

CASE REPORT

Recurrent venous thrombosis during direct oral anticoagulant therapy in a patient with protein S deficiency

Shusuke Yagi^{1,2}, Kumiko Kagawa³, Eiki Fujimoto⁴, and Masataka Sata¹

¹Department of Cardiovascular Medicine, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan, ²Department of Community Medicine and Human Resource Development, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan, ³Department of Hematology, Endocrinology and Metabolism, Tokushima, Japan, ⁴Department of Cardiovascular Surgery, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

Abstract : Protein S (PS) deficiency is an inherited thrombophilia associated with an increased risk of venous thromboembolism (VTE). In Japan, unfractionated heparin followed by warfarin has been historically applied for the treatment of VTE. Recent evidence showed that direct oral anticoagulants (DOACs) were non-inferior to standard therapy with warfarin, with significantly less bleeding in patients with VTE. However, it is unknown whether DOACs are effective for the treatment of VTE in patients with thrombophilia, including protein S deficiency, due to lack of evidence. Here, we report a case of recurrent venous thrombosis during edoxaban therapy in a patient with protein S deficiency, which was successfully treated using high-dose apixaban therapy. *J. Med. Invest.* 66 : 182-184, February, 2019

Keywords : VTE, apixaban, congenital thrombophilia

INTRODUCTION

Protein S (PS) deficiency is an inherited thrombophilia associated with an increased risk of thromboembolism (1). The standard treatment of venous thromboembolism (VTE) consists of unfractionated heparin/low-molecular-weight heparin followed by warfarin, a vitamin K antagonist (2). Recently, direct oral anticoagulants (DOACs), including rivaroxaban, edoxaban, and apixaban, have become available for the treatment of acute VTE in Japan. In studies investigating VTE prevention, DOACs have been shown to be non-inferior to standard therapy with warfarin after initial heparin, with significantly less bleeding (3-5).

However, due to lack of evidence, it is unknown whether DOACs are effective for the treatment of VTE in patients with PS deficiency. Here, we report a case of recurrent venous thrombosis during edoxaban therapy in a patient with PS deficiency, which was successfully treated using high-dose apixaban therapy.

CASE REPORT

A 70-year-old man felt swelling in his right leg and presented to our hospital. He had a history of unprovoked VTE complicated pulmonary embolism (PE) and an inferior vena cava (IVC) filter was implanted 16 years ago. After the onset of previous VTE/PE, he had received anti-coagulation therapy with warfarin, which was switched to 30 mg of edoxaban due to patient preference ; however, his drug adherence was poor. He was also diagnosed with depression and had received 40 mg of paroxetine and 20 mg of baclofen as anti-depressant therapy for years. Blood examination showed elevated D-dimer of 32 µg/mL, suggesting VTE recurrence whilst

receiving edoxaban therapy. Venous echography and enhanced computed tomography (CT) showed thrombosis in the IVC below the IVC filter to the popliteal vein, with no PE (Figure 1A, B, Figure 2A). His blood test results showed decreased PS antigen (54%) and decreased PS activity (44%), indicating he had PS defi-

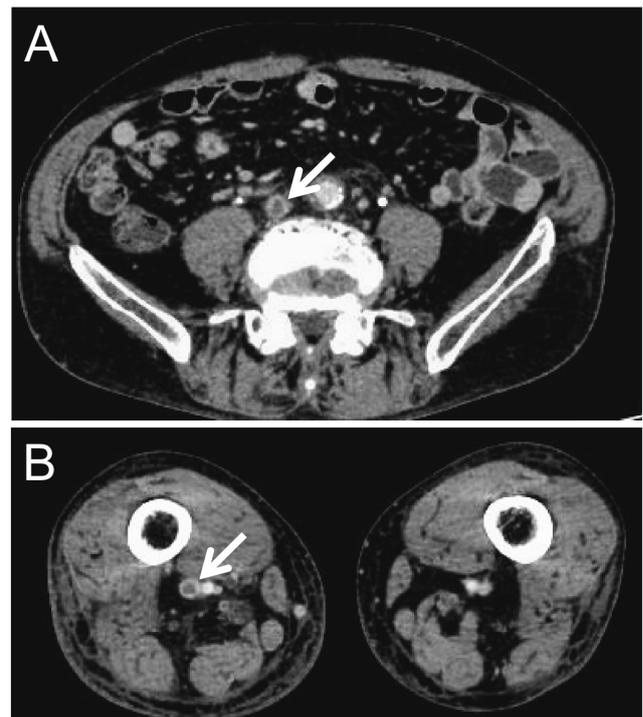


Figure 1. Enhanced CT imaging shows thrombus in the IVC (arrow A) and thrombus in the right femoral vein (arrow B)

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Address correspondence and reprint requests to Shusuke Yagi, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan, and Fax : +81-88-633-7894

