Received: 26 August 2025 / Accepted: 12 November 2025 / Published online: 30 December 2025

DOI 10.34689/SH.2025.27.6.027

UDC 616.61-002-053.2

COMBINATION OF ATYPICAL HEMOLYTIC UREMIC SYNDROME AND IGA NEPHROPATHY : A CASE REPORT AND LITERATURE REVIEW

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Abstract

Atypical hemolytic uremic syndrome (aHUS), which is characterized by thrombotic microangiopathy, is distinct from Shiga-toxin-induced HUS and thrombotic thrombocytopenic purpura. aHUS is associated with dysregulation of the alternative complement system. Eculizumab, an anti-C5 antibody, is effective in limiting complement activation in patients with aHUS. In recent years, a link has been identified between aHUS and some other complement-mediated nephropathies, in particular C3 glomerulopathy and immune-complex–mediated membranoproliferative glomerulonephritis. A common genetic component may be a unifying factor in these situations. At the same time, the possible combination of aHUS with IgA nephropathy (IgAN) remains poorly understood. We herein report the case of a 10-year-old girl, who was admitted to our hospital with symptoms of jaundice, anemia, thrombocytopenia, and acute kidney injury. Clinical and laboratory assessments led to a diagnosis of atypical hemolytic uremic syndrome (aHUS). The patient was initially treated withplasma exchange and hemodialysis. Eculizumab treatment was initiated on hospital day 6.Remission of her thrombotic microangiopathy was achieved, however during her follow-up, the patient experienced several episodes of acute respiratory infections with macrohematuria. Kidney biopsy was performed and her histological findings were consistent with immunoglobulin A nephropathy (IgAN). The patient showed improvement following treatment with eculizumab and ramipril. This case prompts a discussion on the potential relationship between aHUS and IgAN.

Key words: *Hemolytic uremic syndrome, immunoglobulin A nephropathy, acute kidney injury, glomerulonephritis, childhood.*

For citation:

Kagan M.Yu., Issanguzhina Zh.H., Seipenova A.N., Puxovikova N.N. Combination of atypical hemolytic uremic syndrome and IGA nephropathy: a case report and literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (6), pp. 244-250. *doi 10.34689/SH.2025.27.6.027*

Резюме

СОЧЕТАНИЕ АТИПИЧНОГО ГЕМОЛИТИКО-УРЕМИЧЕСКОГО СИНДРОМА И IGA-НЕФРОПАТИИ. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ И ОБЗОРЛИТЕРАТУРЫ.

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Атипичный гемолитико-уремический синдром (аГУС) обусловлен нарушением регуляции системы комплемента, приводящей к повышенной её активации по альтернативному пути. Этот механизм отличает аГУС от других вариантов тромботической микроангиопатии (ТМА), прежде всего таких, как гемолитико-уремический синдром, обусловленный шига-токсином (STEC-ГУС) и тромботической тромбоцитопенической пурпуры (ТТП). Экулизумаб, моноклональное антитело к С5, эффективно блокирует активацию комплемента у пациентов с аГУС. В последние годы была выявлена связь между аГУС и некоторыми другими нефропатиями, развитие которых опосредованно активацией системы комплемента, вчастности С3-гломерулопатией и иммунокомплексным мембранопролиферативным гломерулонефритом. Общий

генетический механизм может быть объединяющим фактором в этих ситуациях. В то же время возможное сочетание аГУС с IgA-нефропатией (IgAN) остаётся плохо изученным. В настоящем сообщении мы приводим наблюдение за 10-летней девочкой, которая поступила в нашу больницу с симптомами желтухи, анемии, тромбоцитопении и острого повреждения почек. Клинические и лабораторные исследования привели к диагностике аГУС. Первоначально пациентка получала лечение инфузиями свежезамороженной плазмы, плазмаобменом и гемодиализом. Лечение экулизумабом было начато на 6-й день госпитализации. Была быстро достигнута ремиссия ТМА, однако во время последующего наблюдения у пациентки сохранялись изменения в анализах мочи и отмечалось несколько эпизодов острых респираторных инфекций, сопровождавшихся кратковременными эпизодами макрогематурии. Была проведена биопсия почки. Гистологическое исследование выявило IgAN. С нефропротективной целью был добавлен пероральный рамиприл, что привело к стойкому улучшению анализов мочи. Мы приводим литературные данные, обсуждающие подобные клинические случаи и возможную связь между аГУС и IgAN.

