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Hereditary atypical hemolytic uremic syndrome in a solitary kidney patient: a case report

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ABSTRACT

Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy (TMA) primarily driven by uncontrolled activation of the alternative complement pathway. Genetic mutations in complement regulatory proteins are identified in most cases, highlighting the hereditary nature of the disease.

Case Presentation: This report describes the case of a male in his late 40s with a solitary kidney (following a prior living donor nephrectomy for his father) who presented to an outpatient nephrology clinic with worsening renal function, newly diagnosed microangiopathic hemolytic anemia, and progressive thrombocytopenia. After comprehensive testing ruled out underlying secondary causes, targeted genetic testing identified a pathogenic heterozygous variant in complement factor H, supporting a diagnosis of suspected complement-mediated TMA. Despite the nephrologist prescribing targeted terminal complement inhibition (ravulizumab), insurance authorization was denied. Following a period of conservative management and the resolution of an unidentified trigger, the patient's renal function spontaneously stabilized. He was referred to a specialty clinic and is currently undergoing close clinical monitoring, with a contingency to initiate alternative complement-directed therapies if his condition acutely deteriorates.

Conclusion: This case highlights the clinical complexities of diagnosing suspected adult-onset hereditary aHUS, particularly in vulnerable patients with a solitary kidney. It underscores the challenges of treatment accessibility, the importance of interpreting genetic and familial data cautiously, and the necessity of vigilant monitoring as disease penetrance increases with age.

Keywords: Atypical hemolytic uremic syndrome, thrombotic microangiopathy, solitary kidney, complement factor H, genetic mutation.

Type of Article: CASE REPORT **Specialty:** Nephrology

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Introduction

Hemolytic uremic syndrome (HUS) is clinically defined by the triad of nonimmune microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure [1]. These clinical features are the result of a pathological lesion known as thrombotic microangiopathy (TMA), characterized by fibrin and platelet thrombi within the microcirculation, particularly the renal arterioles and capillaries [1,2].

While typical HUS is most commonly associated with gastrointestinal infections from Shiga toxin-producing *Escherichia coli* (STEC), atypical HUS (aHUS) represents a distinct, complement-mediated disorder [1]. Atypical HUS is an extremely rare condition; the incidence in industrialized nations is estimated at ~0.3 cases per million inhabitants, accounting for roughly 5%-10% of all HUS cases [1,3].

Atypical HUS is predominantly hereditary, with genetic abnormalities in the complement system found in ~60%-70% of patients [3,4]. These pathogenic variants primarily affect genes encoding alternative pathway regulators and activators, including complement factor H (CFH), membrane cofactor protein (CD46 or MCP), complement factor I (CFI), C3, and complement factor B [2,4]. Additionally, in about 10% of pediatric cases and 3% of adult cases, the disease is acquired via anti-CFH autoantibodies, which frequently occur in the context of a homozygous deletion of CFH-related proteins (CFHR1 and CFHR3) [2].

The alternative complement pathway acts as a primary innate immune defense and is continuously active at a low level due to the spontaneous hydrolysis of C3 [2]. To prevent this constant activation from damaging host tissues, the pathway is tightly regulated by fluid-phase and membrane-bound proteins. Factor H (FH) serves as a

critical fluid-phase regulator, utilizing its 20 short consensus repeats (SCRs) to differentiate between self and non-self surfaces [5]. SCRs 19 and 20 at the C-terminus of FH are essential for binding to polyanions on host endothelial cells [2,5].

In aHUS, mutations often cluster in this C-terminal region; consequently, the mutated FH retains its regulatory activity in the plasma but fails to attach to the host endothelium, exposing these cells to complement attack [5,6]. This leads to uninhibited formation of the C3 convertase (C3bBb) on the cellular surface, rapid amplification of C3b, and subsequent formation of the C5 convertase [2]. The terminal complement cascade is then triggered, resulting in the assembly of the Membrane Attack Complex (MAC or C5b-9) [1,2]. Excessive MAC deposition damages the endothelial lining, promotes local thrombosis, and activates platelets, a process further exacerbated if terminal pathway regulators, such as clusterin, are mutated and fail to inhibit MAC assembly on platelets [1,7]. This lysis and subsequent prothrombotic state drive the devastating microvascular occlusion seen in aHUS [5]. Given the severity of the disease and high risk of end-stage renal disease (ESRD), prompt differentiation from other TMAs and appropriate targeted therapy are essential [8].

Case Presentation

A male patient in his late 40s presented to the outpatient nephrology clinic for the evaluation of progressively worsening renal function. His past medical history was significant for having a solitary kidney following a living donor nephrectomy in 2015; he had donated a kidney to his father. Family history was notable for his father ultimately passing with ESRD while on hemodialysis. While the father reportedly experienced severe unexplained hypertension and anemia prior to requiring dialysis, no definitive records were available to establish the father's original renal diagnosis or genetic status.

