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C3 Glomerulonephritis associated with Monoclonal Gammopathy

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Abstract

Background—C3 Glomerulonephritis (C3GN) is a proliferative glomerulonephritis resulting from glomerular deposition of complement factors due to dysregulation of the alternative pathway of complement. The dysregulation of the alternative pathway of complement may occur as a result of mutations or functional inhibition of complement regulating proteins. Functional inhibition of the complement regulating proteins may result from a monoclonal gammopathy.

Study Design—Case series

Setting and Participants—32 Mayo Clinic patients of C3GN, of which 10 patients (31.25%) had evidence of a monoclonal immunoglobulin in the serum.

Outcomes—Clinical features, hematological and bone marrow biopsy findings, kidney biopsy findings, renal outcomes, complement pathway abnormalities, treatment and follow-up of patients with C3GN that was associated with a monoclonal gammopathy.

Results—The mean age of patients with C3GN associated with monoclonal gammopathy was 54.5 years. Bone marrow biopsy done in 9 patients revealed monoclonal gammopathy of undetermined significance (MGUS) in 5 patients, small lymphocytic lymphoma/chronic lymphocytic leukemia (CLL) in one patient, and no abnormal clones in the remaining 3 patients. Kidney biopsy showed a membranoproliferative glomerulonephritis with bright capillary wall C3 staining in all 10 patients. Evaluation of the alternative pathway of complement showed abnormalities in 7 of the 9 patients tested. None of the patients had a mutation in the complement regulating proteins. As an index case, one patient with C3GN and CLL was treated with Rituximab, cyclophosphamide, vincristine and prednisone and one patient with C3GN and MGUS

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was treated with dexamethasone and bortezomib. Both patients showed significant decrease in hematuria and proteinuria, and stabilization of renal function.

Limitations—Studies to show evidence of direct activation of the alternative pathway by the monoclonal immunoglobulin were not done.

Conclusions—The study highlights the association of C3GN and monoclonal gammopathy, in particular in the older population, and the importance of targeting the underlying hematologic malignancy as an approach to treating C3GN.

Keywords

C3 glomerulonephritis; MPGN; C3GN; monoclonal gammopathy; MGUS

In monoclonal gammopathies, clonal proliferation of immunoglobulin (Ig) producing lymphocytes or plasma cells results in circulation of monoclonal Ig. The clinical spectrum of disease associated with monoclonal gammopathies is wide and includes monoclonal gammopathy of undetermined significance (MGUS), lymphoproliferative disorders and multiple myeloma. Glomerulonephritis resulting from glomerular deposition of monoclonal Ig is well-established. Thus, deposition of monoclonal Ig with immune-type deposits along the capillary walls gives rise to membranoproliferative glomerulonephritis.^{1, 2} Alternatively, deposition of monoclonal Ig along the glomerular basement membrane and tubular basement membranes can give rise to monoclonal Ig deposition disease (MIDD) and depending on the type of deposit can be divided into light chain (LC), heavy chain (HC) or both LC and HC.^{3, 4}

Monoclonal Ig may also cause kidney injury indirectly through dysregulation of alternative pathway (AP) of complement, which could result in C3 glomerulonephritis (C3GN).^{5, 6} C3GN is a recently recognized glomerulonephritis characterized by a proliferative pattern of injury on light microscopy (LM), dominant C3 staining with minimal or negative staining for Ig on immunofluorescence microscopy (IF) and mesangial, subendothelial and occasionally subepithelial deposits on electron microscopy (EM).⁵⁻⁷ While C3GN may occur in the 'de novo' setting, secondary causes or insults that result in unmasking of an AP abnormality may also cause C3GN. Infections are an important secondary cause of C3GN.⁸ We postulate that monoclonal Ig may also be another important secondary cause of C3GN. In this study, we present a comprehensive review of 10 patients with C3GN that had an associated monoclonal gammopathy in the serum or urine. We also review the renal outcomes, complement pathway abnormalities, treatment and follow-up of these patients.

