Proliferative glomerulonephritis with monoclonal immunoglobulin G deposits is associated with high rate of early recurrence in the allograft

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The characteristics of allograft proliferative glomerulonephritis with monoclonal immunoglobulin G deposits (PGNMID) are not well defined. To better characterize this disease we retrospectively identified 26 patients with allograft PGNMID, including 16 followed with early protocol biopsies. PGNMID was found to be a recurrent disease in most (89%) patients. A diagnostic biopsy was done for proteinuria and/or increased creatinine in most patients. Median time from transplant to diagnostic biopsy was 5.5 months, with detection within three to four months post-transplant in 86% of patients. Mesangial proliferative glomerulonephritis was the most common pattern on the diagnostic biopsy with 89% of cases showing immunoglobulin G3 subtype restriction. A detectable serum paraprotein was present in 20% of patients. During a mean follow up of 87 months from implantation, 11 of 25 patients lost their allograft largely due to PGNMID within a mean of 36 months from diagnosis. Median graft survival was 92 months. Independent predictors of graft loss were a higher degree of peak proteinuria and longer time from implantation to diagnosis. Sixteen patients were treated with immunosuppressive therapy which resulted in over 50% reduction in proteinuria in 60%, and improvement of glomerular pathology in nine of 13 patients. However, 44% of responders subsequently relapsed. Thus, PGNMID has a high recurrence rate in renal allografts occurring early with detection enhanced by protocol biopsies. Graft outcome is guarded as nearly half of patients lose their graft within three years from diagnosis. Hence, there is a need for better treatment strategies for this disease.

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Proliferative glomerulonephritis (PGN) with monoclonal IgG deposits (PGNMID) is a recently described entity resulting from deposition of an intact monoclonal IgG in glomeruli.[1] PGNMID is currently classified under monoclonal gammopathy of renal significance (MGRS) lesions characterized by nonorganized deposits.[2,3] Clinicopathologic and outcome characteristics of PGNMID in the native kidney were analyzed in relatively large retrospective studies[4,5] and numerous case reports. PGNMID in the native kidney has a biopsy incidence of 0.17% to 3.7%, is more common in white female adults, and manifests with nephrotic-range proteinuria, hematuria, and renal insufficiency.[4–6] Despite the monotypic nature of glomerular deposits, only 20% to 30% of patients have detectable serum monoclonal Ig, and hematologic malignancy is rare.[4,5] Histologically, most cases exhibit membranoproliferative or endocapillary PGN. On immunofluorescence, deposits are seen exclusively in the glomeruli and show light chain isotype and IgG isotype and subclass restriction, most commonly IgG3 kappa.[4] On electron microscopy, most glomerular deposits are granular and without substructure and are localized to the mesangium, the subendothelial zone, and/or the subepithelial zone. Current immunosuppressive therapy has had limited success, except for the small subset of PGNMID cases associated with CD20-expressing clones that tend to respond to rituximab.[7,8] Prognosis of PGNMID is variable, with nearly one-fourth of patients progressing to end-stage renal disease (ESRD) within 2.5 years, despite immunosuppressive therapy.[4] Eventually, most patients with PGNMID will probably develop ESRD and be faced with the decision whether to pursue kidney transplantation.

In 2011, we reported the first cases of recurrent PGNMID in the allograft.[9] The cohort included 4 patients who presented with renal insufficiency, proteinuria, and hematuria

early posttransplantation, and disease recurrence was documented on transplant (Tx) biopsy (TxBx) after a mean of 3.8 months post-Tx. Monotypic deposits in the glomeruli of the allograft and the native kidney were identical with respect to IgG light and heavy chain isotypes (IgGκ in 3 and IgGλ in 1).[9] Subsequently, 11 more case reports, or small series specifically addressing recurrent and/or *de novo* PGNMID in the renal allograft, have been reported, of which the largest with adequate clinical data included 4 patients.[10–20] The current report enlarges our experience with PGNMID in the renal allograft to 26 cases. Our aim was to define the rate of recurrence, natural history, histologic evolution, presenting features, graft outcomes, and risk factors for graft loss.

RESULTS

Patient and transplant characteristics

Patient and Tx characteristics are summarized in Table 1. Mean age at Tx was 52 years of age (range 26–76 years of age), and 50% were male. Twenty-three patients (88%) were white, 2 were African Americans, and 1 was Asian. The donor kidney source was a living donor in 58% of patients and a deceased donor in 42%. Most patients (78%) received thymoglobulin or basiliximab induction. Seventy-seven percent of patients were receiving a triple-maintenance immunosuppression regimen, and the remaining patients (23%) were receiving steroid-free regimens. The mean number of human leukocyte antigens (HLA mismatched antigens) was 2.6 (range 0–6). One patient had a positive crossmatch Tx, and 1 had an ABO-incompatible Tx. Two patients received preconditioning with rituximab. The nature of allograft PGNMID was definite recurrence in 65% of patients (with a recurrence rate of 89% [see Methods]), probable recurrence in 19%, *de novo* in 4%, and indeterminate in the remaining 12% (see Methods).

