Case Report

DOI: 10.6966/EDMJ.202412_11(4).0003

An Unusual Presentation of C3 Glomerulonephritis and Atypical Hemolytic Uremic Syndrome in a 69-Year-Old Woman

Yahn-Bor Chern[1,2], Shih-Yuan Hung[1,2], Gong-Kai Huang[3], Po-Jui Chi[1,2,]*

We report the case of a 69-year-old woman who presented with 2 weeks course of progressive dyspnea, associated with severe peripheral edema and gross hematuria. She was eventually diagnosed with C3 glomerulonephritis-related crescentic glomerulonephritis, and atypical hemolytic uremic syndrome (aHUS) complicated her admission course. We conducted complete studies on thrombotic microangiopathy to support the diagnosis of aHUS. Renal biopsy was performed after successful treatment of the urinary tract infection and correction of thrombocytopenia. The pathological analyses revealed C3 and crescentic glomerulonephritis. The patient was treated with hemodialysis owing to the presence of medically refractory severe azotemia with uremic symptoms and fluid overload. Plasma exchange was performed for aHUS followed by corticosteroid administration. No recovery in renal function was observed after the treatment, and the patient was discharged in a dialysis-dependent state. Both aHUS and C3 glomerulonephritis are potentially life-threatening diseases that involve dysregulated complement activation. These two diseases may occur simultaneously, and clinicians should raise their awareness for timely diagnosis.

Key words: C3 glomerulopathy, C3 glomerulonephritis, crescentic glomerulonephritis, atypical hemolytic uremic syndrome

Introduction

C3 glomerulopathy is a rare complement-mediated renal disease with a reported incidence of 1/1,000,000 to 2 – 3/1,000,000 in one US registry data cohort study.[1] It is characterized by dysregulated complement activation, which leads to predominant C3 deposition within the glomerulus.[1] The clinical manifestations of C3 glomerulopathy range from asymptomatic hematuria, proteinuria and acute glomerulonephritis. Renal biopsy is the cornerstone for its diagnosis.[2] C3 glomerulopathy can be further divided into two subcategories using electron microscopy: dense deposit disease

From the [1]Division of Nephrology, Department of Medicine, E-Da Hospital, I-Shou University; [2]School of Medicine, College of Medicine, I-Shou University; [3]Department of Anatomic Pathology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan.

Received: July 10, 2022 Accepted: September 20, 2022

* Address reprint request and correspondence to: Po-Jui Chi, Division of Nephrology, Department of Medicine, E-Da Hospital, No. 1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 824005, Taiwan
Tel: +886-7-615-0011 ext. 5121, E-mail: chipojui44@hotmail.com

and C3 glomerulonephritis. Distinctive dense osmiophilic intramembranous deposits are present in dense deposit disease, whereas light dense amorphous mesangial deposits are found in C3 glomerulonephritis.[3]

Atypical hemolytic uremic syndrome (aHUS) is another rare disease with a prevalence of 2.2 – 9.4/1,000,000 and presents with the classic clinical triad of renal injury, microangiopathic hemolytic anemia, and thrombocytopenia.[4] The pathological mechanism of aHUS is dysregulation of the alternative complement pathway, which results in microthrombi formation and endothelial dysfunction.

Although aHUS and C3 glomerulopathy are both complement-mediated diseases that are often caused by secondary triggers (such as infection, autoimmune disease, malignancy, transplant, or drugs) superimposed on genetic mutations, simultaneous occurrence of these two diseases is very rare. We report the case of a patient with an initial presentation of acute kidney injury (AKI) requiring dialysis who was subsequently diagnosed with aHUS. The pathological diagnosis after performing two renal biopsies revealed crescentic glomerulonephritis caused by C3 glomerulonephritis. The unusual presentation of simultaneous occurrence of C3 glomerulonephritis and aHUS is worth further discussion regarding the diagnosis, pathogenesis, and treatment of these two diseases.

Case Report

A 69-year-old woman with a history of diabetes, hypertension, dyslipidemia, and colon cancer that was treated with complete surgical resection for 1 year (chemotherapy was not required according to her statement) was transferred from a regional hospital for further management of deteriorating renal function. Tracing back her history, she had a gastroenteritis episode 2 months before admission. Although there was an improvement in gastrointestinal symptoms, she developed progressive shortness of breath (exertional and orthopnea) in the last 2 weeks. The associated symptoms included gross hematuria, peripheral edema, and poor appetite. Because of worsening symptoms, she visited the emergency department (ED) at a regional hospital, where advanced renal insufficiency was detected. The patient was transferred to our hospital for further management of renal disease.

