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Case Report

# Hypercoagulability and Cavernous Sinus Thrombosis due to Protein C Deficiency. A Case Report

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## Abstract

**Background:** Thrombophilia due to Protein C deficiency is a rare condition, present in 0.2% of general population. Cerebral venous thrombosis has an incidence of 3-4 cases per million in adults. A combination of both is very uncommon. Patients with these conditions are prone to life-threatening superinfections. **Case:** A 51-year-old woman presented with pressing frontal headache accompanied with left periorbital edema, fever, diplopia, and disorientation. Laboratory findings showed low protein C levels. Computed tomography demonstrated sphenoidal rhinosinusitis. Magnetic resonance venography revealed cavernous sinus thrombosis. The patient was started on empiric antibiotic treatment (vancomycin, ceftriaxone, and metronidazole) and anticoagulants. **Conclusion:** This case report emphasizes the importance of early diagnosis and appropriate management of patients with protein C deficiency complicated by septic cavernous sinus thrombosis.

**Key Words:** Thrombophilia; Protein C deficiency; Cavernous sinus thrombosis; Case report (Source: MeSH-NLM).

## Introduction

Protein C deficiency (PCD) is a rare disorder with a prevalence of approximately 0.2% in general population.[1,2] Protein C is a vitamin K-dependent glycoprotein activated by the thrombin-thrombomodulin complex on the endothelial surface. Activated Protein C degrades factors Va and VIIIa of the coagulation cascade, thereby inhibiting coagulation. In addition, it is involved in regulating the expression of endothelial proteins related to inflammation and cell survival.[3] PCD, therefore, promotes thrombus formation. Inheritance of the gene can be either an autosomal dominant inherited disease with an alteration of the Protein C Inactivator of Coagulation (PROC) gene or, less commonly, as an acquired disease.[4] Expression of the PROC gene can be decreased in certain pathological states, including right heart failure, severe liver disease, acute inflammation, and respiratory syndromes, by consumption and the dysfunctional production of activated Protein C.[2] There are two phenotypes of PCD: Type 1 is described as a mutation that reduces the plasmatic concentration of Protein C antigen and its activity, whereas Type 2 is characterized by normal concentrations of the protein, but with dysfunctional activity.[2] This deficiency has a wide range of manifestations from asymptomatic to life-threatening conditions.[4]

Cavernous sinus thrombosis (CST) belongs to the group of cerebral venous thromboses. It has nonspecific clinical manifestations such as headache, painful ophthalmoplegia, conjunctival chemosis, and ocular proptosis.[5,6] CST can be either septic or aseptic; septic form being the most common, with Methicillin-resistant Staphylococcus aureus (MRSA), followed by Methicillin Sensitive Staphylococcus aureus (MSSA) being the most reported causative organisms.[7,8] In a literature review, it was found that 57% of patients with septic CST had sphenoidal rhinosinusitis (inflammation of the nasal mucosa (rhinitis) and the mucosa of the paranasal sinuses (sinusitis)).[8]

### Highlights:

- Patients with undiagnosed thrombophilia have a 3-8% risk of developing cerebral venous thrombosis.
- 3-4 per million cases may develop cerebral venous thrombosis, which can be later complicated by a septic cavernous sinus thrombosis.
- Patients complicated with septic cavernous sinus thrombosis demonstrated to have sphenoidal rhinosinusitis in 57% of the cases.
- A middle-aged patient without any medical or family history of thrombophilia, can develop a cerebral venous thrombosis due to Protein C Deficiency.
- A combination of a septic cavernous sinus thrombosis and a thrombophilia can be correctly managed with early anticoagulation and antibiotic treatment.

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## The Case

A 51-year-old female patient with an unremarkable medical history (no previous similar events, nonsmoker, no surgical history, no miscarriages, no contraceptive pill use) and without family history of thrombophilia, presented to the emergency department with a bilateral pressing frontal headache present for 3 months that gradually increased in severity and did not respond to acetaminophen. A non-contrast computed tomography showed sphenoidal rhinosinusitis and a parenchymal lesion was excluded. The patient was diagnosed with migraine and NSAIDs were prescribed. No treatment for rhinosinusitis was indicated.

