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ORIGINAL ARTICLE

Membranoproliferative glomerulonephritis associated with autoimmune diseases

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Abstract Membranoproliferative glomerulonephritis (MPGN) has been classified based on its pathogenesis into immune complex-mediated and complement-mediated MPGN. The immune complex-mediated type is secondary to chronic infections, autoimmune diseases or monoclonal gammopathy. There is a paucity of data on MPGN associated with autoimmune diseases. We reviewed the Mayo Clinic database over a 10-year period and identified 12 patients with MPGN associated with autoimmune diseases, after exclusion of systemic lupus erythematosus. The autoimmune diseases included rheumatoid arthritis, primary Sjögren's syndrome, undifferentiated connective tissue disease, primary sclerosing cholangitis and Graves' disease. Nine of the 12 patients were female, and the mean age was 57.9 years. C4 levels were decreased in nine of 12 patients tested. The serum creatinine at time of renal biopsy was 2.2 ± 1.0 mg/dl and the urinary protein was 2,850 ± 3,543 mg/24 h. Three patients required dialysis at the time of renal biopsy. Renal biopsy showed an MPGN in all cases, with features of cryoglobulins in six cases; immunoglobulin (Ig)M was the dominant Ig, and both subendothelial and mesangial electron dense deposits were noted. Median follow-up was 10.9 months. Serum creatinine and proteinuria improved to 1.6 ± 0.8 mg/dl and 428 ± 677 mg/24 h, respectively, except in 3 patients with end-stage renal disease. In summary, this study describes the clinical features, renal biopsy findings, laboratory evaluation, treatment and prognosis of MPGN associated with autoimmune diseases.

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Introduction

Membranoproliferative glomerulonephritis (MPGN), also known as mesangiocapillary glomerulonephritis, is a pattern of glomerular injury that results from deposition of immune-complex and/or complement in the mesangium and along the glomerular capillary walls. MPGN is classified as immune-complex mediated when immunoglobulins (Ig) with or without complement are noted on immunofluorescence microscopy, and complement-mediated when only complement factors (±trace/1 + Ig) are noted on immunofluorescence microscopy [1, 2]. Complement mediated-MPGN is due to a dysregulation of the alternative pathway of the complement system [3–5]. On the other hand, immune-complex mediated MPGN, as the name suggests, is related to the presence of immune complexes in the glomeruli.

Immune-complex mediated MPGN is seen in conditions where there is persistent or episodic antigenemia, resulting in circulating antigen–antibody complexes that are then deposited in the glomeruli. Alternatively, the antigen may be deposited in the kidneys first with subsequent binding of the antibody [6]. In either scenario, the deposition of immune-complexes in the glomeruli results in activation of the classical pathway of the complement system and glomerular injury. Persistent antigenemia can be seen with chronic infections, in particular hepatitis C. Immune-complex mediated glomerulonephritis can also result from autoimmune diseases and paraproteinemia. Even though autoimmune diseases are a known cause of MPGN, there is a paucity of data regarding the frequency, clinical

presentation and renal outcome of these patients. There are only a few reports of MPGN associated with autoimmune diseases [7–13]. In this study, we identified and reviewed all cases of biopsy-proven MPGN with a concomitant diagnosis of an autoimmune disease at our institution, excluding systemic lupus erythematosus. We report the clinical, biopsy and laboratory findings, as well as the renal outcome in these patients.

Methods

We searched the Mayo Clinic database from 2002 to 2012 to identify individuals who had a diagnosis of MPGN with an associated autoimmune disease. We excluded patients with systemic lupus erythematosus since lupus nephritis is a well-known cause of proliferative glomerulonephritis [14]. The Institutional Review Boards at the Mayo Clinic approved the study.

Clinical information was obtained from review of the Mayo Clinic medical records. All patients were evaluated by rheumatologists and clinicians at the Mayo Clinic. A total of 12 patients with the following autoimmune diagnoses were identified: rheumatoid arthritis (RA), primary Sjögren's syndrome (PSS), undifferentiated connective tissue disease (UCTD), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and Graves' disease. Two additional patients with MPGN associated with Raynaud's and Castleman's disease were also identified but their biopsies did not have immunofluorescence evaluation and were not included in the study. One further patient with rheumatoid arthritis was excluded due to presence of monoclonal immunoglobulins (Ig)G3 kappa on immunofluorescence microscopy. The diagnosis of RA and PSS was confirmed based on American College of Rheumatology (ACR) diagnostic criteria [15, 16]. Diagnosis of UCTD was confirmed based on the classification proposed by Mosca et al. [17]. Diagnosis of PSC was confirmed based on laboratory and radiological findings. Diagnosis of Graves' disease was confirmed based on laboratory evaluation. All patients had negative serology for hepatitis B and C except for one (patient 12) in whom hepatitis serology was not available.

