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Case Report

When the Genetic Counts: A Case of Venous Thromboembolism

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Abstract

Venous thrombosis is a common condition with multifactorial etiology, affecting, on average, 1 in 1000 adults per year. Protein S deficiency (PSD) is an autosomal dominant hereditary thrombophilia, prevalent in 1.5% of individuals with deep vein thrombosis (DVT). A 49-year-old patient with a family history of venous thrombosis and autosomal dominant polycystic kidney disease was admitted due to left lower limb pain, accompanied by edema. Elevated D-dimers prompted a computed tomography angiogram, which revealed venous thrombosis of the left lower limb veins. Anticoagulation therapy was initiated with apixaban 10 mg twice daily for one week, followed by 5 mg twice daily. The patient was referred for further evaluation to determine the etiology, and neoplastic, infectious, and immunological causes were excluded. Anticoagulation was suspended for 48 hours to study thrombotic disorders, revealing a PSD. The presence of this deficiency increases the risk of developing DVT and should be investigated in cases of typical presentation.

Keywords: Thromboembolism, Protein S Deficiency, Coagulation, Hereditary Thrombophilia.

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Clinical Case

A 49-year-old male patient with a history of autosomal dominant polycystic kidney disease (Mayo classification 1A), smoking, dyslipidemia, and medicated hypertension was admitted. He had a direct family history of lower limb venous thrombosis, which was under investigation. He was admitted to the emergency department due to left leg pain. On physical examination, there was edema of the entire left lower limb with localized pain in the leg and popliteal fossa. D-dimer levels were elevated (600 ng/mL). A computed tomography angiography (CTA) showed signs suggestive of venous thrombosis in the left lower limb veins – posterial tibial artery (Fig. 1). Pulmonary embolism (PE) was excluded with a thoracic CTA. The patient was started on apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily, and was referred to an outpatient clinic for further evaluation.

In the subsequent study, a thoracoabdominal-pelvic CT showed no abnormalities, and there were no signs of anemia or other alterations in the blood tests. PSA was negative, as were autoimmune studies, HIV, and antiphospholipid syndrome (APS) tests. Endoscopic studies revealed no abnormalities. Anticoagulation was temporarily suspended for 48 hours to conduct a thrombophilia study, which revealed a deficiency in free protein S (38.7%), confirmed by two measurements. A genetic test was requested and is pending. The patient remains on anticoagulation with improvement in symptoms.

Discussion/Conclusion

Venous thrombosis is a common condition with a multifactorial etiology, affecting approximately 1 in 1,000 adults annually. Its incidence varies with age, being rare in childhood but increasing exponentially after age 60. The clinical presentation depends on the vascular territory involved, with DVT of the lower limbs and/or PE being the most common manifestations. The high morbidity and mortality associated with venous thrombosis are influenced by the severity of the acute event, the risk of recurrence, and the often debilitating chronic sequelae, such as post-thrombotic syndrome or, more rarely, thromboembolic pulmonary hypertension.

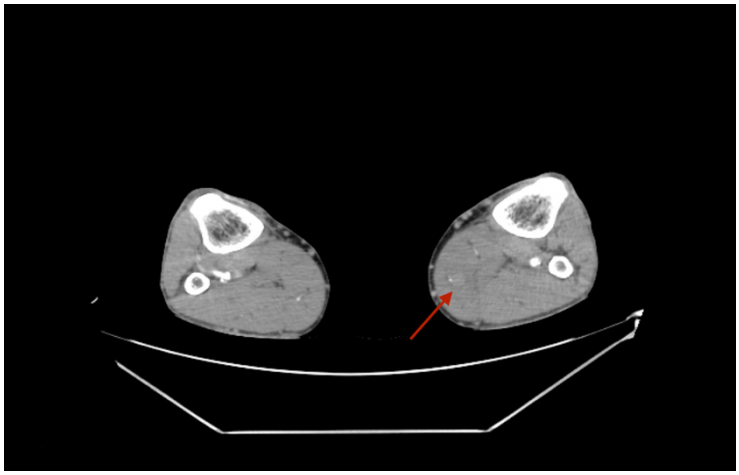

Figure 1. *Absence of contrast filler in venous phase in the posterior tibial vein on CT angiography*

In about 40% of cases, a hereditary or acquired thrombophilia can be identified. Thrombophilias are conditions characterized by an increased risk of venous, and occasionally arterial, thrombosis due to hematological abnormalities that promote blood hypercoagulability.

Protein S deficiency is the fourth most common hereditary thrombophilia, with a relative risk of a first venous thromboembolism (VTE) event being five times higher than in the general population. Protein S, named after Seattle, where it was first discovered, is a vitamin K-dependent glycoprotein. Unlike other coagulation factors, it is not a zymogen but serves as a cofactor for activated protein C, which inactivates procoagulant factors Va and VIIIa, thereby reducing thrombin generation. Protein S also aids in enhancing fibrinolysis and can inhibit prothrombin activation through interactions with other coagulation factors. PSD is an autosomal dominant hereditary thrombophilia, found in about 1.5% of individuals with DVT. Most individuals with hereditary PSD are heterozygous for a PROS1 mutation, although rare cases of homozygous or compound heterozygous individuals with more severe clinical features have been reported.

PSD is one of the most challenging hereditary thrombophilias to diagnose accurately. Protein S levels vary widely in the general population compared to protein C or antithrombin. Inherited PSD can be classified based on whether the abnormality affects total protein S antigen levels, free protein S antigen levels, or protein S function (activity). Free protein S levels are preferred for screening, as they provide the most reliable measure of true deficiency. In patients with a strong family history of VTE, only those with a free protein S antigen level below 41 international units/dL are at increased risk for a first venous thrombosis event. Combining free protein S levels with other tests, such as functional assays, does not significantly improve diagnostic accuracy. Unlike plasma-based tests, genetic testing for protein S deficiency is neither feasible nor widely available outside of research settings.

The absolute risk of VTE, the typical age of onset, and the risk of recurrence vary depending on the study population, with higher risks and earlier onset typically seen in thrombophilic families and individuals with combined inherited or acquired risk factors, as seen in our patient. Hereditary PSD is a rare risk factor for VTE in the absence of a family history. In addition to DVT and PE, thrombosis in the axillary, mesenteric, and cerebral veins has also been reported in patients with protein S deficiency.

The clinical utility of laboratory screening for thrombophilia remains controversial. Current evidence suggests that identifying thrombophilia can potentially help stratify individual risk for recurrent DVT and guide secondary prevention strategies. The initial management of acute VTE in patients with inherited protein S deficiency is similar to that in patients without an inherited thrombophilia, typically involving anticoagulation for at least three to six months. PSD does not alter the choice of anticoagulant or dosing. Indefinite anticoagulation is recommended for many patients with an unprovoked thromboembolic event, regardless of whether an inherited thrombophilia is identified. Documenting protein S deficiency may strengthen the case for indefinite anticoagulation, particularly if there is a strong family history of VTE. If a direct oral anticoagulant (DOAC) is chosen for long-term prevention of recurrent VTE, a higher dose regimen (e.g., rivaroxaban 20 mg once daily or apixaban 5 mg twice daily, rather than rivaroxaban 10 mg once daily or apixaban 2.5 mg twice daily) is generally recommended, provided the individual's bleeding risk is not excessive. This approach is taken because protein S deficiency is one of the more thrombogenic hereditary thrombophilia. It is important for both the prescribing physician and the patient to understand that evidence for the optimal dose in such patients is still lacking.

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