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Atypical hemolytic uremic syndrome: A case-based review

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Abstract

Atypical hemolytic uremic syndrome (aHUS) is an uncommon but potentially fatal form of thrombotic microangiopathy driven by dysregulation of the alternative complement pathway, frequently linked to genetic alterations affecting complement-regulatory proteins. Its clinical presentation is heterogeneous and overlaps with other thrombotic microangiopathies, frequently delaying diagnosis and increasing the risk of irreversible organ damage. Advances in complement biology have substantially improved understanding of disease mechanisms and enabled the development of targeted C5 inhibitors, which have transformed patient outcomes. This review summarizes current knowledge regarding the epidemiology, genetic landscape, pathophysiology, clinical manifestations, diagnostic approach, and contemporary management of aHUS, with particular emphasis on complement inhibition strategies. The discussion is contextualized by a representative clinical case illustrating real-world diagnostic complexity, systemic involvement, and therapeutic decision-making. Evidence indicates that both eculizumab and ravulizumab provide effective and sustained complement blockade, with ravulizumab offering extended dosing intervals and potential advantages in treatment burden and patient preference. Despite therapeutic progress, important challenges remain, including early recognition, interpretation of complex genetic findings, determination of optimal treatment duration, and discontinuation strategies. Continued research and improved epidemiological surveillance are essential to refine risk stratification and optimize long-term outcomes in this rare but severe complement-mediated disorder.

Keywords: Atypical hemolytic uremic syndrome; Ravulizumab; Thrombotic microangiopathy; Atypical hemolytic uremic syndrome

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1. Introduction

Thrombotic microangiopathies (TMAs) comprise a diverse group of disorders that differ in their underlying pathophysiological mechanisms but share the common feature of thrombotic occlusion within the microvascular and, in some cases, macrovascular

circulation.[1] Clinically and laboratory-wise, they are typically defined by the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and evidence of ischemic injury affecting one or more organs.[1] Within this spectrum, atypical hemolytic uremic syndrome (aHUS) represents a unique pathological entity. It is defined as a form of hemolytic uremic syndrome that is not attributable to streptococcal infection, cobalamin deficiency, Shiga toxin-producing bacteria, or other infectious causes, including influenza A (H1N1) and human immunodeficiency virus.[2,3] Clinically, aHUS is characterized by thrombocytopenia, MAHA, and microvascular occlusion-associated end-organ damage, which may affect major organs, including the kidneys, eyes, brain, heart, and gastrointestinal system.[4] The disease is primarily driven by dysregulation of the alternative complement pathway. If it is not recognized promptly and treated appropriately, uncontrolled complement activation may lead to severe organ damage and can ultimately be fatal.[4] Due to the rarity of aHUS, its epidemiology remains challenging to characterize precisely, and available data are relatively limited. Incidence and prevalence estimates are frequently reported alongside those for other thrombotic microangiopathies, further complicating accurate assessment.[3] In a systematic review, Yan *et al.*[3] estimated the annual incidence of aHUS to range from 0.23 to 1.9 cases per million population, with variation according to geographic region and age group. Reported prevalence estimates similarly differed across populations, ranging from approximately 2 to 10 cases per million.[3] Because of its significant clinical overlap with other forms of TMA, particularly thrombotic thrombocytopenic purpura (TTP) and typical hemolytic uremic syndrome (HUS), early and accurate diagnosis of aHUS is critical to ensure timely initiation of appropriate treatment.[5] Delayed diagnosis is associated with worse clinical outcomes, including a greater risk of permanent kidney damage, longer hospital stays, and increased healthcare-related costs.[5] Acute kidney injury (AKI) is one of the most common presenting features of the disease and, in the absence of appropriate treatment, may progress to end-stage renal disease.[2] During the acute phase, patients may also develop serious neurological, cardiovascular, and gastrointestinal complications.[2] The management of aHUS has changed substantially over the past two decades. Historically, therapeutic options were limited to supportive care and plasma exchange, together with strict blood pressure control and renal replacement therapy.[6] Plasma exchange may provide temporary benefit by replacing deficient or dysfunctional complement regulators and removing circulating pathogenic factors, such as anti-complement factor H autoantibodies.[7] However, this approach does not directly block terminal complement activation and therefore does not specifically target the central mechanism of complement-mediated endothelial injury.[7] The introduction of terminal C5 inhibitors, first eculizumab and later ravulizumab, has therefore markedly changed the prognosis of patients with aHUS by allowing targeted inhibition of complement-driven thrombotic microangiopathy.[8] Compared with eculizumab, ravulizumab provides sustained complement blockade with a longer dosing interval, which may reduce treatment burden while maintaining clinical efficacy.[9] This review summarizes current knowledge on aHUS and complement-targeted therapy, illustrated by a representative clinical case reflecting real-world diagnostic and management considerations.

2. Case presentation

A 49-year-old woman was admitted with severe arterial hypertension (250/150 mmHg) and AKI. On presentation, blood pressure remained markedly elevated (230/130 mmHg), and she reported malaise, weakness, and persistent vomiting for approximately two weeks. Her medical history was significant for long-standing, poorly controlled hypertension and treated hypothyroidism. The day prior to admission, she had noticed a rash on the posterior side of her ankles. The initial laboratory results obtained in the emergency department are presented in Table 1.

Table 1. Laboratory findings on admission to the emergency department

Parameter	Result	Reference range
Serum creatinine	4.96 mg/dL	0.51–0.95 mg/dL
Urea	127 mg/dL	20–45 mg/dL
Potassium	2.4 mmol/L	3.50–5.20 mmol/L
Sodium	127 mmol/L	137–146 mmol/L

The hyponatremia and hypokalemia were considered most likely secondary to prolonged vomiting, reduced oral intake, and volume depletion at presentation. Hematologic evaluation demonstrated findings consistent with thrombotic microangiopathy, including elevated lactate dehydrogenase (834 U/L), markedly decreased haptoglobin (<0.1 g/L), reticulocytosis (39%), and schistocytes on the peripheral blood smear. Platelet count was 153 $\times 10^9$/L. Urine analysis showed an albumin-to-creatinine ratio of

430 mg/g. Complement component levels, including C3 and C4, were within the reference range. ADAMTS13 activity was preserved, and testing for Shiga toxin-producing *Escherichia coli* (STEC) was negative. These findings made thrombotic TTP and typical hemolytic uremic syndrome unlikely. Given the suspicion of aHUS, a kidney biopsy was performed. Histopathological examination revealed features of corrugation of the glomerular basement membrane, indicating acute ischemia of the vascular bundle (Figure 1), cortical thinning with mild fibrosis, glomerular crowding due to ischemic atrophy (Figure 2), and vascular congestion with fragmented erythrocytes within arterial walls (Figure 3), and expansion of the inner lamina rara, a change typical of acute TMA (Figure 4).

