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Unveiling the enigma: A challenging case of protein C deficiency concealed by fever and epistaxis

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Abstract

Protein C deficiency is a rare genetic disorder caused by mutations in the protein C, inactivator of coagulation factors Va and VIIA gene, affecting approximately 1 in 200–500 individuals. It leads to a hypercoagulable state, increasing the risk of blood clots. Symptoms vary with age, ranging from life-threatening purpura fulminans in neonates to venous thromboembolism, particularly deep vein thrombosis, in adults. A recent case involved a 21-year-old South Asian male presenting with persistent fever, weight loss, epistaxis, abdominal tenderness, and acute pain in the right thigh and leg, raising suspicion of deep vein thrombosis. Tests confirmed deep vein thrombosis in multiple leg veins and a pulmonary embolism. The patient was diagnosed with protein C deficiency and received anticoagulant therapy, thrombolysis, and an inferior vena cava filter. Complications of protein C deficiency include deep vein thrombosis, pulmonary embolism, stroke, and ischemic colitis. Diagnosis involves immunoassays and genetic analysis. Treatment includes heparin followed by anticoagulation therapy with warfarin. In severe cases, an inferior vena cava filter may be implanted. The described case required extensive treatment due to multiple deep vein thrombosis and a pulmonary embolism, with lifelong anticoagulant therapy. Early diagnosis and appropriate management are crucial in young patients with a history of venous thromboembolism to prevent and manage complications associated with protein C deficiency.

Keywords

Protein C deficiency, DVT, PE, case report

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Background

Protein C (PrC) deficiency is a rare genetic disorder with an estimated prevalence of approximately 1 in 200–500 individuals in the general population.[1] Protein C, inactivator of coagulation factors Va and VIIA (PROC) mutations are inherited in an autosomal dominant manner; however, they can be due to spontaneous gene mutations. More than 160 PROC gene mutations have been discovered till now. Type I PrC deficiency refers to low levels and type II refers to dysfunction of protein C. Both these cause loss of its ability to inactivate coagulation factors Va and VIIIa leading to a hypercoagulable state.[2]

Clinical presentation of protein C deficiency hugely depends on the age of onset, the severity of the deficiency, and other contributing factors such as additional genetic mutations or acquired risk factors. PrC deficiency in neonates can manifest as purpura fulminans, a life-threatening condition characterized by widespread blood clotting and skin necrosis.[3] While in adults, the most common manifestation is venous thromboembolism, particularly deep vein thrombosis (DVT).[4] Patients may present with symptoms such as swelling, pain, warmth, and redness in the affected limb. Clot dislodging and traveling to the lungs can cause pulmonary embolism, which can be life-threatening.

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The current treatment for severe PrC deficiency consists of PrC replacement and the use of oral anticoagulant medication to treat and prevent thrombosis. Exogenous protein can be provided in the form of fresh frozen plasma or, preferably, as pure PrC concentrate.[5] However, the use of medical treatment alone may not be sufficient in certain situations, such as when there is a high risk of clot dislodgement or recurrence. The decision to place an IVC filter is usually tailored taking into consideration the patient's individual risk factors, clot burden, and bleeding risk the placement of an inferior vena cava (IVC) filter may be indicated.[6] An IVC filter is a device that is inserted into the IVC, acting as a physical barrier, trapping clots and preventing them from traveling to the lungs causing pulmonary embolism.

Here we present you with a case of a young male who presented to the emergency department with fever, chills, abdominal pain, and a history of epistaxis. Later on, an inquiry into a history of leg pain raised suspicions of DVT, ultimately leading to the diagnosis of PrC deficiency. This case report highlights the importance of recognizing unusual symptoms and considering underlying conditions such as PrC deficiency in the diagnostic process.

Case presentation

An emergency department was visited by a 21-year-old South Asian male who was experiencing a persistent fever of 103°F for a month. He also complained of rigors and chills. During the same period, he noticed a significant weight loss of 2.5 kg. Two weeks before his hospital visit, he had an episode of epistaxis.

The patient initially exhibited symptoms of fever, nosebleeds, and abdominal pain, which led to a suspicion of an infectious disease. Upon further inquiry, the patient reported experiencing intense and acute pain in their right thigh and leg, despite no history of physical injury and no evidence of a long period of immobility. This raised suspicions of DVT. A thorough evaluation of disorders running in the family was conducted, and the patient did not report any major family history of bleeding disorders or other clotting disorders. As a result, investigations were conducted to determine the underlying cause of DVT.

On hospital admission, his vital signs were stable, with a blood pressure of 133/82 mmHg, pulse rate of 100 bpm, and SpO2 of 98% at room air. He also had a fever of 103°F. On physical examination, the patient was awake, and no immediate concerning findings were observed. However, tenderness was noted during the abdominal examination. Neurological examination revealed no significant findings and the patient's Glasgow coma scale was 15/15.