METHODS

A total of 41 Mayo Clinic patients with the diagnosis of C3GN between 2009 and 2012 were evaluated for this study. Renal biopsies of all patients were evaluated to confirm the diagnosis of C3GN. In all cases, routine work up including LM, IF and EM was performed. Nine patients did not have any work up for monoclonal gammopathy. The Institutional Review Boards at the Mayo Clinic and University of Iowa approved the study.

Functional Assays of Complement Activity

C3 Nephritic factor (C3Nefs) and Factor H autoantibodies were detected, and the hemolytic assay, alternative pathway functional assay (APFA) and soluble membrane attack complex (sMAC) assay were completed, as previously described.^{6,9}

Genetic Testing

Coding regions and intron-exon boundary junctions of *CFH* (MIM#134370; NM_000186), *CFHR5* (MIM#608593; NM_030787.3), *CFI* (MIM#217030; NM_000204.3), *CD46* (MIM#120920; NM_002389.3), *CFB* (MIM#138470; NM_001710.5) and *C3* (MIM#120700; NM_000064.2) were amplified and screened for mutations and polymorphisms using bi-directional sequencing as previously described.¹⁰

Copy Number Variation

Multiplex-ligation probe amplification to detect deletion of *CFHR3-CFHR1* was completed as described.¹¹

RESULTS Clinical features (table 1)

A total of 41 patients with biopsy proven diagnosis of C3GN were reviewed for this study. Of those, 32 patients had evaluations to identify monoclonal proteins. Of the 32 patients, 10 had monoclonal gammopathy either based on serum or urine (estimated prevalence of 31.25%). Two of the ten patients were included in a recent report of C3GN.⁶ The mean average age of C3GN patients without monoclonal gammopathy was 31.5 years as compared to mean age of 54.5 years for those with evidence of monoclonal gammopathy ($p=0.0013$). Of the 10 patients with monoclonal gammopathy the age ranged from 22 to 69 years (mean of 54.5 years). There were 6 males and 4 females. One patient was on dialysis at time of evaluation at the Mayo Clinic (7 years after his initial renal biopsy). The average creatinine at time of evaluation for the other 9 patients was 1.78 mg/dL and ranged from 0.8 to 3.0 mg/dL with a mean estimated glomerular filtration rate (eGFR) of 42.8 ml/min/1.73m² and range of 21 to 79 ml/min/1.73m², based on the Modification of Diet in Renal Disease (MDRD) Study equation.

Of the nine urine microscopies available for review, all patients had hematuria. Twenty-four hour urinary protein was available for 9 patients (not available for the patient on dialysis) and ranged from 74 to 9000 mg/24 hours (mean, 4604 mg/24hour). Complement 3 level was low in 6 out of 9 patients and ranged from 12 to 62 mg/dL (mean 53.5 mg/dL; normal range 75 – 175mg/dL). C4 level was low in only one patient at 4 mg/dL (normal range 14–40 mg/dL). All patients were negative for hepatitis B and C. Cryoglobulins were negative in all patients except for patients # 2, 3, and 9 who did not undergo evaluation. ANA was negative in all patients except for patient # 3 and # 4 who did not have the studies performed. All patients were negative for ds-DNA antibody except for patients # 3, 4, 8 and 10 who did have the studies performed.

Monoclonal and Hematological studies (table 2)

At time of diagnosis, 8 patients had M-spike in the γ region on serum electrophoresis; the remaining 2 patients had hypogammaglobulinemia. All patients showed monoclonal bands on serum immunofixation studies. The most common monoclonal gammopathy was IgG kappa (6 patients). Other gammopathies included 2 patients with IgG lambda, 1 patient with IgA lambda, and 1 with IgM lambda.

Urine monoclonal studies were performed in 6 of the 10 patients and were positive in all 6 patients. Two patients had monoclonal kappa in addition to IgG kappa, 2 patients had monoclonal lambda in addition to IgG lambda. One patient had IgA lambda and one had IgG kappa.

Eight patients had evaluation of their free light chains and 6 had abnormal kappa to lambda ratio (normal range 0.26–1.65). Bone marrow biopsy was performed in 9 patients. Three patients did not have any evidence of abnormal plasma cell clones although one had a hypocellular marrow; five patients had between 5–10% light chain restricted plasma cells and one patient had 30% involvement of the bone marrow with small lymphocytic lymphoma cells.

