Deep Vein Thrombosis in Protein S Deficiency

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ABSTRACT

Protein S is a vitamin K–dependent anticoagulant protein. It functions as a cofactor of activated protein C to inactivate activated factor V (FVa) and activated factor VIII (FVIIIa). Its deficiency is a rare condition and can lead to deep vein thrombosis, pulmonary embolism or stroke. It is often treated with long-term anti-coagulant therapy.

Protein S deficiency may be hereditary or acquired; the latter is usually due to hepatic diseases or a vitamin K deficiency. Protein S deficiency manifests as an autosomal dominant trait; manifestations of thrombosis are observed in both heterozygous and homozygous genetic deficiencies of protein S. This case report is of DVT due to Protein S deficiency in a 53 year old male. Venous Doppler was used to diagnose DVT and free Protein S level measured by ELISA. IVC filter was placed on the third day of admission.

Key Words: *antithrombotic, deep venous thrombosis, inferior venacaval filter, protein S*

INTRODUCTION

Protein S (PS) deficiency is an autosomal-dominant inherited disorder of coagulation, either homozygous or heterozygous. However acquired deficiencies of PS have been described recently in several conditions such as malignancy, pregnancy, nephrotic syndrome and acute phase reactions. The true prevalence of inherited PS deficiency is unknown as not all individuals develop thrombosis. Some studies have indicated a frequency of 2-5% in patients with deep venous thrombosis (DVT) or pulmonary embolism (PE). This is as prevalent as protein C deficiency (5-8%) but less common than antithrombin III deficiency (12-15%).[1] Patients with phenotypic PS deficiency have a 50% chance of developing recurrent thrombosis before age 45.[2] In homozygous individuals, a severe life threatening form of thrombosis called purpura fulminans can result in early infancy. The case report

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describes our experience in treating massive DVT extending up to and completely occluding the right external iliac vein.

CASE REPORT

A 58 year male had unilateral swelling of right lower limb for a day. It started in the calf region and grew upwards. He also complained of mild pain in the right thigh region. There was no history of trauma, hypertension, diabetes or any major surgery in the past. There was no complaints of chest pain or shortness of breath. On examination, the right lower limb was swollen up to the thigh (66 cm) compared to the left thigh (51 cm). The right calf measured 37 cm, and left calf 34.5 cm. General and systemic examinations were within normal limits. Venous Doppler showed hypoechoic thrombus within the lumen of right external iliac and common/superficial femoral, popliteal, and greater saphenous veins signifying complete occlusion. The veins were non compressible and did not show any flow. The diagnosis of DVT involving right ilio-femoral segment was made. Electrocardiogram was normal.

Thrombophillic screen showed free PS levels of 0.5%. Antithrombin III and Protein C levels were normal. Treatment with intravenous heparin infusion was started on the day of admission. Activated partial thromboplastin time (APTT) monitoring was done every six hourly and dose adjusted accordingly. Warfarin was started on the third day of heparin infusion and permanent inferior vena cava (IVC) filter was also inserted on the same day. Heparin was discontinued on the 10th day of admission. At discharge the lower limb swelling had significantly decreased and the patient could mobilize by himself. Repeat venous doppler showed flow augmentation of the distal 2/3rd of superficial femoral and popliteal vein. Deep veins of the leg also showed flow in augmentation, but there was complete occlusion of external iliac and common femoral. The patient is currently on Warfarin 5 mg per day and is maintaining an INR of 2.3.

DISCUSSION

Protein S, a vitamin K–dependent anticoagulant protein, functions as a cofactor of activated protein C to inactivate factor Va and factor VIIIa. It exists in the body in free and protein-bound forms. The free form is functionally active. PS deficiency, a genetic trait, predisposes to the formation of venous clots. Protein S deficiency was first described in 1984.[3] The association of protein S deficiency with arterial thrombosis appears coincidental or weak at best.[4] Acquired causes of PS deficiency are vitamin K deficiency, treatment with Warfarin, systemic sex hormone therapy, pregnancy, liver disease and certain chronic infection e.g. HIV.

