# A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits

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**The optimal treatment for the monoclonal gammopathies of renal significance is not known, but there is consensus among experts that treatment should be specific for the underlying clone. The majority of patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) do not have an identifiable clone, and prior studies have found poor renal outcomes for patients with PGNMID treated with a variety of regimens. Here we present a retrospective case series of 19 patients with PGNMID with a more uniform, clone-directed approach. A circulating paraprotein was detected in 37% of patients, and the overall clone detection rate was 32%. Treatment was directed at the underlying clone or, for patients without a detectable clone, empirically prescribed to target the hypothesized underlying clone. Of the 16 patients who underwent treatment, the overall renal response rate was 88%, and 38% of patients experienced complete renal response (proteinuria reduction to under 0.5 gm/24 hours) with initial treatment. All patients were End Stage Renal Disease-free at last follow-up (median 693 days after diagnosis), and treatment was well tolerated. Thus, a clone-directed approach may lead to novel, targeted treatment strategies that could significantly improve outcomes for patients with PGNMID.**

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Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID) is a renal-limited glomerular disease diagnosed by a kidney biopsy showing membranoproliferative or endocapillary proliferative glomerulonephritis on light microscopy, monoclonal Ig and complement (commonly C3) deposition on immunofluorescence microscopy, and nonorganized electron-dense deposits on electron microscopy.[1] PGNMID is caused by monoclonal gammopathy of renal significance (MGRS): a hematologic disorder associated with a paraprotein causing kidney injury that does not meet the criteria for malignancy (systemic multiple myeloma [plasma cell]) or lymphoma [B cell]).[2] Patients typically present with renal insufficiency, proteinuria, and microscopic hematuria.[1] The optimal treatment for most subtypes of MGRS is not known, but there is consensus among experts that treatment should be specific for the underlying clone.[3] However, the majority of patients with PGNMID do not have an identifiable clone.[4] Previous studies found poor renal outcomes for patients with PGNMID treated with a variety of regimens.[1] Here we report a retrospective case series of 19 patients with PGNMID who were managed at the University of Pennsylvania with a more uniform, clone-directed approach.

## RESULTS

Nineteen patients with PGNMID were identified, all of whom were comanaged by nephrologists and hematologists at the University of Pennsylvania. The clinical and histologic characteristics at the time of diagnosis are presented in Table 1. The mean age at diagnosis was 58 years (range, 25–83 years); 63% (12/19) of patients were male and 32% (6/19) were black. The median estimated glomerular filtration rate (eGFR) at diagnosis was 38 (interquartile range [IQR], 23–58 ml/min per 1.73 $m^2$, and the median proteinuria was 3.6 (IQR, 2.3–8.0 g/g or g/24 h). The median follow-up time after diagnosis was 693 days (IQR, 354–1355 days). Two patients (patients 9 and 10) had PGNMID diagnosed in the allograft after kidney transplantation. The presumed cause of end-stage renal disease (ESRD) in both patients had been hypertensive nephrosclerosis, and neither patient had undergone a native kidney biopsy. No patient was on dialysis at the time of diagnosis.

**Table 1 | Baseline characteristics of patients with PGNMID the time of diagnosis**

| Patient | Age | Sex | Race | eGFR | SCr (mg/dl) | Proteinuria[a] | % GS | Light microscopy pattern | IFTA | Kidney Bx IF | Circulating paraprotein (method of detection) | Clone (% bone marrow involvement) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group 1: clone detected, clone-directed therapy | | | | | | | | | | | | |
| 1 | 26 | M | W | 30 | 2.8 | 6.70 | 42 | MPGN | Mild | IgGλ | IgGλ (sIFE, sFLC) | Lympho-plasmacytic (20% B-cell aggregates, 5% plasma cells) |
| 2 | 50 | M | W | 58 | 1.4 | 3.44 | 2 | MPGN | Mild | IgGλ | None | B cell[b] |
| 3 | 51 | F | B | 58 | 1.2 | 2.20 | 0 | Mesangioproliferative and ECPGN | Mild | IgGκ | IgGκ (sIFE) | B cell (>80%) |
| 4 | 53 | M | W | 45 | 1.7 | 3.00 | 0 | MPGN | Moderate | IgG3κ | IgGκ (SPEP, sFLC) | Plasma cell (5%–10%) |
| Group 2: Clone-detected, nondirected therapy | | | | | | | | | | | | |
| 5 | 72 | M | W | 39 | 1.7 | 5.90 | 50 | MGPN | Severe | IgG3κ | None | Plasma cell (<5%) |
| 6 | 57 | M | W | 18 | 3.6 | 4.30 | 83 | MPGN | Severe | IgGκ | IgGκ (SPEP, sFLC, UPEP) | Plasma cell (5%) |
| Group 3: No clone detected, empirical therapy | | | | | | | | | | | | |
| 7 | 67 | F | W | 23 | 2.1 | 3.56 | 33 | MGPN and ECPGN | Mild | IgG1λ | None | None |
| 8 | 65 | M | W | 34 | 2.0 | 9.52 | 13 | MPGN | Moderate | IgMκ | IgGκ, IgG λ (SPEP) | None |
| 9[c] | 57 | F | B | 55 | 1.3 | 1.94 | 0 | MGPN and ECPGN | Mild | IgG1κ | None | None |
| 10[c] | 38 | F | W | 35 | 1.8 | 0.56 | 0 | MPGN | Mild | IgG3κ | None | None |
| 11 | 34 | M | H | 51 | 1.7 | 15.00 | 39 | MPGN | Moderate | IgGλ | None | None |
| 12 | 43 | M | B | 66 | 1.5 | 3.90 | 14 | MPGN | Severe | IgGλ | None | None |
| 13 | 25 | F | W | 35 | 2.0 | 2.70 | 20 | MPGN, MN | Moderate | IgG1κ | None | None |
| 14 | 36 | M | B | 68 | 1.5 | 24.00 | 0 | MPGN, MN | Mild | IgGκ | None | None |
| 15 | 69 | M | W | 38 | 1.8 | 3.43 | 86 | MGPN | Mild | IgGλ | IgGλ (sIFE) | None |
| 16 | 75 | F | W | 14 | 3.1 | 1.47 | 56 | MGPN and ECPGN | Severe | IgGκ | None | None |
| Group 4: not treated | | | | | | | | | | | | |
| 17 | 78 | M | B | 15 | 4.0 | 8.50 | 43 | MPGN | Severe | IgMκ | None | None |
| 18 | 59 | M | B | 58 | 1.5 | 8.00 | 77 | MGPN and ECPGN | Moderate | IgG1λ | None | None |
| 19 | 83 | F | W | 14 | 2.9 | 2.28 | 0 | MPGN | Severe | IgG3λ | IgGλ (sIFE) | None |