At our ED, the patient presented with nausea, emesis, poor appetite, and orthopnea. No fever, hypotension, or arrhythmia was observed. Her initial oxygen saturation level on room air was 94%. The use of herbal medicine or any analgesic agent was denied by the patient and excluded after reviewing the cloud pharmacy data. Physical examination revealed pale conjunctiva, bilateral basilar rales, and prominent bilateral leg edema. No rash, petechia, open wounds, or throat lesions were observed. Hemograms revealed no leukocytosis but an increased neutrophil component and microcytic anemia. Biochemistry data showed severe azotemia (blood urea nitrogen: 100.6 mg/dL), AKI (creatinine level [11.55 mg/dL] was higher than that 3 months before admission [1.0 mg/dL]), and hypoalbuminemia (2.3 g/dL). Venous blood gas analysis revealed metabolic acidosis (pH 7.31, HCO_3: 17.6 mmol/L, and pCO_2: 35 mmHg). Urinalysis revealed pyuria (WBC: 50 – 100/high power field), hematuria (RBC > 100/high power field), and bacteriuria. Chest radiography revealed mild pulmonary congestion with cardiomegaly (Fig. 1). Abdominal computed tomography was performed without intra-abdominal infection, and bilateral nephromegaly with normal cortical thickness indicated that the course of the patient's renal disease was acute.

Emergent hemodialysis was performed 2 days after her ED visit because of severe azotemia with active uremic symptoms and fluid overload refractory to maximal medical treatment. Renal biopsy was not performed then because of an active urinary tract infec-

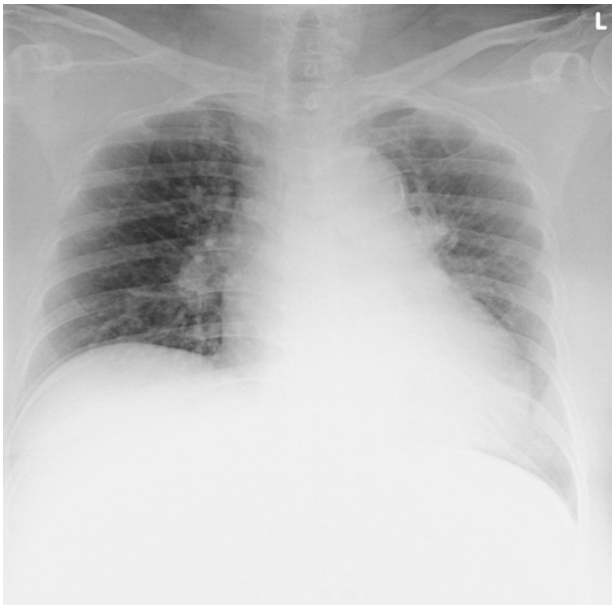

Fig. 1 Chest X-ray showing mild pulmonary congestion with cardiomegaly.

tion. She was administered an empiric antibiotic agent for urinary tract infection and subsequently admitted to the nephrology ward. During admission, progressive anemia (decrease from 9.6 to 6.6 g/dL in 1 week) and acute thrombocytopenia (29,000/μL) were noted without any signs of active bleeding. A peripheral blood smear revealed schistocytes (Fig. 2). Associated findings included low haptoglobin, elevated lactate dehydrogenase (LDH), negative direct/indirect Coombs tests, and normal prothrombin time/activated partial thromboplastin time; thrombotic microangiopathy (TMA) was highly suspected. Mild confusion without any focal neurologic sign was observed at that time. Under the impression of TMA, plasma exchange was initiated following which her thrombocytopenia improved. Cystoscopy was conducted for surveying gross hematuria; no bladder lesion was detected, indicating a hematuria of glomerular origin. Heavy proteinuria was also detected with a urine protein creatinine ratio of 32,691 mg/g. Serial studies including autoimmune profiles were collected due to acute nephritic syndrome and suspicion of rapidly progressive glomerulonephritis. The results of autoimmune profile (including antinuclear antibody, rheumatoid factor, anti-ENA screening, and anti-phospholipid antibody syndrome), cryoglobulin, serum/urine electrophoresis, viral hepatitis markers, immunoglobulin, syphilis, anti-neutrophil cytoplasmic antibody, and anti-streptolysin O were negative. The only positive finding was low C3 (68.5 mg/dL) and normal C4 levels.

ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif,

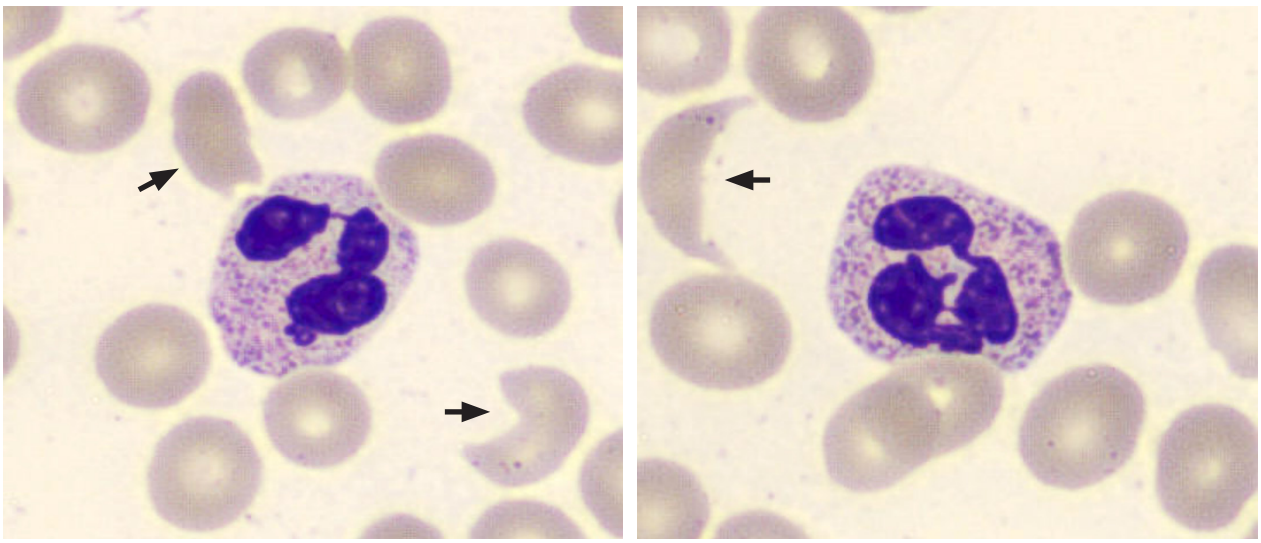

Fig. 2 Peripheral blood smear showing fragmented red blood cells (also termed schistocytes) (arrow). The presence of schistocytes is a hallmark of microangiopathic hemolytic anemia (MAHA).

