

Recurrent Deep Vein Thrombosis Caused by Inherited Coagulopathy in a Japanese Male

Wen-Rui Hao,¹ Pai-Feng Kao,¹ Yat-Lon Leong,² Yu-Tien Tzeng,¹ Ju-Chi Liu,¹ H-Eugene Liu¹ and Paul Chan^{1,2}

Deep vein thrombosis is a common disease entity to which attention should be paid due to its complication of pulmonary embolism. This disease usually has precipitating factors such as obesity, varicose veins or non-ambulation. Congenital coagulation defects should be suspected if patient has recurrent deep vein thrombosis without identifiable precipitating factors. We report a case of 44-year-old Japanese male, who had three events of deep vein thrombosis within four years. Doppler ultrasound study at the time of the first event showed extensive thrombosis of femoral veins. Coagulation factors study revealed that patient had antithrombin III deficiency. This patient's sister in Japan also had this defect. This patient is using warfarin 5 mg daily and has been followed up uneventfully. In patients with recurrent deep vein thrombosis, hereditary coagulation defect should be suspected and warfarin should be used indefinitely.

Key Words: Antithrombin III • Coagulation defect • Deep vein thrombosis • Warfarin

INTRODUCTION

Deep vein thrombosis (DVT) is an important cause of illness in developed countries; its annual incidence is about 1 in 1000 in normal population in Western countries.¹ DVT can occur in the veins of upper extremities, cerebral veins, mesenteric veins or retina, although it more commonly affects lower extremities. It is necessary to pay attention to DVT because it is a disease entity that is commonly associated with post-phlebotic syndrome and even can complicate with pulmonary embolism, which is fatal in about 10% of in-patients.²

Broadly, the causes of DVT can be classified into

two categories: hereditary or acquired.² Clinical suspicion should focus on known risk factors for DVT such as prolonged non-ambulation, recent surgery, obesity, prior episodes of venous thrombosis, lower extremity trauma, neoplastic diseases, female hormone usage, post-partum status and stroke. A positive family history or unusual presentation of venous thrombosis may suggest the presence of hereditary defect.²

We report a case of a Japanese male computer engineer, who had a history of 3 events of recurrent DVT in the past few years although under warfarin therapy. Intensive blood examinations showed that this patient had inheritable coagulation defects (antithrombin III deficiency) leading to his recurrent DVT, which is unusual in the past medical reports in this country.

Received: June 23, 2007 Accepted: January 31, 2008
¹Department of Medicine, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan; ²Department of Medicine, University Hospital, Macau University of Science and Technology, Taipa, Macau, SAR, China.

Address correspondence and reprint requests to: Dr. Paul Chan, Division of Cardiovascular Medicine, Taipei Medical University-Wan Fang Hospital, No. 111, Hsing-Lung Road, Section 3, Wen Shan District, Taipei 116, Taiwan. Tel: 886-2-2930-7930; E-mail: chanpaul@wanfang.gov.tw

CASE REPORT

A 42-year-old Japanese male computer engineer visited our cardiology clinic in November, 2004 due to history of recurrent DVT in his left lower leg. He was apparently healthy, with a body mass index of about 20

kg/m². The first event occurred during October, 2001 when he visited the United States; at that time he felt his left leg had numbness. Two months later in Singapore, he visited a cardiothoracic surgeon clinic because of remarkably painful left leg swelling. Doppler ultrasound examination showed extensive DVT of the left lower leg which involved calf and popliteal veins, the superficial and common femoral veins (Figures 1, 2). He was then admitted to a hospital in Singapore and then received warfarin treatment for 6 months. No coagulation factors were examined in Singapore.

About 2 years later, this patient had left leg swelling again and visited a local hospital in Taipei, where DVT was diagnosed and warfarin was given. He was then referred to our hospital for a study of recurrent DVT. However, Doppler ultrasound did not reveal any throm-

bus inside the left leg. Pletysmography showed the patient had venous insufficiency. He was then given aspirin 100 mg daily for prevention of DVT after another treatment course of 6 months of warfarin therapy.

