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Coexistence of Atypical Hemolytic Uremic Syndrome and Immunoglobulin A (IgA) Nephropathy Without Readily Detectable Glomerular C3 Deposition: A Case Report

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Abstract

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy in which uncontrolled activation of the complement alternative pathway (AP) plays a central role in disease pathogenesis. Immunoglobulin A (IgA) nephropathy (IgAN), another disease associated with complement activation, is the most common primary glomerular disease worldwide. The coexistence of aHUS and IgAN appears to be rare. Previous studies have hypothesized that pathological IgA in IgAN may induce persistent AP activation, thereby contributing to aHUS development. We herein report a 27-year-old woman presenting with malignant hypertension and severe renal impairment. Her clinical and histological findings supported a diagnosis of aHUS with coexisting IgAN. However, immunofluorescence revealed no detectable glomerular C3 deposition despite the severe clinical presentation. Following combined treatment with the humanized anti-C5 monoclonal antibody eculizumab, corticosteroids, and blood pressure control, the patient showed substantial hematologic and renal improvement over approximately eight months of follow-up and remained dialysis-independent. This case highlights an unusual pathological finding in patients with coexisting aHUS and IgAN and underscores the need for further studies to clarify the mechanisms underlying this coexistence.

Categories: Nephrology
Keywords: atypical hemolytic-uremic syndrome (ahus), complement activation, complement inhibitor, iga nephropathy (igan), thrombotic microangiopathy (tma)

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy (TMA) characterized by consumptive thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and multi-organ dysfunction, primarily affecting the kidneys. Its diagnosis is based on the exclusion of other causes of TMA, including thrombotic thrombocytopenic purpura, Shiga toxin-associated HUS, and secondary TMA [1]. Immunoglobulin A (IgA) nephropathy (IgAN), however, is the most common primary glomerular disease worldwide and typically presents with some or all elements of the nephritic syndrome [2]. Mechanistically, aHUS arises from the dysregulation of the complement alternative pathway (AP) [1], while IgAN involves complement activation of both the AP and lectin pathways (LP) [3]. Although IgAN can be associated with TMA lesions, which indicate a poor renal prognosis [4], few cases of aHUS with coexisting IgAN have been reported. Previous studies have hypothesized that pathological IgA in IgAN may induce persistent AP activation, thereby contributing to the development of aHUS [5]. As a humanized anti-C5 monoclonal antibody, eculizumab inhibits terminal complement activation and is therefore an established treatment for aHUS and a rescue therapy for selected patients with refractory IgAN [1,6]. We herein present a patient with coexisting aHUS and IgAN who showed substantial hematologic and renal improvement following combined treatment with eculizumab, corticosteroids, and blood pressure (BP) control. However, immunofluorescence revealed no detectable glomerular C3 deposition, an unusual finding in patients with coexisting aHUS and IgAN. This finding raises questions about the mechanisms underlying their coexistence.

Case Presentation

A 27-year-old woman was admitted with malignant hypertension (BP, 209/129 mmHg) and severe renal impairment, with a serum creatinine (Scr) of 438.4 μmol/L (reference range, 41.0-72.0 μmol/L) and an estimated glomerular filtration rate (eGFR) of 11.25 mL/min (reference range, >90 mL/min). More than one year before admission, she was incidentally noted to have mildly elevated BP (approximately 140/100 mmHg), microscopic hematuria (43 red blood cells (RBCs)/μL; reference range, ⩽13 RBCs/μL), proteinuria (3+), and impaired renal function, with a Scr of 103.2 μmol/L and an eGFR of 65.09 mL/min. However, no further evaluations were performed. She subsequently took two antihypertensive medications of unknown names but later discontinued them. Other medical history was negative. No further monitoring of BP or renal function was performed. One week before admission, she experienced blurred vision in the right eye with occasional nausea and vomiting, but no abdominal pain, diarrhea, or other gastrointestinal symptoms.