Genetic analysis identified a heterozygous complement factor B variant (Val750Leu) of uncertain significance, as well as the complement factor H (*CFH*) H3 haplotype, the Y402H polymorphism in *CFH*, and three components of the membrane cofactor protein (*MCP*)ggaac haplotype, collectively indicating increased genetic susceptibility to aHUS. Interestingly, family screening revealed the same *CFB* and *MCP* variants in two of the patient's sisters. The patient underwent four sessions of plasmapheresis and was subsequently enrolled in a ravulizumab treatment program. After meningococcal vaccination, therapy was initiated with a 2.4 g loading dose, followed by maintenance dosing according to body weight. Treatment was well tolerated, with no adverse events. During hospitalization, the patient experienced recurrent hypertensive crises and developed transient neurological symptoms; brain magnetic resonance imaging demonstrated a fresh ischemic lesion in the pontine region, consistent with extrarenal involvement of aHUS. Over the following months, renal function gradually improved (serum creatinine decreased to 3.18 mg/dL), and hemolytic parameters

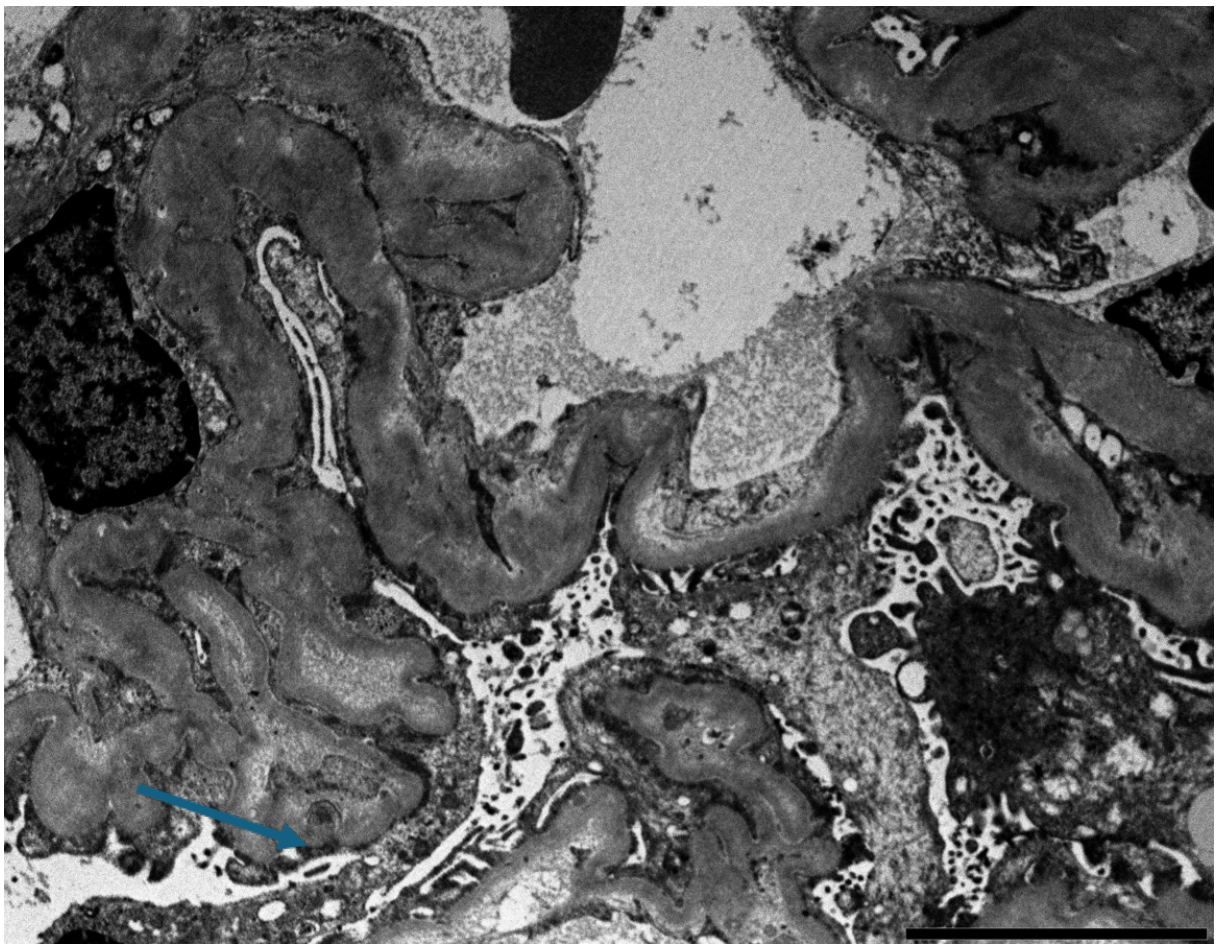

Figure 1. Pathologic findings of the kidney biopsy. The arrow highlights the corrugation of the glomerular basement membrane, a finding consistent with acute ischemia of the vascular bundle.