B, black; Bx, biopsy; eGFR, estimated glomerular filtration rate (expressed as ml/min per 1.73 $m^2$ calculated by the Chronic Kidney Disease Epidemiology Collaboration equation); ECPGN, endocapillary proliferative glomerulonephritis; F, female; GS, glomerulosclerosis; H, Hispanic; IFTA, interstitial fibrosis/tubular atrophy; M, male; MN, membranous; MPGN, membranoproliferative glomerulonephritis; SCr, serum creatinine; sFLC, serum κ/λ free light chain assay; sIFE, serum immunofixation; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; W, white.
[a]Proteinuria expressed as g/g of creatinine or g/24 h.
[b]Bone marrow biopsy results for patient 2 not available (performed before electronic medical record).
[c]Patients 9 and 10 were diagnosed with PGNMID in the allograft after kidney transplant.

Kidney biopsy characteristics are listed in Table 1. Light microscopy showed endocapillary, mesangioproliferative, and/or membranoproliferative glomerulonephritis in all cases. Immunofluorescence microscopy showed dominance of IgGκ staining in 9 cases, IgGλ in 8 cases, and IgMκ in 2 cases. γ Heavy chain subclass staining was performed in 8 of 17 cases and revealed IgG1 in 4 cases and IgG3 in 4 cases. The median percentage of globally sclerotic glomeruli was 20% (IQR, 0–50%). Interstitial fibrosis was mild in 8 cases, moderate in 5 cases, and severe in 6 cases.

Details of the hematologic evaluation are shown in Table 1. A circulating paraprotein was detected in the serum or urine of 7 patients (37%), and of these patients, there was concordance between the circulating and kidney biopsy monoclonal Ig in 6 of 7 cases. Seventeen of 19 patients underwent bone marrow biopsy. A detectable clone was found in 6 patients (32% overall, 35% of patients who underwent clone work up). The underlying clone was a plasma cell in 3 cases, a B cell in 2 cases, and a lymphoplasmacytic clone in 1 case (Table 1). Four of the 6 patients with a detectable clone also had a detectable circulating paraprotein.

Sixteen patients underwent treatment. Three patients were not treated at their physician's discretion due to severe renal insufficiency, moderate-to-severe scarring observed on kidney biopsy, and/or additional comorbid conditions (Group 4). Details regarding therapy and response to initial treatment regimens are presented in Table 2 and Supplementary Table S1. Thirteen of 17 (76%) treated patients had a response to their initial therapy, 6 (35%) of whom experienced a complete response (CR). All 4 patients in Group 1 experienced a renal response, with 3 patients achieving a CR. One patient in Group 2 experienced a PR, whereas the second patient died 2.5 months after starting treatment of complications of recurrent hemothorax that were not attributed to his kidney disease or its treatment. Eight of 10 patients (80%) in Group 3 experienced renal response with initial therapy, 3 (30%) of whom had a CR. In responders, the median time to a PR ($N = 13$) was 5.2 months (IQR, 2.5–10.1 months), and the median time to a CR ($N = 6$) was 12.5 months (IQR, 6.5–21.2 months). Complete renal response was not contingent on resolution of paraproteinemia, as was noted in patients 1 and 4, both of whom experienced a CR but still had a small but detectable monoclonal spike on serum protein electrophoresis. No patient who underwent treatment developed ESRD during follow-up. All patients who did not undergo treatment (Group 4) progressed to ESRD during the follow-up period.