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Recurrent and Denovo PGNMIDD Post Renal Transplant – A Case Series

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Abstract: We present two cases diagnosed with PGNMID post-transplant. The first case is that of a 42 year old lady who was diagnosed as chronic glomerulonephritis with MPGN pattern of injury, the aetiology of which wasn't identified despite two native kidney biopsies. Her immunofluorescence in both biopsies was incomplete. She progressed to end stage renal disease and underwent a cadaver transplant. Four months post transplant she developed allograft dysfunction and was diagnosed with PGNMID after two allograft biopsies. Despite chemotherapy her renal functions worsened and was reinitiated on dialysis. The second case is that of a 59 year old lady who was transplanted in 2001 and was stable until 2020. She developed allograft dysfunction with proteinuria and her allograft biopsy showed mesangial and endocapillary proliferation with kappa light chain restriction clinching the diagnosis of PGNMID which was denovo post-transplant eventually resulting in graft loss.

Keywords: Recurrence, Denovo, Myeloma, MGRS.

INTRODUCTION

Kidney disorders caused by a monoclonal protein (M-protein) secreted by a small plasma cell clone or other B-cell clones in patients who do not meet the diagnostic criteria for multiple myeloma or other B-cell malignancies come under the umbrella term of Monoclonal gammopathy of renal significance (MGRS).(Amaador, K. *et al*., 2019)

MGRS can present as glomerular diseases, tubulopathies, and vascular involvement with varying clinical presentations like proteinuria, hematuria, hypertension, renal dysfunction, nephritic syndrome. MGRS is divided into renal lesions caused by organised and unorganised deposits.(Bridoux, F. *et al*., 2015) Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a recently recognized entity caused by monoclonal deposition of IgG. The monotypic immunoglobulin deposits seen on immunofluorescence (IF) clinches the diagnosis.(Fatima, R. *et al*., 2014)

CASE SUMMARY

Case 1

A 42 year old lady in 2012, presented with proteinuria and lower limb swelling with normal renal functions. She underwent her first kidney biopsy which showed segmental and global endocapillary proliferation in 13 glomeruli with immunofluorescence showing IgG and c3 deposits. She was treated with steroids for 6 months and did not show any response. She was subsequently treated with azathioprine and then mycophenolate mofetil to which she did not show any response either and started developing worsening renal functions. She underwent a second renal biopsy which showed 4 out of 13 glomeruli were sclerosed. Glomerular basement membrane showed variable thickening with diffuse proliferation and lobular accentuation. Mesangial, endocapillary and extracapillary proliferation with karyorrhectic debris was also noticed. 5 glomeruli showed presence of cellular / fibrocellular crescents. Immunofluorescence in this biopsy too showed IgG and c3 deposits. She was treated with intravenous cyclophosphamide for 6 months and did not show any response, her renal functions continued to worsen and reached 5mg/dl. She was subsequently initiated on hemodialysis a year later in 2016 due to uremic symptoms. Her ANA was negative and hepatitis C serology was negative. Myeloma work up and cryoglobulins were not tested. After 3 years on hemodialysis she underwent a deceased donor renal transplant in 2020 January, and was discharged on tacrolimus, mycophenolate mofetil and prednisolone with normal renal functions. Four months post transplant her creatinine increased to 2.8 mg/dl with urine protein estimation of 7.1 grams in 24 hours. An allograft biopsy was done which showed diffuse mesangial proliferative glomerulonephritis. No IF core was taken. She was treated with 2500mg of Methylprednisolone and was continued on triple immunosuppression. Her renal functions normalized and proteinuria also reduced to sub nephrotic range only to worsen again to 3.5 mg/dl and proteinuria increased to 4 grams in the next 4 months. A repeat allograft biopsy showed diffuse mesangial proliferation with diffuse membranous glomerulonephritis 'pattern' as shown in **Figure 1**. Immunoflorescence showed lambda light chain restriction as shown in **Figure 2**. Electron microscopy showed subepithelial electron dense

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deposits, no substructure was identified, diffuse effacement of visceral epithelial cell foot processes was noticed and there was no evidence of GBM reduplication. Complement C3 and C4 were normal.

Myeloma work up in the form of serum electrophoresis, serum immunofixation and free light chain assay was negative and bone marrow biopsy did not show any increase in the plasma cells. She was subsequently treated with rituximab, bortezomib and dexamethasone under haematology but did not respond to therapy and was reinitiated on hemodialysis after 18 months.