Unfortunately, without any antithrombotic treatment, the patient had a third event of recurrent left leg painful swelling in October, 2004, but it was milder than the first episode. He was suspected to have DVT again, but ultrasound study and venography did not show any thrombus inside the left leg. Since this patient had recurrent DVT, inherited coagulation defect was suspected. He received blood examination of coagulation factors.

Laboratory examinations revealed that patient had normal biochemistry (including homocysteine) and hemogram. His international normalized ratio (INR) was remaining around 2-3. The factor IX was 36% (normal range: 70-140%); antithrombin III 61% (normal range: 80-120%); protein C 153.1% (normal range: 70-140%); and protein S < 10% (normal range: 60-150%). Fibrinogen was 279 mg/dl (normal range: 200-400 mg/dl) and factor VIII was 106% (normal range: 70-140%). The D-dimer test was 947 ng/ml (normal range: 0-500 ng/ml). Since the above data were examined while this patient was taking warfarin, we suggested to the patient that he could take aspirin 325 mg daily for one week and quit warfarin, and all the coagulation factors were re-examined. The results were normal except antithrombin III deficiency of 51.9% (normal range: 80-120%).

This patient informed us that his younger sister in Japan also had a history of DVT and was diagnosed to have antithrombin III deficiency. His father had passed away when he was young, and his mother did not have any thrombembolic disease.

During his whole clinical course, the patient did not experience any respiratory or chest symptoms such as dyspnea, tachypnea, chest pain or tachycardia. So pulmonary embolism was not evaluated. The patient was suggested to take warfarin indefinitely and to avoid standing or sitting for a long time. He has been followed up at the cardiology clinic uneventfully, with INR controlled at around 2-3.

DISCUSSION

Coagulation defect leading to thrombotic disease is

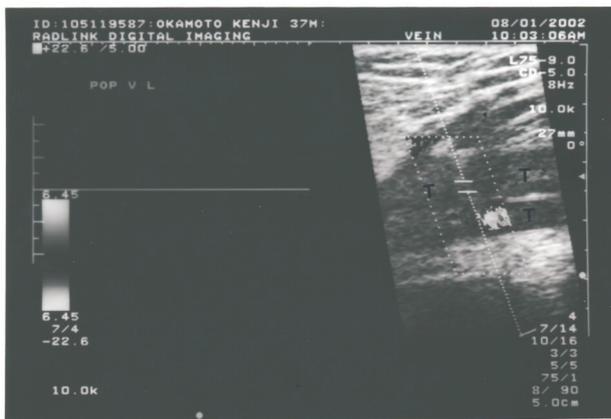


Figure 1. Doppler ultrasonography shows extensive thrombosis (T) of popliteal vein, superficial and common femoral veins; no Doppler wave form was noted.



Figure 2. Doppler ultrasonography showed extensive thrombosis (T) of popliteal vein; no Doppler wave form was noted.

not a rare disorder in Western population.³ In a recent prospective study of outpatients in Dutch presenting with DVT, the prevalence of antithrombin III, Protein S or plasminogen deficiency was 8.3%, compared to 2.2% in normal controls.³ The patient we report here had some important clues to suggest he had hereditary coagulation defect: (1) he was apparently healthy but had 3 events of DVT within 4 years; (2) the first DVT event had extensive thrombosis which involved popliteal, superficial and common femoral veins according to the report of Singapore Gleneagle Hospital; and (3) his younger sister in Japan also had DVT and was reported to have antithrombin III deficiency.

So when approaching patients with DVT, the following clinical features should suggest congenital coagulation disorders and prompt a laboratory screening: (1) thrombosis occurred at an early age; (2) a family history of thrombotic disease; (3) thrombosis occurred at extraordinary positions, such as mesenteric vein thrombosis or central vein thrombosis; (4) recurrent thrombosis with or without apparent precipitating factors; (5) recurrent thrombosis during anticoagulation therapy and/or warfarin-induced skin necrosis. The case we reported had extensive thrombosis, including recurrent thrombosis during anticoagulation therapy with no precipitating factors.