Kidney biopsy findings (table 3)

On light microscopy, a membranoproliferative pattern of injury was present in all 10 patients. There was a range of 0 to 30% focal global glomerulosclerosis, with an average of 15%. The tubular atrophy and interstitial fibrosis varied from 0 to 50% with an average of 24%. Immunofluorescence microscopy showed mesangial and capillary wall staining for C3 (2–3+ out of 3) in all cases. Four cases showed mild segmental staining for IgM and one case showed mild segmental staining for IgG (trace-1+). Electron microscopy showed mesangial and capillary wall deposits in 9 out of 10 cases. Of the capillary wall deposits, all biopsies showed subendothelial deposits and 4 cases also showed subepithelial deposits. In one biopsy, even though C3 was noted on IF studies, electron dense deposits were not present on EM studies, which showed subendothelial fluffy material, raising the possibility of a patient with features of both C3GN and aHUS. Representative biopsy findings are shown in Figure 1 (Patient #4)

Evaluation of alternative complement pathway (table 4)

Functional and genetic studies of the alternative pathway showed abnormalities in 7 out of 9 patients tested. Patient #3 was not tested. Two patients were positive for C3 nephritic factor (C3Nefs). Six patients had functional abnormalities of the AP and two patients showed elevated levels of soluble membrane attack complex (sMAC) in the serum. Risk alleles were identified in 3 patients and included Factor H risk polymorphisms H402 (c.1204C, p.His402). None of the patients had mutations in CFH, CFI, CFB, MCP, C3 or CFHR5.

Laser Dissection and Mass-Spectrometry

We performed laser dissection and mass spectrometry to determine the glomerular proteomic profile in a patient with CLL and C3GN (patient # 9), as previously described.^{6, 12} Mass spectrometry showed large spectra of C3 and smaller spectra numbers

of C9, indicating activation of the AP of complement and the terminal complement pathway (Figure 2). Surprisingly, relatively large spectra numbers of C4 were also detected. The presence of C4 likely indicates activation of classical pathway of complement as well by the monoclonal Ig. CFHR-1 and small spectra numbers of CFHR-5 were also detected which is consistent with the proteomic profile of C3GN.⁶ Importantly, monoclonal immunoglobulins were not identified in glomerular proteomic profile, indicating that the glomerulonephritis was not due to direct deposition of monoclonal Ig.

Treatment and follow-up (table 5)

Treatment regimen was variable amongst the group. Patient # 1, # 3, # 5, and # 6 were treated conservatively. Patient # 3 developed end stage renal disease (ESRD) 7 years after his initial renal biopsy. After undergoing dialysis for 5 years, he received a deceased donor renal transplantation with primary non-function and remains on dialysis. Interestingly, his kidney transplant biopsy 8 months after transplantation showed recurrence of C3GN. He did not receive any therapies for his C3GN prior to transplantation but did receive tacrolimus and mycophenolate mofetil following transplantation but despite this developed recurrence of C3GN. Patient # 1 and # 5 had proteinuria and stable renal function despite lack of treatment. Patient # 1 had repeat renal biopsy two years after diagnosis which did not show any significant changes from the previous biopsy. Patient # 6, on the other hand, had significant progression of his renal disease with increase in proteinuria and progressive renal failure.

Patients # 2, 7, 8, and 10 received either prednisone alone or in combination with immunosuppressive therapy including azathioprine, cyclophosphamide or mycophenolate mofetil with variable response. Patients # 7, 8 and 10 had improvement in proteinuria and relatively stable renal function with repeat biopsies showing presence of C3GN with minimal increase in fibrosis. This was in contrast to patient # 2 who had progression of proteinuria and progressed to ESRD with repeat biopsy showing extensive global sclerosis.

Patient # 4 was treated with dexamethasone and bortezomib which resulted in normalization of the free light chain ratio, with lambda light chains decreasing from 7.35 to 1.93 in follow up. Renal function had remained stable after 13 months of follow-up with improvement in hematuria and lack of proteinuria.

