International Journal of Medical and Health Research
www.medicalsciencejournal.com
ISSN: 2454-9142
Received: 19-12-2021, Accepted: 04-01-2022, Published: 20-01-2022
Volume 8, Issue 1, 2022, Page No. 49-53

Clinico-pathological profile and outcomes of C3 glomerulopathy in north India: A single centre study

Shivendra Singh[1], Prem Shankar Patel[2*], Archana[3], Harish Saini[4], Khushboo Rani[4]

[1] Professor and HOD, Department of Nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

[2] Assistant Professor, Department of Nephrology, India Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India

[3] Senior Resident, Department of Microbiologist, All India Institute of Medical Sciences, Patna, Bihar, India

[4] Senior Resident, Department of Nephrology Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Abstract

Introduction: C3 glomerulopathy is a rare variety of complement mediated glomerulonephritis includes C3GN and DDD. Its histological hallmark is dominant C3 deposition in glomerulus. The clinical presentation and outcome of C3G is widely variable.

Material and Methods: 22 cases with only C3 deposits on kidney biopsy were enrolled in the study during January 2018 to January 2020. They were classified into C3GN and DDD. All received supportive and immunosuppressive therapy and were followed up for 6 months. Outcomes were measured as remission rate and progression to CKD or ESRD.

Results: C3G constituted 22 cases (2.8%) of total renal biopsy. 19 cases had C3GN and 3 had DDD. Mean age was 25.5 years in C3GN and 27.7 years in DDD. RPGN was commonest (47%) presentation in C3GN followed by NS (26%) and AUA (21%). Presentations of DDD were AUA, RPGN, and CKD one in each patient. Mean proteinuria was 3.6 gm/ 24 hours in both groups. Mean serum creatinine was 3.64 mg/dl in C3GN and 4.2 mg/dl in DDD. MPGN was predominant lesion in both groups. Crescents found in both C3GN (47%) and DDD (33.3%). 57.8% patients with C3GN had complete or partial remission; while only one DDD had complete remission. Rest of the C3GN and DDD patients progressed to either CKD or ESRD.

Conclusion: C3G noted in 2.8% of biopsies. RPGN was commonest clinical presentation, and MPGN was commonest histological lesion in C3G. Overall, C3GN had better treatment response than DDD. Despite treatment 8 out of 19 C3GN and 2 out of 3 DDD cases progressed to either CKD or ESRD.

Keywords: C3 glomerulopathy, C3 glomerulonephritis, CKD, dense deposoit disease, outcome

Introduction

C3 glomerulopathy is an umbrella term, which encompasses both C3 glomerulonephritis (C3 GN) and Dense Deposit Disease (DDD). [1] It is recently described term and form rare variety of glomerulonephritis that affect both children and adults. Formerly morphologically on Light and Electron microscopy findings, DDD was classified as membranoproliferative glomerulonephritis (MPGN) type 2 and C3 GN as type 1 or type 3 MPGN. Both diseases result from abnormal regulation of the alternative complement pathway and histologically characterized by dominant C3 deposition in the glomerulus. [2, 3] With growing knowledge's of aetiopathogenesis, recently on basis of immunofluorescence study complement mediated MPGN is reclassified into C3GN and DDD. [4-7] histologically, the diagnosis of C3G is made by immunofluorescence study. It may be difficult to distinguish C3GN and DDD each other on Light & immunofluorescence studies. However, electron dense deposits are found in mesangium and/or sub endothelial, intramembranous and sub epithelial in C3GN, while dense osmiophilic deposits are predominantly present along the glomerular basement membranes (GBM) in DDD. [4-6] Both C3GN and DDD are distinguished from immune-complex mediated glomerulonephritis by the lack of immunoglobulin staining on IF. Incidence of C3G is between 1 and 3 per million. [7] The clinical presentation and outcome is widely variable. The clinical presentation can vary from asymptomatic hematuria and proteinuria with preserved renal function, nephrotic syndrome, and chronic kidney disease to rapidly progressive glomerulonephritis. [8, 9] C3G is a slowly progressive disease and often progressed into chronic kidney Disease with variable speed. Few studies have been published describing the clinical characteristics and outcomes of C3G. [7-10] The aim of this study was to present a comprehensive description of the clinical features, histology, outcomes in C3 glomerulopathy at our centre.