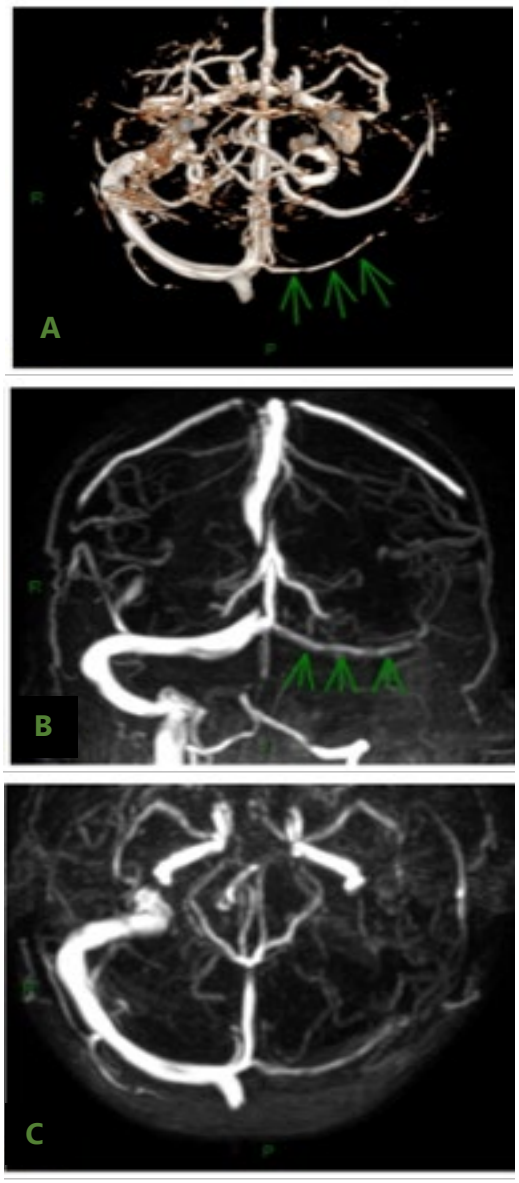
After 2 weeks, the headaches worsened, and her family took her back to the emergency department. During this admission, the patient had left periorbital edema, diplopia, and disorientation to time and place. Physical examination revealed left eye proptosis, nystagmus, limitation of extraocular movements, and papilledema with tortuous left retinal veins on fundoscopy. Remarkable vital signs included a respiration rate of 22/min, temperature of 38.1°C, and pulse rate of 110/min. Based on clinical presentation, differential diagnosis was: subarachnoid hemorrhage, epidural hematoma, bacterial/viral meningitis, and periorbital infection.

Procalcitonin level was 0.783 ng/ml (<0.5 ng/ml normal range); neutrophil level was 14107 $mm^3$ (2000-8000$mm^3$ normal range); C-reactive protein level was 235.9 mg/L (0-10mg/L normal range); and D-Dimer level was 819 mg/ml (0-500 normal range). Prothrombin time, INR, and Partial Thromboplastin Time were within normal ranges. Lipid panel, liver, and renal function markers were normal. Antinuclear antibodies and anti-dsDNA were negative. Due to the possibility of periorbital cellulitis and infection, intravenous empiric antibiotic treatment was started with vancomycin (loading dose of 15mg/kg/ BID), ceftriaxone (2g/BID), and metronidazole (500mg/ TID). Urine and blood cultures were taken prior to antibiotic treatment, and both resulted negative. Based on the neurological findings, imaging studies of the brain were indicated. Magnetic Resonance Venography showed filling defects of the left cavernous sinus compatible with cavernous sinus thrombosis. As a result of the radiological findings, anticoagulation therapy was started with enoxaparin (1mg/kg BID, total dose 60mg BID). Hemorrhage and infections of the central nervous system were excluded based on clinical presentation and laboratory and imaging studies.

Hypercoagulability tests revealed a Type 1 Protein C deficiency with reduced functionality and antigenic plasmatic Protein C levels at 30.98% (70%-140% normal ranges). Antiphospholipid antibodies, protein S, antithrombin III, and homocysteine levels were within normal ranges. Factor V Leiden and prothrombin mutations were not detected.

After seven days of hospitalization, laboratory findings were consistent with resolution of the infectious process (procalcitonin of 0.208 ng/ml, C-reactive protein of 40.10mg/L, and neutrophils of 5239$mm^3$). Blood and urine cultures remained negative. The patient showed significant clinical improvement and was discharged on oral antibiotics (amoxicillin/clavulanic acid 1g/ BID for 5 weeks) and long-term oral anticoagulants (Dabigatran 150mg/ BID). Follow-up with hematology department was indicated after 6 months of discharged and then every year. At eight months follow up, imaging studies were consistent with complete resolution of the thrombotic event and the sphenoidal rhinosinusitis.

