CLINICAL VIGNETTE

Progressive Kidney Dysfunction due to Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID)

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Introduction

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a recently identified condition defined by immune-mediated glomerulonephritis from monoclonal immunoglobulin deposition. We present a 28-year-old female admitted with rapidly progressive renal dysfunction complicated by associated anemia. Renal biopsy revealed proliferative glomerulonephritis with monotypic IgG3-Kappa deposits consistent with PGNMID, requiring steroids and rituximab to stabilize kidney function.

Case

A 28-year-old female recently-recognized renal dysfunction presented to the emergency department with low grade fevers and progressive generalized weakness. She was admitted for substantial deterioration of renal function with severe associated anemia.

The patient had established care with a new provider several months prior. Routine labs revealed a creatinine level of 1.3 mg/dL, with associated proteinuria, prompting referral to nephrology. She as seen by nephrology two weeks prior to hospital presentation. At that time, creatinine had risen to 2.44 mg/dL. Additional labs included urine albumin/creatinine ratio of 6.586. Serologies included: positive ANA 1:40 titer with speckled pattern. C4 at 72, with normal C3. Negative autoimmune tests included: dsDNA, SM Ab, RNP Ab, SSA Ab, SSB Ab, C-ANCA, P-ANCA, myeloperoxidase Ab, and proteinase-3 Ab. Kidney biopsy had been planned but had not been scheduled. Hemoglobin was 7.1 g/dL at initial nephrology visit.

On arrival to the emergency department, the patient was hypertensive, with systolic blood pressures of 160-170 mm Hg despite taking her home labetalol. Physical exam was otherwise unremarkable, notably negative for peripheral edema or significant volume overload. ED labs revealed creatinine increased to 6.3 mg/dL and hemoglobin had decreased to 6.3 g/dL. CT scan showed no acute process or occult malignancy, and she was admitted.

Nephrology was consulted and requested additional serologic investigation. She had nephrotic range proteinuria as well as non-anion gap metabolic acidosis. Infectious evaluation was negative. Renal biopsy was performed shortly after admission. It revealed proliferative glomerulonephritis with monotypic IgG3-Kappa deposits and focal fibrocellular crescents, consistent with diagnosis of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID). The patient was evaluated by hematology and underwent bone marrow biopsy which was unremarkable other than hypocellularity. Serum and urine immunofixation electrophoresis demonstrated a normal pattern without identifiable monoclonal proteins. With these findings, the patient was diagnosed with monoclonal gammopathy of renal significance without plasma cell dyscrasia. She was treated with high dose IV methylprednisolone, followed by oral prednisone. Creatinine initially peaked at 7.97 mg/dL, but steadily declined after IV steroids, reaching 2.89 mg/dL by discharge and did not require hemodialysis.

She received two units of RBC transfusion with appropriate response. Her anemia was felt to be most directly related to renal dysfunction along with active menstruation. After adequate response to initial steroid dosing and sustained response to blood transfusion, she was discharged home.

She has been followed by nephrology and hematology. Six weeks after, she required re-admission for volume overload associated with renal dysfunction. She was aggressively diuresed and initiated on rituximab and erythropoietin after intravenous iron supplementation. She has been effectively managed by nephrology and hematology. After four doses of rituximab, she was slowly weaned off oral steroids. Creatinine level reached a nadir of 1.99 mg/dL and hemoglobin stabilized around 10 g/dL.

After stopping rituximab and steroids, the patient's Creatinine increased to 3-4 mg/dL range. Rituximab and prednisone were resumed with stabilization of Creatinine. Chemotherapy will be discussed should she fail to improve on her current regimen.

Discussion

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) was recently described under the broader categorization of monoclonal gammopathy of renal significance (MGRS).[1] Monoclonal gammopathy involves the secretion of monoclonal immunoglobulins (M proteins) by

plasma or B cells which can cause significant harm from hematological malignancies (i.e multiple myeloma) or specific end organ damage (such as MGRS). A subset of patients have monoclonal gammopathy of undetermined significance (MGUS). While MGUS may not have immediate consequence, there is risk of progression to malignancy as well as end organ damage.

Nasr et al. first described and categorize PGNMID in 2004. The condition is defined by immune-mediated glomerulonephritis due to *monoclonal* Ig deposition which leads to membrano-proliferative glomerulonephritis finding on light microscopy and mesangial, subendothelial, or subepithelial granular deposits under electron microscope.[2,3] Immunofluorescence staining is necessary to confirm PGNMID. It reveals positivity for a single Ig class deposited in the glomeruli. IgG is the most commonly reported heavy chain subclass. Additional studies have recently demonstrated cases of IgA, IgM and light chain deposition. IgG3 with high molecular weight increases restriction at the glomerular filtration barrier.[1,3,4]

PGNMID is thought to cause nephrotoxicity via activation of the classical complement pathway from M protein deposition in glomeruli. Patients often present with microscopic hematuria, edema, and proteinuria, with a majority of patients having nephrotic syndrome and renal insufficiency.[1,3,4] Rapidly progressive glomerulonephritis has been reported, but occurs more rarely. PGNMID typically involves 50-60 aged range patients but has been reported in younger individuals. It is rarely diagnosed, found on less than one percent of renal biopsies, about 1/7th the frequency of light chain amyloidosis.[1,4]