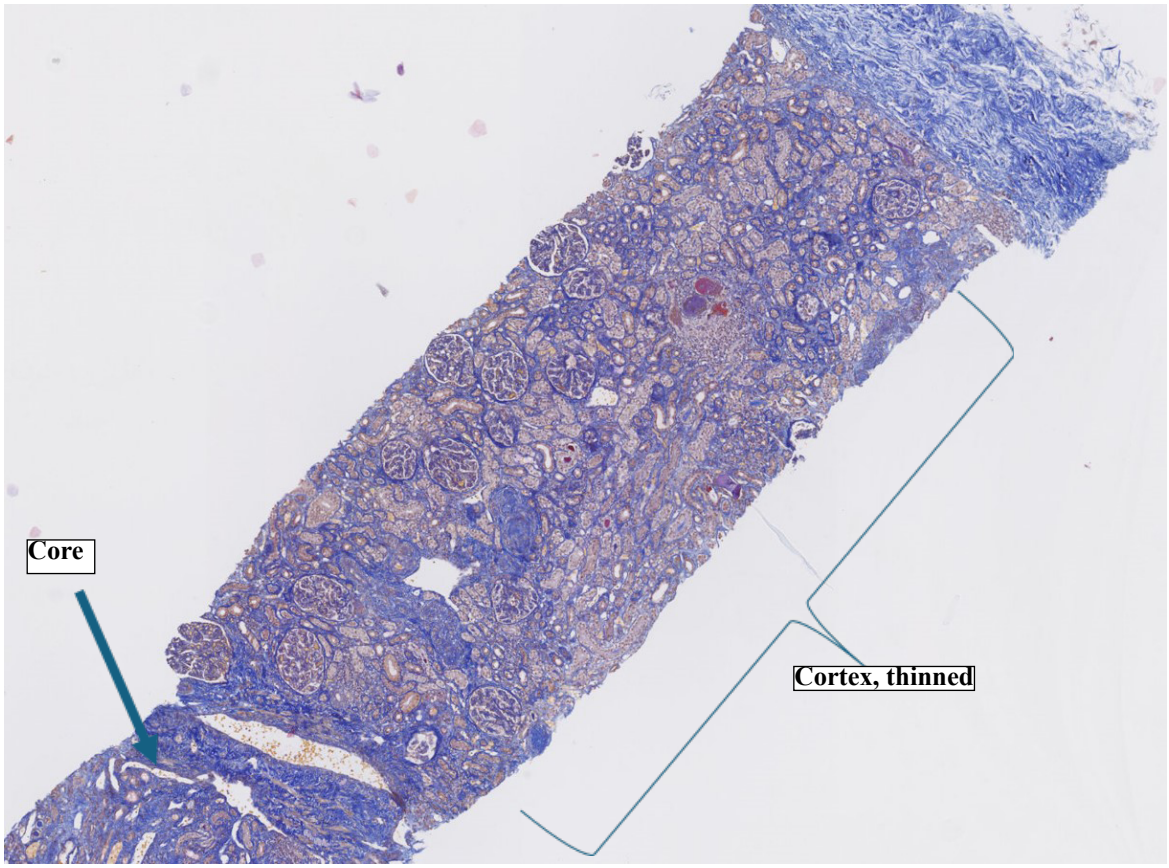

Figure 2. Pathologic findings of the kidney biopsy. Mild fibrosis, glomerular thickening. Cortical atrophy associated with ischemia.

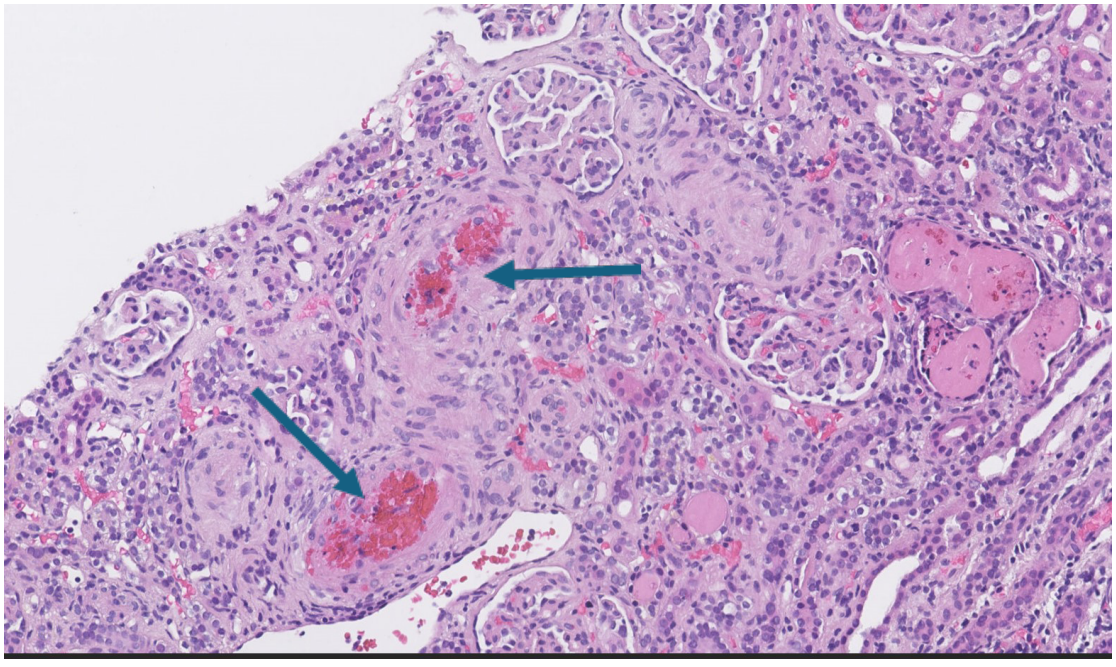

Figure 3. Pathologic findings of the kidney biopsy. The arrows indicate two blood vessels with blood stasis; fragmented erythrocytes are visible in the arterial wall.

