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Case Report

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition: Report of Two Cases and Review of Literature

Abstract

Here we report two cases of proliferative glomerulonephritis with monoclonal IgG deposits, a form of renal involvement by monoclonal gammopathy that mimics immune complex glomerulonephritis. Case 1 presented with incidental proteinuria and a renal biopsy showed mesangioproliferative glomerulonephritis with monoclonal IgG kappa deposits on immunofluorescence examination. He remains stable after one year follow up. Case 2 presented with rapidly progressive renal failure and renal biopsy showed crescentic membranoproliferative glomerulonephritis with monoclonal IgG kappa deposits on immunofluorescence study. He showed no response to aggressive immunosuppressive medication and plasmapheresis and remained anuric. He underwent renal transplantation three months later but disease recurred in the allograft, which was diagnosed on a biopsy one and a half months post-transplant. Extensive work up for underlying paraprotein disease was negative in both patients. Our aim is to expand awareness and highlight the heterogeneity in the clinical presentation, histology and outcome of this rare entity.

Introduction

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a newly added entity in the spectrum of monoclonal gammopathy associated renal disease. PGNMID resembles immune complex glomerulonephritis (GN) on light (LM) and electron microscopy (EM). It commonly presents with a membranoproliferative pattern and rarely with crescent formation. EM shows granular, non-organized deposits, typically in a sub endothelial and mesangial distribution. The glomerular deposits on immunofluorescence (IF) are monoclonal, staining for a single light-chain isotype and a single heavy-chain subtype, most commonly IgG3. Thirty percent of patients have a detectable circulating monoclonal protein with the same heavy and light chain isotypes as the glomerular deposits; however, the presence of an underlying hematologic malignancy is rare. Patients typically present with nephritic or nephrotic syndrome. The prognosis of this disease is variable. We hereby present two cases of PGNMID with different clinical presentation, pathologic findings and outcome.

Case Report

Case 1

42 year old male patient presented with incidentally

detected proteinuria. On admission, blood pressure was 140/80 mm Hg. Systemic examination was unremarkable. Laboratory investigations showed hemoglobin 13.6 gm/dl, total leucocyte count 7500/cumm, platelets 2, 84,000/cumm, blood urea 16mg/dl, serum creatinine 1 mg/dl, serum albumin 3.7gm/dl, sodium/potassium 139/4.6mMol/l. Urine examination showed proteinuria of 1.42 gm/day. Serology for hepatitis B, C and HIV were negative. Serum complement levels were normal. ANA, dsDNA, ANCA, anti GBM antibodies and cryoglobulins were not detected. Ultrasonography showed normal sized isoechoic kidneys. A renal biopsy was done.

Biopsy showed renal cortical tissue with 12 glomeruli, 3 obsolescent (25%). Nonobsolescent glomeruli showed diffuse mild mesangial proliferation (Figure 1) and focal segmental endocapillary proliferation. No double contouring was seen. There were no crescents or tuft necrosis. Interstitium showed focal (1015%) fibrosis and tubular atrophy. Blood vessels were unremarkable.

Immunofluorescence microscopy showed intense (3+) glomerular mesangial granular staining for IgG,C3 and less intense (2+) staining for C1q. Kappa light chain was strongly positive in a similar distribution and lambda light chain was negative (Figure 1). IgA and IgM were also negative. These findings led to a diagnosis of PGNMID, IgG kappa. Electron microscopic studies were not done.

Patient underwent complete work up for dysproteinemia. Serum/Urine electrophoresis, free light chain assay and bone marrow examination were negative. He remains stable after one year follow up with normal creatinine but persisting proteinuria.

Case 2

35 year old male patient presented in April 2015 with rapid worsening of renal functions. He had been on treatment for membranoproliferative glomerulonephritis (MPGN) since December 2010, which was diagnosed on a renal biopsy at another hospital. Light chain studies were not done at that time. Patient was on immunosuppressants for 4 years, after which he discontinued the medications in 2014 and restarted 2 months prior to present admission. General examination showed pallor, pedal oedema, blood pressure 152/105 mm Hg. Systemic examination was unremarkable. Laboratory investigations revealed haemoglobin 6.2gm/dl, total leucocyte count 8600/cumm, platelets 180,000/cumm, Na/K138/4.1mMol/l, calcium 8.7mg/dl, serum total protein/albumin 3.8/2 gm/dl, blood urea 64mg/dl and serum creatinine 2.5mg/dl. Urine analysis showed nephritic nephrotic picture with protein creatinine ratio 8.1:1. Serology for hepatitis B, C and HIV were negative. Serum C3 was marginally reduced and C4 level was normal. ANA, dsDNA, ANCA, antiGBM antibodies and cryoglobulins were not detected. In view of rapid deterioration of renal functions, crescentic transformation of MPGN was considered and a second renal biopsy was performed.