Patient # 9 was diagnosed with CLL and underwent treatment with 6 cycles of Rituximab, cyclophosphamide, vincristine and prednisone (R-CVP). Following treatment, there was marked decrease in proteinuria and significant improvement in renal function. Repeat bone marrow biopsy showed no evidence of SLL/CLL (Figure 3).

DISCUSSION

In this study we describe the clinical features, hematologic evaluation, kidney biopsy, treatment and follow-up of patients with C3GN associated with a monoclonal gammopathy. To our knowledge this is the largest series evaluating the clinicopathologic characteristics and outcomes of patients with C3GN and monoclonal gammopathy.

C3GN is a rare type of glomerulonephritis resulting from dysregulation of the AP of complement. The hallmark of the disease is the presence of C3 on immunofluorescence microscopy with minimal or no Ig. Electron microscopy reveals mesangial and subendothelial electron dense deposits; often small intramembranous and subepithelial deposits may also be present. This is in contrast to Dense Deposit Disease (DDD), which shows sausage shaped diffuse intramembranous deposits. Both C3GN and DDD are grouped under C3 glomerulopathy to reflect a common underlying pathogenic mechanism, i.e. abnormality in the AP of complement.^{13–15} The abnormalities include antibodies to or mutations in complement regulating proteins or both.^{5, 6, 16, 17} Allele polymorphisms in complement regulating proteins are also a risk factor to the development of C3GN or DDD.^{10, 18}

In many patients, however, mutation in genes regulating the alternative complement pathway or the allele variation in the regulatory proteins may not be enough to trigger the disease and a second hit is required before C3GN or DDD develops.¹⁹ In many patients, infection might be such a trigger.⁸ We propose that monoclonal Ig might be another trigger that may impede the regulation of the AP of complement by interfering with the function of complement regulating proteins. This causes over activation of AP resulting in C3GN or DDD.

Association of DDD with monoclonal gammopathy has been previously reported.^{20–22} The largest series was by Sethi et al who reported 10 patients of DDD with associated monoclonal gammopathy. Similar to our study the most common monoclonal Ig was IgG kappa. The average age of patients was slightly older (61.2 years) compared to 54.5 years in our study. More recently Bridoux et al. reported a series of 6 patients with C3GN with associated monoclonal gammopathy.²³ In contrast to the study by Bridoux, patient 1 and 2 in our study had circulating C3NeF indicating that stabilization of C3 convertase by auto-antibody may play a role. Similar to their study, we found the CFH 402 allele in 3 patients but did not find any mutations in complement regulating proteins. The CFH 402H allele is present in 60% of the general population (allele frequency 0.37 in 1000 genomes database) indicating that the CFH 402H allele on its own does not result in C3GN. Thus in these patients the C3GN does not develop due to allele polymorphisms or mutations in complement regulating proteins. On the other hand, this suggests that the monoclonal Ig activate the alternative pathway via inhibition of complement regulating proteins probably by acting as an autoantibody. The prevalence of monoclonal gammopathy is estimated to be 1–2% in general population and increases to 3.2% in adults over age of 50.²⁴ In our study, of the 32 patients with C3GN that had workup for monoclonal studies 31.25% had monoclonal gammopathy, which is much higher than expected in the general population. There were more males than females in our study. This may be due to the small number of patients. Alternatively, it may be reflection of the fact that the age-adjusted rate of monoclonal gammopathy is higher in males than females (4% versus 2.7%).²⁴

The mechanism by which monoclonal Ig results in activation of AP of complement is not entirely known but likely involves activation of the alternative pathway by the aberrant protein.²⁵ In an elaborate study by Meri et al. monoclonal lambda light chains from a patient were found to result in activation of AP through directly interacting with Factor H²⁶ and

development of DDD. Later, Jokiranta et al. showed that the lambda light chains did this by binding to the third short consensus repeat domain and inhibited Factor H.²⁷ There is also the possibility of dysregulation of complement by monoclonal proteins even in the absence of kidney disease.

