

Case Report

Deep venous thrombosis in a patient with therapeutic INR for PS deficiency

Motahareh Vamegh*, Ahmad Hallak, Wael Abousherif

Department of Internal Medicine, Al Qassimi Hospital, Sharjah, United Arab Emirates

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*Correspondence:

Dr. Motahareh Vamegh,

E-mail: motahareh.vamegh@gmail.com

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ABSTRACT

We have reported a rare case of DVT in a 25-year-old patient with a known case of Protein S deficiency with INR within therapeutic index. He was seen in the ED and transferred to the Medical ward after diagnosis in the ED using doppler US. The patient was successfully treated with heparin and warfarin with a higher than usual optimal INR. This case adds to the growing evidence that PS deficiency is one of the rare causes of DVT, and also raises awareness that thrombosis can still occur in the current optimal INR for such patients. This case report necessitates the revision of what should be the optimal INR for patients with Protein S deficiency who develop thrombosis in the current optimal INR.

Keywords: Deep vein thrombosis, Optimal INR, Protein S deficiency, Thrombosis

INTRODUCTION

Protein S (PS) is a vitamin K-dependent serum protein, of 75kDa, that has a pivotal role in the anticoagulant system.¹ The major function of protein S is as a cofactor to facilitate the action of activated protein C (APC) on its substrates, activated factor V (FVa) and activated factor VIII (FVIIIa). The deficiency is rare in the caucasian population, with studies concluding a prevalence of 0.03%.² Protein S deficiency may be hereditary or acquired. Protein S deficiency usually manifests clinically as venous thromboembolism (VTE).

CASE REPORT

A 25-year-old male with a known history of partial epilepsy with secondary generalization managed with Levitiracetam 1.5g BD and Topiramate 150mg, migraine without aura, and Protein S deficiency diagnosed 15years ago managed with warfarin 5mg, presented to the emergency department (ED) of Al-Qassimi Hospital,

Sharjah, UAE with sudden onset of right leg pain, swelling, warmth, and an inability to walk that started the night before presentation after training in the gym. The pain was from the upper thigh extending to the knee, constant, which was aggravated by walking and alleviated by placing ice at the location of swelling and rest. The patient was fatigued but denied any history of trauma, shortness of breath, cough, palpitations and chest pain. On questioning his dietary habits, it was found that he was not aware of the interactions of certain foods with warfarin. His brother and father have also been diagnosed with Protein S deficiency.

The patient physical examination showed 70kg (154lbs) and 68.9 in (175cm) weight and height, respectively. There were no features of jaundice, pallor, leukonychia, clubbing, edema, lymphadenopathy. His vital signs were within normal limits. The right leg was swollen with an approximate circumference difference of 3cm between both legs. The overlying skin was congested, warm, firm, and tender on palpation. The respiratory, gastrointestinal,

cardiovascular, and central nervous system examinations were all normal. Color coded duplex examination of the venous system of Right lower limb revealed obstruction of the deep venous system of the right lower limb by an acute thrombus at the right iliac vein extending to the superficial femoral vein, popliteal vein and proximal parts of the leg veins (Figure 1). Investigations revealed an INR of 2.36, which is within the optimal range of 2-3. All other blood tests were unremarkable. Activated

partial thromboplastin time (APTT) was also 43. The patient was admitted, and started on low molecular weight heparin (LMWH) 60mg BID along with warfarin which was titrated up to a revised therapeutic range of 3-4. Prothrombin time (PT) and INR (International Normalized Ratio) were monitored. Patient was stable and discharged on the seventh day of hospital stay, on warfarin 6.5mg once a day with INR 3.07. He was advised to follow-up monthly to monitor INR.