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She had no history of pregnancy, and there was no family history of kidney disease. Physical examination revealed no abnormalities in the neurological, cardiopulmonary, abdominal, or cutaneous examinations. Fundoscopic examination revealed edema, hemorrhages, and cotton-wool spots at multiple sites in the posterior pole of the retina, with mild exudation in the macula.

Further laboratory tests revealed moderate anemia (hemoglobin, 76 g/L; reference range, 113-151 g/L), schistocytosis (1.2%; reference range, <1.0%), reticulocyte percentage (2.60%; reference range, 0.58-1.59%), lactate dehydrogenase (563 U/L; reference range, 120-250 U/L), haptoglobin (<0.07 g/L; reference range, 0.30-2.00 g/L), and thrombocytopenia (platelet count, 64×10^9/L; reference range, $100\text{-}300\times10^9$/L). Urinalysis revealed microscopic hematuria (26 RBCs/μL; reference range, ⩽13 RBCs/μL) and massive proteinuria (urinary albumin-to-creatinine ratio, 3422.22 mg/g Cr; reference range, <25.00 mg/g Cr). Serum C3 (0.77 g/L; reference range, 0.70-1.40 g/L), C4 (356 mg/L; reference range, 100-400 mg/L), and soluble C5b-9 (135ng/mL; reference range, 72-252ng/mL) were within the normal ranges. No monoclonal protein was detected by serum immunofixation, and free light chain κ/λ ratio was within the normal range. Autoimmune serologies (antinuclear antibody (ANA), anti-dsDNA, anti-ENA, anti-phospholipid, antineutrophil cytoplasmic antibody (ANCA), anti-GBM (glomerular basement membrane), and anti-PLA2R antibodies) were negative. The upright aldosterone-to-renin ratio was 31.45, and thyroid hormones were normal. A Coombs test was not performed. The ultrasound showed increased parenchymal echogenicity in both kidneys. Additional findings included parathyroid hormone (212 pg/mL; reference range, 15-65 pg/mL), HbA1c (3.9%; reference range, 4.0-6.0%), serum albumin (38.5 g/L; reference range, 35.0-52.0 g/L), negative indicators for hepatitis viruses, and normal tumor markers (alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and CA19-9). Catecholamines, cortisol, growth hormone, and renal artery ultrasound were not measured. Based on these findings, hemolytic uremic syndrome (HUS) was strongly suspected. Further tests, including stool cultures for *Salmonella* and *Shigella*, serum ADAMTS13 activity (76.77%; reference range, 70-120%) and ADAMTS13 inhibitor level (0.00 Bethesda, reference range, <0.6 Bethesda), were normal. A kidney biopsy was therefore performed.

Histopathological examination showed global glomerulosclerosis in 14 of 22 glomeruli (63.6%) and cellular or circumferential crescents in five (22.7%). Significant mesangial hypercellularity and matrix expansion were observed, along with segmental double-contour formation of the glomerular basement membrane. Severe tubulointerstitial injury was characterized by multifocal tubular atrophy involving approximately 40% of the tubules, with tubular degeneration and intratubular cast formation. The interstitium showed edema, diffuse fibrosis, and dense inflammatory cell infiltration, predominantly by lymphomononuclear cells. Vascular lesions included arterial and arteriolar intimal thickening, endothelial swelling, myxoid or hyaline changes, severe luminal narrowing, and segmental microthrombus formation, consistent with TMA. Immunofluorescence revealed segmental granular mesangial staining for IgA (2+) and weak IgG (+/-), with no C3 staining (Figure *1*).