The majority of patients in our study had diagnosis of MGUS based on serum, urine and bone marrow biopsy results. Only patient # 4 in our study was treated with chemotherapy for the MGUS with favorable renal outcomes. Patient # 9 was the only patient in our cohort who had CLL in association with monoclonal gammopathy. He was treated with 6 cycles of R-CVP which resulted in improvement in his proteinuria, improvement in creatinine and normalization of his complement levels (Figure 3). The evaluation of his AP revealed elevated sMAC level indicative of activation of his complement pathway. The absence of any detectable antibodies may have been due to the fact that his serum was tested after he had already received one cycle of therapy.

Monoclonal gammopathy, is present in up to 20% of cases of CLL, and correlates with a poor prognosis.²⁸ Hill *et al* described three patients with CLL and MPGN, all of whom had monoclonal proteins detectable in either the serum or urine; in two of these patients, there was intense glomerular C3 staining on immunofluorescence studies in the absence of any immunoglobulins, consistent with a diagnosis of C3GN. All three patients were treated with chlorambucil and prednisone and had improvement in their renal parameters.²⁹ Our patient also had significant improvement in his hematuria, proteinuria and blood pressure control after treatment for his CLL.

We have previously reported the association of MGUS with MPGN and noted that the term “undetermined significance” in these patients is misleading as the monoclonal Ig deposition results in direct kidney injury which is of significance.¹ In this study, we show that monoclonal Ig are indirectly associated with kidney injury as a result of activation of the alternative pathway of complement. We propose that in all patients with C3GN, evaluation for monoclonal gammopathy should be part of the evaluation. There is no specific therapy available for C3GN. Targeting the monoclonal Ig may serve as a novel therapeutic approach in such patients.

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Figure 1.

Representative light, immunofluorescence, and electron microscopy in a C3GN patient with monoclonal gammopathy (patient # 4). A–B. Light microscopy showing a membranoproliferative pattern of injury (PAS stain, A 10x, B 40x). C. Immunofluorescence studies show bright C3 in the mesangium and along capillary walls (40x). D–E. Electron microscopy showing mesangial deposits (thick white arrows), subendothelial deposits (thick black arrows), and subepithelial deposits (thin black arrows) and intramembranous deposits (thin white arrows). (D- 7830x, E- 17900x).

Probability Legend:					
over 95%					
80% to 94%					
50% to 79%					
20% to 49%					
0% to 19%					
Bio View:					
#	Identified Proteins (382)	Accession Number	Molecular Weight	S1	S2
1	Complement C3	CO3_HUMAN	187 kDa	27	23
2	Complement C4-B	CO4B_HUMAN	193 kDa	17	13
3	Complement factor H-related protein 1	FHR1_HUMAN	38 kDa	8	5
4	Complement factor H-related protein 5	FHR5_HUMAN	64 kDa	2	2
5	Complement component C9	CO9_HUMAN	63 kDa	3	1
6	Complement factor H	CFAH_HUMAN	139 kDa	1	2
7	Ig gamma-1 chain C region	IGHG1_HUM...	36 kDa	1	

Figure 2.

Laser microdissection and mass spectrometry analysis of glomerular proteins in C3GN associated with CLL (patient # 9) in 2 samples (S1 and S2). The proteomic data show large spectra for C3, C4, and CFHR-1. Small spectra numbers for C9 and CFHR-5 are also present. Kappa or lambda light chains were not detected and spectra for IgG-1 C region in sample 1 was below the level that is deemed clinically valid.

Figure 3. C3GN associated with CLL (patient #9). Change in renal parameters in months after diagnosis, number of cycles of R-CVP completed is marked with thick black arrows.

Table 1A

Patient demographics and laboratory evaluation of 10 patients with C3GN with monoclonal gammopathy (out of 32 C3GN patients tested).