Ключевые слова: *гемолитико-уремический синдром, иммуноглобулин А нефропатия, острое почечное повреждение, гломерулонефрит, детство.*

Для цитирования:

Каган М.Ю., Исангужина Ж.Х., Сейпенова А.Н., Пуховикова Н.Н. Сочетание атипичного гемолитико-уремического синдрома и IGA-нефропатии. Клиническое наблюдение и обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (6), С.244-250. *doi 10.34689/SH.2025.27.6.027*

Түйіндеме

АТИПИЯЛЫҚ ГЕМОЛИТИКО-УРЕМИЯЛЫҚ СИНДРОМ МЕН IGA НЕФРОПАТИЯСЫНЫҢ ҮЙЛЕСІМІ. КЛИНИКАЛЫҚ БАҚЫЛАУ ЖӘНЕ ӘДЕБИЕТКЕ ШОЛУ

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Атипиялық гемолитикалық-уремиялық синдром (аГУС) комплемент жүйесінің реттелуінің бұзылуымен байланысты, бұл оның альтернативті жол арқылы шамадан тыс белсендірілуіне әкеледі. Бұл механизм аГУС-ті тромботикалық микроангиопатияның (ТМА) басқа түрлерінен, ең алдымен шигатоксинмен байланысты гемолитикалық-уремиялық синдромнан (STEC-ГУС) және тромботикалық тромбоцитопениялық пурпурадан (ТТП) ерекшелендіреді. Экулизумаб - С5-ке қарсы моноклоналды антидене - аГУС-пен ауыратын науқастарда комплемент белсендірілуін тиімді түрде тежейді. Соңғы жылдары аГУС пен кейбір басқа нефропатиялар арасындағы байланыс анықталды, олардың дамуы комплемент жүйесінің белсендірілуімен байланысты, атап айтқанда, С3-гломерулопатия және иммундық кешенмен байланысты мембранопролиферативті гломерулонефрит. Бұл жағдайларда ортақ генетикалық механизм біріктіруші фактор болуы мүмкін. Сонымен қатар, аГУС пен IgA-нефропатиясының (IgAN) қатар жүруі әлі толық зерттелмеген. Осы мақалада біз сарғаю, анемия, тромбоцитопения және жедел бүйрек зақымдануы белгілерімен ауруханаға түскен 10 жастағы қыздың жағдайын сипаттаймыз. Клиникалық және зертханалық зерттеулер аГУС диагнозын растады. Бастапқыда науқас жаңа мұздатылған плазма инфузиясы, плазма алмасу және гемодиализ арқылы ем қабылдады. Экулизумабпен емдеу ауруханаға жатқызылғаннан кейін 6-шы күні басталды. ТМА ремиссиясына тез қол жеткізілді, алайда кейінгі бақылау кезеңінде науқастың зәр талдауларында өзгерістер сақталып, жедел респираторлық инфекция эпизодтарымен қатар жүретін қысқа мерзімді макрогематурия байқалды. Бүйрек биопсиясы жасалды. Гистологиялық зерттеу IgAN диагнозын көрсетті. Бүйрек қорғаушы мақсатта ішке қабылдайтын рамиприл қосылды, бұл зәр талдауларының тұрақты жақсаруына алып келді. Біз осындай клиникалық жағдайларды сипаттайтын әдеби деректерді ұсынып, аГУС пен IgAN арасындағы мүмкін байланыс мәселесін талқылаймыз.

