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Membranous glomerulonephritis is a manifestation of IgG4-related disease

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IgG4-related disease (IgG4-RD) is a systemic immune-mediated disease that typically manifests as fibro-inflammatory masses that can affect nearly any organ system. Renal involvement by IgG4-RD usually takes the form of IgG4-related tubulointerstitial nephritis, but cases of membranous glomerulonephritis (MGN) have also been described. Here we present a series of 9 patients (mean age at diagnosis 58 years) with MGN associated with IgG4-RD. All patients showed MGN on biopsy, presented with proteinuria (mean 8.3 g/day), and most had elevated serum creatinine (mean 2.2 mg/dl). Seven patients had known extrarenal involvement by IgG4-RD, with 5 patients having concurrent IgG4-related tubulointerstitial nephritis. Immunohistochemical analysis for the phospholipase A2 receptor, a marker of primary MGN, was negative in all 8 biopsies so examined. Six of 7 patients with available follow-up (mean 39 months) were treated with immunosuppressive agents; one untreated patient developed end-stage renal disease and underwent transplantation, without recurrence at 12 years after transplant. All 6 treated patients showed decreased proteinuria (mean 1.2 g/day), and most showed decreased serum creatinine (mean 1.4 mg/dl). Thus, MGN should be included in the spectrum of IgG4-RD and should be suspected in proteinuric IgG4-RD patients. Conversely, patients with MGN and an appropriate clinical history should be evaluated for IgG4-RD.

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IgG4-related disease (IgG4-RD) is a recently recognized systemic immune-mediated disease, typically characterized by mass-forming fibroinflammatory lesions. Autoimmune pancreatitis was the first recognized form of the disease, first described by Sarles *et al.*[1] in 1961. Since then, some form of IgG4-RD has been described in nearly every organ system.[2–6] IgG4-RD is well recognized in the form of tubulointerstitial nephritis (IgG4-related TIN), which may present either as a mass-like lesion or renal failure or both.[7,8] Glomerular disease has been reported in a few case reports and has been noted incidentally in some series of IgG4-related TIN.[9,10] The specific glomerular diseases reported have been membranous glomerulonephritis (MGN), IgA nephropathy/Henoch–Schönlein purpura, membranoproliferative glomerulonephritis, and a mesangioproliferative immune complex glomerulonephritis.[8–21] MGN is the most commonly described glomerular disease in IgG4-RD and is present in ~7% (4/58) of patients in two biopsy series of IgG4-related TIN.[8,11]

Here we present the first case series of MGN in the setting of IgG4-RD, in patients with or without IgG4-related TIN. In this series of nine patients with IgG4-related MGN, we describe the histopathologic, immunophenotypic, and ultrastructural features, radiographic and serologic findings, as well as clinical outcomes, including response to therapy. This series emphasizes the need to recognize 'IgG4-related MGN' as a form of secondary MGN in IgG4-RD, distinct from the more typically recognized cellular inflammatory IgG4-RD processes.

RESULTS

Clinical features of IgG4-related MGN

The average age of the 9 patients was 58 years (range 34–75 years); 6 (67%) of them were men. All patients presented with proteinuria, and all but one with nephrotic range proteinuria, with a mean value of 8.3 g/day (range 1.7–16). Six patients had known full nephrotic syndrome, and all seven patients with known values had low serum albumin (mean 2.0 g/dl; range 0.7–2.8). The serum creatinine (SCr) was elevated in 6 of 8 patients with available data, with a

mean creatinine of 2.2 mg/dl (range 0.8–6.6). In 7 of 9 patients, the primary indication for biopsy was heavy proteinuria or nephrotic syndrome, and the two other patients had acute renal failure along with proteinuria.

Of the 9 patients, 7 had known current or previous clinical, radiographic, and/or histologic evidence of other organ involvement by IgG4-RD, and one additional patient (no. 8) had possible lung involvement (see Table 1). The extrarenal organs involved were as follows: pancreas (4 patients), salivary gland (2), orbit or eye (2), lymph node (2), liver (sclerosing cholangitis, 1; possible liver inflammatory mass, 1), lung (1–2), skin (1), and possible thyroid involvement (1). One patient (no. 9) also had ulcerative colitis, an inflammatory condition not typically associated with IgG4-RD.[2] Two patients had typical features of IgG4-related TIN on biopsy and did not have definite involvement of other organs; one of these two patients had renal radiographic lesions and the other had possible lung involvement by reported radiographic studies. None of the patients had clinical features diagnostic of systemic lupus erythematosus or Sjögren syndrome, and they had no evidence of cancer, viral infectious processes such as hepatitis B or C, or other known causes of secondary MGN.