Results

Clinical features

There were total of 308 biopsy-proven diagnoses of MPGN performed at Mayo Clinic between the years 2002 and 2012. Of those, 17 had a concomitant diagnosis of an autoimmune disease (an estimated rate of 5.5 %). Two patients did not give research authorization and were excluded from the study. One patient had monoclonal IgG3 kappa on immunofluorescence microscopy and was excluded. Of the remaining 14, 12 had complete renal biopsy evaluation and were included in this study. Of the 12 patients, 5 had RA, 3 had PSS, 2 had UCTD, 1 had PSC, and 1 had Graves' disease (Table 1). One of the patients with diagnosis of UCTD also had a diagnosis of PBC. The median duration of autoimmune diagnosis to the time of renal biopsy was 9.7 years, ranging from <1 month to over 32 years (mean 12.1 ± 10.6 years).

Patients' mean age at time of renal biopsy for all diagnoses combined was 59.3 ± 12.6 years. The majority of patients (75 %) were female, as expected. Average serum creatinine at time of renal biopsy was 2.1 ± 1.0 mg/dl, ranging from 1 to 4.3 mg/dl. Average 24-h urinary protein at time of renal biopsy was 1,975 ± 1,690 mg/24 h, ranging from 241 mg to 6,110 mg/24 h. Urinalysis of all 10 patients analyzed showed significant hematuria. Three patients required dialysis at the time of renal biopsy.

Serological and monoclonal studies

Results of the serological analysis are presented in Table 2. Anti-nuclear antibodies (ANA) were positive in 8 of the 12 patients. Of the five patients with RA, two had positive anti-citrullinated protein antibody (anti-CCP). Of the three patients with PSS, two had anti-Sjögren syndrome A antibodies (anti-SSA), and one had both positive anti-SSA and anti-SSB antibodies. One patient with UCTD had positive serologic workup for anti-SSA, anti-ribonucleoprotein (anti-RNP), anti-Smith, and anti-topoisomerase I (anti-Scl-70); the other patient with UCTD had positive anti-double stranded deoxy-ribonucleic acid (anti-dsDNA). The patient with Graves' disease had positive thyroid peroxidase (TPO) and thyrotropin receptor antibodies. Of the 11 patients with available rheumatoid factor (RF) data 8 were positive, and of the 10 patients with available serum cryoglobulin data 4 were positive, all of which were type II cryoglobulins. Two of these patients had RA and two had PSS. C4 levels were low in 8 of the 11 patients tested (11.4 ± 12.2), and C3 levels were low in 6 of the 10 patients tested (63 ± 36.3). When both C3 and C4 were considered together, only two of the 11 patients tested had normal complement levels at the time of renal biopsy (Table 2).

Patient's monoclonal and hematological characteristics are presented in Table 3. All except one patient had evaluation for serum monoclonal studies, of which three (patients 3, 4 and 7) were positive for an M-spike. Immunofixation studies in all three patients showed monoclonal IgM kappa. Type II cryoglobulins were detected in the serum of these three patients. Of the 3 patients with

Table 1 Patients' demographics and renal characteristics

Patient	Diagnosis	Age (years)	Gender	Creatinine at renal biopsy (mg/dl)	Dialysis at time of renal biopsy	Proteinuria (mg/24 h)	Duration of AI diagnosis at renal biopsy (years)
1	RA	69	Male	2.8	Yes	241	20.0
2	RA	48	Female	2.0	No	2,900	6.9
3	RA	67	Female	1.5	No	2,250	32.8
4	RA	58	Female	1.0	No	581	5.5
5	RA	69	Male	4.3	Yes	2,780	6.7
6	PSS	70	Female	1.9	No	6,110	17.6
7	PSS	56	Female	1.8	No	548	12.5
8	PSS	54	Female	1.4	No	442	0
9	UCTD	28	Male	1.7	No	2,066	1.8
10	UCTD/PBC	57	Female	1.7	No	885	13.2
11	PSC	75	Female	3.8	Yes	1,510	27.4
12	Grave's	54	Female	1.2	No	3,396	0.3