Түйінді сөздер: *гемолитикалық-уремиялық синдром, иммуноглобулин А нефропатиясы, жедел бүйрек зақымдануы, гломерулонефрит, балалық шақ.*

Дәйексөзүшін:

Каган М.Ю., Исангужина Ж.Х., Сейпенова А.Н., ПуховиковаН.Н. Атипиялық гемолитико-уремиялық синдром мен IGA нефропатиясының үйлесімі. Клиникалық бақылау және әдебиетке шолу // ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 244-250. *doi 10.34689/SH.2025.27.6.027*

Hemolytic uremic syndrome (HUS) represents a group of disorders with diverse etiologies and pathogenic mechanisms. These conditions are grouped under the general term "thrombotic microangiopathy" (TMA), due to the formation of blood clots within the microcirculation. TMA is characterized not only by organ damage, but also by thrombocytopenia caused by platelet consumption and microangiopathic hemolytic anemia. The latter is characterized by the presence of more than 1% schistocytes (red blood cell fragments) in the blood, which can be easily detected by peripheral blood smear analysis. Other laboratory markers of intravascular hemolysis, such as increased lactate dehydrogenase (LDH) levels and decreased plasma haptoglobin, can also be detected [1].

Despite the similarity of clinical and morphological features, primary TMA can be divided into two main categories: thrombotic thrombocytopenic purpura (TTP) and HUS [2]. In the pathogenesis of TTP, a key role is played by a severe deficiency of the ADAMTS13 enzyme, which is responsible for cleaving large multimers of von Willebrand factor into smaller fragments with low thrombogenic capacity. ADAMTS13 deficiency may result from either genetic mutations or the presence of autoantibodies that inhibit its activity. This leads to the formation of uncleaved multimers of von Willebrand factor and the development of microthrombosis. The disease has a systemic nature and can affect various organs; however, ischemic involvement of the central nervous system often predominates in the clinical presentation, while acute kidney injury requiring dialysis is less common [3].

In contrast, HUS is a form of TMA in which the kidneys are the primary target organ. Therefore, severe acute kidney injury (“acute uremia”) becomes one of the main clinical features of this syndrome [2,4]. Historically, HUS has been classified into two forms: with (D+) and without (D-) diarrhea. D+ HUS was previously considered synonymous with HUS caused by Shiga toxin-producing E. coli (STEC). However, the current classification distinguishes between “typical HUS” (STEC-HUS), referring to the Shiga toxin-induced form, and “atypical HUS” (aHUS) for all other cases [4,5]. Atypical HUS is a rare condition characterized by uncontrolled activation of the alternative complement pathway. The pathogenesis of aHUS involves mutations in genes regulating complement activity (such as factor H, factor I, MCP, C3, factor B, and thrombomodulin) or the presence of autoantibodies against these proteins [2]. Potential triggers for disease onset include infections, pregnancy, childbirth, and surgical procedures.

Ideally, aHUS diagnosis should include genetic testing; however, about 40% of patients with clinical manifestations of aHUS have no detectable genetic mutations. This may be due to limitations of current diagnostic methods, as well as the fact that the full spectrum of genes involved in complement regulation is not yet completely understood. Therefore, a negative genetic test result does not exclude the possibility of aHUS diagnosis. Moreover, given the time-consuming nature of genetic testing and the need for prompt therapeutic decisions in active TMA, the diagnosis of aHUS should be based on clinical and laboratory findings after exclusion of other potential causes of TMA in a particular patient [4]. Children with TMA, TTP and STEC-HUS should be excluded first. For this purpose, it is especially important to determine ADAMTS13 activity: levels below 10% of the norm are indicative of TTP, whereas higher activity essentially rules out this diagnosis [6]. The presence of diarrhea during the prodromal phase, along with a positive Shiga toxin test or isolation of Shiga toxin-producing E. coli from feces, confirms the diagnosis of STEC-HUS [5,7].

In addition, it is important to exclude secondary forms of thrombotic microangiopathy (TMA), which may be associated with antiphospholipid syndrome, systemic lupus packed red blood cells, disseminated intravascular coagulation (DIC), and other conditions [8]. In recent years, an association has been established between atypical hemolytic-uremic syndrome (aHUS) and several other complement-mediated nephropathies, such as C3-glomerulopathy and immunocomplex membranoproliferative glomerulonephritis. A shared underlying factor in these cases may be a genetic predisposition [9,10]. At the same time, the coexistence of aHUS with IgA nephropathy (IgAN) remains insufficiently studied [11].