Renal radiographic data were available in seven of the eight patients. Radiographic abnormalities representing IgG4-related TIN were noted in only one patient, who had marked enlargement of both kidneys (>14 cm).

Laboratory features of IgG4-related MGN

Five patients had measurements available for serum IgG4; all of these patients had increased serum IgG4 (mean 484 mg/dl; range 183–1200). Serum IgG was elevated in only one of five patients who had been tested. Of the 6 patients with available data, 2 (33%) had peripheral blood eosinophilia. One of 6 patients had low serum C3 and C4 levels. Two patients had low-titer or transiently positive antinuclear antibody. No patients had a positive anti-neutrophil cytoplasmic antibody or positive tests for hepatitis B or C infection.

Histologic and immunophenotypic features of IgG4-related MGN

All biopsies showed a pattern of MGN with subepithelial deposits in a membranous pattern seen by immunofluorescence (IF), electron microscopy, or light microscopy, including immunoperoxidase staining for IgG4. The biopsies of two of nine patients showed a diffuse segmental membranous pattern, whereas the remaining biopsies showed a global membranous pattern. One biopsy (patient 7) with a segmental membranous pattern also showed segmental endocapillary hypercellularity. No biopsies showed crescents, fibrinoid necrosis, or thrombi. Two biopsies showed glomerular diseases in addition to MGN: one showed IgA nephropathy with mesangial IgA deposits distinct from the glomerular basement membrane (GBM) deposits of MGN, and the other showed concurrent nodular diabetic glomerulosclerosis.

Of the 9 biopsies, 5 (56%) showed IgG4-related TIN on the sample with MGN: 3 biopsies showed diffuse TIN and 2 showed focal TIN. The infiltrates were composed of many plasma cells along with eosinophils and mononuclear cells. Immunoperoxidase staining for IgG4 showed a moderate increase (11–30 cells/40× field) or marked increase (>30/40× field) in IgG4+ plasma cells in the most concentrated areas in 4 biopsies, with an inflammatory infiltrate remaining on the stained slides. Expansile interstitial fibrosis accompanying the TIN was present in two biopsies. Tubular atrophy and interstitial fibrosis ranged from 10 to 50% in biopsies with TIN (a representative biopsy with TIN is shown in Figure 1). In biopsies without TIN, interstitial fibrosis and tubular atrophy affected $<5\%$ of the cortex.

IF studies revealed segmental or global granular GBM staining for IgG and both κ and λ light chains, with the exception of one patient whose biopsy showed dim staining for IgG and λ light chain without κ light chain or other immunoreactants. All but two patients showed GBM staining for C3. Two patients showed dim staining for C1q. One biopsy (patient 7) showed granular mesangial staining for IgG, C3, and κ and λ in addition to the GBM staining. Granular mesangial staining for IgA was noted in one biopsy (patient 3); the GBM deposits did not stain for IgA in this case. Granular tubular basement membrane (TBM) deposits were noted by IF in three biopsies (focal deposits in one biopsy and diffuse in two). IF staining for IgG subclasses 1–4 were performed on four biopsies with available frozen tissue with glomeruli. All four showed that the immune complex deposits contained IgG4, and in three biopsies the deposits were shown to be IgG4 dominant. Other IgG subclasses were variably present (see Table 1).

All biopsies had electron microscopy performed. Subepithelial electron-dense deposits were identified in all biopsies, with a pattern of MGN stage I, II, or III. Three biopsies also showed mesangial deposits (patients 3, 7, and 8), including the biopsy with coexisting IgA nephropathy, which also showed paramesangial deposits. Two biopsies showed small subendothelial deposits segmentally. The electron-dense deposits did not show substructure. One biopsy (patient 9) showed a tubuloreticular inclusion within an endothelial cell. Podocytes showed diffuse ($>50\%$) foot process effacement.

Immunostaining for anti-phospholipase A2 receptor (PLA2R) antibodies was performed on the eight biopsies with available tissue. All eight biopsies had negative staining for anti-PLA2R. Concurrently stained control cases of primary MGN showed positive granular GBM staining for anti-PLA2R (see Figure 2 for representative glomerular features).

The clinical, histologic, and laboratory features are presented in Table 1.

Treatment and clinical follow-up of IgG4-related MGN

Follow-up clinical information was available in 7 of 9 patients, with a mean follow-up time of 39 months (range