AI autoimmune disease, *RA* rheumatoid arthritis, *PSS* primary Sjögren's syndrome, *UCTD* undifferentiated connective tissue disease, *PSC* primary sclerosing cholangitis, *PBC* primary biliary cirrhosis

Table 2 Serological evaluation

Patient	Diagnosis	ANA	ENA	RF	Cryoglobulin	C3 (75–175 mg/dl)	C4 (14–40 mg/dl)
1	RA[a]	Negative	Negative	Negative	Negative	123	26
2	RA	Negative	Negative	Positive	Not done	Low	Low
3	RA	Negative	Negative	Positive	Type II	62	3
4	RA	Negative	Negative	Positive	Type II	41	20
5	RA[a]	Positive	Negative	Positive	Not done	101	37
6	PSS	Positive	Anti-SSA	Positive	Type II	48	4
7	PSS	Positive	Anti-SSA/SSB	Positive	Type II	89	3
8	PSS	Positive	Anti-SSA	Positive	Negative	91	3
9	UCTD	Positive	Anti SSA/RNP/smith/SCL-70	Negative	Negative	47	4
10	UCTD/PBC	Positive	Anti-ds-DNA	Negative	Negative	Not done	3
11	PSC	Positive	Not done	Positive	Negative	Not done	Not done
12	Grave's	Positive	Negative	Not done	Not done	51	11

Anti-SSA/SSB anti-Sjögren syndrome A/B antibodies, *RNP* ribonucleoprotein, *SCL-70* anti-topoisomerase I, *Anti-dsDNA* anti-double stranded deoxy-ribonucleic acid, *ANA* anti nuclear antibody, *ENA* extractable nuclear antigen, *RF* rheumatoid factor, *RA* rheumatoid arthritis, *PSS* primary Sjögren's syndrome, *UCTD* undifferentiated connective tissue disease, *PSC* primary sclerosing cholangitis, *PBC* primary biliary cirrhosis

[a] Positive anti-citrullinated protein antibody

positive serum monoclonal studies, 2 also had positive urine monoclonal studies (one with kappa only and one with IgM only). Two of these patients had bone marrow biopsies done which showed 5 % plasma cells (patients 3 and 4).

Kidney biopsy findings

Renal biopsy findings are presented in Table 4. On light microscopy, an MPGN pattern of injury was present in all 12 cases. There was a range of 0–70 % focal global glomerulosclerosis, with an average of 17 %. The tubular atrophy and interstitial fibrosis varied from 5 to 60 % with an average of 22 %. Immunofluorescence microscopy showed mesangial and capillary wall staining for IgM in 11 of the 12 cases and C3 in all cases. Four cases also showed staining for IgG. Electron microscopy showed mesangial and subendothelial electron dense deposits in all cases (in one case electron microscopy was not performed due to lack of glomeruli). Four cases also showed subepithelial deposits. In addition, features of cryoglobulinemic glomerulonephritis were noted in 4/5 cases of RA and all 3 cases of PSS. These biopsies showed intra-luminal immune microthrombi on light microscopy and intra-luminal

Table 3 Monoclonal and hematological characteristics

Patient	Diagnosis	SPEP	Serum IFE	UPEP	Urine IFE	Cryoglobulins	Bone marrow
1	RA	Negative	Negative	ND	ND	Negative	ND
2	RA	ND	ND	ND	ND	Not done	ND
3	RA	M spike in γ region	IgM Kappa	M spike in γ region	Kappa	Type II	5 % plasma cells
4	RA	M spike in γ region	IgM Kappa	Negative	Negative	Type II	5 % plasma cells
5	RA	Negative	Negative	Negative	Negative	Not done	Normal
6	PSS	Negative	Negative	Negative	Negative	Type II	ND
7	PSS	M spike in γ region	IgM Kappa	Negative	IgM	Type II	ND
8	PSS	Negative	Negative	ND	ND	Negative	ND
9	UCTD	Negative	Negative	ND	ND	Negative	Normal
10	UCTD/PBC	Negative	Negative	Negative	Negative	Negative	ND
11	PSC	Negative	Negative	Negative	Negative	Negative	ND
12	Grave's	Negative	Negative	ND	ND	Not done	ND