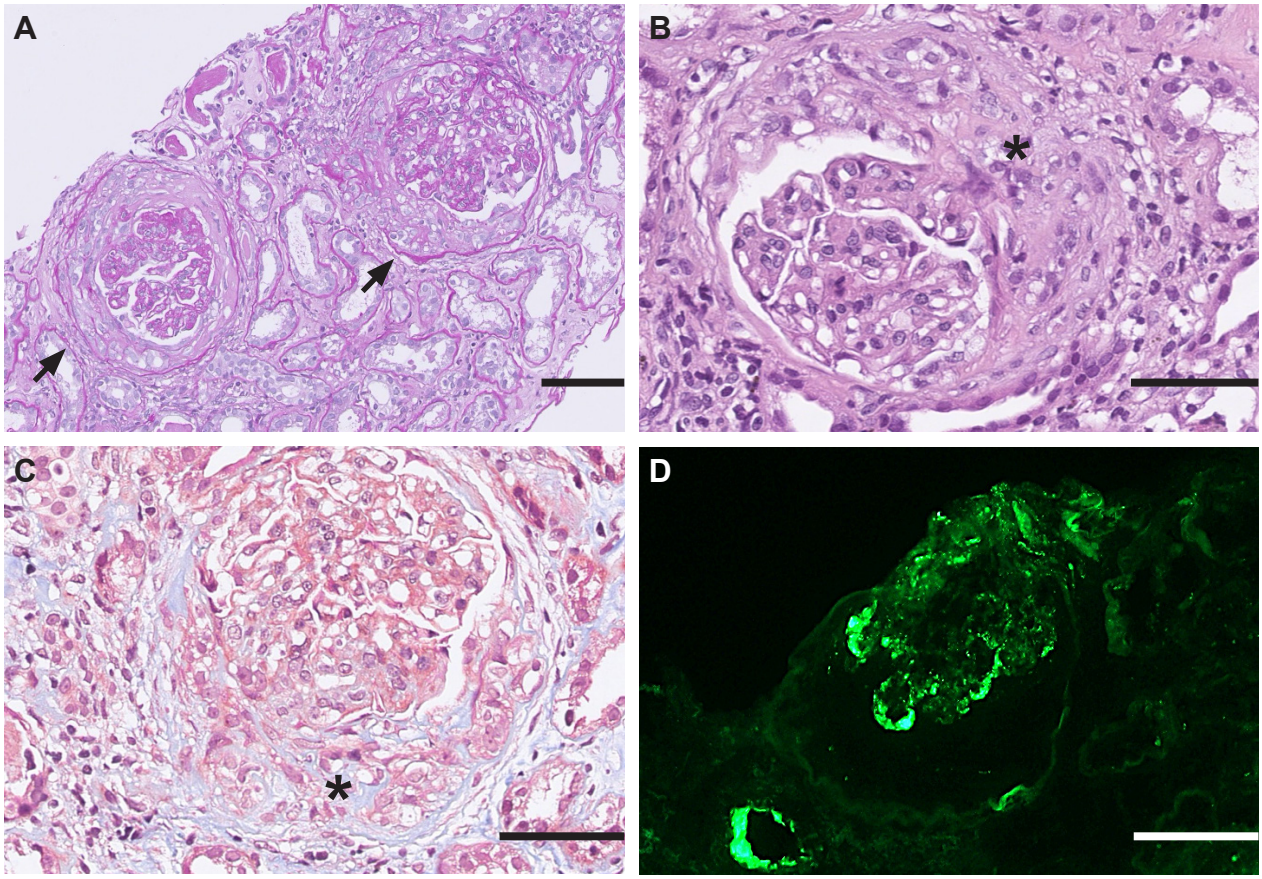

Fig. 3 (A) Hematoxylin and eosin stain showing cellular and fibrocellular crescentic glomeruli (arrow). Moderate acute tubular injury/necrosis and tubular atrophy of cortical tubules are noted. Fibrocellular crescent is found in (B) hematoxylin and eosin stain and (C) periodic acid-Schiff stain (asterisk). (D) C3 staining showing moderately positive staining in the capillary loops of a glomerulus (Scale bar: 50 μm).

member 13) activity before plasma exchange was reportedly 94%. aHUS was favored. After 13 sessions of therapeutic plasma exchange (TPE), TPE was held because of the relatively stationary hemoglobin and platelet counts. Renal biopsy was performed twice (due to inadequate specimen for immunofluorescence stain examination the first time) after urinary tract infection was completely treated and under acceptable platelet levels. Hematoxylin and eosin staining (Fig. 3A & 3 B) and periodic acid-Schiff staining revealed crescentic glomerulonephritis (Fig. 3C). Immunofluorescence staining showed an increase in C3 staining in glomerular capillary loops (Fig. 3D). Electron microscopy showed only scanty electron-dense deposits in the basement membrane (Fig. 4), indicating C3 glomerulonephritis.

Due to the failed application of Eculizumab, prednisolone was administered daily at

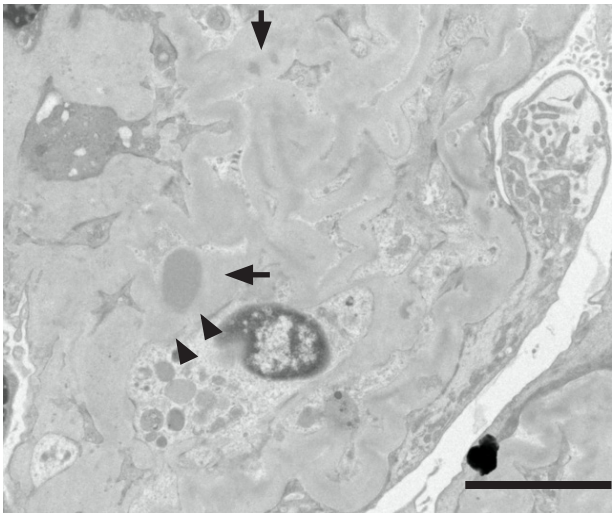

Fig. 4 Scanty electron-dense deposits (arrow) are noted in the basement membrane (arrowhead) in electron microscopy (Scale bar: 5 μm; indicated magnification: 8kx).

0.5 mg/kg body weight. However, the response was poor. The patient was discharged in a dialysis-dependent state.