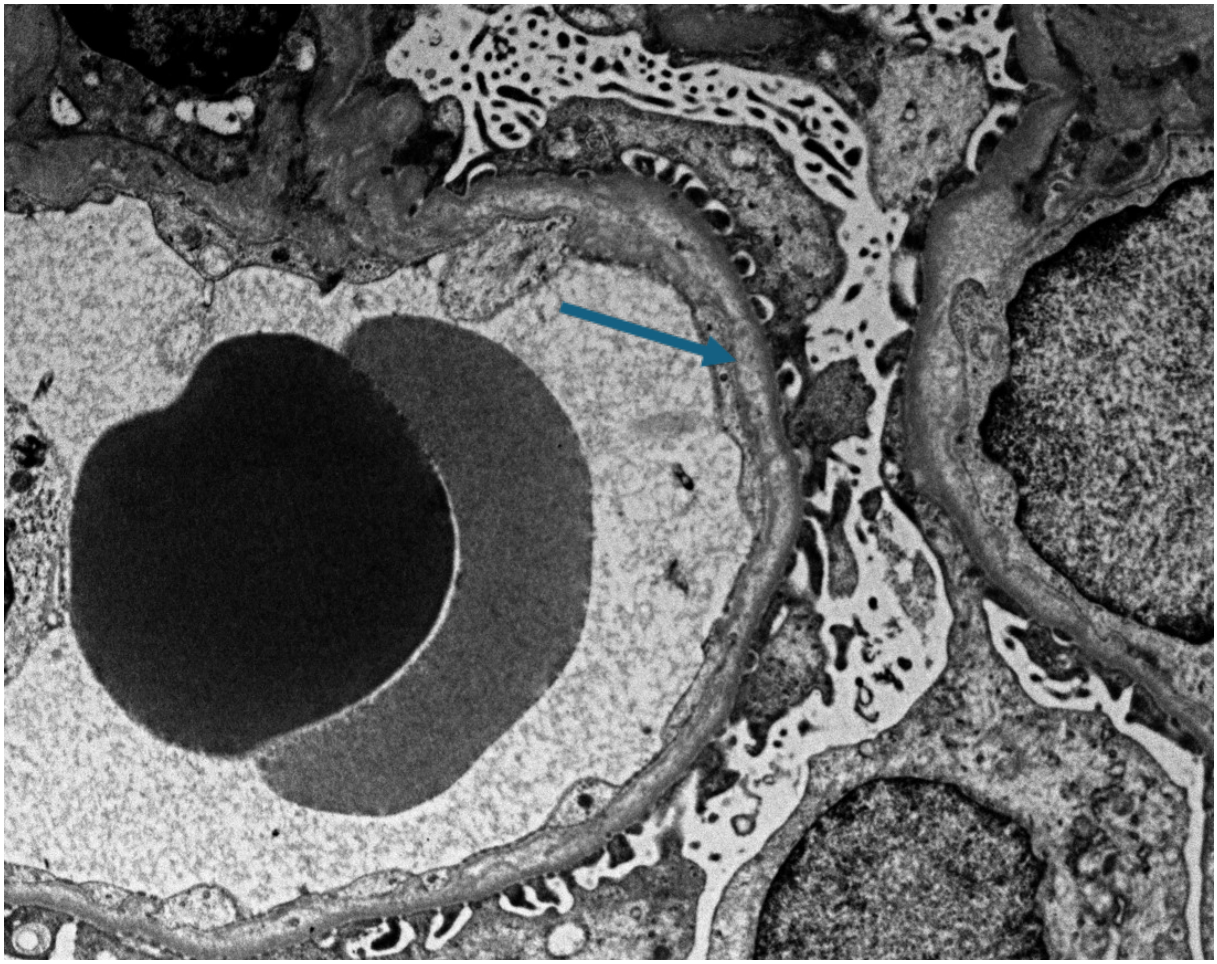

Figure 4. Pathologic findings of the kidney biopsy. The arrow indicates the widened internal thin plate; this swelling is typical of acute thrombotic microangiopathy.

normalized. Five months after initial presentation, a repeat kidney biopsy demonstrated arterionephrosclerosis without active thrombotic microangiopathy. Although complement inhibition was associated with hematologic remission and improvement in renal function, the chronic biopsy abnormalities, including cortical thinning and fibrosis, were not considered reversible; the follow-up biopsy instead showed arterionephrosclerosis without active TMA. In light of the repeat biopsy demonstrating arterionephrosclerosis without features of active thrombotic microangiopathy, and given the patient's sustained clinical improvement, the expert panel recommended discontinuation of ravulizumab therapy. The decision was further supported by the absence of ongoing disease activity and consideration of the patient's genetic profile. In clinical practice, discontinuation of anti-C5 therapy may be considered in cases with stable hematologic and renal parameters, resolution of active symptoms, and a complement mutation profile not associated with a high risk of relapse.[10] The patient was discharged in stable condition with recommendations for close nephrological follow-up. A summary of the clinical course, diagnostic process, treatment, and follow-up is presented in Table 2.

3. Epidemiology of atypical hemolytic uremic syndrome

Atypical HUS represents a relatively small proportion of hemolytic uremic syndrome cases, accounting for approximately 5–10% of all HUS diagnoses, and is closely linked to genetic abnormalities involving regulation of the alternative complement pathway.[3] Owing to the rarity of the disease, its epidemiology remains difficult to characterize precisely, and available population-level data are limited. In many studies, incidence and prevalence estimates are reported alongside those for related thrombotic microangiopathies, further complicating

Table 2. Timeline of clinical course, diagnosis, treatment, and follow-up

Time point	Key events
2 weeks before admission	Malaise, weakness, and persistent vomiting developed
Day 0	Admission with severe hypertension and acute kidney injury; laboratory features of thrombotic microangiopathy identified
Early hospitalization	ADAMTS13 activity was normal, and STEC testing was negative; kidney biopsy confirmed thrombotic microangiopathy consistent with aHUS
Early hospitalization	Genetic testing revealed *CFB*, *CFH*, and *MCP* risk variants; plasmapheresis was performed
During hospitalization	Ravulizumab was initiated after meningococcal vaccination; transient neurological symptoms occurred, and a brain MRI showed a pontine ischemic lesion
1–5 months follow-up	Gradual improvement in renal function and normalization of hemolytic parameters during continued ravulizumab therapy
5 months after presentation	Repeat kidney biopsy showed arterionephrosclerosis without active thrombotic microangiopathy
5 months after presentation	Ravulizumab discontinued; patient discharged in stable condition with close nephrological follow-up

Abbreviations: ADAMTS13: A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; aHUS: Atypical hemolytic uremic syndrome; CFB: Complement factor B; CFH: Complement factor H; MCP: Membrane cofactor protein; MRI: Magnetic resonance imaging; STEC: Shiga toxin-producing *Escherichia coli*.