Antithrombin III deficiency was first reported in a Norwegian family in 1965;⁴ the family members had antithrombin III about 40-50% of normal, with a history of recurrent thrombosis. Antithrombin III is an autosomal dominant hereditary disease. A recent study in the United Kingdom found that the prevalence of antithrombin III deficiency in white population was about 0.2-0.4%.⁶ Review of published cases shows that about 55% of affected patients had DVT episodes.⁷ The common sites of DVT in these patients are deep veins of the legs and mesenteric veins, and approximately 60% had recurrence and about 40% had pulmonary embolism evidence.⁷

A previous investigation by Shen et al. which studied 85 patients with unexplained venous thrombophilia revealed 50 patients had a deficiency of inhibitor proteins, but only 3 (3.5%) had antithrombin III deficiency.⁸ Ho et al. investigated 50 patients with venous thrombosis, reporting that only 2 patients had antithrombin III deficiency.⁹ Both studies did not find any

Factor V Leiden mutation, which is a common form of congenital thrombophilic disease in white population.^{8,9} Data from a Japanese report also presented the similar findings as Taiwanese which showed that antithrombin III deficiency is also not common in Japanese.¹⁰

Two major types of antithrombin III have been shown.¹¹ The classical type (type I) is a result of reduced synthesis of protease inhibitor molecules;¹² type II is a discrete molecular defect within the protease inhibitor.¹³

In conclusion, in patients with unusual clinical presentation of DVT, congenital coagulation defects should be suspected. Oral anticoagulants are highly effective, and treatment with warfarin should be maintained indefinitely in patients with recurrent DVT. Prophylactic anticoagulation in affected kindreds of patients is not suggested unless they have risk factors such as prolonged immobilization.¹⁴

REFERENCES

1. Carter CJ. Epidemiology of venous thromboembolism. In: Hull RD, Pineo GF, Eds. *Disorders of Thrombosis*. Philadelphia: WB Saunders, 1996:159-74.
2. Maheshwari A, Mehrotra A, Henry R, et al. Deep veins thrombosis. Risk and management. In: Abela GS, Ed. *Peripheral Vascular Disease: Basic Diagnostic and Therapeutic Approaches*. Philadelphia: WB Saunders, 2004:452-60.
3. Hijboer H, Brandjes DPM, Buller HR, et al. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep venous thrombosis. *N Engl J Med* 1990;323:1512-6.
4. Egeberg O. Inherited antithrombin deficiency causing thrombophilia. *Thromb Diathes Haemorrh* 1965;13:516-30.
5. Rosenberg RD. Actions and interaction of antithrombin and heparin. *N Engl J Med* 1975;292:146-51.
6. Meade TW, Dyer S, Howarth DJ, et al. Antithrombin III and procoagulant activity: sex differences and effects of the menopause. *Br J Haematol* 1990;74:77-81
7. Thaler E, Lechner K. Antithrombin III deficiency and thromboembolism. In: Prentice CRM, Ed. *Clinics in Haematology*. London: WB Saunders, 1981:369-80.
8. Shen MC, Lin SJ, Tsay W. High prevalence of antithrombin III, protein C and protein S deficiency, but no factor V Leiden mutation in venous thrombophilic Chinese patients in Taiwan. *Thromb Res* 1997;87:377-85.
9. Ho HC, Chau WK, Hsu HC, et al. Causes of venous thrombosis in fifty Chinese patients. *Am J Hemato* 2000;63:74-8.
10. Suehisa E, Nomura T, Kawasaki T, Kanakura Y. Frequency of natural coagulation inhibitor (antithrombin III, protein C and protein S) deficiencies in Japanese patients with spontaneous deep

- vein thrombosis. *Blood Coagul Fibrinolysis* 2001;12:95-9.
11. Lane DA, Ireland H, Olds RJ, et al. Antithrombin III: a database of mutations. *Thromb Haemost* 1991;66:657-61.
 12. Scully MF, De Hass H, Chan P, Kakkar VV. Hereditary antithrombin III deficiency in an English family. *Br J Haematol* 1981;47:235-40.
 13. Harper P, Luddington R, Daly M, et al. The incidence of dysfunctional antithrombin variants: four cases in 210 patients with thromboembolic disease. *Br J Haematol* 1991;77:360-4.
 14. Demers C, Ginsberg JS, Hirsh J, et al. Thrombosis in antithrombin-III-deficient persons: report of a large kindred and literature review. *Ann Intern Med* 1992;116:754-61.