C3 Glomerulopathy, a pathology with scarce evidence. A case report

Nefrologo in Corsia

Andrés Felipe Barragán[1], Elías Quintero-Muñoz[1], Daniel Quintero-Muñoz[2], Paula V Rodriguez-Segura[3]


Andres Felipe Barragan Amado

1 Internal Medicine Resident; La Sabana University, Chía, Colombia
2 MD, La Sabana University, Chía, Colombia
3 MD, Internist, Nephrologist, Hospital Universitario de La Samaritana - Grupo de investigación UROHUS, Bogotá, Colombia.

Corrispondenza a:
Elías Quintero Muñoz, M.D.
Universidad de La Sabana
Chía, Colombia
Phone: +57 311 2388078
E-mail: eliasquintero121@gmail.com

ABSTRACT
C3 Glomerulonephritis (C3GN) is a rare disease with an estimated incidence of 1-2 cases per million, caused by an alteration in the alternative complement pathway, although its complete physiopathology remains uncertain. Treatment evidence is poor. Immunosuppressive therapy can be initiated in more severe cases. Progression rates to end stage kidney disease are of up to 50% within a decade, and the posttransplant recurrence rates of 45-60%. We describe the case of a young man without any past medical history, with lower extremities edema, dyspnea, and kidney function deterioration. The patient was ultimately diagnosed with C3GN.

PAROLE CHIAVE: C3 glomerulopathy, glomerulonephritis, alternative complement pathway

Introduction

C3 Glomerulopathy (C3G) is a renal disease caused by a primary alteration in the complement, presenting a dysregulation in the alternative complement pathway, which induces hyperactivity. The term was first described in 2007 in a series of 19 patients characterized by the histopathological finding of C3 deposits in renal tissue without any other significant immunocomplex [1]. The renal symptoms were hypertension, kidney disease, proteinuria, hematuria, and nephrotic syndrome.

C3G has been classified as an independent glomerulopathy in the 2013 consensus of International Society of Nephrology, organized by Mathew Pickering and Terence Cook. Included in this pathology are two entities: Dense Deposit Disease (DDD) and Complement 3 Glomerulonephritis (C3GN). The difference lies in the appearance and distribution of deposits on electron microscopy of the glomerulus: DDD is characterized by the presence of highly electron-dense deposits within the glomerular basement membrane (GBM), while in C3GN the deposits are located in the mesangium or along the subendothelial side of the GBM [2,3]. Another classification has arisen from the need to correlate pathophysiological, clinical, histological, and genetic data. This new classification could be more useful to clinicians because, unlike the pathological one, addresses the underlying pathogenesis of the disease. It recognizes 4 different groups, indicating four different pathogenic patterns. Patients in groups 1-3 show predominantly fluid phase complement activation, often present with low serum C3 levels, and have a high prevalence of genetic complement abnormalities; patients in group 4 have predominantly solid phase complement activation, normal serum C3 levels, and are associated with worse renal outcomes. This classification, however, has not yet been validated and may be subject to limitations [4].

The rarity of this disease has made it difficult to estimate precise epidemiologic data; the data available comes from small cohort studies. The United States estimates an incidence of C3G of 1-3 cases per 1.000.000 of the population and a prevalence of <5 cases per 1.000.000. Other European data show a lower incidence, estimated in 0.2-1 cases per 1.000.000 people and a prevalence of 1.4 per 1.000.000 [5]. The progression rates to end stage kidney disease are of up to 50%, and in renal allografts transplantation the recurrence rate is 45-60% [6].

Treatment recommendations for C3GN are based on a series of cases, case reports, and a few open-label trials. Poor evidence with immunosuppression, plasma infusion, or plasmapheresis has been described in small cohorts with inconclusive results. However, new evidence indicates an alternative treatment with Eculizumab, a humanized monoclonal antibody that binds C5 to prevent the formation of the membrane attack complex [6].

We describe here the case of a young man, without any relevant medical history, who came to the emergency room with signs and symptoms compatible with nephrotic syndrome and was ultimately diagnosed with C3GN through histopathology. This case illustrates the clinical presentation of this disease and the importance of being aware of it for an adequate diagnostic and therapeutic approach.