Initial laboratory results revealed a hemoglobin level of 10 g/dl, a platelet count of 504×10^9/μl, a total leukocyte count of 12×10^8/μl, and CRP (C-reactive protein) levels of 31.6 mg/dL (normal range 0.3–1.0 mg/dL). His coagulation profile revealed a PT (Prothrombin time) of 12.6 s, APTT (activated partial thromboplastin time) of 30.6 s and an INR of 1.28. Laboratory analysis via ELISA (Eenzyme-linked immunosorbent assay) revealed that the patient's PrC levels were measured at 9 IU/dL, indicating a low concentration. The renal profile, including blood urea nitrogen, urea, and creatinine, fell within normal ranges. Molecular testing could not be performed as the patient had financial constraints.

After the administration of antibiotics (azithromycin 500 mg, once daily for 3 days) and paracetamol initially, the patient's fever subsided, but his leg pain persisted. Further radiological investigation, specifically a venogram, was conducted, which revealed the presence of a thrombus in several veins of the right leg, including the right popliteal vein, right superficial femoral vein, right common femoral vein, right external iliac vein, and right common iliac vein. In addition, a pulmonary embolism was detected in the descending branch of the right pulmonary artery. The patient also had a femoral sheath hematoma, which was later drained. These findings led to the diagnosis of DVT in the right leg.

To manage the condition, the patient received intravenous heparin (10,000 IU) and was prescribed rivaroxaban tablets for continued treatment. The patient was later scheduled for thrombolysis of the right-sided DVT with tPA (Tissue plasminogen activator) balloon placement. In addition, he was started on Aggrastat infusion as a maintenance therapy. Further management involved the placement of an MRI-compatible IVC filter below the right renal veins, with its hook positioned at the inferior end plate of L1. Low molecular weight heparin was also prescribed for 3 months.

Discussion

PrC is a plasma zymogen that relies on vitamin K and has a molecular weight of 62 kDa. Once it is activated into a serine protease, PC plays a crucial role in the physiological regulation of blood coagulation.[7] PrC deficiency is a rare qualitative blood disorder that is linked to an elevated risk of developing abnormal blood clots which leads to thrombosis. The active form of protein C, known as APC, possesses potent anticoagulant properties. A deficiency in this protein can disrupt the blood coagulation process, leading to an increased production of blood clots. The underlying cause of PrC deficiency is a mutation in the PROC gene. This mutation is more frequently observed in Asian patients and tends to affect children more often than adults. PrC deficiency can either be acquired or present from birth (congenital). In terms of disease severity, the mild form of the condition is estimated to occur in approximately 1 in 200 to 1 in 500 individuals, while severe clinical cases are extremely rare.[1] PrC deficiency can present as deep venous thrombosis, pulmonary embolism, stroke, or ischemic colitis. Ischemic colitis can cause abdominal pain, but there was no such finding in this particular patient. Hence, understanding the body's intrinsic anticoagulants and thrombophilic conditions can aid in the prevention and treatment of these frequently

life-threatening complications.[8,9] Various cases have been reported of PrC deficiency which leads to the development of ischemia in the brain, intestines, pulmonary vasculature, and even eyes. Tina et al. reported a case of a 59-year-old woman who presented with recurrent transient monocular vision loss and a history of stroke, which was attributed to PrC deficiency.[10] Another case report by Luis MHR et al. described a case of a 15-year-old female who presented with diffuse abdominal pain and was diagnosed with acute mesenteric ischemia secondary to combined protein C and S deficiencies.[11]

PrC deficiency can be diagnosed through immunoassays such as ELISA, as well as genetic analysis to identify mutations in the PROC gene.[12] The initial acute treatment for this rare qualitative disorder involves the administration of heparin, followed by a gradual introduction of anticoagulation therapy, with warfarin being the most effective agent. The duration of treatment varies based on the number of thrombotic events. Patients experiencing their first thrombotic event are typically treated with oral anticoagulants for a period of 3–6 months, whereas those who encounter subsequent episodes require lifelong treatment with warfarin or low molecular weight heparin.[13] As part of early treatment or in cases where anti-coagulation has been ineffective or contraindicated, an IVC filter may also be implanted.[14]

In our case, the patient presented with extensive DVTs in several vessels of the right lower limb. In addition, there was also a pulmonary embolism detected in the descending branch of the right pulmonary artery. The patient then underwent thrombolysis and IVC filter placement and was prescribed lifelong oral anticoagulants.

Limitations

This study has its limitations. First, molecular testing was not possible due to the financial constraints of the patient. In addition, the patient did not return for follow-up visits, which hindered our ability to record long-term management and outcomes.

Conclusion

In young patients, the presence of typical symptoms such as abdominal tenderness, fever, and chills may sometimes be due to atypical manifestations of DVT and PE. These unusual presentations can be attributed to rare disorders that typically emerge during adolescence. One potential cause of thrombotic disorders is protein C deficiency, which should be taken into account in these individuals, particularly if they have a history of DVT or other vascular thromboses.

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Ethical approval

This report does not contain any personal information that could lead to the identification of the patient. Therefore, it is exempted from ethical approval. Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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