accurate assessment of the true disease burden.[3] Nevertheless, in a systematic literature review, Yan *et al.*[3] estimated that the annual incidence of aHUS ranges from 0.23 to 1.9 cases per million population, with differences observed according to geographic region and age group.[3] Reported prevalence estimates also vary between populations, ranging from approximately 2 to 10 cases per million individuals.[11] Similarly, Yerigeri *et al.*[11] reported in a recent review that the prevalence among adults aged 20 years and older ranges from 2.2 to 9.4 cases per million, which is broadly consistent with previous epidemiological estimates. Notably, most of these epidemiological studies originated in Europe, Australia, or New Zealand, leaving the global picture incomplete.[3] Additional insights have emerged from regional studies. In China, Zheng *et al.*[12] identified 372 unique patients with aHUS, of whom 45.6% were male. The age distribution demonstrated a bimodal pattern, with peaks in childhood and among women in their thirties, suggesting a higher overall susceptibility in children and women. Similarly, a retrospective study from Japan[13] that included 217 patients with aHUS reported a slight female predominance (51.2%), reinforcing the notion that women may be more prone to developing this disorder. European data provide an additional perspective. A French study conducted between 2009 and 2016, which included patients of all ages, identified 15 cases of aHUS

and reported an annual incidence of 1.9 cases per million population.[14] In a multinational European study conducted by Wühl *et al.*[15] across 11 countries between 2007 and 2011, 815 patients with HUS were identified, including 81 patients younger than 20 years of age. The estimated annual incidence of aHUS was 0.39 cases per million population, while the prevalence was 4.96 cases per million population. Massart *et al.*[16] provided further nationwide data from Belgium using the Global aHUS Registry, which prospectively and retrospectively collected data from patients of all ages with a clinical diagnosis of aHUS. A total of 121 Belgian patients were included, corresponding to a prevalence of 10.4 patients per million inhabitants. This cohort also showed a female predominance, with women comprising 57.9% of cases compared with 42.1% in men. A population-based study from Italy reported an annual incidence of HUS of 6.3 cases per million children, with a higher incidence of 15.7 cases per million among children younger than 5 years.[17] Although aHUS was historically regarded mainly as a pediatric disorder, it is now recognized that the disease may develop at any stage of life.[18] This broader age distribution is supported by data from a large cohort of 851 patients, in which the mean age at disease onset was 21.4 years.[19] Notably, the Japanese nationwide study documented only 217 diagnosed cases over a nine-year period—substantially fewer than earlier projections estimating 200–300 new cases annually.[10] This discrepancy highlights the likelihood of underdiagnosis or misclassification within the broader TMA spectrum and underscores the need for improved epidemiological surveillance, standardized diagnostic criteria, and greater access to complement and genetic testing.[17]

4. Complement genetics in atypical hemolytic uremic syndrome

Atypical HUS is closely linked to genetic abnormalities that disrupt normal regulation of the alternative complement pathway. However, genetic susceptibility alone is often insufficient to cause overt disease, and clinical onset frequently requires an additional environmental or physiological trigger, such as infection, pregnancy or the postpartum period, transplantation, severe hypertension, malignancy, drug exposure, autoimmune disease, or systemic inflammation.[18] Rare triggers have also been described, including acute pancreatitis, suggesting that any condition capable of inducing marked endothelial stress, systemic inflammation, or complement activation may potentially unmask an underlying complement-regulatory defect.[20] This concept is commonly explained by the "multiple-hit" model of aHUS, according to which inherited complement susceptibility, acquired complement abnormalities, and environmental or clinical triggers interact to exceed the threshold for uncontrolled complement activation and clinically trigger thrombotic microangiopathy.[21] In this model, genetic variants or risk haplotypes create a predisposed background, but additional insults are required to initiate endothelial injury and sustain the cycle of microvascular thrombosis.[21] Pathogenic variants or structural abnormalities in complement-regulatory and complement-activating genes are identified in approximately 60–70% of patients with aHUS.[21] These mutations can be broadly classified into two main categories: loss-of-function mutations (involving factor H, factor H-related proteins, membrane cofactor protein, and factor I) and gain-of-function mutations (involving factor B and C3).[22] In addition to inherited mutations, acquired drivers such as anti-CFH autoantibodies—frequently associated with *CFHR1*/*CFHR3* gene deletions—also contribute to dysregulation of the alternative pathway.[23] Józsi *et al.*[23] demonstrated that factor H autoantibodies in aHUS are closely associated with homozygous *CFHR1*/*CFHR3* deficiency, supporting the concept that anti-CFH antibody-mediated disease represents a distinct acquired form of complement dysregulation. These autoantibodies impair the regulatory activity of factor H, particularly its ability to control complement activation on host cell surfaces, thereby promoting excessive alternative pathway activation and endothelial injury.[23] Although *CFHR1*/*CFHR3* deletion is not sufficient to cause disease in isolation, it appears to increase susceptibility to the development of anti-CFH autoantibodies, thereby linking structural variation within the *CFH–CFHR* genomic region to acquired complement-mediated TMA.[24] Notably, the genetic predisposition underlying aHUS is increasingly recognized as complex and multifactorial rather than strictly monogenic. Ji *et al.*[25] emphasized the remarkable heterogeneity of reported variants, including missense mutations, splice-site alterations, copy number variations, and hybrid *CFH–CFHR* gene rearrangements. In addition, incomplete penetrance is a well-established feature of the disease, and many patients harbor multiple rare variants or risk-associated haplotypes that may interact synergistically to increase susceptibility and influence clinical expression.[25] The composite genetic background of an individual, including multiple variants or haplotypes, influences disease penetrance, clinical phenotype, and relapse risk, although genotype–phenotype correlations remain incompletely defined. Genetic evaluation has important clinical implications beyond diagnostic support. Identification of complement-related variants may help estimate relapse risk, guide decisions regarding the duration or discontinuation of complement inhibition, inform counseling and screening of family members, and support risk assessment before kidney transplantation.[26]

This is particularly relevant because recurrence risk after transplantation varies according to the underlying genetic abnormality, with circulating complement-regulatory defects generally associated with a higher risk of recurrence than isolated membrane-bound defects.[26] However, because genotype–phenotype correlations remain imperfect, genetic results should be interpreted alongside clinical presentation, disease severity, treatment response, and evidence of ongoing thrombotic microangiopathy.