Case report

A 27-year-old man without any past personal or family health history presented to the emergency department with lower extremities edema and dyspnea on moderate exertion; reportedly, the symptoms had appeared 6 days before. When asked about other symptoms, the patient also reported upper respiratory symptoms in the last 15 days. On physical examination, vital signs were: BP, 150/102 mmHg; HR, 144 beats per minute; BR, 18 breaths per minute. Besides hypertension and tachycardia, the only abnormal finding was a grade II lower extremities pitting edema. Laboratory

results indicated the presence of anemia, severely impaired renal function (Figure 1), proteinuria and hematuria. Additionally, the patient was found to have hypocalcemia, hyperphosphatemia, hyperuricemia, hyperparathyroidism (Table I).

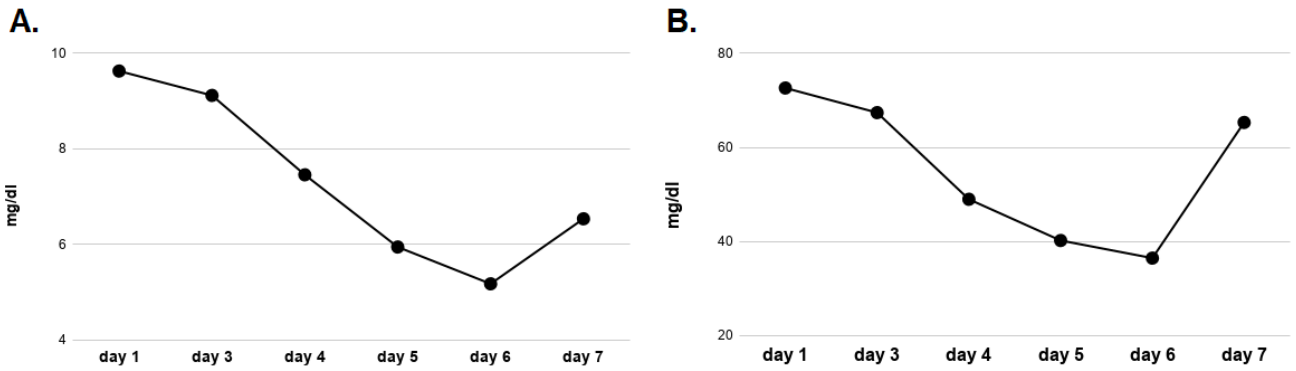

Figure 1: Renal function over time. Renal replacement therapy was initiated on the third day of hospitalization. (A) Serum creatine concentration; (B) Serum BUN concentration

The patient was assessed by the Nephrology department, with a preliminary diagnosis of rapidly progressive glomerulonephritis (RPGN). The diagnosis was supported by the lab results and by the patient's vital signs at admission: hypertension, edema, hematuria, and rapid progression to renal failure. However, findings such as hypocalcemia, hyperphosphatemia, hyperuricemia, hyperparathyroidism, suggested a chronicity element, even though renal ultrasonography findings were normal.

Due to the nephrotic proteinuria and nephritic clinical behavior, additional exams were performed with the following findings: Hypoalbuminemia; Low C3; Normal C4; ANA (1:80); negatives ENA; Anti-neutrophil Cytoplasmic Antibodies (ANCA) with negative anti-proteinase 3 (PR-3) and anti-myeloperoxidase (MPO); Negative Anti–glomerular basement membrane (anti-GBM); abnormal protein electrophoresis. In addition, tests for Hepatitis B, Hepatitis C, Treponema Pallidum, and HIV were negative (Table I). Transthoracic echocardiogram showed a reduced left ventricular ejection fraction (20%) with an associated dilatation of the left cavities.

Considering these data, a working diagnosis of rapidly progressive glomerulonephritis was made, while waiting for the results of the renal biopsy. Therefore, it was decided to start steroid pulses with 1 gram/day of methylprednisolone for 3 days, followed by oral steroids. Before administration of steroids, anthelmintic therapy with ivermectin and albendazole was given and the patient was isolated according to hospital protocol. In addition, cutaneous biopsy was performed, ruling out any deposit disease.

Notwithstanding steroid treatment, BUN and creatinine concentration kept rising, as well as water overload. Renal replacement therapy was thus initiated on the third day of hospitalization. Optimal dry weight and blood pressure control was achieved, also thanks to calcium channel blockers and beta blockers. At the same time, erythropoietin therapy was initiated to treat anemia. The echocardiographic findings (reduced left ventricular ejection fraction and dilatation of left cavities) were thought to be related to water overload. After initiating the renal replacement therapy, the patient managed to lose 15 kg, his functional class improved, and his left ejection fraction achieved normal values.

