Protein S Deficiency and Arterial Thromboembolism: A Case Report and Review of the Literature

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Abstract

Protein S (PS) deficiency is associated with a well documented risk of venous thromboembolism. However, the relation between PS deficiency itself to arterial thrombotic events (ATEs) is not clearly established. In our case, we report an ATE in a patient with a documented novel PROS1 mutation and a family history of PS deficiency. Other etiologies for arterial thrombosis were excluded. The role of precise diagnosis with levels of PS and documentation for mutational analysis are discussed. We highlight the problems with diagnosis in previously reported cases with arterial thrombotic events and discuss the potential for treatment with antiplatelet therapy in a subset of patients with PS deficiency.

Keywords: Protein S deficiency; Arterial thromboembolism; Thrombosis

Introduction

Protein S (PS) is a vitamin K dependent plasma glycoprotein that is synthesized by the liver, vascular endothelium, monocytes and megakaryocytes. PS serves as a cofactor for activated protein C (APC) and the degradation/deactivation of activated coagulation factor V (FV) and activated coagulation factor VIII (FVIIIa), resulting in the restriction of thrombin generation. PS also inhibits the tissue factor pathway. PS deficiency is a thrombophilic condition inherited in an autosomal dominant fashion with mutations in the PROS1 gene on chromosome 3 \[1\]. PS deficiency and the risk of venous thrombosis are well documented in literature \[2\]. This risk is compounded by other factors such as genetic thrombophilic deficiencies and acquired situations i.e. trauma, estrogens, pregnancy, HIV infection, age, immobilization, cancer, hypertension, diabetes, hyperlipidemia, smoking and others. However, the relation of PS deficiency itself to arterial events is not clearly established \[3\].

In this report we document the presentation of an arterial thrombotic event (ATE) in a patient with PS deficiency.

Case Report

A 78-year-old Caucasian female with a history of PS deficiency and on warfarin presented with sudden onset of right arm weakness. As the patient had hematuria 1 week prior to admission, warfarin was currently being withheld. Her past medical history included a diagnosis of PS deficiency for more than 25 years, aortic and mitral regurgitation, iron deficiency anemia secondary to chronic gastrointestinal blood loss, diverticulitis, and an open cholecystectomy. The patient had no history of diabetes, hypertension, dyslipidemia, or smoking. She had no previous thrombotic events and had multiple uneventful pregnancies. She has several family members (son, granddaughter, and grandson) with PS deficiency who had venous thrombotic episodes. Physical exam showed her fully alert and oriented, temperature was 37.0 °C, blood pressure was 112/80 mm Hg, heart rate was 65 beats per minute, respiratory rate was 10 breaths per minute, and oxygen saturation was normal. Cardiac examination showed regular sinus rhythm and a mild apical systolic murmur. Neck exam showed no carotid bruits or venous distension. Lungs were clear to auscultation. Abdomen was non-tender and no organomegaly was detected. Lymph nodes were not palpable. The legs were free of edema and there was no calf tenderness or erythema. Neurological exam revealed 3/5 strength in the right hand and forearm and mild ataxia on the right finger-to-nose test. The remainder of the neurologic exam was normal.

Complete blood count (CBC) revealed hemoglobin of 94 g/L (121 - 157 g/L), hematocrit of 31.5% (35.0 % - 46.1%), white cell count of 8.3 × 10\(^3\)/L (3.4 - 10.3 × 10\(^3\)/L), and a platelet count of 51%. Protein C levels were not done as the patient was on warfarin. Genetic testing revealed the mutation to be PROS1, c.447G>T heterozygous (p.Trp149Cys). Factor V Leiden and
prothrombin mutations were absent, and the antithrombin level was normal. A non-contrast head computed tomography (CT) showed no acute abnormalities. Tissue plasminogen activator (tPA) was administered but was withdrawn due to repeated headaches. The magnetic resonance imaging (MRI) brain revealed bilateral small infarcts and one larger 1.5 cm cortical infarct in the left frontoparietal lobe; these findings were consistent with likely embolic phenomena. The magnetic resonance angiogram (MRA) of the head and neck showed no significant signs of focal stenosis, aneurysms, or vascular malformations. The carotid ultrasound, transthoracic echocardiogram, and transoesophageal echocardiogram all were negative. Cardiac rhythm remained normal during her hospitalization.

Over the course of her hospital stay her arm strength began to improve.

**Discussion**

In our patient the level of PS, family history, and **PROS1** mutations were normal. The antithrombin level was normal.

A non-contrast head computed tomography (CT) showed no acute abnormalities. Tissue plasminogen activator (tPA) was administered but was withdrawn due to repeated headaches. The magnetic resonance imaging (MRI) brain revealed bilateral small infarcts and one larger 1.5 cm cortical infarct in the left frontoparietal lobe; these findings were consistent with likely embolic phenomena. The magnetic resonance angiogram (MRA) of the head and neck showed no significant signs of focal stenosis, aneurysms, or vascular malformations. The carotid ultrasound, transthoracic echocardiogram, and transoesophageal echocardiogram all were negative. Cardiac rhythm remained normal during her hospitalization.

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**Conflict of Interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

**Financial Disclosure**

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