Material and Methods

This prospective observational study was conducted in the department of nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India from January 2018 to January 2020. Out of total 780 kidney biopsy, 22(2.8%) cases with only C3 deposits in the absence of immunoglobulin were enrolled in the study. Details of kidney biopsies (LM, IF and EM reports) were noted, and cases were further classified into C3GN and DDD. C3 glomerulonephritis (C3GN) and DDD were defined by

standard criteria. [1, 4] Crescentic glomerulonephritis was defined by crescent formation over 50% sampled glomeruli in biopsy specimen. Asymptomatic urinary abnormalities (AUA) were defined as abnormalities detected in routine urinalysis in patients with no symptoms of renal or urologic disease. Nephrotic syndrome was defined as proteinuria >3.5 g per 24 hours in association with distinct lowering of serum albumin (<3 gm/dl). Rapidly progressive glomerulonephritis (RPGN) and chronic kidney disease (CKD) was defined as per standard guidelines. [11, 12]

The patient's detail clinical history, physical examination and laboratory data were analyzed. The laboratory investigations including Complete Haemogram, ESR, Renal functions test, Liver function test, Lipid profile, HBsAg, anti HCV, HIV, Serum paraprotein, immunological assay (RA factor, ANA, Anti ds DNA antibody, PR3 ANCA, MPO ANCA and Anti GBM Ab) and serum complement C3 and C4 were performed. 24 hours urinary protein quantification and routine urinalysis was done. Renal biopsy sample were studied under light microscopy (LM), Immunofluorescence (IF) and Electron microscopy (EM). Detail Complement factor analysis, genetic studied and C3 nephritic factor analysis were not done due to lack facility at our centre. All patients received supportive treatment with Angiotensin-converting enzyme (ACE)/inhibitors (ACEi)/Angiotensin II receptor blockers (ARBs). Patients with nephrotic syndrome and asymptomatic urinary abnormality (proteinuria >1 gm/ 24 hours) received oral prednisolone (1 mg/kg/day) for a period of 16 weeks with subsequent tapering (0.1 mg/kg/week) with MMF (1-2 gm/day) for 6 month in some patients. Patients with >50% crescents were treated with pulse intravenous methylprednisolone (15mg/kg/day for 3 days), followed by oral prednisolone at 1 mg/kg for 8 weeks followed by tapering (0.1mg/kg/week) along with pulse intravenous cyclophosphamide (7.5 mg/kg/pulse) monthly for 6 dose. Patient with no recovery from dialysis at third months, further immunosuppressant was discontinued. All patients were followed up with renal function test and 24 hr urinary proteins monthly for a period of 6 months. Complete remission was defined as: reduction of proteinuria to < 0.3 g/d and with creatinine clearance of > 60 ml/min/1.73 m2 and serum albumin > 3.5g/dl. Partial remission was defined as: reduction of proteinuria to 0.3–3.5 g/day, stable serum creatinine (change in serum creatinine < 25%) or a decrease in proteinuria > 50% from the baseline, and stable serum creatinine (change in serum creatinine < 25%). At end of follow-up, patients were categorized into improved (complete + partial remission) and not-improved (progression to CKD/ESRD) groups. Outcomes were measured in term of complete/partial remission and progression to CKD or ESRD.

Results

C3 glomerulopathy (C3G) constituted 22 cases (2.8%) of total native renal biopsies. during. 19 cases had C3GN and 3 had DDD. Patients with C3GN (mean age 25.5 years) and DDD (mean age 27.7 years) had almost similar mean age at the time of diagnosis. Majority (52%) of patients with C3GN were adult, while 2 out of 3 DDD cases were under 18 years. Mostly C3 glomerulopathy were found in male with gender ratio in C3GN (M: F% = 63/37) and DDD (M: F% =100/0). About half (47%) of the C3GN patients presented with rapidly progressive glomerulonephritis (RPGN). Nephrotic Syndrome (NS) and Asymptomatic Urinary Abnormality (AUA) were noted in 26% and 21% C3GN cases respectively. DDD had presented with AUA, RPGN and CKD each in one at the time of presentation. NS was more common in C3GN than DDD. Mean daily urinary protein excretion was similar (3.0 gm/ 24 hours) in both sub- groups. Mean serum creatinine was 3.64 mg/dl in C3GN and 4.2 mg/dl in DDD cases. Mean serum albumin was 3.7 gm/dl (C3GN) and 3.8gm/dl (DDD). The low C3 levels was prevalent in C3GN than the DDD patients. None of the patients had low serum C4 level in either group. Out of 19 C3GN cases, 14 (74%) cases had membranoproliferative glomerulonephritis (MPGN) like morphology with mesangial & endocapillary proliferation and 5(26%) case had diffuse proliferative glomerulonephritis (DPGN) like lesion on light microscopy (LM). All three DDD cases had MPGN morphology. None of the patients with DDD had DPGN. Crescents (on >50% sampled glomeruli) were commonly seen with C3GN than DDD. [Table-1] In C3GN category, majority of patients with AUA (75%, 3 out of 4) and NS (80%, 4 out of 5) had improvement after treatment. While, only 44% (4 out of 9) cases with RPGN had improved. In DDD category, only one patients presented with AUA had improvement and rest 2 patients progressed to CKD. Overall, C3GN had better (57.8% Vs 33.3%) treatment response than DDD. [Table-2] At the end of follow up, 57.8% patients with C3GN had complete or partial remission; while only one DDD case had complete remission. Rest of the C3GN (42.2%) and DDD (2 cases) patients had progressed to either CKD or ESRD. [Table-3]