Laboratory results:	
Hemoglobin	8.9 g/dl
Hematocrit	27.5%
Platelets	327000/microL
Serum Creatinine	9.63 mg/dl
BUN	72.64 mg/dl
Iron	33.8 ug/mL
TIBC	403.66 ug/dL
Folic Ac	15.83 ng/mL
Vitamin B12	674 pg/mL
TSH	1.07
Albumin	2.65 g/dL,
PTH	412 pg/dL (12-88)
Calcium	8.58 mg/dL
Potassium	4.12 mEq/L
Phosphorus	6.72 mg/dL
Total Cholesterol	163.57 mg/dl
High density lipoprotein	62.6 mg/dl
Low density lipoprotein	95.48 mg/dl
Antibodies:	
ANCA	PR-3: Negative – MPO: Negative
C3	39.9 mg/dl (79-152)
C4	31.8 mg/dl (18-55)
DNA, ENA	Negative
ANA	1:80 Homogeneous pattern
Anti GBM	Negative
Protein electrophoresis	low albumin and moderate increase in α fraction
Urine analysis:	
Protein	500.0 mg/dl
Blood	300.00 ery/ul
Sediment	leukocytes: 15 cel/ul low erythrocytes: 120 cel/ul dysmorphic erythrocytes: 12cel/ul cylinders: hialines/3
Proteins in urine 24 hours	4072.88 mg
Urine volume	1400 mL

Table I: Laboratory results

Renal biopsy contained 31 glomeruli, 19 of which were globally sclerotic (61%) and 6 had segmentary sclerosis (19%). There was remarkable glomerulomegaly, endocapillary proliferation, mesangial matrix enlargement, images in double contour, and thickening of the basement membrane (3+). Moreover, there was severe interstitial fibrosis and tubular atrophy (80%). Immunofluorescence showed only bright staining for C3 in capillary wall and mesangium (3+). The vessels were unremarkable. Ultrastructurally, two glomeruli were examined, one was globally sclerotic and the other had segmentary sclerosis. Additionally, there was endocapillary hypercellularity and images in double contour in relation with subendothelial and intramembranous electron-dense deposits (3+). A total renal chronicity score of 8 was calculated (See Figure 2 and Figure 3).