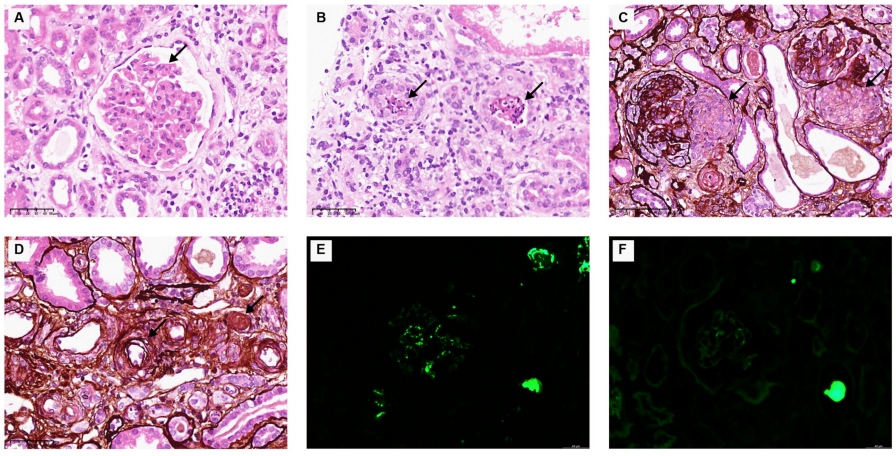


FIGURE 1: Light microscopy and immunofluorescence findings on renal biopsy.

Light microscopy revealed mesangial hypercellularity and expansion (arrow in A), intratubular cast formation (arrows in B), cellular crescents (arrows in C), arteriolar wall thickening (left arrow in D), and segmental microthrombus formation (right arrow in D). Immunofluorescence showed segmental mesangial deposition of IgA (E) and IgG (F) in the glomeruli.

Collectively, these findings supported a clinical diagnosis of aHUS, diffuse proliferative IgAN (grading and classification were deferred because of concomitant kidney disease), and malignant hypertension (MH)-associated kidney injury. Additional complement tests performed nearly five months after admission

revealed an elevated serum complement factor Ba (CFBa) of 2042.60 ng/mL (reference range, 221.3-727.0 ng/mL) and a decreased CH50 of 14.3 U/mL (reference range, 23.0-46.0 U/mL). However, the complement evaluation remained incomplete, as genetic tests for variants in genes (e.g., *C3*, *CFH*, *CFB*, *CFI*, and *CD46*) and assessment of anti-CFH antibodies were not performed.

After admission (day 0), the patient received supportive care focused primarily on BP control, initially with intravenous nicardipine and subsequently with carvedilol, doxazosin, nifedipine, and clonidine. Although BP had decreased to approximately 140/100 mmHg and the platelet count gradually increased to 134×10^9/L (reference range, $100\text{-}300\times10^9$/L), Scr continued to increase, reaching 547.6 umol/L (reference range, 41.0-72.0 μmol/L) on day 4. We consequently treated the patient with eculizumab (900 mg weekly for four weeks, followed by 1200 mg every 14±2 days) on day 5. Her renal function began to improve just one day after the first dose of eculizumab (Scr, 463.3 umol/L; reference range, 41.0-72.0 μmol/L, and eGFR, 10.52mL/min; reference range, >90 mL/min). Given the coexisting IgAN, pulse corticosteroid therapy was administered from day 7 to day 9, followed by gradual dose tapering (Figure *2*).

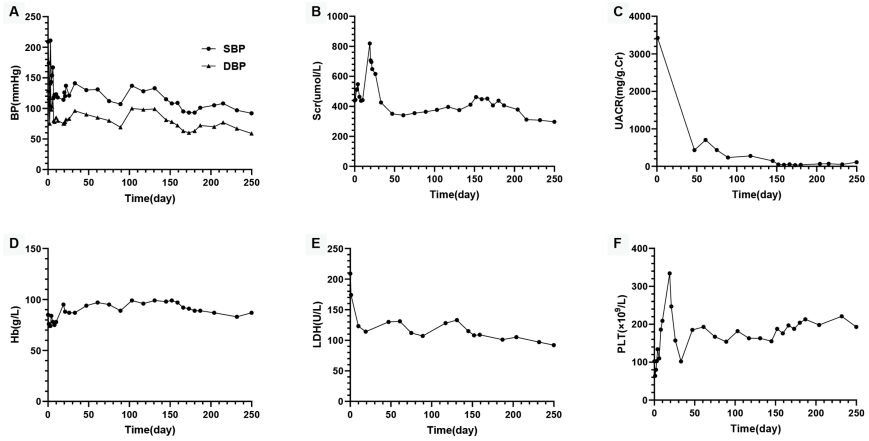


FIGURE 2: Patient clinical course.