IgAN is the most common primary glomerular disease, particularly prevalent in countries of the Asia-Pacific region. It is characterized by dominant or co-dominant mesangial deposition of immune complexes containing IgA. Large cohort studies have identified distinctive light-optical histological changes, including mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), interstitial fibrosis and tubular atrophy (T), and semilunar lesions (C). These findings formed the basis for the Oxford morphologic classification of IgAN [12,13].

In this paper, we present a rare case of the co-occurrence of aHUS and IgAN in a 10-year-old girl.

Clinical Observation. A 10-year-old girl was admitted in June 2024 to the regional children's hospital due to the acute vomiting, profound weakness, marked jaundice of the skin and sclera, and decreased diuresis. No diarrhea was observed. In addition to jaundice, examination revealed isolated petechiae on the trunk and arterial hypertension (BP 145/85 mm Hg). The heart rate was 94 beats per minute, respiratory rate 20 breaths per minute, and body temperature 36.5 ° C. Upon admission to the emergency department, a general blood test revealed anemia with Hb 76 g / L and thrombocytopenia 49 x 109 / L. A peripheral blood smear showed schistocytes of 3-4% (Figure 1) and reticulocytosis of 5%. Urinalysis (UA) revealed a high number of erythrocytes and proteinuria of 2.6 g/L. Biochemical analysis of blood confirmed high bilirubin levels (total bilirubin at 180 μmol/L, indirect fraction at 172 μmol/L) and acute kidney injury, with urea at 22 mmol/L and creatinine at 265 μmol/L. Ultrasound demonstrated bilateral diffuse increased echogenicity of the renal parenchyma. Liver ultrasound showed no signs of biliary obstruction, fibrosis, or any other damage. The patient was admitted to the intensive care unit. From the medical history, it was established that there was no hereditary history of kidney disease. The child had no previous health abnormalities, except for a single episode of macrohematuria that developed three years ago, due to which the patient was hospitalized in the pediatric urology unit with suspected urolithiasis.

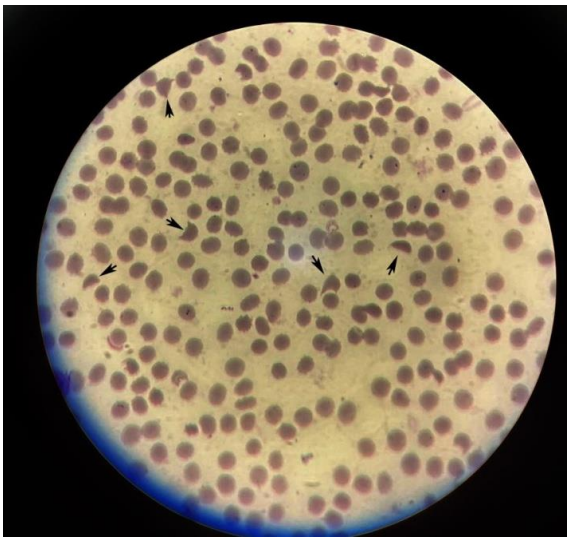

Figure 1. Schistocytes (indicated by arrows) in the patient's peripheral blood smear.