Table 1: Base line clinical and laboratory data of C3 glomerulopathy study population. (n=22)

Characteristics	C3 GN (n=19)	DDD (n=3)
Mean Age at diagnosis & age range (years)	25.5(13-60)	27.7(11-55)
Age group (%)		
< 18 years	37	66.6
18-50 years	52	0
>50 years	11	33
Male/Female (%)	63/37	100/0
Presentation (%)		
Asymptomatic urinary abnormality (AUA)	21	33.3
Nephrotic syndrome(NS)	26	0
RPGN	47	33.3
CKD with hematuria & proteinuria.	5.3	33.3
Mean urinary protein & range (gm /day)	3.0(1.4-10.2)	3.0(1.3-6)
Mean serum Creatinine & range (mg/dl)	3.64(0.6-9.9)	4.2(1.1-6.3)

Mean Serum Albumin & range (gm/dl)	3.7(2-5)	3.8(3.2-4.4)
Low C3 at diagnosis (%)	63	33.3
Low C4 at diagnosis (%)	0	0
Renal histology (%)		
MPGN	74	100
DPGN	26	0
Crescent	47	33.3

C3GN= C3 glomerulonephritis, DDD= Dense Deposit Disease, MPGN= Membranoproliferative Glomerulonephritis, DPGN= Diffuse Proliferative Glomerulonephritis, RPGN= Rapidly Progressive Glomerulonephritis.

Table 2: Response of treatment on C3 glomerulopathy with various clinical syndromes at six months follows up. (n=22)

Clinical presentation	C3GN (n=19)		DDD (n=3)	
	Improved N (%)	Not-improved N (%)	Improved N (%)	Not-improved N (%)
Asymptomatic urinary abnormality	3 (15.8)	1 (5.3)	1 (33.3)	0
Nephrotic syndrome	4 (21.0)	1 (5.3)	0	0
RPGN	4 (21.0)	5 (26.3)	0	1 (33.3)
CKD with hematuria & proteinuria.	0	1 (5.3)	0	1 (33.3)
	Total = 11 (57.8%)	Total = 8(42.1%)	Total = 1(33.3%)	Total = 2(66.6%)

C3GN= C3 glomerulonephritis, DDD= Dense Deposit Disease, RPGN= Rapidly Progressive Glomerulonephritis.

Table 3: Outcomes of C3 glomerulopathy at six month follow up. (n=22)

Outcomes	C3GN n (%)	DDD n (%)
Remission (complete + partial)	11 (57.8)	1(33.3)
Remission (complete)	8 (42.1)	1(33.3)
Progression to CKD	2 (10.5)	0
Progression to ESRD	6 (31.5)	2(66.6)
	Total = 19 (100%)	Total = 3 (100%)

C3GN= C3 glomerulonephritis, DDD= Dense Deposit Disease, CKD= Chronic Kidney Diseas

Discussion

C3 glomerulopathy (C3G) is a newer entity which describes the complement-mediated glomerulonephritis caused by dysregulation of the alternative complement pathway. It is a heterogeneous disease with respect to aetiology, clinical presentation and prognosis. We found C3G in about 2.8% of all kidney biopsy. Prevalence of C3G was about 0.7-1.52% in other Indian studies. [10, 13]This difference in prevalence could be due to difference in duration of study and total number of kidney biopsy performed. In this study, C3glomerulonephritis (C3GN) was about six times more prevalent than Dense Deposits Disease (DDD).