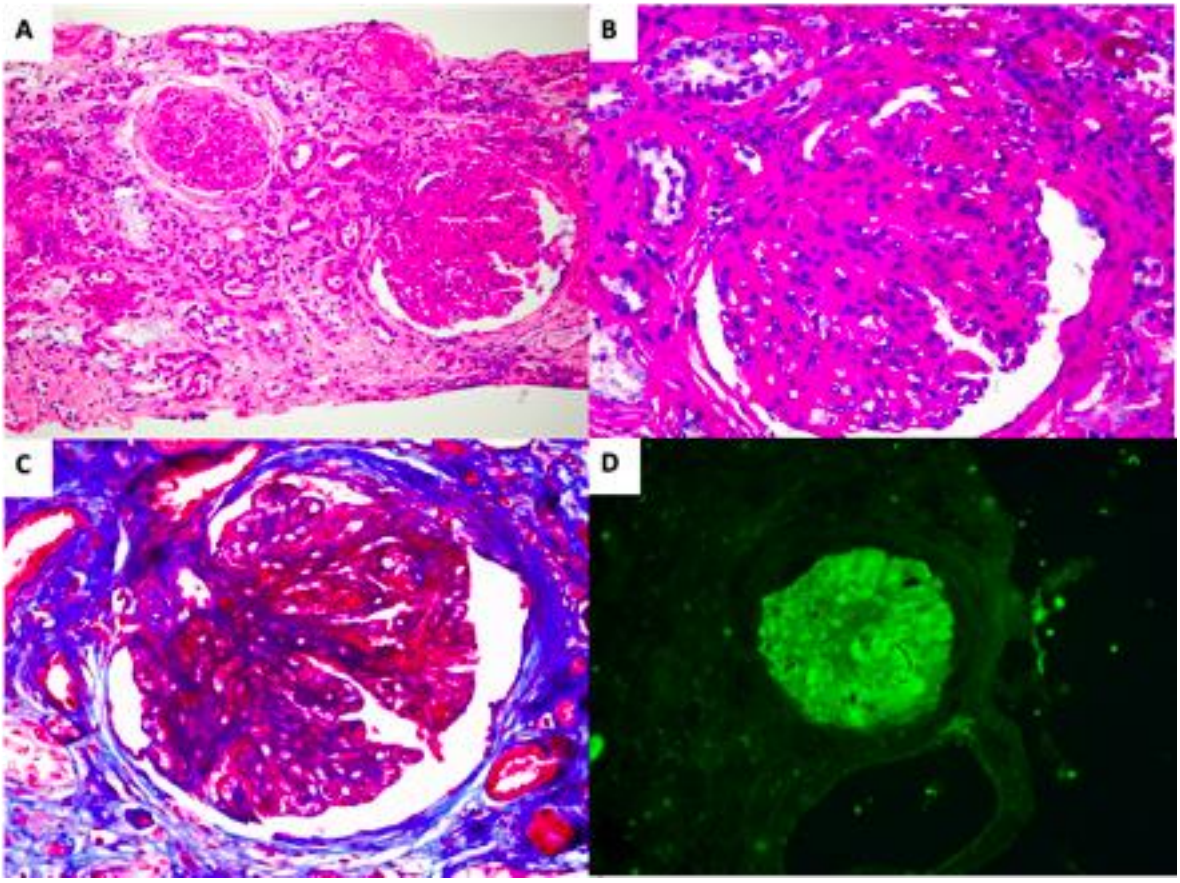

Figure 2: Renal biopsy. (A) Glomerulus with membranoproliferative pattern of injury and globally sclerotic glomeruli. Tubulointerstitial compartment has marked chronic changes with tubular atrophy and interstitial fibrosis (HE stain); (B) Glomerulus with prominent mesangial expansion and mesangial cell hypercellularity. Glomerular basement membrane is thickened (PAS stain); (C) Same glomerulus showing double contours with large mesangial and subendothelial deposits staining red in trichrome stain; (D) Direct immunofluorescence for C3 showing 3+ staining in capillary wall and mesangium.

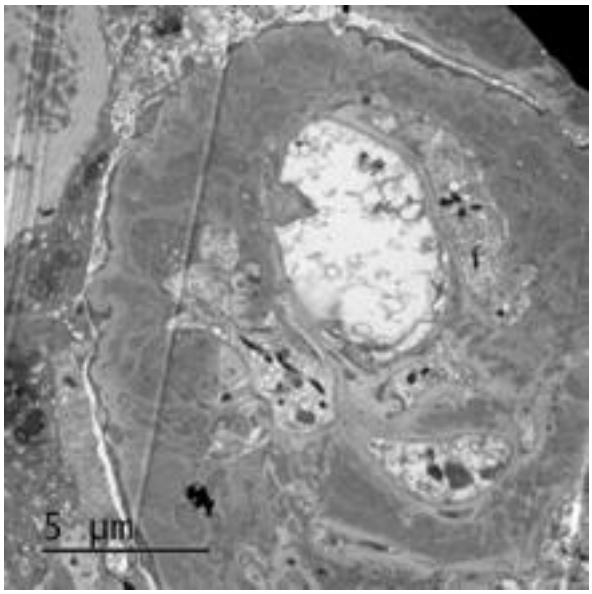

Figure 3: Electron microscopy image. Electron microscopy shows a thickened glomerular basement membrane with cellular interposition associated with the presence of electron-dense subendothelial and intramembranous permeating deposits (so-called "MPGN type 3 patter of Strife and Anders"). In addition, there is overlying podocyte foot process effacement.

After receiving the renal biopsy results and given the lack of response to steroids, it was decided to place a long-term hemodialysis catheter to continue dialysis after discharge. Follow-up in the patient's hometown was arranged, for additional studies and to enlist the patient for a kidney transplant. Unfortunately, however, contact with the patient was lost.

Discussion

C3 glomerulopathy has been gaining recognition since its first description in 2007. However, if knowledge of the diseased has increased, many aspects of its physiopathology and treatment remain unknowns. It was initially considered as a membranoproliferative glomerulonephritis, but was later reclassified in a group of its own [3].

The physiopathology has not been established yet. Evidence shows that activation of the alternative complement pathway can be compromised by the presence of genetic alterations of regulatory and activation processes (H factor, C3 nephritic factor which fulfills regulatory functions over the conversion of activated C3). These genetic alterations affect the functionality of the complement system directly. Moreover, the genetic alterations cause the production of antibodies against these intermediaries. However, a genetic alteration in the complement can be found (H factor, B factor, and FHR proteins) just in 25% of patients with C3 glomerulopathy. On the other hand, acquired factors have been considered to play a role, given that C3G is not a familial disease in most cases; but no trigger has been established. Antibodies against C3bBb can be found in 46% of C3G; likewise, different antibodies against B factor, H factor and C5 convertase have been reported, but their clinical relevance remains uncertain. The resulting aberrant complement activation will ultimately activate the C5 common complement pathway. Regardless, no etiologic agent in the genetic alterations or any acquired factor have so far proved sufficient to explain the phenomena [2,7,8].