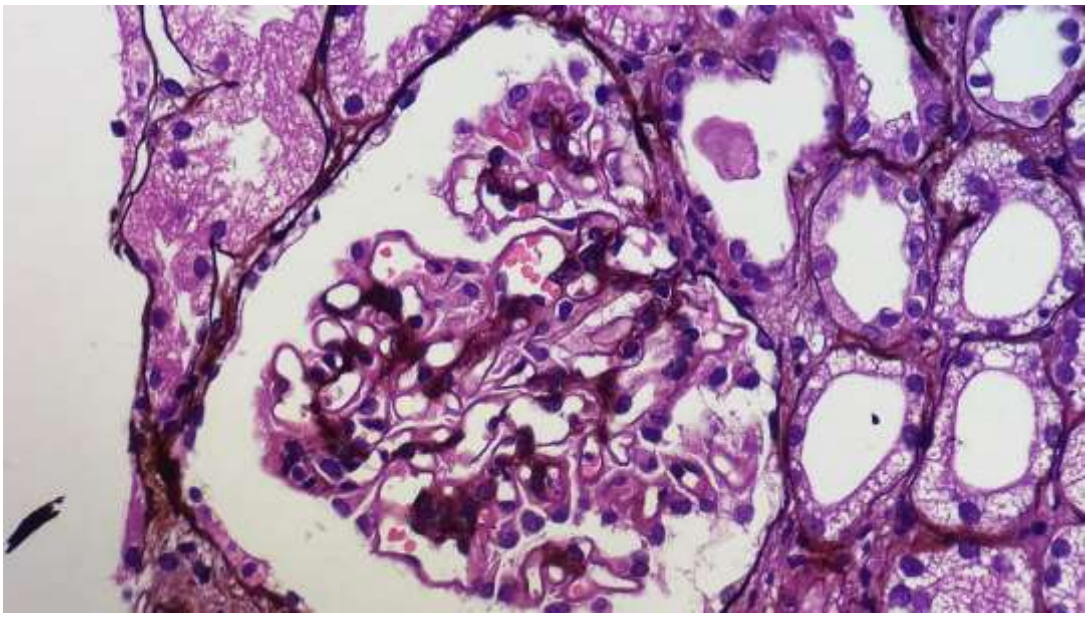

Figure 1: Diffuse mesangial proliferative with Diffuse Membranous glomerulonephritis pattern.

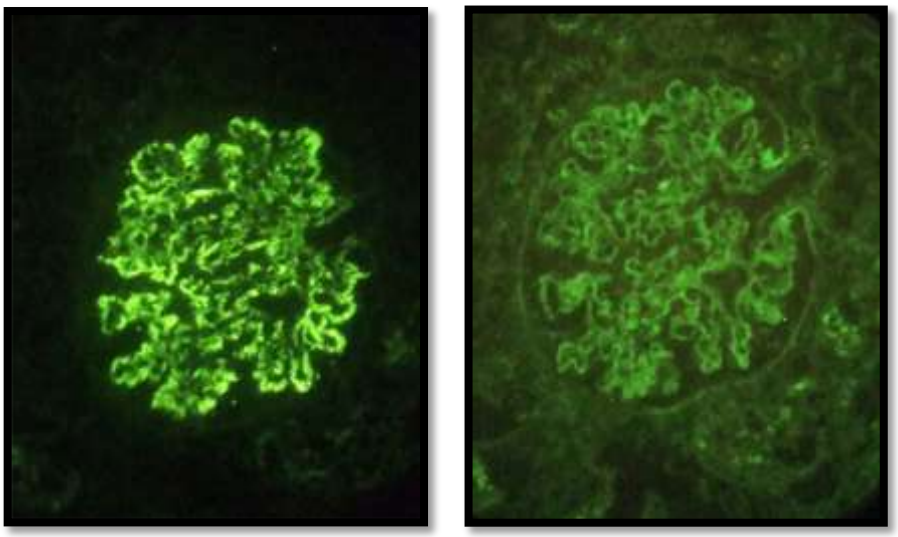

Figure 2: Lamda light chain restriction on Immunoflorescence. Lamda IF is depicted on the left and Kappa IF on the right

Case 2

A 59 year old lady, with a suspected chronic interstitial disease as her native kidney disease, who underwent a living related donor renal transplant in 2001 and was doing well until 2019 when her creatinine was 0.75mg/dl. She came to us in 2020 with a creatinine of 2.5mg/dl, urine microscopy showing RBCs and 24 urinary protein of 2600mg/day. She underwent a renal biopsy which showed 20 glomeruli, one globally sclerosed, 12 showed segmental to global endocapillary proliferation and remaining show mild increased cellularity. 3 showed presence of partial cellular to fibrocellular crescents. Immunofluorescence done showed kappa light chain restriction with subtyping demonstrating

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IgG3κ. The light microscopy is depicted in **Figure 3**. Myeloma work up in the form of serum electrophoresis, serum immunofixation and free light chain assay was negative and bone marrow biopsy did not show any increase in the plasma cells. She was started on chemotherapy, however her renal functions did not improve and progressed to end stage renal disease in 14 months.

