Open Journal of
Clinical & Medical
Case Reports

Volume 7 (2021)
Issue 13

ISSN: 2379-1039

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) associated with underlying haematological malignancy (primary myelofibrosis) with renal extra medullary haematopoesis

Puneet Arora*; Bhawna Bansal; Vimal Pandita

***Corresponding Author: Puneet Arora**

Consultant and Head, Department of Nephrology, Max Super specialty Hospital, Dehradun, 248001, India.

Email: puneetarora2412@gmail.com & puneet.arora2@maxhealthcare.com

Abstract

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID), a rare Monoclonal Gammopathy of Renal Significance (MGRS), is rarely associated with underling haematological malignancy. Similarly, kidneys as the site of extra-medullary haematopoiesis (EMH) is another rare histopathological finding recognized in ante-mortem settings. We present a case of primary myelofibrosis with renal extra medullary haematopoiesis and PGNMID as associated glomerulopathy.

Keywords

MGRS; EMH; PBF; case report; Immunofluorescence.

Introduction

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) [1], a rare monoclonal gammopathy of renal significance (MGRS), mostly have no background diseases but few cases have rarely been associated with viral infections or hematological malignancies [4,5]. Similarly, kidneys as the site of Extra-Medullary Haematopoiesis (EMH) is another rare histopathological finding recognized in ante-mortem settings and often misdiagnosed as allergic interstitial nephritis [9]. Here, we report a case of primary myelofibrosis who presented clinically as nephrotic syndrome without renal insufficiency and on biopsy was found to have renal extra medullary haematopoiesis and PGNMID as associated glomerulopathy.

Case Report

A 60 years old non diabetic, non hypertensive male presented with frothuria and anasarca from last

one month. Patient had palpable splenomegaly with nephrotic range proteinuria and no renal insufficiency (Table 1). He gave no history of weight loss, easy fatigability, bone pain, low grade fever or pruritus. Serum cryoglobulins, hepatitis B surface antigen and hepatitis C antibodies were negative. Renal biopsy was done which revealed increased cellularity and matrix of mesangium with normal thickness of glomerular capillary walls (Figure 1). Interstitium showed lymphoid aggregates with admixed eosinophils, polymorphs and scattered megakaryocytes, nucleated erythroid and myeloid cells (Figure 2) Immunohistochemical stains were performed to confirm erythroid cells (glycophorin stain) and myeloid precursors (myeloperoxidase stain) (Figures 2,3). Megakaryocytes were identifiable by their large size, multilobed nuclei, and large amounts of granular cytoplasm. On Immunofluorescence (IF) confluent IgG & lambda light chain deposits on mesangial and segmental capillary walls were seen. No IgA, IgM and kappa light chains were seen. Congo red and thioflavin T stain for amyloid were also negative. Hence a histopathological diagnosis of proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) and renal Extra Medullary Hematopoiesis (EMH) was made. Prednisolone 60 mg per day was started and oncologist opinion was taken to rule out underlying hematological malignancy. No M-spike was seen on Serum Immunofixation Electrophoresis (SIFE) and free kappa and lambda ratio was also within normal limits. Peripheral Blood Film (PBF) showed anisocytosis, poikilocytosis, thrombocytosis and a left shift (large atypical cells-7%, myelocytes-11%, metamyelocyrtes-4%). There was a dry tap on bone marrow aspiration. (Table 1). On bone marrow biopsy, sections showed intertrabecular bony spaces revealing prominent cellular marrow fibrosis [Reticulin: WHO grade 3/3] with scattered marrow elements. Dyspoetic megakaryocytes in focal clusters and streaming were noted. As features were highly suggestive of Primary Myelofibrosis (PMF), cytogenetic and mutational analysis was planned for confirmation but could not be done as patient refused further allopathic treatment and switched to ayurveda indian drugs, nature of which is not known. Within a month of starting prednisolone, his proteinuria had decreased to <500 mg/24 hours (Table 1) and anasarca had subsided. Subsequently, patient was lost to follow up but returned three months after renal biopsy with anasarca, proteinuria (2.9 gms/24 hours), and leukocytosis (36,800/mm3) (Table1). Patient again refused chemotherapy and later died in another hospital, the cause of which was attributed to complications of underlying malignancy.

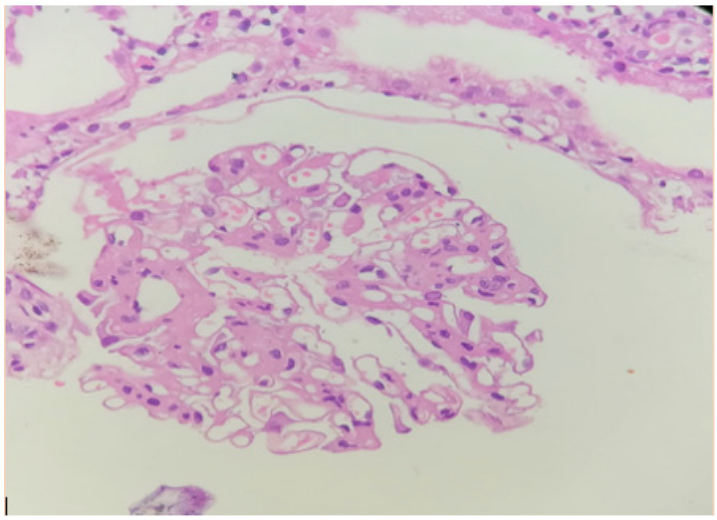

Figure 1: Glomerular capillary wall is of normal thickness with patent capillary lumens which are not bloodless. Mesangium - Shows increased matrix and cellularity.