SPEP serum protein electrophoresis, *IFE* immunofixation electrophoresis, *UPEP* urine protein electrophoresis, *RA* rheumatoid arthritis, *PSS* primary Sjögren's syndrome, *UCTD* undifferentiated connective tissue disease, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *ND* not done

Table 4 Renal biopsy findings

Patient	Pattern of injury	% Globally sclerosed glomeruli	Interstitial fibrosis	Immunofluorescence microscopy (CW and mesangial)	Ultrastructural localization of deposits
1	MPGN	25	50	IgG (2+), C3 (2+), K (2+), L (2+)	SU, MES
2	MPGN	5	10	IgM (2+), C3 (trace), K (trace), L (trace)	SU, MES, SE
3	MPGN	15	20	IgM (3+), C3 (1+), K (3+), L (3+)	SU, MES
4	MPGN	10	5	IgM (3+), IgG (2+), C3 (1+), K (3+), L (2+)	SU, MES, SE
5	MPGN	0	20	IgM (2–3+), C3 (2+), K (trace), L (negative)	No glomeruli
6	MPGN	0	10	IgM (1+), C3 (3+), K (1+), L (1+)	SU, MES
7	MPGN	15	25	IgM (2+), C3 (3+), C1q (1+), K (1+), L (1+)	SU, MES
8	MPGN	10	20	IgM (2+), C3 (1+)	SU, MES
9	MPGN	20	30	IgM (1+), IgG (trace), C3 (3+), C1q (3+), K (1+), L (3+)	SU, SE, MES
10	MPGN	25	25	IgM (1+), C3 (3+), K (trace), L (trace)	SU, MES
11	MPGN	70	60	IgM (2+), IgG (1–2+), IgA (1–2+), C3 (3+), C1q (2+), K (1–2+), L (1–2+)	SU, MES
12	MPGN	10	10	IgM (1+), IgG (3+), C3 (3+), C1q (3+), K (3+), L (3+)	SU, SE, MES

MPGN membranoproliferative glomerulonephritis, *CW* capillary wall, *SE* subepithelial, *SU* subendothelial, *IN* intramembranous, *MES* mesangial

electron dense deposits on electron microscopy. Microtubular substructure was noted focally in two cases. Importantly, none of the cases with features of cryoglobulinemic glomerulonephritis showed monoclonal immunoglobulins on immunofluorescence microscopy. Representative renal biopsy findings from a case of RA (patient 2) and PSS (patient 6) are shown in Fig. 1.

Renal outcome and treatment

Findings on patients' renal outcomes, treatment and follow-up are presented in Table 5. The majority of patients (except for patients 5 and 11) were treated with corticosteroid therapy alone or in combination with other immunosuppressive therapies including mycophenolate mofetil (MMF), cyclophosphamide, or azathioprine. Rituximab was used in all patients with evidence of type II cryoglobulinemia. Patients 5 and 11 did not receive any therapy for treatment of their MPGN. Chronic myelogenous leukemia was detected in Patient 5 at the time of renal biopsy and the patient was entered in a clinical trial for the treatment of chronic myelogenous leukemia. The patient died 4 years after the renal biopsy due to complications of chronic myelogenous leukemia. Patient 11 developed end