***Figure 1.*** Brain Magnetic Resonance Venography Confirming Cavernous Sinus Thrombosis.



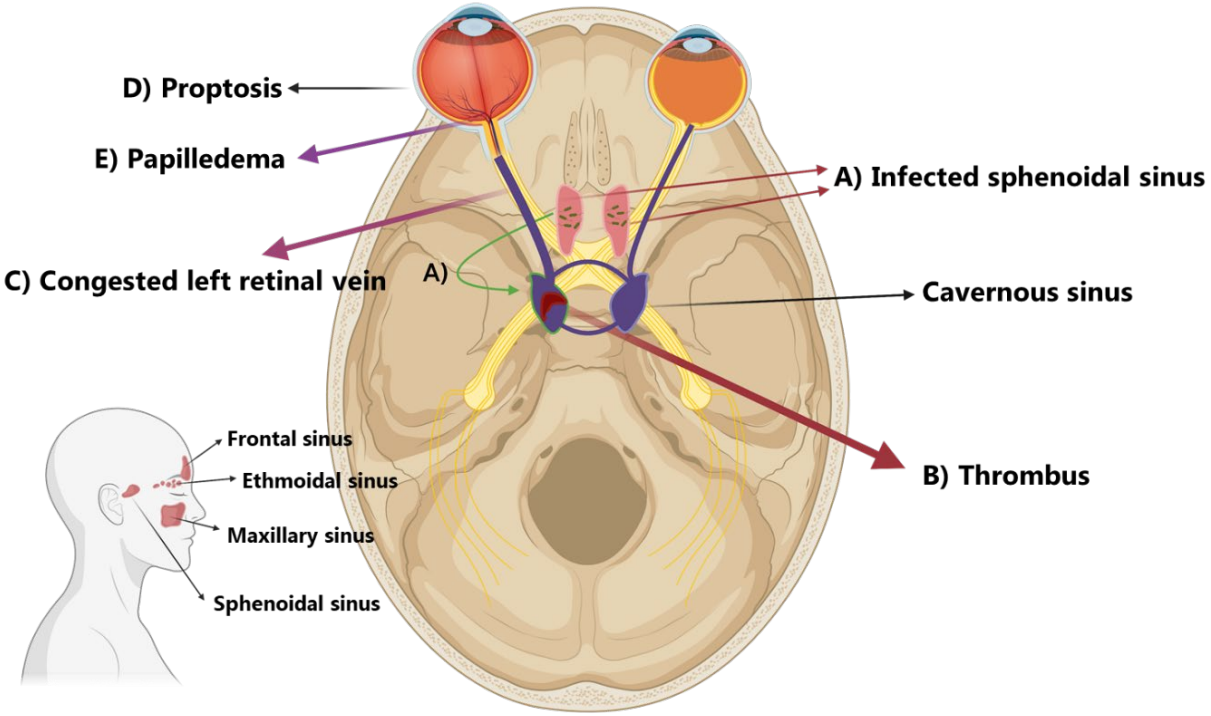

***Legend:*** **A:** 3D Reconstruction of a Magnetic resonance cerebral venography. Axial section, cranial view. **B:** Magnetic resonance cerebral venography. Coronal section. **C:** Magnetic resonance cerebral venography. Axial section, cranial view. All of them show decreased diameter, signal intensity and filling defects of the left transverse sinus and ipsilateral internal jugular vein (green arrows). Tortuosity and dilatation of the left ophthalmic veins are also present.

## Discussion

This case report presents a patient with thrombophilia due to Type 1 PCD complicated by cavernous thrombosis. Septic CST was supported by periorbital cellulitis and laboratory findings. Weerasinghe & Lueck et al. reported a similar case with septic CST caused by MSSA, however the patient did not have a three-month headache history, diplopia, or fundoscopic abnormalities.[8] Type 1 PCD was suspected in this case due to low Protein C plasmatic levels associated with a thrombotic event. This is unlike a case described by Fukushima et al. where normal plasmatic Protein C levels increased the suspicion of type 2 PCD and their patient presented with seizures and paralysis.[9] The diagnosis of our patient was established by referring to the Protein C activity assay using the immunofluorescence method. However, genetic analysis was preferred in Fukushima´s et al report.[9]