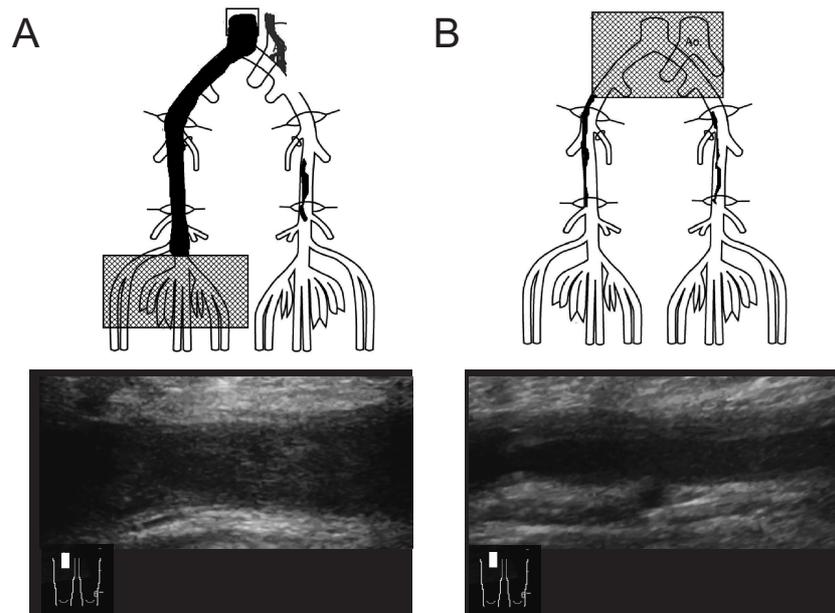


Figure 2. Venous echographic imaging of VTE focused on the right femoral vein before apixaban treatment (A) and after apixaban treatment (B). Filled squares indicate poor imaging sites with venous echography

ciency, although he had no family members who had a history of thrombosis. His protein C (PC) level was within normal range, and both anti-cardiolipin antibodies and lupus anticoagulant were negative, excluding PC deficiency or anti-phospholipid syndrome.

A regular dose of edoxaban was not effective for preventing VTE recurrence, which might be attributable to the patient's poor drug adherence. In addition, a high dose of apixaban but not edoxaban was available for the treatment of acute VTE. Therefore, he was administered a high dose of 20 mg apixaban for 7 days for acute VTE, with no heparin bridging or hospitalization, following administration of a regular dose of 10 mg apixaban. Anti-depressants, which may be a risk factor for the recurrence of VTE, were continued because his depressive state was stabilized by these drugs. His right leg swelling gradually improved and follow-up venous echography after 12 days revealed that the acute thrombus in the IVC to the right femoral vein was almost resolved, and showed only mural thrombus (Figure 2B). It is planned that he will continue to receive apixaban therapy for life, as long as he does not experience major bleeding.

DISCUSSION

In this case, a high dose of apixaban was effective for the treatment of VTE in a patient with PS deficiency who received edoxaban therapy.

PS serves as a cofactor for activated PC, which inactivates procoagulant factors Va and VIIIa, reducing thrombin generation and enhancing fibrinolysis. PS can also directly inhibit prothrombin activation via interactions with other coagulation factors (6, 7). Some genetic variations of the PS gene have been identified as genetic risk factors for VTE, including amino acid substitution of Glu(GAG) for Lys-155(AAG), known as PS Tokushima (1, 8), with an odds ratio of 4.72 (9, 10).

Congenital PS deficiency has been identified in 1-7.5% of patients with VTE and in 0.03-0.13% of the general Caucasian population. However, it has been reported that there is a higher prevalence in

the Japanese population, both for VTE patients (12.7%) and the general population (0.48-0.63%) (11-13). PS deficiency is the most frequent congenital thrombophilia in Japanese people; therefore, we must understand this thrombophilia, and that patients with PS deficiency have an increased risk of VTE and a necessity for prophylactic use of anticoagulants for recurrent VTE (11, 12).

For the treatment of VTE in Japan, unfractionated heparin followed by warfarin has been historically administered. However, vitamin K antagonists could suppress the synthesis of vitamin K-dependent anticoagulation factors, including PC and PS, in addition to coagulation, factors of prothrombin factor VII, IX, and X. Thus, further inhibition of PS could be worsen VTE in patients with PS deficiency. We previously showed that warfarin therapy decreased PS activity to 46% and PC activity to 62%, but that edoxaban therapy maintained PS and PC activity to 90% and 93%, respectively, in patients with VTE (14). Thus, DOACs could be preferable therapy for VTE in patients with PS/PC deficiency. In theory, DOACs should be effective in patients with thrombophilia. However, there has been no clinical trial showing the effects and safety of DOACs in patients with PS deficiency. There have been some reports of PS deficiency complicated with VTE that were successfully treated with rivaroxaban (15) (16), and some recurrent cases of deep vein thrombosis after rivaroxaban treatment (17). A small subset of patients with thrombophilic disorders (5-7%) were included in the EINSTEIN rivaroxaban trial (3) and the AMPLIFY apixaban trial (5), but no specific information was recorded to identify the type of hypercoagulable disorder. The guideline from the American College of Chest Physicians does not describe the treatment of VTE in patients with thrombophilia, but describes thrombophilic disorders as a risk factor for recurrent VTE (18).