Hematologic and serologic characteristics are summarized in Table 1. A monoclonal protein was detected on serum protein electrophoresis with immunofixation (SPEP-SIF) pre- and/or post-Tx in 5 of 25 patients (20%) who were tested, including IgGλ in 3 and IgGκ in 2. In 1 patient with IgG3κ glomerular deposition, a serum monoclonal IgGκ was first detected 7 months post-diagnostic TxBx (85 months post-diagnostic native kidney biopsy). Serum-free light chain ratio tested in 20 patients was normal in 19 (95%) and elevated in 1 patients (5%) who had an IgGκ monoclonal protein on SPEP-SIF assay. Urine protein electrophoresis with immunofixation was positive in 3 of 20 tested patients (15%), all of whom had positive SPEP-SIF results. Bone marrow biopsies performed in 16 patients, including the 5 with positive SPEP-SIF results, were negative for plasma cell dyscrasia in 13, showed 5% κ-restricted plasmacytosis in 1 (a patient who had IgGκ monoclonal protein on SPEP-SIF), and showed 10% involvement by λ-restricted chronic lymphocytic leukemia (CLL) in 1 (a patient who had IgGλ on SPEP-SIF). One patient with IgG3κ PGNMID had a negative bone marrow biopsy result post-Tx but in whom multiple myeloma was diagnosed 12 years pre-Tx (with 30% λ-restricted plasmacytosis) and had a complete hematologic response pre-Tx following stem cell transplantation. Hypocomplementemia was present in 35% of patients (Table 1), including 1 who had confirmed alternative and terminal pathway activation (low total complement, very low C3, normal C4, very low C3 and C5 functional assay results, and elevated soluble C5b-9). No patient had positive test results for hepatitis B or C virus or serum cryoglobulin; and only 5% (1 of 19) had a positive antinuclear antibody. Four patients (15%) had a history of autoimmune disease pre-Tx (rheumatoid arthritis in 1, ankylosing spondylitis in 1, Graves' disease in 1, and primary biliary cirrhosis status post-liver Tx in 1), which were clinically and serologically

Table 1 | Patient and transplant characteristics ($N = 26$ patients)

Parameter	Value
Mean age, yrs, at Tx (range)	52 (26–76)
Number of males/total (%)	13/26 (50%)
Number of whites/total (%)	23/26 (88%)
Number of pre-emptive/total (%)	6/26 (23%)
Number of kidney sources/total (%)	
Living, related	8/26 (31%)
Living, unrelated	7/26 (27%)
Deceased	11/26 (42%)
Mean number of HLA-mismatched antigens (range)[a]	2.6 (0–6)
Number with positive DSA (pre-formed or *de novo*)/total (%)	0/15 (0%)
Number undergoing induction immunosuppressive therapy/total (%)[a]	
Thymoglobulin	9/17 (53%)
Basiliximab	5/17 (29%)
Thymoglobulin and basiliximab	1/17 (6%)
Alemtuzumab	1/17 (6%)
None	1/17 (6%)
Number receiving maintenance immunosuppressive regimens/total (%)	
Prednisone/mycophenolate mofetil/tacrolimus	13/26 (50%)
Mycophenolate mofetil/tacrolimus	5/26 (19%)
Prednisone/mycophenolic acid/tacrolimus	4/26 (15%)
Prednisone/mycophenolate mofetil/cyclosporine	2/26 (8%)
Mycophenolate mofetil/cyclosporine	1/26 (4%)
Prednisone/mycophenolate mofetil/sirolimus	1/26 (4%)
Number of detectable paraproteins on SPEP-SIF/total (%)	5/25 (20%)
Number of detectable paraproteins on UPEP/UIF/total (%)	2/17 (12%)
Number with abnormal serum free light chain ratios/total (%)	1/20 (5%)
Number with hematologic malignancy/total (%)	2/26 (8%)
Number with hypocomplementemia/total (%)	6/17 (35%)
Low C3 with normal C4	4/6 (67%)
Low C3 and C4	2/6 (33%)
Number with positive serum cryoglobulin/total (%)	0/17 (0%)
Number with positive ANA/total (%)	1/21 (5%)
Number with positive hepatitis C antibody/total (%)	0/24 (0%)
Number with positive hepatitis B surface antigen/total (%)	0/25 (0%)

ANA, anti-nuclear antibody; DSA, donor-specific antibodies; HLA, human leukocyte antigen; SPEP-SIF, serum protein electrophoresis with immunofixation; UPEP/UIF, urine protein electrophoresis with immunofixation.
[a]Data were not available for 9 patients who underwent transplantations elsewhere.