Present renal biopsy showed corticomedullary renal cores with 5 glomeruli, none obsolescent. There were circumferential cellular crescents in 4/5(80%) glomeruli with focal segmental tuft necrosis (Figure 2). Glomerular tuft also showed accentuated lobulations, segmental neutrophilic infiltration, complex, capillary wall thickening with segmental double contouring and marked endothelial swelling with occlusion of capillary lumina. >50% cortex showed tubular atrophy and interstitial fibrosis. Blood vessels showed moderate medial hypertrophy and intimal fibrosis.

Immunofluorescence studies showed intense (3+) granular to semi linear staining for IgG and C3 and weaker staining for Clq. Deposits were identified exclusively in the glomeruli, global in distribution and were primarily sub endothelial and mesangial in location. Light chain studies showed kappa light chain restriction (Figure 2). A diagnosis of crescentic PGNMID, IgG kappa was made. Electron microscopic studies were not done.

The patient was maintained on hemodialysis due to severely worsening kidney function. In spite of plasmapheresis and aggressive immunosuppressive medications for three weeks, no improvement in his renal function was observed. Work up for paraprotein disease including serum and urine electrophoresis, serum free light chain assays and bone marrow biopsy were negative.

He continued to be anuric and 3 months later, he underwent renal transplantation from live unrelated donor. Pretransplant cross match was negative. The maintenance immunosuppres-

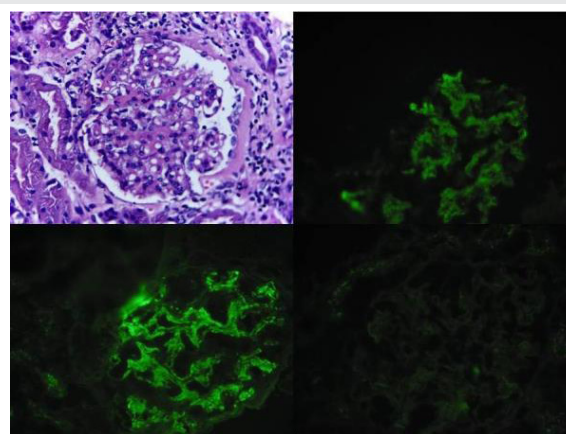


Figure 1: Light microscopy showing glomerulus with mild mesangial proliferation, Hematoxylin and eosin stain, 40x (upper left), positive immunofluorescence staining for IgG, 40x (upper right), kappa light chain, 40x (lower left) and negative immunofluorescence staining for lambda light chain, 40x (lower right).

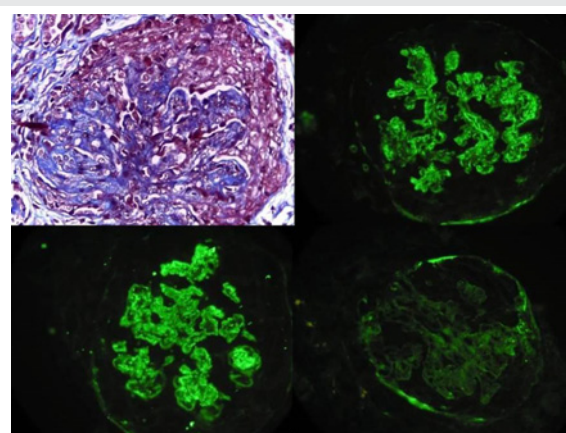


Figure 2: Light microscopy showing glomerulus with cellular crescent and underlying tuft necrosis, Masson Trichrome stain, 40x (upper left), positive immunofluorescence staining for IgG, 40x (upper right), kappa light chain, 40x (lower left) and negative immunofluorescence staining for lambda light chain, 40x (lower right).

sion regimen consisted of tacrolimus, MMF, and prednisolone. His immediate post-transplant period was uneventful. However, one and a half months later, a biopsy taken for allograft dysfunction with serum creatinine 1.6mg/dl showed features of active T cell mediated rejection, type1B and concurrent mild mesangioproliferative glomerulonephritis with monoclonal IgG kappa on IF consistent with recurrent disease. He responded to antirejection treatment and presently has stable renal functions.