Similarly, C3GN was 3-10 times more prevalent than DDD in other studies. [14, 15] The mean age of the patients was almost similar in both C3GN (25.5 yr) and DDD (27.7 yr) group. Majority (52%) of C3GN cases were noted in 18-50 years age group. While, 2 out of 3 DDD and 7 out of 19 C3GN cases were in pediatrics (< 18 yrs) age group. Mean age at diagnosis of C3GN patients was in 22.9– 42.5 years range in various published studies. [2, 10, 16, 17] In DDD too, mean age of patients in studies by *Lu et al.*, and *Smith et al.*, was comparable to the present study [13, 18, 19] We observed male predominance, with male: female ratio(%) inC3GN (63/37) and DDD (100/0), which is similar to the observation of other Indian studies. [10, 13] However, equal number of male and female had been observed in other series. [17-20] Thus, our overall observation on demographic profile of C3G is in accordance with other studies mentioned above.

The clinical presentation of C3G is widely variable ranging from asymptomatic urinary abnormalities, nephrotic syndrome to advance renal failure. We found proteinuria and hematuria in all patients with C3 glomerulopathy.

Sethi et al., and *Habib et al.*, also has reported hematuria & proteinuria in all patients with C3GN and DDD in their study. [17, 20] In C3GN category; about 47% of patients had presented with rapid loss of kidney function.

Nephrotic syndrome was seen in 26% cases, and 21% cases had asymptomatic urinary abnormalities (AUA).

Nephrotic syndrome was more often seen in C3GN than the DDD. *Viswanathan GK et al.,* found nephrotic syndrome in 28.6% patients with C3GN in their study.[13] In C3GN, mean 24 hours urinary protein excretion was 3.0 gm/24 hours and mean serum creatinine was 3.64 mg/dl. *Viswanathan GK et al.*, noted mean 24 hour urinary protein excretion 3.98 gm/24 hr and mean serum creatinine 4.19 mg/dl in C3GN patients, which is similar to this study. [13] However, *Sethi et al.,* had found higher mean 24hr urinary protein excretion 5.76 g/24h (range 0.615g to 15 g) in their study. [17] In DDD category; asymptomatic urinary abnormalities (AUA), RPGN and CKD was noted in one patient each. None of the DDD patients had nephrotic syndrome in this study. While, in various studies nephrotic syndrome has been reported in significant number of patients with DDD. [13, 16, 19, 20] In DDD, mean 24 hours urinary protein excretion was 3.0 gm/24 hours and mean seru creatinine was 4.2 mg/dl. *Kumar A. et al.,* had found mean 24 hr urinary protein excretion 3.2 g/24 hr and mean serum creatinine 3.2 mg/dl in DDD patients, which is similar to this study. [10] Hence, our observation also supports the varied clinical presentation of C3 glomerulopathy. Measurement of serum C3 & C4 level is not a sensitive or specific marker for diagnosis and classification of C3 glomerulopathy. C3 level would be low or it can be normal in patients with C3 glomerulopathy.[3, 8, 9, 17, 21- 23] we found low C3 level in about 2/3rd of C3GN and in 1/3rd of DDD cases. None of the patients had low C4 in this study. Thus, here it is justifiable to be stress that normal level of C3 does not rule out the diagnosis of C3G and vice-versa.

Histological lesion in C3 glomerulopathy is heterogeneous. In this study, majority of C3GN (74%) and all three DDD cases had MPGN like lesion. In about 26% of C3GN cases