The patient was admitted to our hospital on day 0. Eculizumab was initiated on day 5, and methylprednisolone 500 mg daily was administered from day 7 to day 9. By day 250, steroid therapy had been tapered to prednisone 5 mg every other day. During long-term follow-up, the patient's BP was kept under control (A). Scr gradually and persistently decreased, except for a transient increase early in the treatment course (B). Substantial improvements were observed in UACR (C), microangiopathic hemolytic anemia (D and E), and PLT (F).

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; Scr, serum creatinine; UACR, urinary albumin-to-creatinine ratio; Hb, hemoglobin; LDH, lactate dehydrogenase; PLT, platelet count.

During approximately eight months of follow-up, the patient's BP remained well controlled, and she achieved hematologic normalization (a normal platelet count and lactate dehydrogenase (LDH) level, sustained for at least two consecutive measurements over a period of at least four weeks) [7] and renal improvement, with Scr decreasing by over 25% (297.0 μmol/L; reference range, 41.0-72.0 μmol/L) and urinary albumin-to-creatinine ratio decreasing to 112.89 mg/g Cr (reference range, <25.00 mg/g Cr). A transient increase in Scr occurred early in the treatment course, possibly indicating ongoing disease activity, which prompted rehospitalization (Figure *2* and Table *1*). No further hospitalization occurred thereafter. The patient received meningococcal and pneumococcal vaccines three weeks after admission. In terms of safety, the patient developed an asymptomatic urinary tract infection and a mild acute upper respiratory tract infection early in the treatment course, and oral candidiasis approximately six months after admission, despite receiving thymalfasin.

	Day 0	Day 19	Day 117	Day 250
BP (mmHg)	209/129	114/75	128/98	92/59
Scr (μmol/L)	438.4	819.2	396.4	297.0
UACR (mg/g Cr)	3422.22	NA	278.46	112.89
Hb (g/L)	76	95	96	87
LDH (U/L)	563	246	281	166
PLT (×10⁹/L)	64	334	163	193

TABLE 1: Patient clinical course.

The patient was admitted to our hospital on day 0 and rehospitalized on day 19 because of a transient increase in Scr. Day 117 represented the midpoint of follow-up, and day 250 marked the end of follow-up. BP, blood pressure; Scr, serum creatinine; UACR, urinary albumin-to-creatinine ratio; Hb, hemoglobin; LDH, lactate dehydrogenase; PLT, platelet count; NA, not available.

Discussion

TMA is a histological classification describing a constellation of microvascular alterations that primarily affect the kidney. Clinically, it is characterized by consumptive thrombocytopenia, MAHA, and multi-organ dysfunction. aHUS represents a unique entity within the broader spectrum of TMA, with preserved ADAMTS13 activity and negative Shiga toxin-related tests [8]. TMA is also a frequently identified lesion in IgAN and indicates a poor renal prognosis [2,4]. However, the coexistence of aHUS and IgAN appears to be rare, with only a limited number of cases reported to date. Herein, we describe a case of aHUS with coexisting IgAN presenting with acute kidney injury, MH, and hematologic features of TMA. The patient subsequently showed meaningful clinical improvement following combined treatment with eculizumab, corticosteroids, and BP control.

In the reported cases, IgAN either preceded or coincided with the onset of aHUS [5,9-17]. Similarly, our patient had presented with mildly elevated BP, microscopic hematuria, proteinuria, and impaired renal function more than one year before admission, suggesting that IgAN may have been clinically active at that time. Taken together, these observations raise the hypothesis that active IgAN may trigger the development of aHUS in susceptible individuals. This triggering effect may be mediated by infection, uncontrolled BP, transplantation, and medications, or alternatively, by persistent activation of the AP in IgAN [5]. Although persistent, untreated IgAN may have contributed to uncontrolled BP, MH was considered less likely to be the primary trigger of TMA in our patient, as her renal function continued to deteriorate despite an initial BP reduction and Scr increased again despite normal BP during rehospitalization.