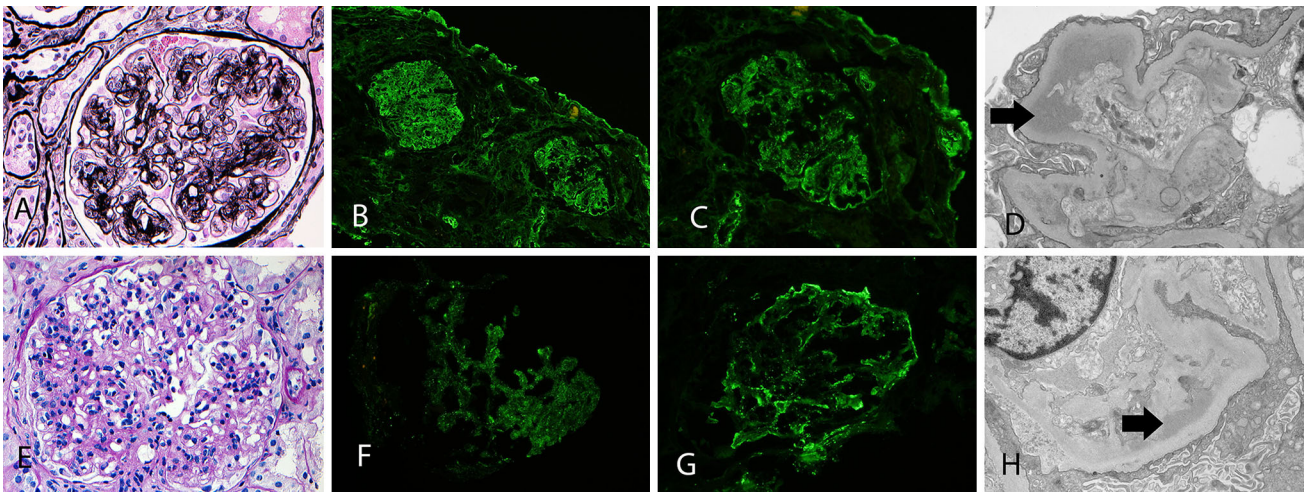

Fig. 1 Representative renal biopsy findings from a case of rheumatoid arthritis (*top panel*) and primary Sjögren's syndrome (*bottom panel*). *Top panel* **a** light microscopy showing a membranoproliferative pattern of injury (Jones-methenamine stain, ×40). **b**, **c** Immunofluorescence microscopy showing granular capillary wall staining for IgM (**b** ×20) and C3 (×40). **d** Electron microscopy showing subendothelial deposits (*black arrow*). *Bottom panel* **e** Light microscopy showing a membranoproliferative pattern of injury (periodic acid Schiff stain, ×40). **f**, **g** Immunofluorescence microscopy showing granular capillary wall staining for IgM (**b** ×40) and C3 (×40). **h** Electron microscopy showing subendothelial deposits (*black arrow*)

Table 5 Renal outcomes, treatment and follow-up

Patient	Diagnosis	F/U serum creatinine (mg/dl)	Dialysis at F/U	F/U proteinuria (mg/24 h)	Duration of F/U in months	Treatment for MPGN
1	RA	1.6	No	67	7	Prednisone
2	RA	1.3	No	NA	0.8	Prednisone
3	RA	0.7	No	15	10.9	Rituximab/PLEX/prednisone
4	RA	NA	NA	NA		Rituximab/cytoxan/dexamethasone
5	RA	4.6	Yes	On dialysis	50.5	None[b]
6	PSS	3.4	No	622	2.8	Rituximab/azathioprine/prednisone
7	PSS	1.2	No	67	38.9	Rituximab/prednisone
8	PSS	1.7	No	68	29.9	Cytoxan/prednisone
9	UCTD	5.1	Yes	On dialysis	2.5	MMF/prednisone
10	UCTD/PBC	1.8	No	1,730	56.4	Azathioprine/prednisone
11	PSC	7.5	Yes	On dialysis	5.8	None
12	Grave's	1.5	No	Not done yet[a]	0.9	MMF/prednisone

F/U follow-up, *MPGN* membranoproliferative glomerulonephritis, *RA* rheumatoid arthritis, *PSS* primary Sjögren's syndrome, *UCTD* undifferentiated connective tissue disease, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *MMF* mycophenolate mofetil

[a] Recent case with <1 month follow-up

[b] Patient with chronic myelogenous leukemia

stage liver disease due to PSC and received a liver transplant, and was listed as a candidate for renal transplant.

Follow-up data was available in eight of the 10 remaining patients. Mean duration of follow-up was 18.7 months, ranging from <1 month to over 56 months (median 7.1). Average follow-up creatinine in patients not on dialysis was 1.65 ± 0.78 mg/dl, which was improved from creatinine at time of renal biopsy (2.1 ± 1.0 mg/dl). Mean proteinuria improved from 1,975 ± 1,690 mg/24 h at the time of renal biopsy to 428 ± 677 mg/24 h at follow-up. Three patients were on dialysis during follow-up, two of whom (patients 5 and 11) were on dialysis at the time of biopsy. Patient 1 who was on dialysis at the time of renal biopsy received therapy with prednisone, with improvement in the renal function and discontinuation of dialysis. On the other hand, a patient with UCTD (patient 9) progressed to end-stage renal disease despite immunosuppressive therapy and required initiation of dialysis.

Discussion

Traditionally MPGN has been categorized into three groups (Type I, II and III) and secondary MPGN based on the electron microscopy findings of renal histology [18]. More recently, MPGN has been divided into immune-complex and complement-mediated MPGN, which puts emphasis on the pathogenesis of MPGN [1]. One of the well-known causes of immune-complex mediated MPGN is autoimmune disease and there are reports of cases in the literature assessing this association. The other etiologies of immune-complex mediated MPGN include chronic infections and monoclonal gammopathy.