During the period of acute decline culminating in August 2025, the deterioration occurred despite adequate renal protective strategies, such as a low sodium diet, weight loss, blood pressure control with an angiotensin-converting enzyme inhibitor, and diabetes control with an sodium-glucose cotransporter-2 (SGLT-2) inhibitor and metformin. Laboratory investigations at that time revealed newly diagnosed microangiopathic hemolytic anemia, a requirement for confirming active TMA. His hemoglobin dropped to 9.2 g/dl. Hemolysis was evident by an elevated lactate dehydrogenase (LDH) of 450 U/l, an undetectable haptoglobin (<10 mg/dl), an indirect bilirubin of 1.8 mg/dl, and an elevated reticulocyte count of 4.5%. A peripheral blood smear confirmed the presence of 2-3 schistocytes per high-power field, while a direct antiglobulin (Coombs) test was negative. His platelet count demonstrated a clear downward trend, falling from a baseline of 220-135 K/µl, and subsequently to a nadir of 98 K/µl, temporally associated with his renal decline. His urine protein-to-creatinine ratio was 1.2 g/g. The acute onset of hemolysis and rapid consumption of platelets clinically differentiated this active TMA from progressive chronic kidney disease, diabetic kidney disease, or hypertensive hyperfiltration injury. A kidney biopsy was considered but ultimately deferred due to the high bleeding risk associated with his thrombocytopenia and solitary kidney status.

An extensive evaluation was initiated to rule out secondary causes of TMA. ADAMTS13 activity was 85%, effectively excluding thrombotic thrombocytopenic purpura. Stool polymerase chain reaction testing for Shiga toxin was negative, ruling out STEC-HUS. Further serological testing for HIV, hepatitis B, hepatitis C, antinuclear antibodies, and antineutrophil cytoplasmic antibodies were all negative. The patient was normotensive upon presentation, excluding malignant hypertension, and severe autoimmune etiologies were deemed unlikely. Complement studies revealed a low-normal serum C3 of 82 mg/dl, a normal C4 of 24 mg/dl, elevated soluble C5b-9, and negative anti-FH antibodies.

Figure 1 depicts the serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) trend of the patient from December 1, 2022, through February 23, 2026. After a period of improvement and stabilization in 2024, there was a progressive decline in function between November 26, 2024, and August 28, 2025, which prompted further workup. The patient subsequently experienced a spontaneous recovery, with kidney function stabilizing through early 2026.

Given the high clinical suspicion of a primary complement-mediated TMA, the patient underwent targeted genetic testing. The panel revealed a heterozygous, pathogenic mutation in the CFH gene on Chromosome 1 (c.3572C>T, p.Ser1191Leu), which localizes to SCR20. This specific variant impairs the ability of FH to anchor to host endothelial cells, providing strong genetic support for a diagnosis of hereditary aHUS. Several variants of uncertain significance were also reported, including alterations in anillin actin binding protein, Inversin, and CYP11A1 on Chromosomes 9 and 15; however, these were carefully evaluated and deemed incidental findings without a causative role in the patient's TMA phenotype.

Based on the evidence of active hemolysis and deteriorating renal function in a highly vulnerable solitary kidney, the diagnosis of complement-mediated TMA was considered sufficiently established to prescribe terminal complement inhibition. Ravulizumab was selected as the preferred first-line agent due to its extended half-life and alignment with current treatment guidelines for complement-mediated TMAs. Before insurance approval, mandatory hepatitis B and tuberculosis testing, as well as baseline LDH levels, returned negative or stable.

