Venous Thrombosis Associated with Complement Factor H Mutation: Highlighting Complement–Coagulation Crosstalk - A Case Report

Abstract

Complement Factor H (CFH) is a key regulator of the alternative complement pathway, and mutations in its gene are commonly associated with atypical hemolytic uremic syndrome (aHUS). Typically linked to renal thrombotic microangiopathy (TMA), CFH also interacts with coagulation factors, suggesting its role in thrombosis. We describe a 22-year-old male with AKI, nephrotic-range proteinuria, and anuria. Renal biopsy revealed chronic TMA. A CT revealed partial thrombosis of the right internal jugular vein (IJV). Thrombophilia workup was unremarkable. Genetic testing identified a pathogenic heterozygous *CFH* mutation (c.3572C>T; p.Ser1191Leu). This case illustrates an unusual CFH deficiency with venous thrombosis in the absence of traditional risk factors. Structural similarities between CFH and β2-glycoprotein I may underlie its anticoagulant function. Complement dysregulation should be considered in the differential diagnosis of unexplained thrombosis, particularly when associated with renal dysfunction.

Keywords: *Atypical hemolytic syndrome, Complement factor H mutation, Thrombotic microangiopathy, Venous thrombosis.*

Introduction

Complement factor H (CFH) is a key inhibitor of the alternative complement pathway. Factor H abnormalities have been linked to renal disorders like C3 glomerulopathy and atypical hemolytic uremic syndrome (aHUS).[1] Evidence suggests that Factor H interacts with multiple coagulation factors, also highlighting its emerging role in the coagulation cascade.[2] We present the case of a 22-year-old male who developed chronic thrombotic microangiopathy (TMA) and venous thrombosis due to CFH deficiency, highlighting the potential compliment coagulation crosstalk.

Case Report

A 22-year-old male presented with fever, vomiting, and headache, followed by anasarca, anuria, and shortness of breath.

On evaluation, the patient was hypertensive (BP-180/100 mmHg). Laboratory tests showed renal dysfunction (serum creatinine: 9.7 mg/dL, blood urea nitrogen [BUN]: 126 mg/dL) and anemia (hemoglobin: 9.2 g/dL, WBC count: 11.3×10^3/µL, platelets: 2.33×10^5/µL). There was no evidence of hemolysis, as the peripheral smear was negative for schistocytes, and lactate dehydrogenase (LDH) was 270 U/L. Urinalysis revealed 4+ protein and 2–4 RBCs per high-power field, with a spot urine protein-to-creatinine ratio (UPCR) of 3.1. Complement levels were normal, and tests for antinuclear antibodies (ANA), anti-glomerular basement membrane (anti-GBM) antibodies, and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Renal biopsy findings were consistent with chronic TMA, revealing 3/12 sclerosed glomeruli, 1/12 with segmental sclerosis, and ischemic changes in the remaining viable glomeruli [Figure 1a]. There was significant interstitial fibrosis and tubular atrophy (50%), along with marked vascular thickening. Immunofluorescence was negative.

Due to anuria, dialysis was planned via the right internal jugular vein (IJV). However, failed cannulation of both IJVs prompted a venous Doppler, which revealed bilateral IJV thrombosis and complete left cephalic vein thrombosis. Anticoagulation was initiated. A computed tomography (CT) venogram performed after 5 days showed partial thrombosis of the right IJV [Figure 1b] and significant attenuation of the left IJV's cranial portion. The patient had no history of prior cannulation. Thrombophilia workup, including Protein C, Protein S, antithrombin III, Factor V Leiden, Prothrombin G mutation, anticardiolipin antibodies, anti-β-2 glycoprotein antibodies, and lupus anticoagulant, was negative. Plasma homocysteine was 6.59 µmol/L (<15 µmol/L).

Whole-exome sequencing identified a pathogenic heterozygous missense mutation in exon 22 of the *CFH* gene (c.3572C>T; p.Ser1191Leu). Due to the lack of venous access, the patient was started on peritoneal dialysis. His hospital course was complicated by recurrent pulmonary edema from refractory hypertension. After stabilization, he was discharged in a hemodynamically stable condition but succumbed to his illness at home 2 months later.

Discussion

CFH mutations are the most common genetic abnormalities associated with aHUS, accounting for 20-30% of cases.[3] These mutations impair CFH's ability to bind surface-bound C3b, reducing the degradation of C3b and C3 convertase, which leads to excessive complement activation. Although our patient had normal complement levels, decreased C3 was observed in only 30-50% of patients with *CFH* mutations.[4]

aHUS is a TMA that primarily involves the arterioles and capillaries of parenchymatous organs. However, our patient also presented with unprovoked venous thrombosis of the bilateral IJV and left cephalic vein. CFH and β2-glycoprotein I (β2-GP-1) share structural similarities and bind to anionic phospholipids like phosphatidylserine on activated platelets. This binding prevents the attachment of clotting factors, such as factor XII, and limits the assembly of the

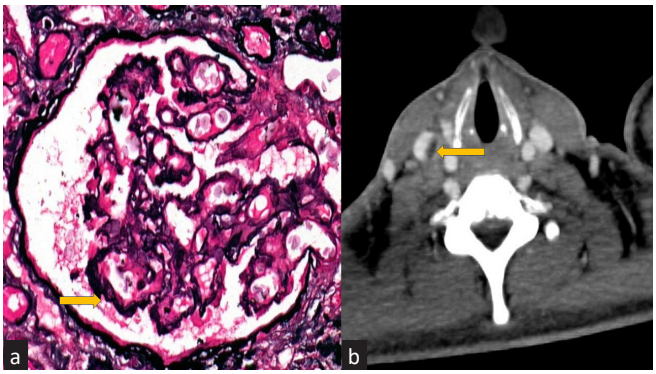

Figure 1: (a) Light microscopy showing a single glomerulus with ischemic changes in the form of wrinkling of basement membrane (yellow arrow) and mesangiolysis on Jones methenamine silver stain 400x. (b) Computated tomography venogram showing a hypodense filling defect (yellow arrow) in the lumen of right internal jugular vein, suggestive of partial thrombosis.

prothrombinase complex, thereby maintaining an anti-thrombotic state.[5] With all prothrombotic tests negative, we propose that factor H deficiency is the underlying cause of venous thrombosis, highlighting its central role in linking the complement and coagulation pathways.

A 4-year-old Indian girl with anti-Factor H-mediated aHUS developed fingertip gangrene due to thrombosis of the digital arteries.[6] Thrombotic involvement of small, medium, and even branches of large arteries leading to stroke, peripheral gangrene, and ischemic pancreatitis has also been reported in adults with aHUS.[7] Greenwood reported aHUS with bilateral retinal arterial and venous occlusion, successfully treated with eculizumab.[8]

Through this case, we aim to highlight a potential mechanistic link between CFH deficiency and thrombotic events, and to propose complement dysregulation as a rare but important consideration in patients with unexplained thrombosis.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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