5. Pathophysiology of atypical hemolytic uremic syndrome

The pathogenesis of aHUS is driven by a self-perpetuating cycle of uncontrolled alternative complement pathway activation.[27] Under normal physiological conditions, this pathway is tightly controlled by both soluble complement regulators and membrane-bound regulatory proteins. When this protective regulation at host cell surfaces is impaired, the alternative pathway amplification loop may remain persistently active, promoting ongoing complement activation and endothelial injury.[27] Excessive generation of C5a and C5b-9 leads to endothelial injury, microvascular thrombosis, and tissue ischemia, which further amplify complement activation and sustain thrombotic microangiopathy.[28] Noris *et al.*[21] emphasized that aHUS develops when complement regulation on host cell surfaces becomes insufficient, allowing the alternative pathway to attack endothelial cells and promote platelet activation within the microvasculature. Importantly, deposition of C5b-9 on endothelial cells promotes cellular activation rather than simple cytolysis, inducing proinflammatory and prothrombotic signaling.[28] C5a acts as a potent anaphylatoxin that promotes inflammation and leukocyte recruitment, whereas sublytic C5b-9 deposition may stimulate endothelial cells to adopt a proadhesive and procoagulant phenotype.[28] The central pathological features of this process include swelling of endothelial cells, their separation from the underlying basement membrane, and activation of pathways that promote thrombosis within the microvasculature.[28] Activated endothelial cells upregulate adhesion molecules, release von Willebrand factor, and promote platelet adhesion and aggregation. Complement activation also interacts with the coagulation cascade by enhancing tissue factor expression and thrombin generation.[27,29] Markiewski *et al.*[30] described an extensive connection between complement and coagulation, showing that activation of one system can amplify the other, thereby reinforcing inflammation, thrombosis, and vascular injury. In this model, complement activation promotes endothelial and platelet activation, while coagulation proteases can further stimulate complement pathways, creating a self-reinforcing cycle of inflammation, thrombosis, and endothelial damage.[30] Interestingly, genetic mutations alone are insufficient for disease manifestation.[31] Additional environmental or clinical triggers are usually required to unmask the underlying defect.[27,31] These include severe hypertension, infections, pregnancy and the postpartum period, transplantation, or autoimmune diseases.[32] In these cases, endothelial injury acts as the initiating event that drives further complement activation, thereby maintaining the self-perpetuating cycle.[31] Frimat *et al.*[32] further supported this "second-hit" concept by demonstrating that heme released during hemolysis can amplify complement activation and endothelial injury, thereby contributing to the progression of thrombotic microangiopathy in genetically susceptible individuals. The interaction between genetic susceptibility and environmental triggers accounts for the heterogeneity of clinical presentation and explains why not all mutation carriers develop aHUS.[32] Atypical HUS is best understood as a complement-mediated thrombotic microangiopathy in which genetic defects confer a predisposition, while external "second hits" initiate and sustain the pathological cascade, reflecting a complex connection between complement activation, endothelial dysfunction, and coagulation pathways.

6. Clinical presentation of atypical hemolytic uremic syndrome

The initial clinical manifestations of aHUS are often nonspecific, with patients commonly presenting with weakness, fatigue, somnolence, malaise, gastrointestinal symptoms such as vomiting, nausea, or abdominal pain, and occasionally headache or reduced appetite.[33] Early symptoms may be vague and variable, which can delay recognition of the underlying thrombotic microangiopathy, particularly when renal or neurological signs are not yet fully developed.[33] As the disease advances, patients usually develop the classic clinical and laboratory triad of thrombocytopenia, microangiopathic hemolytic anemia, and AKI.[34] These early symptoms may progress to signs of AKI, such as uremia, oliguria, and fluid overload. Renal involvement is the dominant clinical feature in most patients and may range from proteinuria and mild elevation in creatinine to severe AKI.[32] Hypertension is also common and may be both a manifestation and an aggravating factor of endothelial injury, making it difficult, in some cases, to distinguish hypertension-associated TMA from complement-mediated aHUS.[34] The risk of progression to stage 3–4 chronic kidney disease or even end-stage renal disease remains high.[33] In contrast to typical HUS, spontaneous recovery of kidney function is uncommon in patients with aHUS.[34] If left untreated, the disease has a poor prognosis, with nearly half of

patients progressing to dialysis dependence and mortality approaching 25%.[34] Clinical presentation can also extend beyond renal involvement. Extrarenal manifestations of aHUS include cardiovascular and neurological complications such as pulmonary hypertension, heart failure, blindness, seizures, and arterial hypertension.[35] Formeck *et al.*[35] highlighted that extrarenal involvement reflects the systemic nature of complement-mediated endothelial injury and may affect the cardiovascular system, central nervous system, lungs, eyes, gastrointestinal tract, and skin. Neurological manifestations may range from confusion, headache, and altered mental status to focal deficits or coma, reflecting systemic microvascular injury.[34] In severe cases, neurological involvement may result from hypertensive encephalopathy, microvascular ischemia, seizures, posterior reversible encephalopathy syndrome, or stroke-like lesions.[36] This is clinically important because neurological symptoms may dominate the presentation or emerge during the acute phase of the disease, as illustrated by patients who develop transient focal deficits or ischemic lesions during active TMA.[36] These manifestations highlight the systemic nature of aHUS and contribute significantly to its morbidity and mortality.[37] The disease may follow a relapsing–remitting course, particularly in genetically predisposed individuals, and recurrence risk is substantial in the context of kidney transplantation without adequate complement inhibition.[34]