Hematuria spontaneously resolved after a few days and, although ultrasound of the urinary system did not reveal a calculus, this episode was assessed as a probable passage of a stone. Recommendations were given to increase the amount of fluid intake. Monitoring of urine tests was not performed subsequently. The hematuria resolved spontaneously within a few days and, although renal ultrasound did not reveal a calculus, this episode was interpreted as a probable passage of a stone. The patient was advised to increase fluid intake. No follow-up urinalysis monitoring was conducted thereafter. The examination in the intensive care unit revealed a high level of LDH at 2160 U / L (< 430). Other biochemical parameters remained within the reference levels: ALT - 18.3 IU/L (0.0 - 39.0), AST - 46.4 IU/L (0.0 - 47.0), CPK - 75.6 U/L (<247), complement factor 3 (C3) - 115 mg/dL (90-180), complement factor 4 (C4) - 34 mg/dL (10-40). There were no deviations in the coagulogram: APTT 28 seconds (24-35), prothrombin index 91% (70-120), fibrinogen 2.57 g/L (1.8-4.0), D-dimer 0.31 μg/ml (0-0.55). Testing for hepatitis A, B, C, CMV, and EBV returned negative results. Autoimmune screening, including antinuclear antibodies, antibodies to double-stranded DNA, ANCA, and antiphospholipid antibodies, did not reveal any values exceeding the reference ranges. Both direct and indirect Coombs tests were negative. ADAMTS13 activity was measured at 71% (93-113). The child was tested for antibody titers against factor H, which found to be within normal limits.

TMA was diagnosed. Over the following days, the patient received infusions of fresh frozen plasma and packed red blood cells. One plasma exchange session was performed with replacement of 60 ml/kg of the patient's plasma and, due to the developed hyperhydration, one hemodialysis session was required. Oral amlodipine was prescribed at a dose of 5 mg per day due to arterial hypertension. Given the absence of diarrheal prodrome, STEC- HUS was ruled out. ADAMTS13 activity level above 10% (blood for the study was taken before the start of plasma therapy) allowed to exclude TTP. Together with negative findings for antiphospholipid syndrome, DIC syndrome, immune hemolytic anemia, and systemic autoimmune diseases, these results allowed to reject other possible causes of TMA and diagnose aHUS, in connection with which complement-inhibiting therapy with eculizumab was initiated on the sixth day of the disease.

Eculizumab was given 600 mg weekly for two doses, then 900 mg every two weeks (maintenance) (patient weight 33 kg). Two days after the first dose, the patient demonstrated a marked increase in diuresis, from 200 ml to 1300 ml per day. This was followed by a rapid normalization of peripheral blood platelet counts, a more gradual decline in serum bilirubin, and eventual resolution of anemia and schistocytosis, with LDH levels decreasing to 280 U / L. Blood pressure normalized, allowing for the discontinuation of amlodipine therapy, and serum urea and creatinine returned to refence levels. However, despite the clear positive dynamics in general urine tests, hematuria (erythrocytes from 30-40 in sight to a large number) and proteinuria (albumin-to-creatinine ratio of 1.0-1.2 mg / mg in spot urine samples) persisted.

To investigate further, targeted next-generation sequencing was performed at the Medical Genetic Center of the National Medical Research Center of Children's Health in Moscow, focusing on genes associated with aHUS (CFH, CFI, MCP, C3, CFB, THBD). Pathogenic genetic variants were not identified. In September and October 2024, the patient experienced two episodes of macrohematuria during acute respiratory viral infection, which could not be explained by aHUS relapse, given the ongoing eculizumab therapy and the absence of laboratory signs of TMA activity. In this regard, in October 2024, 3.5 months after the TMA onset, a puncture biopsy of the lower pole of the left kidney was performed.

Light microscopy was conducted on paraffin sections stained with hematoxylin-eosin, PAS reaction, Masson's trichrome, and Jones methenamine silver stain. The nephrobiopsy material included both cortical and medullary tissue, with a total of 40 glomeruli. The glomeruli were mildly enlarged, with single-contour capillary wall and diffuse expansion of the mesangial space due to the extracellular matrix and its hypercellularity, but without signs of both endocapillary hypercellularity (E0) and formation of crescents (C0) (Figure 2).