The patient had poor drug adherence and recurrent VTE during edoxaban therapy. Recurrent VTE was mostly related to poor drug adherence, which highlights the important role of regular DOACs in high-risk patients. In addition, he had received anti-depressants for years. Depression and anti-depressant therapy have been reported to be risk factors for VTE (19). Furthermore, he had previously had an IVC filter implanted, and it has been reported that these filters do not prevent VTE occurrence (20), indicating that

the IVC filter itself may generate thrombi. We previously reported that IVC filter implantation could cause endovascular damage and fibrin formation, resulting in thrombus formation (21). Activation of the extrinsic pathway by endovascular damage from mechanical stress and activation of the intrinsic pathway triggered by IVC filter contact with XII factor might enhance thrombus formation. In this patient, these risk factors, in addition to PS deficiency, may have contributed to the recurrence of VTE.

DOACs are generally preferred over warfarin for the acute treatment of VTE; however, there is no specific guideline for use in patients with inherited thrombophilia. Additional evaluation of DOAC use in patients with inherited thrombophilia is necessary to provide further evidence.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

REFERENCES

- Hayashi T, Nishioka J, Shigekiyo T, Saito S, Suzuki K. Protein S Tokushima : abnormal molecule with a substitution of Glu for Lys-155 in the second epidermal growth factor-like domain of protein S. *Blood* 83(3) : 683-90, 1994
- Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al : Prevention of VTE in nonsurgical patients : Antithrombotic Therapy and Prevention of Thrombosis, 9th ed : American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141(2 Suppl) : e195S-e226S, 2012
- Investigators E, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al : Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 363(26) : 2499-510, 2010
- Hokusai VTEI, Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, et al : Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 369(15) : 1406-15, 2013
- Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al : Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 369(9) : 799-808, 2013
- Esmon CT : Protein S and protein C : Biochemistry, physiology, and clinical manifestation of deficiencies. *Trends Cardiovasc Med* 2(6) : 214-9, 1992
- Hackeng TM, van't Veer C, Meijers JC, Bouma BN : Human protein S inhibits prothrombinase complex activity on endothelial cells and platelets via direct interactions with factors Va and Xa. *J Biol Chem* 269(33) : 21051-8, 1994
- Shigekiyo T, Uno Y, Kawauchi S, Saito S, Hondo H, Nishioka J, et al : Protein S Tokushima : an abnormal protein S found in a Japanese family with thrombosis. *Thromb Haemost* 70(2) : 244-6, 1993
- Miyata T, Kimura R, Kokubo Y, Sakata T : Genetic risk factors for deep vein thrombosis among Japanese : importance of protein S K196E mutation. *Int J Hematol* 83(3) : 217-23, 2006
- Kimura R, Honda S, Kawasaki T, Tsuji H, Madoiwa S, Sakata Y, et al : Protein S-K196E mutation as a genetic risk factor for deep vein thrombosis in Japanese patients. *Blood* 107(4) : 1737-8, 2006
- Adachi T : Protein S and congenital protein S deficiency : the most frequent congenital thrombophilia in Japanese. *Curr Drug Targets* 6(5) : 585-92, 2005
- Angchaisuksiri P : Venous thromboembolism in Asia—an unrecognised and under-treated problem? *Thromb Haemost* 106(4) : 585-90, 2011
- Skelley JW, White CW, Thomason AR : The use of direct oral anticoagulants in inherited thrombophilia. *J Thromb Thrombolysis* 43(1) : 24-30, 2017
- Yamazaki H, Yagi S, Torii Y, Amano R, Oomichi Y, Sangawa T, et al : Edoxaban improves acute venous thromboembolism while preserving protein C and protein S levels. *J Cardiol* 71 : 305-309, 2018
- Ameku K, Higa M : Rivaroxaban Treatment for Warfarin-Refractory Thrombosis in a Patient with Hereditary Protein S Deficiency. *Case Rep Hematol*. 2018 ; 2018 : 5217301. 1).
- Martinelli I, Bucciarelli P, Artoni A, Fossali EF, Passamonti SM, Tripodi A, et al : Anticoagulant treatment with rivaroxaban in severe protein S deficiency. *Pediatrics* 132(5) : e1435-9, 2013
- Undas A, Goralczyk T : Non-vitamin K : antagonist oral anticoagulants in patients with severe inherited thrombophilia : a series of 33 patients. *Blood Coagul Fibrinolysis* 28(6) : 438-42, 2017
- Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al : Antithrombotic Therapy for VTE Disease : CHEST Guideline and Expert Panel Report. *Chest* 149(2) : 315-52, 2016
- Parkin L, Balkwill A, Sweetland S, Reeves GK, Green J, Beral V, et al : Antidepressants, Depression, and Venous Thromboembolism Risk : Large Prospective Study of UK Women. *J Am Heart Assoc* 6(5), 2017
- Mismetti P, Laporte S, Pellerin O, Ennezat PV, Couturaud F, Elias A, et al : Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism : a randomized clinical trial. *JAMA* 313(16) : 1627-35, 2015
- Yagi S, Yamamoto Y, Nishiyama S, Sata M : An Occluded Hooklet of an Embedded Inferior Vena Cava Filter. *Intern Med* 57(15) : 2275-6, 2018