7. Diagnostic approach to atypical hemolytic uremic syndrome

Laboratory hallmarks include microangiopathic hemolytic anemia, thrombocytopenia, and the presence of schistocytes on peripheral smear.[37] Additional laboratory abnormalities usually include elevated lactate dehydrogenase, decreased haptoglobin, indirect hyperbilirubinemia, reticulocytosis, and a negative direct antiglobulin test. Renal involvement is suggested by increased serum creatinine, reduced estimated glomerular filtration rate, hematuria, proteinuria, or oliguria, although the severity of kidney injury may vary at presentation.[38] The Japanese Society of Nephrology/Japanese Pediatric Society criteria define aHUS by the triad of hemolytic anemia (schistocytes > 1%, increased lactate dehydrogenase), thrombocytopenia (<150,000/μL), and organ damage, most commonly renal, in the absence of Shiga toxin infection or severe *ADAMTS13* deficiency (<10%).[36] Because aHUS belongs to the broader spectrum of thrombotic microangiopathies, the first priority is to exclude conditions requiring different urgent management, particularly thrombotic TTP and STEC-associated HUS. Story *et al.*[5] emphasized that severe *ADAMTS13* deficiency strongly supports TTP, whereas preserved ADAMTS13 activity should prompt consideration of other causes of TMA, including aHUS.[37] Similarly, stool testing or Shiga toxin testing is essential when typical HUS is suspected, especially in patients with diarrheal illness or gastrointestinal symptoms.[38] Secondary TMA should also be considered, particularly in the setting of malignant hypertension, autoimmune disease, pregnancy or postpartum state, transplantation, active malignancy, severe infection, or exposure to drugs.[32] In practice, the diagnostic approach follows a structured pathway, beginning with the recognition of clinical presentation and laboratory abnormalities, followed by exclusion of secondary causes of TMA. This differential diagnosis is clinically important because complement-mediated aHUS may mimic secondary TMA, while some secondary triggers may also unmask underlying complement dysregulation.[37] Complement assessment and genetic testing can support the diagnosis, although normal C3 and C4 concentrations do not rule out aHUS, as alternative pathway dysregulation may occur despite routine complement levels remaining within the reference range.[33] Genetic analysis may reveal pathogenic variants, variants of uncertain significance, susceptibility haplotypes, or genetic backgrounds associated with anti-CFH autoantibodies.[38] However, because these results are frequently not immediately available, initiation of appropriate therapy should not be delayed when clinical suspicion of aHUS is high. Complement serology and genetic testing provide supportive evidence, while a renal biopsy may confirm thrombotic microangiopathy. Renal biopsy is not necessary in all cases, but it may be valuable when the diagnosis is unclear, when malignant hypertension or another form of secondary TMA is part of the differential diagnosis, or when determining the extent of active and chronic kidney injury could affect management.[39] Brocklebank *et al.*[39] emphasized that renal TMA is primarily a histological pattern of endothelial injury rather than a single disease entity, and therefore, biopsy findings must be interpreted in the wider clinical and laboratory context. Typical histological features may include endothelial swelling, mesangiolysis, duplication of the glomerular basement membrane, thrombi in arterioles or arteries, mucoid intimal edema, and chronic ischemic lesions.[40] However, while biopsy can demonstrate thrombotic microangiopathy, it cannot independently determine its etiology; therefore, the final diagnosis requires integration of histology with clinical presentation, hemolysis markers, platelet count, ADAMTS13 activity, Shiga toxin testing, complement evaluation, and genetic findings.[39] This process is illustrated in Figure 5.

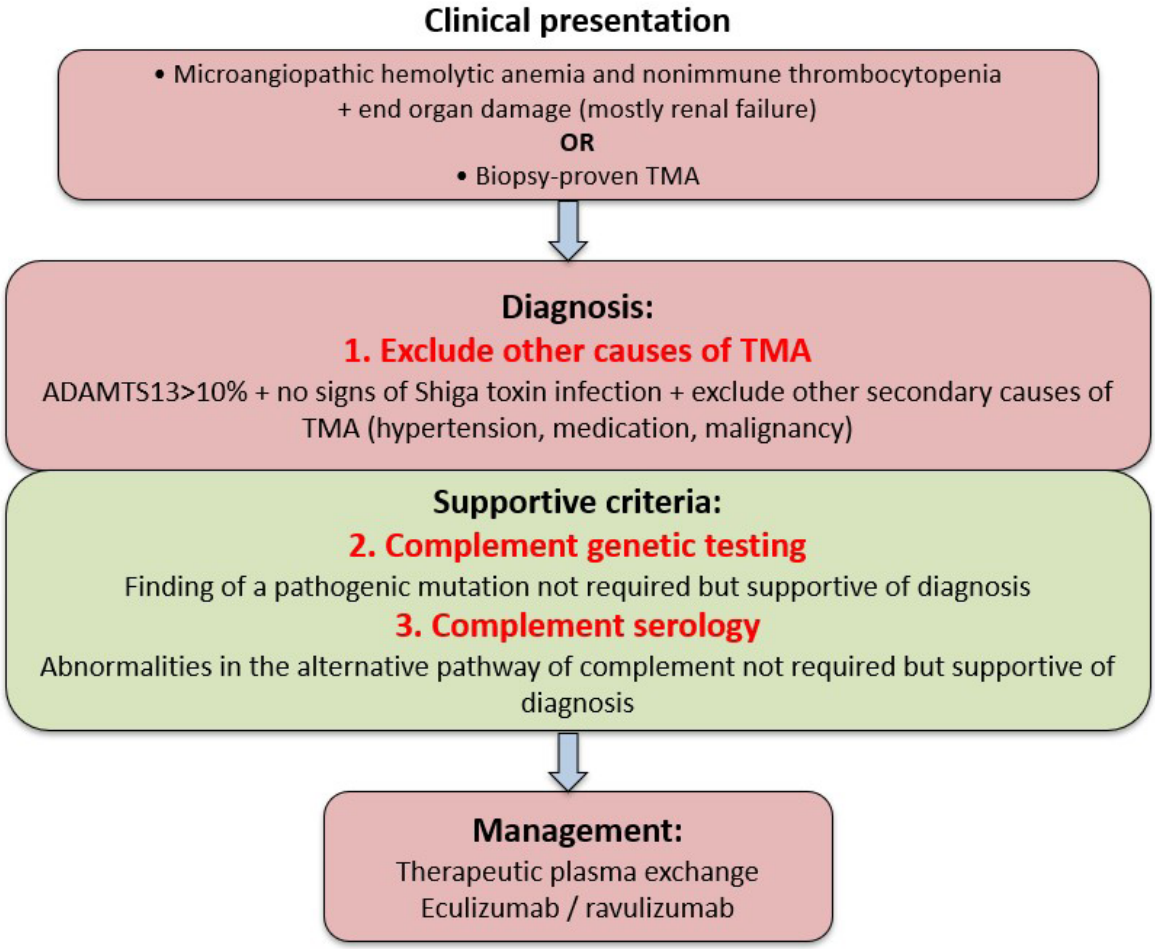

Figure 5. Clinical presentation, diagnosis, and management of aHUS. The image was created by the authors based on Ref.[41]
Abbreviations: ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS: Atypical hemolytic uremic syndrome; TMA: Thrombotic microangiopathy.