The risk of venous thromboembolism in patients with PCD is around 3-8%.[1] Cavernous thrombosis as a complication of an infectious process is more common in patients that have prothrombotic risk factors, such as deficiency of coagulation factors, trauma, smoking, oral contraceptive pills use, or previous surgery (*Figure 2*).[2,5] The aforementioned risk factors were not declared by the patient during the clinical interview. This supports the hypothesis of a possible inherited PCD triggered by an unidentified infection.[4] There have been some cases reported of patients without any family history of hypercoagulable states that developed a thrombotic event and found to have thrombophilia.[2]

***Figure 2.*** Simplified Graphic of an Infected Cavernous Sinus Thrombosis.




***Legend:*** **A)** An infected sphenoid sinus causes septic thrombosis in the cavernous sinus, **B)** In cavernous thrombosis, the facial vein, and superior and inferior ophthalmic veins **C)** cannot drain properly, resulting in facial and periorbital edema, ptosis, proptosis **D)**, chemosis, eye movement discomfort, papilledema (**E)**, retinal vein dilation, and vision loss. This image was created with Biorender.

The imaging studies recommended for the diagnosis of CST are contrast-enhanced computed tomography, magnetic resonance imaging, or magnetic resonance venography.[7] In this case report, all these imaging studies were used. Magnetic Resonance Imaging was normal, and contrast enhanced computed tomography revealed sphenoidal rhinosinusitis. Magnetic Resonance Venography showed enlargement and filling defect in the left cavernous sinus after contrast administration. Tortuosity and dilatation of the left ophthalmic veins were present. Central filling defects in the left transverse and sigmoid sinuses accompany these findings (*Figure 1*).

Due to undetermined timeline of sphenoidal rhinosinusitis, the recommended 10 days antibiotic treatment was extended to 5 weeks by the infectious disease department. According to the management of chronic rhinosinusitis described by Baron & Durand in 2017, a minimum of 3 weeks of antibiotic course is recommended. Some symptoms of chronic rhinosinusitis tend to reappear after 10 days of treatment.[10]

At 8 months, imaging studies were consistent with complete resolution of the thrombotic event and sphenoidal rhinosinusitis. The continuation of anticoagulation with a direct oral anticoagulant (Dabigatran) after hospitalization showed no

recurrence of thrombotic events, similar to what was reported by Fukushima et al. [9]

The limitation of this case is the uncertainty about its infectious etiology. Cultures resulted negative and a nasopharyngeal swab for bacteria was not performed. Due to a possible chronic sphenoidal rhinosinusitis as the infectious source, empirical prolonged antibiotic treatment was prescribed (this is debatable). Moreover, because of diplopia, confrontation visual field examination could not be assessed correctly

### Conclusions

Although rare, a patient without medical and family history of thrombophilia may develop cerebral venous thrombosis because of Protein C Deficiency. Sinus infection may worsen the clinical state. Early recognition with clinical examination and imaging studies, followed by prompt intervention with anticoagulation and broad-spectrum antibiotics, is associated with a good prognosis for patients with septic CST due to hypercoagulability.

## Summary – Accelerating Translation

Este reporte de caso presenta a un paciente con trombofilia debido a una deficiencia de proteina C (DPC) tipo 1 complicado por una trombosis del seno cavernoso (TSC). La TSC séptica fue confirmada por celulitis periorbitaria y hallazgos de laboratorio. El paciente también presentaba historia de dolores de cabeza de 3 meses, diplopía y anormalidades fundoscópicas. La sospecha de DCP tipo 1 surgió debido a bajos niveles plasmáticos de Proteína C asociados con un evento trombótico. La tomografía computarizada mejorada con contraste y la resonancia magnética venográfica mostraron un aumento y un defecto de llenado en el seno cavernoso izquierdo después de la administración de contraste, así como tortuosidad y dilatación de las venas oftálmicas izquierdas. Se recomendó un tratamiento prolongado de 5 semanas con antibióticos debido a una posible rinosinusitis esfenoidal crónica como fuente infecciosa. En el seguimiento a los 8 meses, se observó una resolución completa del evento trombótico y de la rinosinusitis esfenoidal. Se realizó anticoagulación oral (Dabigatrán) después del alta hospitalaria, lo que evitó la recurrencia de eventos trombóticos. Las limitaciones del caso incluyen la falta de cultivos positivos y la ausencia de una muestra de hisopado nasofaríngeo para bacterias.

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