Clinical manifestations are variable. Hematuria or proteinuria is found in 100% of patients but it has been demonstrated that nephrotic syndrome or nephritic syndrome can occur as initial manifestation in 30-50% and 16-38% of cases, respectively (or both, as in our case). Regarding renal function, it can oscillate between a preserved renal function, rapidly progressive glomerulonephritis, or even advanced chronic renal disease, as in the case described [5,9,10].

C3G can affect both the pediatric and adult population, with an average age of onset of 25 years, as described in the literature. It has been associated more commonly with dense deposit disease among the pediatric population. In the case of the adults, especially those older than 50, associated monoclonal gammopathy must be ruled out [11].

Regarding treatment, there are no randomized clinical trials or clinical guides at the moment. Recommendations are based on a series of cases, case reports and clinical expertise extrapolated from others glomerulopathies. Regardless of the complexity of the disease, in all patients the treatment consists in optimal nutrition, controlling dyslipidemia and blood pressure, prioritizing the use of ACE inhibitors or Angiotensin I receptor blockers to inhibit the renin-angiotensin system and reduce urinary protein [2,12,13].

Immunosuppressive treatment with Mycophenolate and steroids is indicated in patients with proteinuria over 500 mg in 24 hours despite supportive treatment, those at risk of progressive disease, or with moderate inflammation on biopsy [12]. This treatment has been used in 2 case series with a small population group, showing partial or complete response in up to 66% of the patients; those who did not respond were characterized by a worse proteinuria and renal function deterioration upon admission [13,14].

Eculizumab (Monoclonal Antibodies against C5) has been tested on small samples, showing partial

or complete response in 46% of the cases, especially on those with creatine >1,5 upon admission and a rapid progression [15]. Likewise, Welte T. et al used eculizumab in seven patients previously diagnosed with C3G, including five patients with C3GN and 2 with DDD. Four patients showed improved or stable renal function, defined as a decrease of serum creatinine, urinary protein, or hematuria after 3 months of treatment of 30% or around 30%, respectively. The time of response was between 2 weeks to 6 months [6].

Regarding other therapies, such as rituximab or plasma therapy, there is not enough data at present to give any recommendation. McCaughan reported the case of 29-year-old woman who required a kidney transplant for a DDD. After 4 weeks of transplantation, because of worsening proteinuria and renal function, treatment with rituximab, corticosteroid and plasmapheresis was initiated but the deterioration in renal function continued [16].

There are ongoing trials investigating novel therapeutic anti-complement drugs such as avacopan, danicopan, pegcetacoplan or iptacopan. Avacopan, an oral C5aR1 inhibitor, is being tested in a phase 2 randomized, double blind, placebo-controlled trial (NCT03301467). The objective is to evaluate efficacy based on histologic changes in kidney biopsies taken at baseline and after 26 weeks of treatment. Danicopan (ACH-0144471), an oral factor D inhibitor, is being evaluated in three different trials (NCT03369236, NCT03459443 and NCT03124368). Pegcetacoplan (APL-2), a subcutaneously a C3 inhibitor, is being tested for proteinuria reduction (NCT03453619). Finally, iptacopan (LNP023) is an oral, reversible inhibitor of factor B, evaluated for change in proteinuria and histopathological changes in kidney biopsy (NCT03832114). No results are available yet.

In terms of prognosis, there is no difference between dense deposit disease or rapidly progressive glomerulonephritis and has been reported that more than 50% of the patients will progress to chronic renal disease despite treatment [2]. According to the series published in 2014 by Ladan Z. et al, 66.7% of patients with kidney transplantation developed recurrent C3GN in the allograft, with a median time of 28 month; most of these patients had hematuria (45%), low C3 (78%) and all had proteinuria at the time of recurrence. Allograft biopsies showed bright C3 staining (2–3+), with six biopsies also showing trace/1+ staining for IgM and/or IgG. Finally, 50% had lost their graft secondary to recurrence. Three patients had a second recurrence, and four cases of recurrence were identified by protocol kidney allograft biopsies, which showed C3 deposits in the absence of clinical symptoms [17].