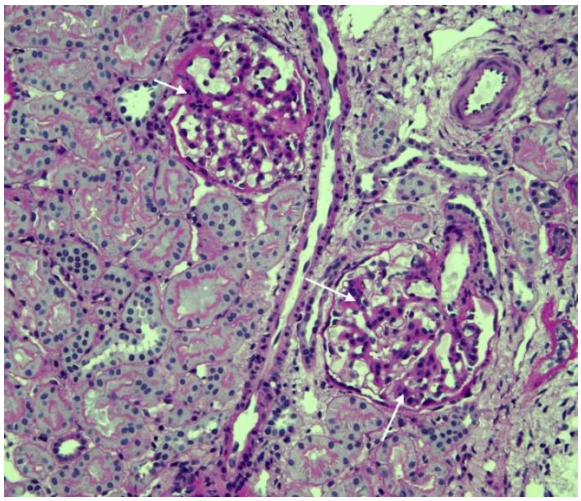

Figure 2. Histological examination of renal tissue. Mesangial proliferation and expansion of the mesangial matrix (indicated by arrows). PAS stain, magnification ×200.

The GBM was not visually thickened, had a single contour, and showed uniform silver impregnation. Segmental glomerulosclerosis (S1) was noted in 6 glomeruli (15%), without reaction of glomerular epithelium. Cytoplasm of tubular epithelium was granular, with preserved brush border, and tubular lumens were patent. There were no signs of tubular atrophy and interstitial fibrosis (T0). Arterioles and small-caliber arteries exhibited no pathological changes.

Immunofluorescence analysis was performed on cryostat sections using FITC-conjugated antibodies against human IgA, IgG, IgM, C3, C1q, fibrinogen, and kappa and lambda light chains. The staining revealed diffuse mesangial granular deposition of IgA graded as 3+ (Figure 3), along with C3 (1+), kappa (2+), and lambda (2–3+).

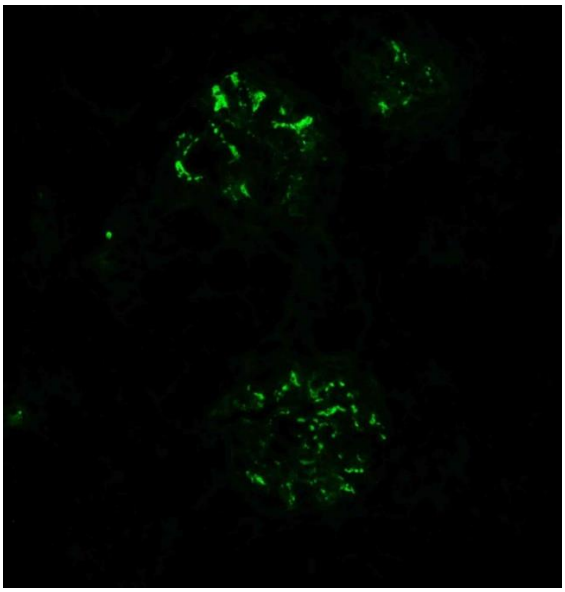

Figure 3. Immunofluorescence analysis of kidney biopsy, magnification ×100. Diffuse mesangial granular expression of IgA (+++).

Electron microscopy was performed on semithin sections stained with toluidine blue and ultrathin sections stained with uranyl acetate and lead citrate, with double contrast with osmium. Seven glomeruli were examined on semithin sections. All of them showed focal, mild mesangial hypercellularity; with no evidence of endocapillary hypercellularity or crescent formation. One glomerulus exhibited secondary segmental glomerulosclerosis. The GBM was of uniform thickness (240-260 nm), with preserved lamina densa, lamina rara interna and lamina rara externa, without signs of disorganization and with a smooth external contour. Podocyte foot processes were preserved and discretely arranged throughout, and the slit diagram between them was clearly visualized. Electron-dense deposits were determined in the mesangial matrix, mainly in the paramesangial area (Figure 4). No electron-dense deposits were found in the subendothelial or subepithelial spaces. No pathological inclusions were observed in the cytoplasm of epithelial, endothelial, or mesangial cells. A weakly expressed subendothelial edema was noted. CONCLUSION: IgA nephropathy, Oxford-2016 classification: M1E0S1T0C0. Mild subendothelial edema of glomerular capillaries is not a highly specific sign; however, in the context of a confirmed diagnosis of atypical HUS, it may be consistent with the disease.