Since *CFH* mutations were first reported to be associated with aHUS in 1998, mutations in other complement-related genes (e.g., *C3*, *CFB*, *CFI*, and *CD46*), as well as hybrid *CFHR1/CFH* genes, have subsequently been identified in aHUS. Uncontrolled AP activation is now widely recognized as a central driver of aHUS pathogenesis [18]. In IgAN, complement activation has also emerged as an important mediator of renal inflammation through both the AP and LP, particularly in patients with microangiopathic lesions. Glomerular C3 deposition is frequently observed in patients with IgAN, and a higher intensity of glomerular C3 deposition has been associated with more severe renal lesions and poorer long-term renal survival [19,20]. In previous cases with both aHUS and IgAN, glomerular C3 deposition was consistently observed, and a substantial proportion of patients exhibited hypocomplementemia [5,9-17]. Collectively, these findings suggest a shared pattern of complement activation in both disorders. In our patient, the elevated serum CFBa level detected nearly five months after admission provides additional evidence of AP activation. However, despite the severe clinical presentation, immunofluorescence staining revealed no detectable glomerular C3 deposition. This finding should be interpreted with caution because the immunofluorescence specimen contained only one glomerulus. Nevertheless, this unusual pathological finding raises questions about the mechanisms underlying the coexistence of aHUS and IgAN.

Eculizumab, a humanized anti-C5 monoclonal antibody, has been approved for the treatment of aHUS. By inhibiting C5 cleavage, it prevents C5a generation and membrane attack complex formation, thereby attenuating complement-mediated inflammation and thrombosis [1]. Given the important role of complement activation in IgAN, eculizumab has also been used as rescue therapy for refractory IgAN in some reported cases. These cases were characterized by rapid disease progression, crescent formation, and poor responses to conventional therapies, with some exhibiting TMA features. All of them showed glomerular C3 deposition, whereas evidence of complement activation in blood was limited. Despite heterogeneous clinical responses, some patients experienced partial improvement following eculizumab treatment [6]. Moreover, favorable responses to eculizumab have also been reported in some patients with

coexisting aHUS and IgAN [14,15,17]. In our patient, substantial hematologic and renal improvement was observed following combined treatment with eculizumab, corticosteroids, and BP control. This clinical improvement may have reflected treatment effects on both aHUS and IgAN, rather than on aHUS alone. Although the effects of these treatments cannot be fully disentangled, eculizumab was considered the key therapeutic intervention, as Scr began to decline just one day after its administration. Thus, the clinical response supports a role for complement activation in the disease process.

Several limitations should also be acknowledged. First, the complement evaluation was incomplete, as genetic tests for complement-related variants and assessment of anti-CFH antibodies were not performed, leaving the underlying complement abnormalities insufficiently characterized. In addition, a Coombs test was not performed, limiting the evaluation of alternative causes of hemolytic anemia.

Conclusions

We herein describe a rare case of aHUS with coexisting IgAN. Immunofluorescence revealed no detectable glomerular C3 deposition despite the severe clinical presentation. This unusual pathological finding raises questions about the mechanisms underlying this coexistence. The patient showed substantial hematologic and renal improvement after treatment, likely driven in large part by eculizumab, a humanized anti-C5 monoclonal antibody. Together with the elevated serum CFBa level, this clinical response supports an important role for complement activation in the disease process.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Zhaoting Ren, Kunling Ma

Acquisition, analysis, or interpretation of data: Zhaoting Ren, Lijun Mou

Drafting of the manuscript: Zhaoting Ren

Critical review of the manuscript for important intellectual content: Lijun Mou, Kunling Ma

Supervision: Lijun Mou, Kunling Ma

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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