Patient	Age/ sex	Serum Cr at presentation (mg/dL)	eGFR (ml/min/1.73 m ²)	Urinary protein (mg/24hr)	Urine microscopy at renal bx	C3/C4 (mg/dL)
1	61/M	1.1	68	1190	50–100 RBC, 20–30 WBC	57/35
2	22/M	2.0	42	7741	50–100 RBC, 10–20 WBC	12/31
3	46/M	On dialysis	On dialysis	On dialysis	On dialysis	53/18
4	69/F	2.0	25	74	40–50 RBC(>25 dysmorphic), 4–10 WBC	100/19
5	49/F	1.2	48	2805	<3 RBC, 4–10 WBC	80/16
6	69/M	3.0	21	5896	3–10 RBC	130/21
7	41/F	0.8	79	9000	3–10 RBC, 1–3 WBC ^a	NA/NA
8	63/M	2.0	34	1872	30–40 RBC, 3–10 WBC ^b	73/23
9	63/M	1.8	38	5081	>100 RBC, 4–10 WBC	62/4
10	62/M	2.2	30	7779	3–10 RBC ^c	64/38

^a 12 years after renal biopsy

^b 6 years after renal biopsy

^c 8 months after renal biopsy

NA- not available

Table 1B

Patient demographics and laboratory evaluation of patients with C3GN without monoclonal gammopathy (out of 32 C3GN patients tested).

Patient	Age/sex	Serum Creatinine at presentation (mg/dL)	eGFR(ml/min/1.73m ²)	Urinary protein (mg/24hr)	C3/C4 (mg/dL)
1	73/F	1.4	37	614	46/24
2	52/F	1.24	45	6389	76/26
3	47/F	3.1(on dialysis)	16	204	56/47
4	19/M	8.2 (on dialysis)	8	7503	100/22
5	19/M	2.8	29	1970	130/36
6	42/F	0.6	110	1737	17/18
7	22/M	1.8	47	3 ⁺	N/N
8	19/F	2.2	29	8200	28/N
9	17/F	0.64	121	1027	115/20 [*]
10	18/F	2.7	23	1765	75/12
11	20/M	1.9	45	501	10/35
12	61/F	0.8	73	2299	108/33 ⁺
13	11/M	0.5	123	4800	L/N
14	20/M	2.9	34	21614	40/27
15	29/M	1.57	52	700	20/28
16	69/M	1.5	46	196	87/26 ^ψ
17	37/M	1.1	75	9740	93/14 [‡]
18	21/M	0.9	107	4000	83/15
19	22/F	0.72	101	7800	38/15
20	49/F	1.3	44	448	93/25
21	8/F	0.8€	67	1+€	L/N
22	18/F	2.4£	26	2509£	116/18£

^{*} Patient 9, complement studies 2 months after renal biopsy

⁺ Patient 12, complement studies 1 month after renal biopsy

^ψ Patient 16, complement studies 1 year after renal biopsy

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⌘ Patient 17, complement studies 3 months after renal biopsy
⌘ Patient 21, creatinine and urinary protein, 1 year after renal biopsy
⌘ Patient 22, creatinine, urinary protein and complement studies, 18 years after renal biopsy
C3 normal range (75–175mg/dl), C4 normal range (14–40mg/dl)
L: low, N: normal

Table 2

Hematologic evaluation of patients with C3GN and monoclonal gammopathy.

Patient	SPEP	Immunofixation (serum)	UPEP	Immunofixation (urine)	Kappa/ Lambda *	Bone marrow biopsy	Hematological diagnosis
1	M spike in γ region	IgG kappa	No M-spike	IgG kappa	1.45	8% kappa restricted plasma cells	MGUS
2	Hypogammaglobulinemic	IgM lambda	No abnormalities	No abnormalities	1.42	No B-cell clones	MGUS
3	M spike in γ region	IgA lambda	All fractions present	IgA lambda	0.1	5–10% lambda restricted plasma cells	MGUS
4	M spike in γ region	IgG lambda	All fractions present	Lambda + IgG lambda	0.24	10% lambda restricted plasma cells	MGUS
5	M spike in γ region	IgG kappa	Abnormality in γ region	Kappa + IgG kappa	2.0	No B-cell clones	MGUS
6	M spike in γ region	IgG kappa	M spike in γ region	Kappa + IgG kappa	1.97	5% kappa restricted plasma cells	MGUS
7	M spike in γ region	IgG kappa	NA	NA	NA	5% kappa restricted plasma cells	MGUS
8	M spike in γ region	IgG kappa	NA	NA	1.74	Not done	MGUS
9	Hypogammaglobulinemic	IgG kappa	NA	NA	2.29	Small lymphocytic leukemia involving 30% of bone marrow	CLL
10	M spike in γ region	IgG lambda	M spike in γ region	Lambda + IgG lambda	NA	Hypocellular, No plasma-cell clones	MGUS