After receiving the results of the histological examination, ramipril was added to eculizumab therapy at a dose of 2.5 mg per day for nephroprotective and antiproteinuric purposes, the dose of which was gradually increased to the maximum tolerated, reaching 5 mg per day. By November 2024, the patient's urine tests had normalized and remained within normal limits at the time of preparing this publication. In the absence of any signs of TMA activity, a decision was made to discontinue eculizumab therapy and continue nephroprotective treatment with ramipril.

Discussion. We present a case of a rare combination of IgAN and aHUS in a 10-year-old girl. Initially, we attributed all of the patient's symptoms solely to TMA; however, despite the prompt initiation of eculizumab therapy and complete resolution of hematologic abnormalities, hematuria and proteinuria persisted. This, combined with a prior unexplained episode of macroscopic hematuria three years earlier, led us to suspect glomerulonephritis and perform a nephrobiopsy. Histological examination revealed dominant, diffuse mesangial IgA (+++) deposition. Additionally, secondary segmental glomerulosclerosis was observed in 15% of glomeruli—characteristic of chronic IgAN. These findings suggest that the onset of glomerulonephritis likely preceded the development of aHUS, potentially dating back to the earlier episode of macroscopic hematuria noted in the patient's history.

Several publications report that TMA may be a histological finding in IgAN [14,15]. In such cases, TMA may either represent a direct complication of the glomerulonephritis—mediated by its underlying mechanisms—or an independent coexisting pathology such as TTP, aHUS, or STEC-HUS. The development of TMA as a complication of IgAN may require multiple contributing factors, with complement activation within the glomeruli—triggered by IgA deposition—being a key element. In these situations, TMA may manifest solely at the histological level without overt clinical signs [14,15]. In contrast, the pronounced clinical manifestations of TMA observed in our patient strongly suggest the presence of a second, distinct disease [14]. We believe that the rapid resolution of TMA symptoms following the initiation of eculizumab, and the absence of histological signs of TMA 3.5 months after disease onset under ongoing complement-inhibiting therapy, support the diagnosis of aHUS superimposed on pre-existing IgAN. An interesting question arises: should the co-occurrence of these two diseases be regarded as coincidental, or is there an underlying connection? Given that these two conditions did not arise simultaneously in our patient—with IgAN likely preceding aHUS—the most straightforward explanation is that the initial disease may have triggered the development of the second [16].

Nonetheless, several studies have identified genetically determined dysregulation of the complement system in some patients with isolated IgAN. This dysregulation may potentially contribute both to the pathogenesis of glomerulonephritis and to the development of aHUS. Cases reported by Nakamura H. et al., Hou W. et al., and Schmitt R. et al. describe various mutations in complement factor H associated with the co-occurrence of IgAN, TMA, and aHUS

[17, 19]. In such scenarios, eculizumab may provide therapeutic benefits for both diseases [16, 17].

Some reports also highlight elevated circulating levels of complement factor H-related proteins (CFHR1–5) in patients with IgAN, which further indicates activation of the alternative complement pathway. In the case presented here, eculizumab effectively and completely resolved the manifestations of TMA, but had no significant impact on the persistent hematuria and proteinuria, which were most likely driven by IgAN. The use of the maximally tolerated dose of ramipril led to marked improvement in urine parameters, offering hope for slowing disease progression.

In conclusion, we describe a patient with both clinical and histological features of aHUS and IgAN. Despite the rarity of this combination, this case underscores the importance of considering such a dual diagnosis to avoid misinterpretation and ensure appropriate management.

Author's contribution.

Mikhail Kagan *– conceptualization, literature search and analysis, text writing and editing, responsibility for the integrity of all parts of the article.*

Zhamilya Issanguzhina *– critical revision and editing of the article.*

Aniya Seipenova *– systematic review and analysis of the literature.*

Natalia Pukhovikova *–systematic review and analysis of the literature.*

Acknowledgments. *The authors express their gratitude to renal pathologist Dr. Olga Vorobyova from the National Center for Clinical Morphological Diagnostics, St. Petersburg, Russian Federation, for performing the histological examination of kidney tissue.*

The authors declare no conflicts of interest.

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