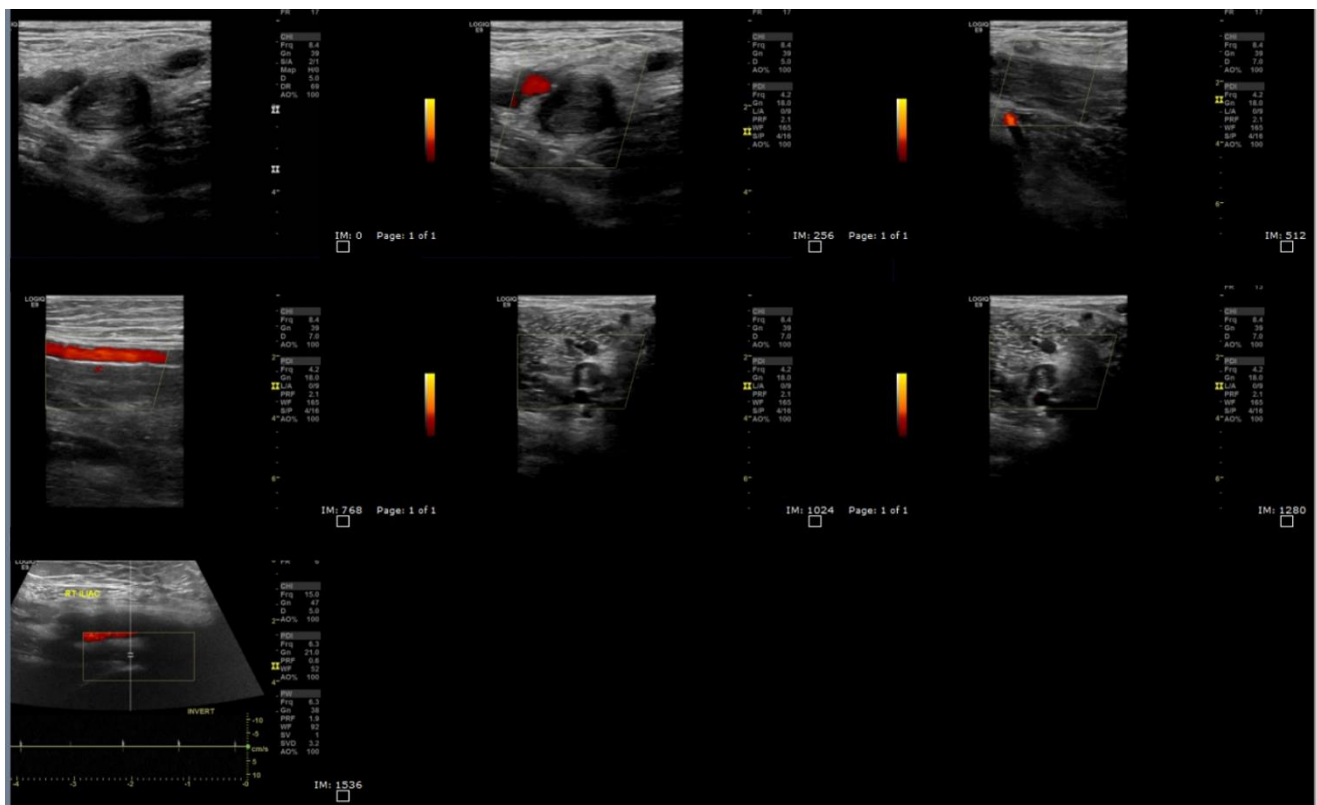


Figure 1: Obstruction of the deep venous system of the right lower limb by an acute thrombus at the right iliac vein extending to the superficial femoral vein, popliteal vein and proximal parts of the leg veins.

DISCUSSION

Protein S is a vitamin K-dependent anticoagulant protein which 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 and 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 infections like HIV.⁵

The present case raises concern about the possibility of developing recurrent thrombosis in patients diagnosed with PS deficiency within the current guidelines of the INR range between 2-3.⁶⁻⁸ This seems to be a rare occurrence due to the lack of literature with similar cases, however there have been documented cases of patients with recurrent venous thrombosis despite optimal INR in cases of Anti-Phospholipid Syndrome (APS).⁹

In the absence of guidelines for this situation, we decided that raising the therapeutic INR range from 2-3 to 3-4, keeping in mind the increased risk of bleeding with intracerebral hemorrhage being the most worrisome.

Another important aspect that we need to consider when setting a new therapeutic INR range is the possibility of warfarin-induced skin necrosis.¹⁰

Another important aspect of patient care for this case is educating patients on diet-drug interactions especially for drugs with narrow therapeutic windows like warfarin. We believe that dietary consultation during the initiation of warfarin therapy could play a crucial role in stabilizing INR to stay within the optimal range.

On the other hand, emerging oral anticoagulants, direct thrombin inhibitors and direct factor Xa inhibitors, such as dabigatran and rivaroxaban, with a predictable anticoagulant response and little potential for food or drug interactions, have been designed to be administered in fixed doses without coagulation monitoring and could be the treatment choice for these patients.

CONCLUSION

We reported a rare case of a deep vein thrombosis in presence of optimal therapeutic INR due to protein S deficiency in a 25-year-old male. Clinicians should have a high index of suspicion of recurrent DVTs even in presence of optimal INR and increasing INR range should be considered to prevent worrisome life-threatening complications.

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