had DPGN. Crescents were seen in about 47% cases with C3GN and one cases with DDD. MPGN had been predominantly seen in C3G in various studies by *Sethi et al*., *Fakhouri et al*., *Servais et al., Viswanathan GK et al.,* and *Nasr et al.*, both in paediatric and adult population. [1, 3, 9, 13, 16] However, *Walker et al.,* found mesangioproliferative glomerulonephritis in majority (45%) of the patients with DDD. [24] *Viswanathan GK et al.,*, had reported MPGN and Mesangioproliferative GN in equal number of patients with C3GN. [13] Other morphologically distinct DPGN like lesion was also seen in various series. [3, 13, 16, 24] Crescents were seen more often in the present study as compared to other published series.[13, 16, 24] High prevalence of crescentic lesion in the present study could be due to presentation in late symptomatic stage, difference in kidney biopsy protocol and geographical differences in population. Hence, our observation also supports the heterogeneous nature of lesion in C3 glomerulopathy. At the end of follow up; overall remission rate of C3GN was better than DDD (57.8 Vs 33.3%). Majority of C3GN patients presenting with nephrotic syndrome (80%) and asymptomatic urinary abnormality (75%) had remission after treatment. While, majority 2outof 3 DDD patients not improved. Complete or partial remission was achieved in 11 with C3GN and in 1 with DDD. Two C3GN patients didn't respond with treatment and progressed to CKD. One of these patients was presented with NS and other with CKD. Total 36% (n=8, C3GN=6, DDD=2) patients progressed to End Stage Renal Failure. Clinical presentation in these six C3GN patients was RPGN (n=5) and AUA (n=1). Two DDD patients had presented with RPGN and CKD each in one. Majority (60%, 6 out of 10) of C3G patients presented with RPGN had poor outcome and progressed to ESRD. However, follow up in this study was short and it is limitation of the study. In an Indian study *Kumar A et al.,* found complete or partial remission in about 25% patients with C3G and 40% had progressed to ESRD [10]. In a study from Columbia reported remission in 38% of C3GN and 25% of DDD. [15] In series by *Sethi et al.*, had reported ESRD in about 26% patients with C3 glomerulopathy. [17] However, a study from Columbia ESRD has been reported in about 50% of patients. [15] Thus, overall outcome of C3G in this study is comparable to various studies from United Kingdom [8], France [9], Columbia [15], Japan [25], Italy [26], Turkey [27] and Spain [28]. To summarize, present study has demonstrated that C3 glomerulopathy has varied clinical presentation, renal histology, treatment response and outcomes. It carries poor prognosis and high risk of disease progression especially in subgroup of patients with RPGN presentation. Although, this study has multiple limitations like small number of participants, short follow-up and limited complement factor & genetic workup.

Conclusion

C3 glomerulopathy was noted in 2.8%. C3GN was more frequent than DDD. RPGN was commonest clinical presentation, and MPGN was commonest histological lesion in C3G. Overall, C3GN had better treatment response than DDD. Limited follow up revealed, C3G carried poor prognosis and despite treatment 8 out of 19 C3GN and 2 out of 3 DDD cases progressed to either CKD or ESRD. However, longer follow-up, large sample size and genetic workup is needed to understand the prognosis of C3 glomerulopathy.

Disclosure of potential conflicts of interest

None and results presented in this paper have not been published previously in whole or part.

Funding

This study was not funded by any organization.

Informed consent

Informed consent was obtained from participant included in study.

Limitations of Study

Short follow up, small sample size and limited complement factor/genetic analysis.

Acknowledgements

We thank all the C3G patients who participated in this study.

References

1. Fakhouri F, Frémeaux-Bacchi V, Noël LH, Cook HT, Pickering MC. C3 glomerulopathy: a new classification. *Nat Rev NephrolM,*2010:6(8):494-499. doi:10.1038/nrneph.2010.85
2. Servais A, Frémeaux-Bacchi V, Lequintrec M, et al. Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. *JMed Genet,*2007:44(3):193-199. doi:10.1136/jmg.2006.045328
3. Sethi S, Fervenza FC, Zhang Y et al. Proliferative glomerulonephritis secondary to dysfunction of the alternative pathway of complement. *ClinJ Am Soc Nephrol,*2011:6(5):1009-1017. doi:10.2215/CJN.07110810
4. Bomback AS, Appel GB. Pathogenesis of the C3 glomerulopathies and reclassification of MPGN. *Nat Rev Nephrol,*2012:8(11):634-642. doi:10.1038/nrneph.2012.213
5. Barbour TD, Pickering MC, Terence Cook H. Dense deposit disease and C3 glomerulopathy. *Semin Nephrol,*2013:33(6):493-507. doi:10.1016/j.semnephrol.2013.08.002
6. Appel GB, Cook HT, Hageman G et al. Membranoproliferative glomerulonephritis type II (dense deposit disease): an update. *J Am Soc Nephrol*. 2005;16(5):1392-1403. doi:10.1681/ASN.2005010078
7. Smith RJH, Appel GB, Blom AM et al. C3 glomerulopathy - understanding a rare complement-driven renal disease. *Nat Rev Nephrol,*2019:15(3):129-143. doi:10.1038/s41581-018-0107-2
8. Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. *Clin JAm Soc Nephrol,*2014:9(1):46-53. doi:10.2215/CJN.04700513
9. Servais A, Noël LH, Roumenina LT et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. *Kidney Int,*2012:82(4):454-464. doi:10.1038/ki.2012.63
10. Kumar A, Nada R, Ramachandran R *et al.* Outcome of C3 glomerulopathy patients: largest single-centre experience from South Asia. *J Nephrol,*2020:33:539-550.

11. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*,2012:120(4):c179-c184. doi:10.1159/000339789
12. Levey AS, Eckardt KU, Tsukamoto Y et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*,2005:67(6):2089-2100. doi:10.1111/j.1523-1755.2005.00365.x
13. Viswanathan GK, Nada R, Kumar A et al. Clinico-pathologic spectrum of C3 glomerulopathy-an Indian experience. *Diagn Pathol*,2015:10:6. Published 2015 Mar 17. doi:10.1186/s13000-015-0233-0
14. Ravindran A, Fervenza FC, Smith RJH, De Vriese AS, Sethi S. C3 Glomerulopathy: Ten Years' Experience at Mayo Clinic. *Mayo Clin Proc*,2018:93(8):991-1008. doi:10.1016/j.mayocp.2018.05.019
15. Bomback AS, Santoriello D, Avasare RS et al. C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy. *Kidney Int*,2018:93(4):977-985. doi:10.1016/j.kint.2017.10.022
16. Nasr SH, Valeri AM, Appel GB, et al. Dense deposit disease: clinicopathologic study of 32 pediatric and adult patients. *Clin J Am Soc Nephrol*,2009:4(1):22-32. doi:10.2215/CJN.03480708.
17. Sethi S, Fervenza FC, Zhang Y et al. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. *Kidney Int*, 2012:82(4):465-473. doi:10.1038/ki.2012.212
18. Lu DF, Moon M, Lanning LD, McCarthy AM, Smith RJ. Clinical features and outcomes of 98 children and adults with dense deposit disease. *Pediatr Nephrol*,2012:27(5):773-781. doi:10.1007/s00467-011-2059-7
19. Smith RJ, Harris CL, Pickering MC. Dense deposit disease. *Mol Immunol*,2011:48(14):1604-1610. doi:10.1016/j.molimm.2011.04.005.
20. Habib R, Gubler MC, Loirat C, Mäiz HB, Levy M. Dense deposit disease: a variant of membranoproliferative glomerulonephritis. *Kidney Int*,1975:7(4):204-215. doi:10.1038/ki.1975.32
21. Lachmann PJ. The amplification loop of the complement pathways. *Adv Immunol*,2009:104:115-149. doi:10.1016/S0065-2776(08)04004-2
22. Leroy V, Fremeaux-Bacchi V, Peuchmaur M et al. Membranoproliferative glomerulonephritis with C3NeF and genetic complement dysregulation. *Pediatr Nephrol*,2011;26(3):419-424. doi:10.1007/s00467-010-17
23. Hawfield A, Iskandar SS, Smith RJ. Alternative pathway dysfunction in kidney disease: a case report and review of dense deposit disease and C3 glomerulopathy. *Am J Kidney Dis*,2013:61(5):828-831. doi:10.1053/j.ajkd.2012.11.045
24. Walker PD, Ferrario F, Joh K, Bonsib SM. Dense deposit disease is not a membranoproliferative glomerulonephritis. *Mod Pathol*,2007:20(6):605-616. doi:10.1038/modpathol.3800773
25. Okuda Y, Ishikura K, Hamada R et al. Membranoproliferative glomerulonephritis and C3 glomerulonephritis: frequency, clinical features, and outcome in children. *Nephrology (Carlton)*,2015:20(4):286-292. doi:10.1111/nep.12382
26. Iatropoulos P, Noris M, Mele C, et al. Complement gene variants determine the risk of immunoglobulin-associated MPGN and C3 glomerulopathy and predict long-term renal outcome. *Mol Immunol*,2016:71:131-142. doi:10.1016/j.molimm.2016.01.010
27. Caliskan Y, Torun ES, Tiryaki TO et al. Immunosuppressive Treatment in C3 Glomerulopathy: Is it Really Effective?. *Am J Nephrol*,2017:46(2):96-107. doi:10.1159/000479012
28. Rabasco C, Cavero T, Román E et al. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. *Kidney Int*,2015:88(5):1153-1160. doi:10.1038/ki.2015.