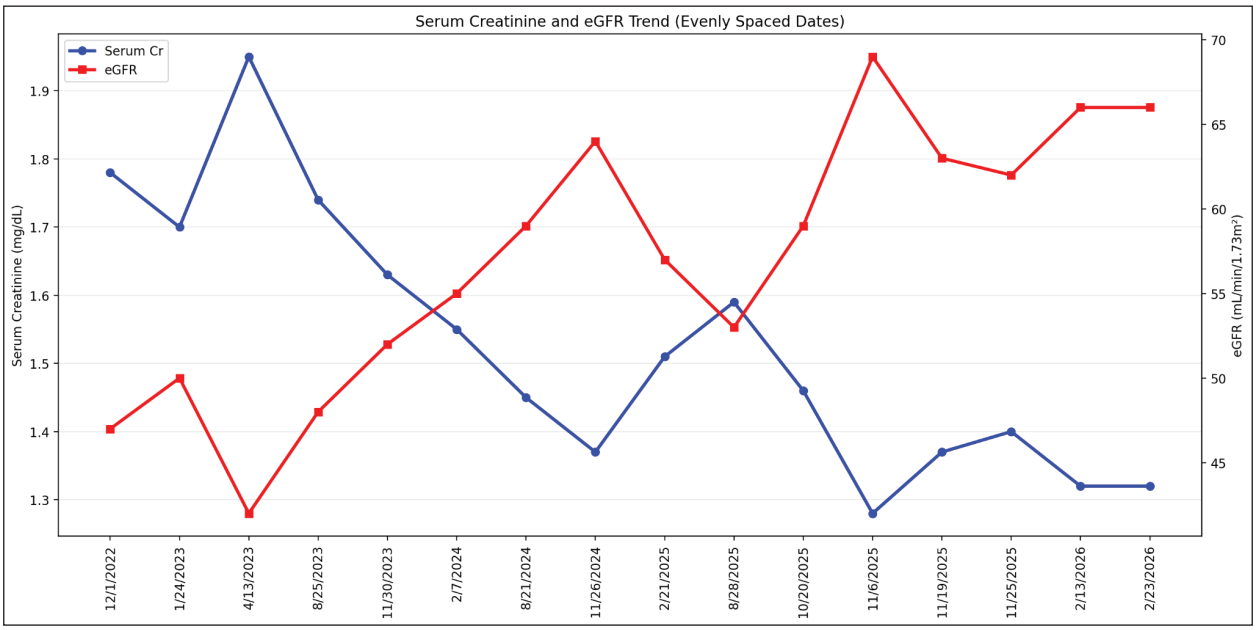


Figure 1. *Serum creatinine and glomerular filtration rate trend.*

However, the patient's insurance provider denied authorization for the medication. Consequently, the patient was referred to a tertiary specialty clinic for further management and to handle the appeals process. By February 2026, the patient experienced spontaneous clinical stabilization without complement inhibition, possibly due to the resolution of an unidentified viral or environmental trigger. At his most recent follow-up, his SCr had improved to 1.32 mg/dl, his eGFR was 66 ml/min/1.73 m^2, his platelet count had recovered to 185 K/µl, and his hemoglobin was stable at 11.4 g/dl. This spontaneous remission dictates his current management strategy: the clinical team is maintaining vigilant, continuous monitoring to determine if future signs of microangiopathic deterioration will warrant an immediate transition to alternative immunomodulatory treatments, such as therapeutic plasma exchange, or an emergency appeal for terminal complement inhibition.

To establish a clear clinical sequence, the patient's medical timeline was carefully reconstructed:

From late 2022 through mid-2024, the patient experienced fluctuating renal function, with an eGFR dipping to 43 ml/min/1.73 m^2 and serum creatinine peaking at 1.95 mg/dl in April 2023. His kidney function subsequently improved, reaching a peak eGFR of 64 ml/min/1.73 m^2 and a SCr of 1.37 mg/dl by November 26, 2024. However, an asymptomatic, progressive renal deterioration began shortly thereafter, with eGFR dropping to 55 ml/min/1.73 m^2 (SCr 1.51 mg/dl) by February 21, 2025, and hitting a low of 53 ml/min/1.73 m^2 (SCr 1.59 mg/dl) on August 28, 2025. This steady 9-month decline prompted a comprehensive TMA workup in late August 2025. Following an insurance denial for targeted therapy in the fall of 2025, the patient was closely monitored. His kidney function spontaneously recovered by November 2025 (eGFR 69 ml/min/1.73 m^2, SCr 1.28 mg/dl) and stabilized through February 23, 2026, with an eGFR of 66 ml/min/1.73 m^2 and a SCr of 1.32 mg/dl.

Discussion

This patient's presentation illustrates several critical components of aHUS management, specifically the importance of detailed family history, the concept of age-related penetrance, the complex "multiple-hit" genetic etiology, and the severe clinical vulnerability of living kidney donors.

The patient's family history of a father who died with ESRD on dialysis presents a compelling, albeit speculative, hypothesis for familial TMA. While no evidence is available to definitively establish the father's original renal diagnosis or genetic status, hereditary aHUS frequently demonstrates an autosomal dominant pattern with incomplete penetrance, meaning familial clusters across multiple generations are not uncommon [9].

The timing of the patient's clinical manifestation in his late 40s highlights the concept of age-related penetrance. Epidemiological data indicate that disease penetrance among mutation-positive index probands generally increases cumulatively with age, reaching roughly 67% by age 40 and approaching 100% by age 65 [10]. However, these estimates are derived from heterogeneous cohorts and cannot perfectly predict an individual patient's clinical course. Asymptomatic relatives carrying exact mutations often exhibit a much lower lifetime penetrance (11% by age 40), reflecting the necessity of secondary factors [10].