Conclusions

In the case described here, the patient initial manifestations were related to a nephritic syndrome with a nephrotic component, with a severe impaired renal function, depletion of C3 complement, and without response to steroid pulse, therefore requiring hemodialysis. Prognosis was bad, even upon admission. Renal biopsy showed mesangioproliferative glomerulonephritis with C3 staining and severe chronic changes greater than 80%. This rare disease is a diagnostic and therapeutic challenge given its poor prognosis. More studies must be conducted, clinical guides must be established in order to manage this disease, and protocols should emphasize pre-transplant studies of complement pathologies.

Acknowledgment

We thank Dr. Lina María Espinosa and Fundación Santa Fe de Bogotá for providing microscopic biopsy images and their description.

BIBLIOGRAFIA

1. Servais A, Frémeaux-Bacchi V, Lequintrec M, Salomon R, Blouin J, Knebelmann B, et al. Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. J Med Genet 2007; 44:193–9.
2. Pickering MC, D'agati VD, Nester CM, Smith RJ, Haas M, Appel GB, et al. C3 glomerulopathy: Consensus report. Kidney Int 2013; 84(6):1079-89.
3. Bomback AS, Appel GB. Pathogenesis of the C3 glomerulopathies and reclassification of MPGN. Nat Rev Nephrol 2012; 8(11):634-42.
4. Iatropoulos P, Daina E, Curreri M, Piras R, Valoti E, Mele C, et al. Cluster analysis identifies distinct pathogenetic patterns in c3 glomerulopathies/immune complex-mediated membranoproliferative GN. J Am Soc Nephrol 2018; 29(1):283-94.
5. Smith RJH, Appel GB, Blom AM, Cook HT, D'Agati VD, Fakhouri F, et al. C3 glomerulopathy — understanding a rare complement-driven renal disease. Nat Rev Nephrol 2019; 15(3):129-43.
6. Welte T, Arnold F, Kappes J, Seidl M, Häffner K, Bergmann C, et al. Treating C3 glomerulopathy with eculizumab. BMC Nephrol [Internet] 2018; 19(1):7.
7. Sethi S, Fervenza FC, Zhang Y, Zand L, Vrana JA, Nasr SH, et al. C3 Glomerulonephritis: Clinicopathologic findings, complement abnormalities, glomerular proteomic profile, treatment and follow-up. Kidney Int 2012; 82(4):465-73.
8. Barbour S, Gill JS. Advances in the understanding of complement mediated glomerular disease: Implications for recurrence in the transplant setting. Am J Transplant 2015; 15(2):312-9.
9. Cavero T, Praga M. Glomerulopatía C3 : ¿qué sabemos de esta entidad ? NefroPlus 2017; 8(2):95-107.
10. Rabasco C, Cavero T, Román E, Rojas-Rivera J, Olea T, Espinosa M, et al. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. Kidney Int 2015; 88(5):1153-60.
11. Ravindran A, Fervenza FC, Smith RJH, Sethi S. C3 glomerulopathy associated with monoclonal Ig is a distinct subtype. Kidney Int 2018; 94(1):178-86.
12. Goodship THJ, Cook HT, Fakhouri F, Fervenza FC, Frémeaux-Bacchi V, Kavanagh D, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. In: Kidney International. Elsevier, 2017; p. 539-51.
13. Rovin BH, Caster DJ, Cattran DC, Gibson KL, Hogan JJ, Moeller MJ, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019; 95(2):281-95.
14. Avasare RS, Canetta PA, Bomback AS, Marasa M, Caliskan Y, Ozluk Y, et al. Mycophenolate mofetil in combination with steroids for treatment of C3 glomerulopathy: A case series. Clin J Am Soc Nephrol 2018; 13(3):406-13.
15. Le Quintrec M, Lapeyraque AL, Lionet A, Sellier-Leclerc AL, Delmas Y, Baudouin V, et al. Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerulopathy. Am J Kidney Dis 2018; 72(1):84-92.
16. McCaughan JA, O'Rourke DM, Courtney AE. Recurrent dense deposit disease after renal transplantation: An emerging role for complementary therapies. Am J Transplant 2012; 12(4):1046-51.
17. Zand L, Lorenz EC, Cosio FG, Fervenza FC, Nasr SH, Gandhi MJ, et al. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. J Am Soc Nephrol 2014; 25(5):1110-7.