8. Treatment of atypical hemolytic uremic syndrome

Modern treatment of aHUS relies on two complement C5 inhibitors: eculizumab and ravulizumab.[42] Legendre *et al.*[42] showed that terminal complement inhibition with eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with progressive improvement in renal function, establishing C5 blockade as a disease-modifying strategy in aHUS. Eculizumab is a humanized monoclonal antibody (IgG2/4κ), and in adults, therapy begins with an induction phase of 900 mg administered as a 25–45 minute intravenous infusion once weekly for the first four weeks.[43] In the fifth week, patients receive 1,200 mg, followed by a maintenance regimen of 1,200 mg every 14 days, also given over 25–45 minutes.[43]

Ravulizumab is a newer engineered antibody derived from eculizumab but modified to achieve a longer half-life.[44] This pharmacokinetic modification enables ravulizumab to be administered as maintenance therapy every eight weeks, rather than every two weeks as with eculizumab. In adults, ravulizumab dosing is based on body weight. The recommended loading dose is 2,400 mg for patients weighing 40–60 kg, 2,700 mg for those weighing 60–100 kg, and 3,000 mg for patients weighing more than 100 kg.[44] The first maintenance dose is given two weeks after the loading dose, followed by subsequent maintenance infusions every eight weeks, with an allowable dosing window of up to seven days, except for the first maintenance administration.[44] Rondeau *et al.*[45] reported that ravulizumab was effective and safe in adults with aHUS who were naive to complement inhibitor therapy, with rapid improvement in thrombotic

microangiopathy parameters and renal outcomes during treatment. Switching from eculizumab to ravulizumab has been shown to be both safe and effective, ensuring sustained hematological stability and preservation of renal function.[46] Notably, Shahid *et al.*[47] reported that while eculizumab and ravulizumab demonstrate comparable safety and efficacy, patients and caregivers often prefer ravulizumab because of its lower financial burden and less frequent dosing schedule. Similarly, Mauch *et al.*[48] conducted two surveys, one among adult patients with aHUS and another among caregivers of pediatric patients. Both groups expressed an overall preference for ravulizumab over eculizumab, primarily due to the reduced infusion frequency. Notably, both ravulizumab and eculizumab are associated with a broad spectrum of adverse events. Most are mild but can still negatively impact quality of life, including pyrexia, diarrhea, vomiting, headache, abdominal pain, constipation, and nausea.[49] A particular concern with C5 inhibition is the increased risk of meningococcal infection.[50] The Centers for Disease Control and Prevention emphasizes that patients receiving complement inhibitors remain at markedly increased risk of meningococcal disease, even after vaccination, and therefore require vaccination, education regarding early symptoms, and consideration of antimicrobial prophylaxis according to local practice.[50] For this reason, patients are required to receive meningococcal vaccination and often short-term antibiotic prophylaxis. Interestingly, recent reports suggest that the incidence of meningococcal disease among patients receiving ravulizumab or eculizumab has decreased, likely due to increased awareness, preventive strategies, and broader vaccine use.[51] Plasma exchange also remains an important component of supportive management in aHUS, particularly in the early phase of treatment.[51] In clinical practice, it is often initiated within 24 hours of diagnosis while awaiting the results of genetic and complement testing.[52] Kaplan *et al.*[52] noted that, before the availability of complement inhibitors, plasma therapy was a central therapeutic approach in aHUS, although outcomes remained variable and the treatment did not specifically block terminal complement activation. The purpose of this therapy is to replace deficient or dysfunctional circulating complement regulators, such as CFH, and, in selected cases, to remove pathogenic anti-CFH autoantibodies.[52] Although the precise mechanisms by which CFH abnormalities lead to disease are not yet fully understood, plasma exchange may provide temporary control of complement dysregulation until targeted therapy is established. In patients with severe AKI, continuous hemodiafiltration may also be required as supportive renal replacement therapy to manage fluid overload, electrolyte disturbances, acid–base imbalance, and uremic complications.[11] The frequency and duration of treatment are individualized and depend on the patient's clinical and laboratory response.[4] Notably, its clinical utility has also been illustrated in selected reports, including rapid response in an individual treated with high-dose corticosteroids and plasma exchange, as well as successful perioperative use in combination with eculizumab during combined liver-kidney transplantation in CFH-associated aHUS.[53,54]

9. Conclusion

Atypical HUS is a rare but severe complement-mediated thrombotic microangiopathy characterized by substantial clinical heterogeneity and a significant risk of renal and systemic complications. Its presentation may overlap with other forms of TMA, particularly TTP, STEC–HUS, secondary TMA, and hypertension-associated TMA, making early diagnosis challenging. The presented case illustrates this diagnostic complexity, as severe arterial hypertension, AKI, laboratory evidence of microangiopathic hemolysis, and biopsy-proven thrombotic microangiopathy required careful integration of clinical, laboratory, histological, and genetic findings. Advances in complement biology have substantially improved understanding of aHUS pathogenesis. The disease is now recognized as a multifactorial condition in which inherited susceptibility, acquired complement abnormalities, environmental, or clinical triggers interact to produce uncontrolled activation of the alternative pathway and endothelial injury. Genetic testing may identify pathogenic variants, variants of uncertain significance, risk haplotypes, or structural abnormalities that support the diagnosis and assist in risk stratification. The introduction of terminal complement inhibition has transformed the prognosis of aHUS. Eculizumab and ravulizumab provide targeted C5 blockade, control complement-mediated thrombotic microangiopathy, and may promote hematologic remission and renal recovery. Ravulizumab offers the additional practical advantage of an extended dosing interval, which may reduce treatment burden while maintaining sustained complement inhibition. In the presented case, ravulizumab was well tolerated and was associated with normalization of hemolytic parameters and gradual improvement in renal function, although chronic biopsy changes such as cortical thinning, fibrosis, and arterionephrosclerosis were not reversible. Contemporary management of aHUS requires a multidisciplinary approach combining early recognition of TMA, prompt exclusion of TTP and STEC–HUS, assessment for secondary triggers, complement and genetic evaluation, renal biopsy in selected cases, supportive care, and timely initiation of complement inhibition when clinically indicated. Further

epidemiological surveillance, standardized diagnostic algorithms, prospective discontinuation studies, and improved biomarkers of disease activity are needed to refine risk stratification and optimize long-term outcomes in this complex complement-mediated disorder.

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Conflict of interest

The authors declare they have no competing interests.

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