses during adulthood, with a 50% probability of remaining free of thrombosis at age 45.^[7]

Screening for inherited deficiency thrombophilia is accomplished by assessing activity levels. A decreased activity level may be due to reduced antigenic level of normal protein or to a dysfunctional protein. The activity level of protein S is more complicated as protein S activity can fluctuate with the level of its C4 binding protein.^[2] Therefore, the total and free levels of protein S should be determined.

Management of thrombophilia involves measuring the available risk factors of patients in developing thrombosis. In this particular patient, he has an inherited thrombophilic state which puts him at higher risk in developing venous thrombosis. His hypercholestromic state will increase his risk of developing arterial thromboembolism. The role of vitamin K

antagonist here in protecting against recurrence thrombotic episodes is mandatory as it reduces the event. However, there is risk of bleeding and it may be fatal in 0.25% of subjects. [4] With increasing age and co-morbid conditions, such as cancer, the risk of developing thrombosis may increase. Major disadvantages of vitamin K antagonist would be (i) the need for regular monitoring, (ii) risk of bleeding, and (iii) life long anticoagulants.

Asymptomatic carriers of inherited thrombophilic defects have 0.4% to 1.6% chances of developing thrombotic episodes. [4] As his brothers had severely low levels of protein S, they are asymptomatic carriers and thus long term anticoagulation is not justified. However, these carriers are required to be put on anticoagulants when exposed to high risk situations such as surgery, trauma or prolonged immobilisation, usually for a duration of 2-4 weeks following surgery or hospitalisation of this high risk situation.

Low intensity warfarin therapy or novel anticoagulants such as oral direct thrombin inhibitors may prove effective strategies for preventing recurrent thromboembolism in patients with thrombophilia. [8] Danazol, a synthetic anabolic steroid has been shown to be effective in protein S deficient patients. [9] This is reported in the study done by Ledford MR *et al.* (1997) whereby the patient had a eleven-year history of venous thrombosis and was not compliant to warfarin therapy. He was free from thrombotic event after 36 months of starting on danazol. Danazol acts by suppression of platelet activation through thrombin inhibition and simply through elevation of protein S. [9]

CONCLUSION

Hereditary thrombophilias is not as common as acquired thrombophilias. Awareness of hereditary thrombophilias is important when a person is presented with pulmonary thromboembolism at an early age. Family screening is important as it helps to diagnose asymptomatic carriers who are at risk.

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