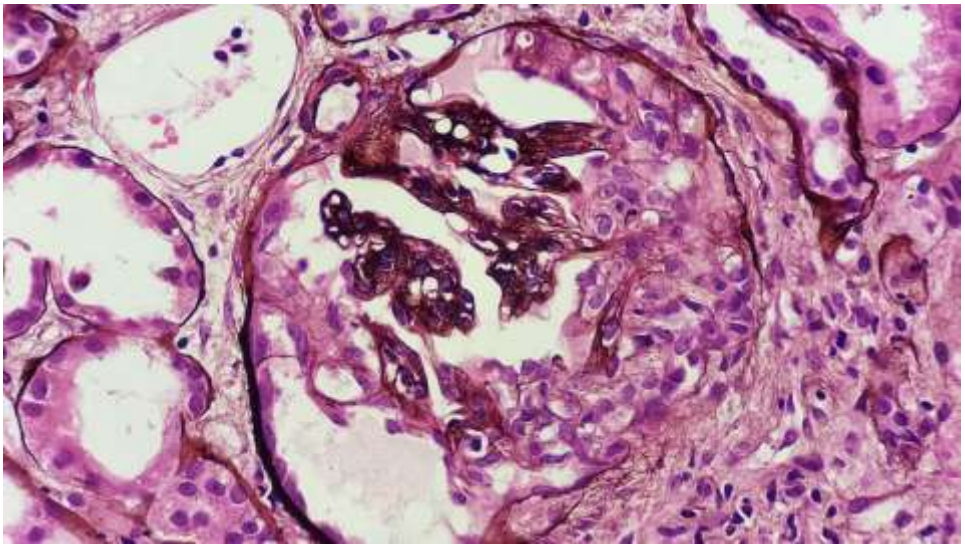

Figure 3: Mesangial, endocapillary and extracapillary proliferation with karyorrhectic debris and cellular crescent

DISCUSSION

The diagnosis of MGRS primarily requires the presence of : Renal biopsy for identification of the pattern of renal parenchymal damage and demonstration of monoclonal protein, if present. Identification of the corresponding monoclonal protein in the serum and/or urine. Demonstration of the underlying clonal population of cells secreting the monoclonal protein, and characterization of extrarenal manifestations of the clonal disorder.(Amaador, K. *et al*., 2019)

Multiple myeloma is the most frequent monoclonal gammopathy to involve the kidney and may present with glomerular and tubular immunoglobulin deposition. Other glomerular diseases associated with monoclonal gammopathies include monoclonal immunoglobulin deposition disease (light chain deposition disease, and heavy chain deposition disease), Type 1 cryoglobulinemic glomerulonephritis (GN), immunotactoid GN, light and heavy chain amyloidosis, light chain proximal tubulopathy, and rarely fibrillary GN.(Leung, N. *et al*., 2012) They are all distinguished by the monoclonal immunoglobulin (or component) deposits in immunofluorescence (IF) study. Ultrastructurally, electron-dense deposits (EDD) can be categorized into two distinct patterns: One with organized EDD formation, as seen in immunotactoid glomerulopathy, fibrillary GN, amyloidosis, and the other particularly with nonorganized powdery EDD, often seen in light/heavy-chain deposition disease. In this group of monoclonal gammopathy of renal significance (MGRS), a unique category of renal disorder characterized by proliferative GN and associated with monoclonal immune deposits of IgG (PGNMID) has been added.(Nasr, S.H. *et al*., 2009)

Proliferative glomerulonephritis with monoclonal Immunoglobulin G (IgG) deposits (PGNMID) presents with intact monoclonal IgG (single light-chain isotype and single γ heavy chain subtype) deposition. It is characterized by intact monoclonal IgG deposition, the most common type was IgG3κ (47%- 53.1%), followed by IgG1κ (21.9%- 26%), IgG3λ (5%- 12.5%), IgG1λ (6.3%-16%), and IgG4κ(0%- 5%).6 In our case subtyping wasn't done in the first case, but showed lambda light chain restriction and the second case showed IgG3κ on subtyping.