Discussion

We present the case of a 69-year-old woman with rapidly progressive glomerulonephritis that was proven to be caused by C3 glomerulonephritis after renal biopsy. aHUS complicated the patient's clinical course. Her renal function was not restored after serial plasma exchange sessions and steroid administration. C3 glomerulonephritis and aHUS are rare but challenging diseases both in terms of diagnosis and optimal treatment selection for patients.

C3 glomerulopathy, which comprises dense deposit disease and C3 glomerulonephritis, is a group of kidney diseases caused by dysregulation of the alternative complement pathway.[5,6] Renal biopsy is indicated for its diagnosis. The pattern of C3 glomerulopathy observed by light microscopy may be diverse, and an accurate diagnosis relies on immunofluorescence staining. Membranoproliferative glomerulonephritis (MPGN) is the most common pattern, however, endocapillary/mesangial proliferative glomerulonephritis or crescentic and necrotizing glomerulonephritis can also be present.[2] Immunofluorescence studies shows dominant C3 staining with minimal or no immunoglobin. Electron microscopy of C3 glomerulonephritis, quite different from dense deposit disease, usually reveals amorphous mesangial deposits with or without capillary wall deposits.[7] The genetic predisposition linked to C3 glomerulopathy remains unclear, but aHUS and C3 glomerulopathy share some common genetic defects.[1] Through the understanding of complement factor H-related proteins (CFHR 1 – 5) recently,[8,9] it is now known that different defects in CFHR 1 – 5 result in either aHUS or C3 glomerulopathy. In addition to genetic mutations (C3, factor H, I, and B), autoantibodies (C3 and C4 nephritic factors) are increasingly being recognized to play an important role in the pathogenesis of C3 glomerulopathy.[10] These antibodies work against the regulatory components of the complement system, resulting in over-activation of the alternative complement system. In addition, studies have demonstrated the limited efficacy of eculizumab in C3 glomerulopathy, indicating the presence of upstream complement dysregulation, which requires further research.[10]

aHUS diagnosis requires a physician to be highly alert for TMA, especially for patients presenting with AKI with unexplained anemia and thrombocytopenia. It is crucial for physicians to order peripheral blood smears (to search for schistocytes) and tests for hemolytic anemia (LDH, bilirubin, haptoglobin, and direct/indirect Coombs test) to demonstrate the presence of non-immune-mediated hemolytic anemia. ADAMTS13 should be checked before plasma exchange to differentiate two major categories of TMA: thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS).[2] In our patient, the ADAMTS13 level was not low, which suggested that HUS was favored. Viral gastroenteritis 2 months before her admission and a recent urinary tract infection were considered precipitating factors for aHUS. According to the International Hemolytic Uremic Syndrome group classification, aHUS is reasonably suspected after excluding infection-associated (Shiga toxin associated, viral infections such as influenza and HIV) and co-existing conditions (such as organ transplantation, autoimmune diseases, malignancy, malignant hypertension, and offending drugs).[11] aHUS is an ultra-rare variant of TMA caused by complement dysregulation. Genetic or acquired complement dysregulation was detected in 40% – 60% of patients with aHUS indicating a genetic predisposition.[11]

According to the Kidney Disease: Improving Global Outcomes (KDIGO) consensus report, important tests minimally required for patients with suspected C3 glomerulopathy

and aHUS include serum (C3, C4, C3 nephritic factor, factor H antibodies, serum paraprotein detection) and genetic [*C3, CFH, CFB, CFI, CD46, THBD* (Thrombomodulin), *CFHR1, CFHR5*, and *DGKE* (diacylglycerol kinase epsilon) mutations] screening.[2,3,7] The genetic analysis for aHUS in our patient showed two related mutations, *VWF* (von Willebrand factor): c.7437 + 18T > C and CFHR5: c.*20A > C. Previous studies have shown that CFHR5 mutation is a well-characterized cause of C3 glomerulopathy. However, the mechanism between this mutation and aHUS is not well established and requires further investigation to clarify their relationship.