* normal range 0.26–1.65

Table 3

Kidney Biopsy findings of patients with C3GN and monoclonal gammopathy.

Patient	Pattern of Injury	% globally sclerosed glomeruli	Interstitial Fibrosis	Immunofluorescence Microscopy (CW and mesangial)	Ultrastructural localization of deposits
1	MPGN	0	10	C3 (2+), IgM (1+)	SE, SU, MES
2	MPGN	24	0	C3+, IgM (trace)	SE, SU, IN, MES
3	MPGN	30	30	C3 (3+)	SE, SU, MES
4	MPGN	20	20	C3 (3+)	SE, SU, IN, MES
5	MPGN/?tma	5	30	C3 (3+)	No deposits
6	MPGN	30	40	C3 (3+)	SU, MES
7	MPGN	25	10	C3 (3+), IgM and C1q (trace)	SU, IN, MES
8	MPGN	15	50	C3 (3+)	SU, IN, MES
9	MPGN	10	40	C3 (3+), IgG (trace)	SU, MES
10	MPGN	5	10	C3 (3+), IgM (trace)	SU, IN, MES

MPGN- membranoproliferative, CW- capillary wall, SE- sup epithelial, SU- subendothelial, IN- intramembranous, MES- mesangial

Table 4
Alternative complement pathway evaluation of patients with C3GN and monoclonal gammopathy.

Patient	CFH	C3Nef	APFA	Hemolytic assay	sMAC (mg/L)
1	H402- 2 copies; No mutation	Positive	1%, very low	Normal	1.23
2	H402-0; No mutation	Positive	14.1%, very low	Normal	ND
4	H402- 2 copies; No mutation	Negative	86.2%, normal	Normal	0.09
5	No mutation	Negative	24.7% low	Normal	0.1
6	H402-1 copy; No mutation	Negative	143.2%, abnormal	Normal	0.2
7	H402-0; No mutation	Negative	54% low	Normal	0.23
8	H402-0; No mutation	Negative	61% low	Normal	0.2
9	H402-0; No mutation	Negative	85% normal	Normal	0.44
10	H402-0; No mutation	Negative	67% low normal	Normal	0.17

sMAC= serum membrane attack complex (normal 0.3 mg/L), APFA=alternate pathway functional assay (normal 65% - 130%)

Table 5
Treatment and renal outcome at follow up of patients with C3GN and monoclonal gammopathy.

Patient	Therapy	ACEI/ARB use	Time to f/u (month s)	Serum Cr at f/u (mg/dL)	eGFR (ml/min/1.7 3m ²)	Urinary protein at f/u (mg/24h)	C3 in f/u (mg/dl)	Kappa/ Lambda at f/u
1	Conservative	No	53	1.3	41	2265	45	1.35
2	Prednisone, azathioprine, Cyclophosphami de	Yes	20	5.9	12	10390	22	1.04
3	Conservative	No	158	On dialysis	On dialysis	On dialysis	91	0.26
4	Dexamethasone, bortezomib	Yes	13	1.8	28	40	131	1.15
5	Conservative	Yes	9	1.4	40	1464	NA	1.95
6	Conservative	No	4	5.9	10	15416	NA	NA
7	Cyclophosphami de, Mycophenolate mofetil	Yes	144	0.9	65	4535	93	1.3
8	Prednisone	Yes	78	2.8	23	204	80	NA
9	Rituximab, cyclophosphamid e, vincristine, prednisone	Yes	6	1.6	44	1500	108	NA
10	Prednisone	Yes	15	1.8	38	588	116	NA

* f/u - follow up