This incomplete penetrance heavily supports the "multiple-hit" hypothesis, which states that a genetic

susceptibility alone is rarely sufficient to cause aHUS; it must be unmasked by an environmental trigger or compounded by additional genetic modifiers [6,8,9,11]. Predisposition to aHUS often requires the concurrence of a primary mutation alongside common susceptibility alleles, such as specific single nucleotide polymorphism haplotype blocks located within the regulators of complement activation gene cluster on chromosome 1q32 [12]. The patient's spontaneous stabilization following the acute episode further supports the likelihood that a transient "second hit" triggered the temporary TMA manifestation.

The specific gene affected heavily dictates the clinical phenotype and prognosis. In this patient, the identified CFH mutation in SCR20 severely disrupts the protein's C-terminal polyanion binding sites. Consequently, mutated FH retains regulatory activity in plasma but fails to attach to the host endothelium, exposing cells to complement attack [5,6]. Zygosity is also an important variable; while heterozygous CFH deficiencies present exclusively as aHUS, homozygous deficiencies can present as membranoproliferative glomerulonephritis [13]. Generally, CFH mutations carry the poorest prognosis, with the highest rates of mortality and ESRD, while MCP mutations typically have a better renal survival rate despite a relapsing clinical course [3]. This genotypic influence extends to transplantation outcomes; patients with CFH, CFI, and C3 mutations face an extremely high risk of post-transplant recurrence [2,3].

From a management perspective, treatment has been revolutionized by targeted terminal complement (C5) inhibitors, which effectively halt the MAC formation and microangiopathy [4,8]. However, this case exposes a significant real-world barrier to care: the high cost and insurance denial of first-line therapies. The delay in optimal treatment is especially critical for a patient with a solitary kidney, where any further endothelial damage and nephron loss directly accelerates the trajectory to ESRD.

Conclusion

This case demonstrates the complex diagnostic workup of suspected adult-onset hereditary aHUS in the outpatient setting, while exposing critical systemic challenges in healthcare access. A thorough clinical evaluation including comprehensive hemolysis panels, targeted genetic analysis, and the exclusion of secondary TMA causes is essential for establishing an accurate diagnosis. A family history of ESRD and the recognition of age-dependent penetrance serve as important tools in identifying at-risk individuals, though they must be interpreted cautiously. Due to the high risk of rapid progression in this highly vulnerable solitary-kidney patient, the current clinical plan involves continuous monitoring and readiness to deploy targeted therapy should symptoms recur. Resolving insurance barriers to terminal complement inhibitors remains a significant hurdle in the ethical and effective management of patients with genetic complement dysregulation.

What is new

This case highlights the manifestation of adult-onset hereditary aHUS in a highly vulnerable patient with a solitary kidney following a living donor nephrectomy. It emphasizes the importance of utilizing family history to recognize age-related penetrance, while exposing significant systemic insurance barriers to accessing targeted anti-complement therapies.

List of Abbreviations

aHUS	Atypical hemolytic uremic syndrome
C3	Complement component 3
C3bBb	C3 convertase
C5	Complement component 5
C5b-9	Membrane attack complex
CD46	Cluster of differentiation 46
CFB	Complement factor B
CFH	Complement factor H
CFHR1	Complement factor H-related protein 1
CFHR3	Complement factor H-related protein 3
CFI	Complement factor I
ESRD	End-stage renal disease
FH	Factor H
GFR	Glomerular filtration rate
HUS	Hemolytic uremic syndrome
MAC	Membrane attack complex
MCP	Membrane cofactor protein
MPGN	Membranoproliferative glomerulonephritis
RCA	Regulators of complement activation
SCr	Serum creatinine
SCRs	Short Consensus Repeats
SGLT-2	Sodium-glucose cotransporter-2
SNP	Single nucleotide polymorphism
STEC	Shiga toxin-producing *Escherichia coli*
TMA	Thrombotic microangiopathy
TTP	Thrombotic thrombocytopenic purpura

Conflict of interests

The authors declare no financial relationships or conflicts of interest from the past three years regarding the publication of this manuscript.

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Consent for publication

Informed consent was obtained from the patient for the publication of this case report.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

Patient (gender, age)	Male, late 40s
Final diagnosis	Hereditary aHUS
Symptoms	Worsening renal function, thrombocytopenia, anemia
Medications	ACE inhibitor, SGLT-2 inhibitor, metformin; Ravulizumab (prescribed but denied by insurance)
Clinical procedure	Genetic testing
Specialty	Nephrology