Over the past decade, our understanding of aHUS pathogenesis and treatment modalities has increased. Eculizumab (an anti-C5 monoclonal antibody) and ravulizumab (a long-acting C5 inhibitor) are therapeutic options for aHUS that have demonstrated favorable outcomes.[4,10] The results of immunosuppressive therapy for C3 glomerulopathy are controversial because previous studies have focused on the treatment of primary MPGN. C3 glomerulopathy has been a new disease category derived from MPGN type 2 in the past decade;[6] hence, the efficacy of immunosuppressants for C3 glomerulopathy requires further study. Plasma exchange has been observed to be effective in some cases of C3 nephropathy.[1] Patients lacking factor H may benefit from plasma replacement.[7] Prognostic data regarding C3 glomerulopathy and aHUS are limited due to the small number of cases. Previous studies have shown that patients with C3 glomerulonephritis have a better prognosis than those with dense deposit disease.[7] The prognosis of aHUS is poor. The chance of progression to end-stage renal disease within 5 years ranges from 38% to 73%, according to different genetic mutations.[7]

Conclusions

Here, we describe the case of a patient with simultaneous crescentic glomerulonephritis caused by C3 glomerulonephritis and aHUS. The key to the diagnosis of aHUS relies on the clinician's high awareness of AKI in patients with unexplained anemia and thrombocytopenia. Early diagnosis, followed by plasma exchange, is life-saving. Due to advances in understanding the pathogenesis of aHUS, we now have a new therapeutic choice with the anti-C5 monoclonal antibody agents, eculizumab and ravulizumab, for the treatment of aHUS. C3 glomerulonephritis, now considered a subgroup of C3 glomerulopathy mediated by complement activation, presents with crescentic glomerulonephritis. The renal prognosis in patients with aHUS and C3 glomerulonephritis is poor; thus, our patient eventually became dialysis-dependent. Both aHUS and C3 glomerulonephritis are potentially life-threatening diseases that involve dysregulated complement activation. These two diseases may occur simultaneously, and clinicians should raise their awareness for timely diagnosis.

Author Contributions

Case provide: Po-Jui Chi and Shih-Yuan Hung; Data collection and interpretation: Yahn-Bor Chern and Po-Jui Chi; Pathologic report interpretation: Gong-Kai Huang; Literature search: Shih-Yuan Hung; Manuscript preparation: Yahn-Bor Chern and Po-Jui Chi. All authors have read and agreed to the published version of the manuscript.

Funding

The authors gratefully acknowledge the financial support of E-Da Hospital, Taiwan (EDAHC111003).

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Smith RJH, Appel GB, Blom AM, et al: C3 glomerulopathy - understanding a rare complement-driven renal disease. Nat Rev Nephrol 2019;15:129-43. doi: 10.1038/s41581-018-0107-2.
2. Angioi A, Fervenza FC, Sethi S, et al: Diagnosis of complement alternative pathway disorders. Kidney Int 2016;89:278-88. doi: 10.1016/j.kint.2015.12.003.
3. Goodship TH, Cook HT, Fakhouri F, et al: Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 2017;91:539-51. doi: 10.1016/j.kint.2016.10.005.
4. Anliker-Ort M, Dingemanse J, van den Anker J, et al: Treatment of rare inflammatory kidney diseases: drugs targeting the terminal complement pathway. Front Immunol 2020;11:599417. doi: 10.3389/fimmu.2020.599417.
5. Kaartinen K, Safa A, Kotha S, et al: Complement dysregulation in glomerulonephritis. Semin Immunol 2019;45:101331. doi: 10.1016/j.smim.2019.101331.
6. Pickering MC, D'Agati VD, Nester CM, et al: C3 glomerulopathy: consensus report. Kidney Int 2013;84:1079-89. doi: 10.1038/ki.2013.377.
7. Zipfel PF, Wiech T, Stea ED, et al: CFHR gene variations provide insights in the pathogenesis of the kidney diseases atypical hemolytic uremic syndrome and C3 glomerulopathy. J Am Soc Nephrol 2020;31:241-56. doi: 10.1681/ASN.2019050515.
8. Togarsimalemath SK, Sethi SK, Duggal R, et al: A novel CFHR1-CFHR5 hybrid leads to a familial dominant C3 glomerulopathy. Kidney Int 2017;92:876-87. doi: 10.1016/j.kint.2017.04.025.
9. Kant S, Kronbichler A, Sharma P, et al: Advances in understanding of pathogenesis and treatment of immune-mediated kidney disease: a review. Am J Kidney Dis 2022;79:582-600. doi: 10.1053/j.ajkd.2021.07.019.
10. Turkmen K, Baloglu I, Ozer H: C3 glomerulopathy and atypical hemolytic uremic syndrome: an updated review of the literature on alternative complement pathway disorders. Int Urol Nephrol 2021;53:2067-80. doi: 10.1007/s11255-020-02729-y.
11. Raina R, Krishnappa V, Blaha T, et al: Atypical hemolytic-uremic syndrome: an update on pathophysiology, diagnosis, and treatment. Ther Apher Dial 2019;23:4-21. doi: 10.1111/1744-9987.12763.