Diagnosis of PGNMID is confirmed on renal biopsy with microscopy and immunofluorescence examination. Other causes of renal deposition disease must be ruled out, including type 1 cryoglobulinemia, fibrillary glomerulopathy, lupus and anti-GBM nephritis, and light chain amyloidosis.[1,3,4] Once PGNMID has been diagnosed, determining the source of monoclonal gammopathy can be challenging. Circulating monoclonal proteins are found in approximately 30% of patients with PGNMID.[1,3,4] Thorough diagnostic testing should be performed including serum and urine electrophoresis and immunofixation, light chain testing, bone marrow examination, flow cytometry evaluation, and PET-CT scan to rule out underlying malignancy if prior testing is unrevealing. While a subset of patients with PGNMID are found to have underlying hematologic malignancies, there are case reports of patients with PGNMID induced by viral infection; including Parvovirus B19 and Hepatitis C, as well as solid tumors.[3]

Treatment of PGNMID depends on the source of monoclonal protein production. Testing patients with underlying malignancies such as multiple myeloma or lymphoma, should be treated with appropriate systemic chemotherapy. Patients with PGNMID with a circulating plasma cell clone or a detectable monoclonal non-IgM protein are treated similarly to those with multiple myeloma with a goal to eradicate the pathologic clone. Typically, regimens of cyclophosphamide, bortezomib, and dexamethasone are used. Patients with pathologic B cell clone or an IgM monoclonal protein are typically treated with rituximab.[1,3,4]

However, there is no treatment consensus for the majority of PGNMID patients without detectable circulating monoclonal proteins. Risk/benefit discussions should balance treatment side effects versus watchful waiting. Patients with subacute presentations and milder renal insufficiency with < 1gm proteinuria per day could be treated initially with ACE-I/ARB therapy. Recent studies have reported good clinical outcomes treating PGNMID with empiric clone-directed therapy. Regimens including cyclophosphamide, bortezomib, and/or rituximab. comes. A 2018 small retrospective study by Gumber et al. reported 88% of patients had at least partial renal response (improved eGFR and proteinuria) to clone therapy, with 38% achieving complete renal recovery, and no patients developing ESRD by end of study. Importantly, 90% of treated patients who did not have a detectable clone showed renal improvement with empiric clone-directed treatment.[5]

Patients with PGNMID are reported to have poor renal prognosis with 25% of patients developing end-stage renal disease (ESRD) within 30 months.[4] Patients with PGNMID, post-transplant have high rates of recurrence (up to 89%) within the allograf.[1,6] Further studies are needed to better characterize PGNMID and optimal treatment strategies.

Conclusion

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) was newly characterized in 2004. It defined by immune-mediated glomerulonephritis due to monoclonal immunoglobulin deposition within the glomerulus. Identification of the cause of monoclonal gammopathy is needed as well as excluding other causes of renal deposition disease. Treatment is targeted against the underlying pathologic plasma or B cell clone. However, the majority of PGNMID cases, fail to identify a circulating clonal protein. Optimal treatment is challenging. Recent small studies employing empiric clone-directed therapy have promising favorable outcomes.

REFERENCES

1. **Lin L, Chen N**. A Review on the Diagnosis and Treatment of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits. *Int J Gen Med*. 2022 Dec 14;15:8577-8582. doi: 10.2147/IJGM.S386733. PMID: 36540764; PMCID: PMC9760043.
2. **Nasr SH, Markowitz GS, Stokes MB, Seshan SV, Valderrama E, Appel GB, Aucouturier P, D'Agati VD**. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. *Kidney Int*. 2004 Jan;65(1):85-96. doi: 10.1111/j.1523-1755.2004.00365.x. PMID: 14675039.
3. **Li M, Xu G**. An update of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Clin Kidney J*.

2021 Dec 14;15(6):1041-1048. doi: 10.1093/ckj/sfab269. PMID: 35664272; PMCID: PMC9155251.

4. **Bridoux F, Javaugue V, Nasr SH, Leung N**. Proliferative glomerulonephritis with monoclonal immunoglobulin deposits: a nephrologist perspective. *Nephrol Dial Transplant*. 2021 Jan 25;36(2):208-215. doi: 10.1093/ndt/gfz176. PMID: 33494099.
5. **Gumber R, Cohen JB, Palmer MB, Kobrin SM, Vogl DT, Wasserstein AG, Nasta SD, Bleicher MB, Bloom RD, Dember L, Cohen A, Weiss BM, Hogan JJ**. A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Kidney Int*. 2018 Jul;94(1):199-205. doi: 10.1016/j.kint.2018.02.020. Epub 2018 May 11. PMID: 29759418.
6. **Aucouturier P, D'Agati VD, Ronco P**. A Fresh Perspective on Monoclonal Gammopathies of Renal Significance. *Kidney Int Rep*. 2021 May 4;6(8):2059-2065. doi: 10.1016/j.ekir.2021.04.026. PMID: 34386655; PMCID: PMC8343799.