Monoclonal IgG can be produced in response to either intrinsic or extrinsic antigens. These monoclonal IgG can self aggregate as a result of their intrinsic physical properties, high avidity for glomeruli and could rapidly deposit in glomeruli by interacting with the negatively charged glomerular constituents. This monoclonal IgG was so little in serum/urine that it cannot be detected by serum electrophoresis or immunofixation.(Nasr, S.H. *et al*., 2009)

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Guiard, E. *et al*., reported that both of membranous nephropathy and MPGN were the two common pathologic patterns. Our first case showed a membranous nephropathy pattern. Other studies reported cases of MN correlated with IgG1, and MPGN correlated with IgG3.While dominant C3 staining with the intensity of C3 staining at least two orders of magnitude greater than any other immunoreactant is seen in C3GN, our cases showed IgG to be more dominant ruling out the possibility of C3GN. The electron dense deposits are very similar to polyclonal immune-complex mediated glomerulonephritis which can be deposited in the subendothelial, mesangial, occasionally subepithelial and/or intramembranous areas. These deposits mostly showed nonorganized granular pattern, but organized structures, including fibrils (15-21 nm in diameter) and lattice-like structures (15 nm) were also reported in 32.4% of PGNMID patients, but very focally.(Guiard, E. *et al*., 2011)

Seventy percent of the PGNMID patients failed to identify monoclonal immuoglobulins or MIg-producing cells in the serum, urine and bone marrow. Rare patients (3%) developed monoclonal spike during follow up.5,6 The prognosis of PGNMID is poor, during a mean follow up of 30.3 months, 21.9% patients progressed to ESRD, and 37.5% had persistent renal dysfunction. Only 3.7% M-spike negative patient at presentation developed M-spike during follow up, and none of patients with M-spike at presentation developed multiple myeloma or lymphoma. Higher serum creatinine level, higher percentage of global glomerulosclerosis, greater degree of tubular atrophy, interstitial fibrosis and arteriosclerosis were associated with ESRD, which is very similar to other kidney diseases.(Rajkumar, S.V. *et al*., 2010)

In case 1 we see that the patient's native kidney disease was not diagnosed as immunofluorescence wasn't done in the first native kidney biopsy and the second biopsy IF for light chains wasn't done and hence the diagnosis of PGMIDD was missed and recurred as early as 4 months after transplant.PGNMID may recur early after renal transplantation (5–19 months).(Nasr, S.H. *et al*., 2011)The clinical outcomes are variable, with approximately 25% of patients developing ESRD refractory to immunosuppressive treatment within 2.5 years.8 A recent study of protocol biopsies revealed that PGNMID had a high recurrence rate (89%) early after transplantation. In most studies, approximately half of the patients lost graft function within 3 years after diagnosis.(Albawardi, A. *et al*., 2011)

De novo proliferative GN with monoclonal IgG deposits (PGNMID) is an extremely rare disease. While the recurrent PGNMID presents early (within the initial two years after renal transplantation), *de novo* PGNMID appears several years later like in our case. A handful of cases of *de novo* PGNMID have been reported in the literature with review of literature showing 7 cases to be reported.10 After a 30 month follow up of these patients, 38% had complete or partial recovery, 22% developed ESRF, and (38%) of these patients experienced persistent allograft dysfunction. Only 10% of patients expressed low complement level.(Abbas, F. *et al*., 2017)

Treatment of PGNMIDD depends on the underlying clone detected if any. A B cell clone would require treatment with rituximab while a plasma cell clone would require treatment with bortezomib, in addition to cyclophosphamide and dexamethasone in both regimens. However, if a clone isn't detected the treatment would depend on the isotype of the clone detected in the serum. IgM clone is treated with rituximab while a non-IgM clone would be treated with bortezomib. If the bone marrow and serum do not display any clone or monoclonal protein respectively, the chemotherapy would be decided based on the monoclonal protein within the kidney deposits.(Noto, R. *et al*., 2017)

CONCLUSION

The first case emphasizes the importance of determining the native kidney disease before a transplant and that every MPGN/DPGN pattern of injury needs to be evaluated. Both the cases highlight the importance of two cores, one for immunofluorescence in the post transplant setting. They also show the necessity to do IF with kappa and lambda to demonstrate light chain restriction and clinch the diagnosis of PGNMIDD. It also emphasizes the poor graft outcome associated with PGNMIDD post transplant – recurrence and de novo alike

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