Protein S deficiency can be classified into three types, Type I, II, and III.[5]

PS deficiency is associated with the occurrence of dural sinus thrombosis which has a high mortality rate.[6] A case of DVT associated with protein S deficiency which was treated conservatively with Aspirin 150mg per day has also been reported.[7] An IVC filter was placed in the patient to prevent any pulmonary thromboembolism as the clot was massive which is similar to a case report with placement of IVC filter in a case of pulmonary and deep venous thrombosis.[8] Not many cases have been reported where IVC filter has been placed in a case of DVT, ours case was unique in the sense that the DVT was massive and it could have led to a fatal embolism of the main pulmonary artery had it occurred. Keeping in mind about the risks and benefit ratio of the procedure we decided that the patient would benefit out of it. The indications for IVC filter placement according to various texts and journals are when anticoagulation is contraindicated in a patient or when new pulmonary embolism occurs in a patient on anticoagulation.

Therapy is mainly antithrombotics and long term anti coagulants. During the initial phase, heparin as intravenous unfractionated heparin or as subcutaneous low molecular weight heparin (LMWH) should be continued for a minimum of five days. Warfarin administration can start on day 1 or 2 of heparin therapy. After two consecutive therapeutic international normalized ratio (INR) and a minimum of five days of heparin therapy the patient can continue on warfarin alone. In most patients the recommendation for initial warfarin treatment is for six to nine months. The question of whether to continue lifelong warfarin with identified PS deficiency is controversial. If the first thrombotic event was life threatening or occurred in multiple or unusual sites (e.g. - cerebral veins, mesenteric veins), most experts recommend lifelong therapy initially. If precipitated by a strong event (e.g. - trauma, surgery) and the thrombosis did not meet the criteria of life threatening or unusual sites, some experts argue that these patients may have a lower risk of recurrence and deserve a trial without warfarin after nine months. In patients who are asymptomatic carriers of PS deficiency the goal of therapy is prevention of the first thrombosis. In such patients, avoid drugs that predisposes to thrombosis, including oral contraceptives. In these patients, if surgery or orthopedic injury occurs, prophylaxis with heparin is mandatory. In pregnancy prophylaxis with heparin is recommended, however the timing is controversial. Most experts would treat from the second trimester through 4-6 weeks postpartum.[4]

Overall we present a case of PS deficiency presenting with DVT involving all the major superficial and deep

veins of the lower limb extending up to the external iliac vein and the principles of management of life threatening DVT and prevention of major embolic complication by insertion of permanent IVC filter.

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REFERENCES

1. Finazzi G, Barbui T. Different incidence of venous thrombosis in patients with inherited deficiencies of antithrombin III, protein C and protein S. Thromb Haemost. 1994;71:15-8.

2. Borgel D, Gandrille S, Aiach M. Protein S deficiency. Thromb Haemost. 1997;78:351-6.

3. Schwarz HP, Fischer M, Hopmeier P, Batard MA, Griffin JH. Plasma protein S deficiency in familial thrombotic disease. Blood. 1984 Dec;64(6):1297-300.

4. Godwin JE. Protein S deficiency. [Online]. 2007 [cited 2009 Jun 5]; [5]. Available from: URL: http://emedicine.medscape.com/article/205582-overview.

5. Moll S, White II GC. Coagulation disorders. In: Runge MS, Patterson C, editors. Principles of molecular medicine. 2nd ed. New Jersey (USA): Humana press Inc; 2006. p. 876.

6. Kuroki K, Taguchi H, Sumida M, Onda J. Dural sinus thrombosis in a patient with protein S deficiency-case report. Neurol Med Chir. 1999;39(13):928-31.

7. Khandekar AA, Kumbhalkar SD, Salkar HR, Parakkadavathu RT, Salkar RG. Protein S deficiency presenting as deep vein thrombosis-a case report. Angiology. 2003; 54(5):605-8.

8. Kobayashi R, Yamashita A, Gohra H, Furukawa S, Oda T, Hamano K. Pulmonary and deep vein thrombosis in a young patient with protein S deficiency: report of a case. Surg Today. 2007;37(8):660-3.