Despite the well-established association of autoimmunity and MPGN, there are limited reports in the literature evaluating this relationship, with little information regarding the renal outcomes particularly with the current available therapy. To the best of our knowledge, our study is the first to systematically evaluate this association and investigate the clinical characteristics and renal outcomes in these patients. The most common autoimmune diseases in our cohort included RA and PSS. Patients in our cohort had a mean follow up of 18.7 months with an overall good renal prognosis as evidenced by improvement in renal function and proteinuria following therapy.

Kidney biopsy of 6 patients—3 with RA (patients 2, 3, 4) and all 3 patients with PSS (patients 6, 7, 8)—showed features of cryoglobulinemic glomerulonephritis. Laboratory evaluation confirmed type II cryoglobulins in four of these patients: two with RA and two with PSS (Table 1). IgM was the dominant immunoglobulin in 11 of the 12 cases. Furthermore, electron microscopy confirmed the subendothelial and mesangial electron dense deposits in all 11 cases and few subepithelial deposits in 4 of the 11 cases (in 1 case electron microscopy was not done due to lack of glomeruli). The findings suggest that IgM-dominant deposits in the setting of hepatitis-negative MPGN should raise the suspicion for an underlying autoimmune disease.

Hematological evaluation revealed monoclonal IgM in 3 patients; all three were positive for type II cryoglobulins (monoclonal IgM and polyclonal IgG). Cryoglobulins are common in patients with PSS and can be present in patients with rheumatoid arthritis [19]. Patients with PSS mainly develop type II cryoglobulins compared to other connective tissue diseases such as systemic lupus erythematosus that are associated with type III cryoglobulins. In a study of 30 patients with PSS, one-third of the patients had type II cryoglobulins in their serum [20]. It is not uncommon for patients with type II cryoglobulins to have a monoclonal gammopathy, in particular a IgM istoype [19]. However, it is important to note that although IgM was present in 11 of our 12 patients on immunofluorescence studies, there was staining for both kappa and lambda light chains indicating a polyclonal component of immune-deposits. Bone marrow biopsy done in two patients with RA and cryoglobulins showed evidence of underlying lymphoproliferative disorder with 5 % plasma cells. Both higher rates of cryoglobulins and lymphoproliferative disorders have been reported in patients with RA and our data likely reflect these associations, which may be due to increased autoreactivity of B-cells [21, 22].

Serological evaluation was negative for cryoglobulins or monoclonal proteins in patients with UCTD, PSC, and Graves' disease. Renal biopsy in these cases showed MPGN with immunofluorescence microscopy showing IgM in the two cases of UCTD, IgG and IgM in PSC, and predominantly IgG in Graves' disease. Electron microscopy showed subendothelial and mesangial deposits.

Overall, the renal prognosis in these 12 patients was good. Patients 1, 5 and 11 were on dialysis at the time of renal biopsy. Of these, patient 1 recovered renal function following therapy with prednisone, with subsequent discontinuation of dialysis, patient 5 died of complications of chronic myelogenous leukemia, and patient 11 still remained on dialysis at time of follow-up and was listed as a candidate for renal transplant. This patient also received a liver transplant due to end stage liver disease due to PSC. Therapies in our patients were variable but included prednisone in all regimens and rituximab therapy for all patients who had detectable serum cryoglobulins with overall good outcomes. Other treatments included MMF, cyclophosphamide or azathioprine or in combination (Table 5). One patient with UCTD (patient 10) progressed to end stage kidney disease and required dialysis.

In conclusion, this study describes the clinical features, kidney biopsy findings, laboratory evaluation, treatment and prognosis of MPGN associated with autoimmune diseases. MPGN associated with autoimmune diseases is uncommon, tends to develop in females who have had the disease for many years, and presents with hematuria and proteinuria and is often associated with low C4 levels. Kidney biopsy shows an MPGN with predominantly IgM and C3 on immunofluorescence studies, while cryoglobulins are likely to present in the setting of RA and PSS. Limited data on immunosuppressive therapy for the underlying autoimmune disease shows that it appears to have a favorable impact on renal function and proteinuria.

Conflict of interest Authors do not have any conflict of interest.

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