Discussion

In 2004, Nasr et al., described a novel form of glomerular injury related to monoclonal immunoglobulin (IgG) deposition, the so called proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) [1]. Subsequently, in 2009, the same group reported the largest series of PGNMID [2] which included 37 patients, most of whom were white (81%), female (62%) and older than 50 yr (65%). In 30% of the patients, a monoclonal serum protein with the same heavy- and light-chain isotypes as the glomerular deposits (mostly IgG1 or IgG2) were detected, but only one patient had myeloma. Histologic

pattern was predominantly membranoproliferative (57%). During an average of 30.3 months of follow-up for 32 patients with available data, 38% had complete or partial recovery, 38% had persistent renal dysfunction, and 22% progressed to ESRD. Correlates of ESRD on univariate analysis were higher creatinine at biopsy, percentage of glomerulosclerosis, and degree of interstitial fibrosis but not immunomodulatory treatment or presence of a monoclonal spike. On multivariate analysis, higher percentage of glomerulosclerosis was the only independent predictor of ESRD. Only one patient lacking a monoclonal spike at presentation subsequently developed a monoclonal spike and no patient with a monoclonal spike at presentation subsequently developed a hematologic malignancy. They conclude that proliferative glomerulonephritis with monoclonal IgG deposits does not seem to be a precursor of myeloma in the vast majority of patients.

In a study by Sethi and colleagues [3], a serum M protein was detected in 28 of the 61 patients (46%) with proliferative glomerulonephritis after exclusion of systemic lupus erythematosus and viral hepatitis B and C. Monoclonal gammopathy of undetermined significance was the most common (57%) underlying monoclonal gammopathy in these patients.

The variability in histological pattern in PGNMID is well documented, the most common pattern being membranoproliferative. Crescents were present in 32.4% cases in Nasr et al., series [2]. The two cases presented here, demonstrate the heterogeneity of glomerular alterations and its correlation with clinical outcome.

There is no standardized protocol for treatment of PGNMID and controlled studies are lacking. The International Kidney and Monoclonal Gammopathy. Research Group recommends adapting the therapeutic approach to the severity of renal disease [4].

Membranoproliferative glomerulonephritis of any etiology tends to recur in the allograft. In PGNMID, recurrence tends to be early and is often more severe clinically than the native disease. A study by Nasr et al. [5], provides a detailed report of recurrent PGNMID in 4 patients with monotypic IgG3 on kidney biopsy who underwent renal transplant, all 4 patients had early recurrence despite negative results of serum studies for M protein at the time of transplant.

The pathogenesis of PGNMID remains elusive. Because up to two thirds of patients have no detectable M protein (by standard SPEP/UPEP/IFE) even after long follow-up, it is possible that this unique glomerulonephritis may arise in the course of normal immune responses. It is hypothesized that during an immune response (to extrinsic or intrinsic antigens), one or more clones of B cells proliferate and produce monoclonal IgG molecules (particularly IgG3) with ability to self-aggregability

and rapidly deposit in glomeruli through entrapment and/or interaction with negatively charged glomerular constituents. The small quantity of this monoclonal IgG may elude detection by conventional methods because of its high avidity for the glomeruli and rapid aggregability favored by its intrinsic physical properties and glomerular sieving itself [2].

Conclusion

PGNMID is a newly recognized entity caused by monoclonal deposition mostly of IgG. Clinical presentation and outcome are variable and correlate with LM findings. This is demonstrated clearly by the two cases presented here. Case 1 presented with subnephrotic proteinuria and normal renal functions. LM showed primarily mesangioproliferative pattern. Patient remains stable after one year follow up. On the contrary, case 2 presented with rapidly deteriorating renal functions with crescentic membranoproliferative pattern on LM. There was no response to treatment, patient underwent renal transplantation but developed early recurrence. Monoclonal IgG kappa glomerular deposits were present on IF in both cases. However, circulating monoclonal protein was not detected in either of these patients. There is no consensus regarding treatment and is mostly dictated by histology.

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