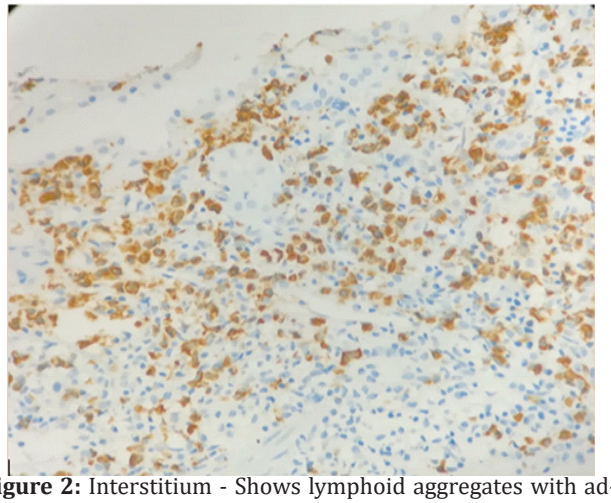

Figure 2: Interstitium - Shows lymphoid aggregates with admixed eosinophils, polymorphs and scattered megakaryocytes, nucleated erythroid and myeloid cells. Myeloid series cells are highlighted by Myeloperoxidae IHC staining.

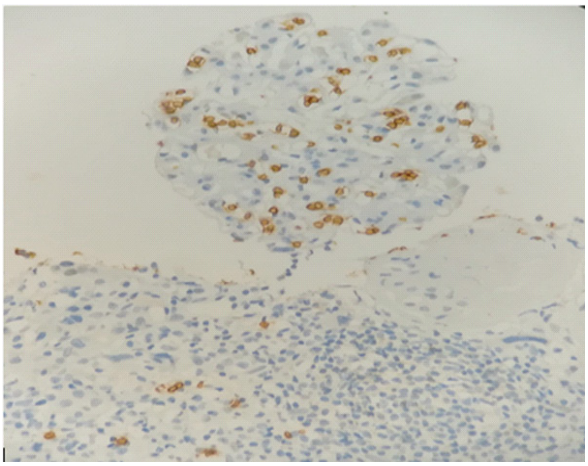

Figure 3: Glycophorin IHC highlights the RBCs inside the glomerulus and scattered in the interstitium.

Table 1

Investigation	At the time of Renal Biopsy	4 weeks after Renal Biopsy	12 weeks after Renal Biopsy
Hemoglobin (14-17 g/dL)	12.7	12.2	12.7
TLC (4000-11000/mm^3)	14600	19400	36800
Platelets (150,000-450,000/mm^3)	5.56	6.67	8.09
Creatinine (0.7-1.2 mg/dL)	0.81	0.9	0.85
Urine RM	4+ protein	Traces protein	2+ protein
24hour Urine Protein (<150 mg)	10762 mg	259 mg	2900 mg
Renal Biopsy	PGNMID and renal extramedullary hematopoiesis		
PBF		Leucoerythroblastic peripheral smear	
SIFE		No M Spike	
Kappa: Lambda Ratio (0.26 – 1.65)		1.09	
LDH (60-100 U/L)		792	
BMA		Dry Tap	
BM Biopsy		Myelofibrosis ; Reticulin: (WHO Grade 3/3)	
Cytogenetic and Mutational Analysis		Not Done	

TLC: Total Leucocyte count; PBF: Peripheral Blood Film; SIFE: Serum Immunofixation Electrophoresis; LDH: Lactate Dehydrogenase; BMA: Bone Marrow Aspiration; BM Biopsy: Bone Marrow Biopsy.

Discussion

PGNMID is a rare monoclonal gammopathy of renal significance (MGRS) first reported by Nasr et al in 2004 [1]. The key diagnostic features of PGNMID [2] are 1) Monoclonal staining of glomeruli for one IgG subclass (mostly IgG3) and a single light chain (kappa or lambda) with negative staining of IgA and IgM heavy chains. The Immunofluorescence (IF) pattern is often the one which clinches the diagnosis. 2) Predominantly membranoproliferative pattern and occasionally only mesangial proliferation [3] is found on light microscopy. A membranous pattern has rarely been observed. 3) Sub endothelial and mesangial (rarely sub epithelial) deposits apparent upon electron microscopy resemble Immune complex GN. The histopathological findings of our case (mesangial proliferation) with glomerular deposits of single immunoglobulin class (IgG) and a single light chain (lambda) and negativity of IgA & IgM stains are

consistent with the conception of classic PGNMID.

The etiology of PGNMID is not fully understood. Majority (70-80%) of patients with PGNMID are negative for a Monoclonal (M) spike, as seen in our case too, and patient rarely develops an M spike during follow up. PGNMID seems not to be a precursor of myeloma in most cases. The diagnosis is usually established when these patients undergo kidney biopsy for evaluation of proteinuria or renal insufficiency. Most of the PGNMID cases have no background diseases but few cases have rarely been associated with viral infections or hematological or lymphoproliferative malignancies [4,5]. Association of PGNMID with underlying PMF has never been reported till date.

PGNMID is thought to be due to a clonal proliferation of B lymphocytes or plasma cells that hypersecrete abnormal IgG capable of self aggregation and deposition in the glomerulus as electron dense deposits. Because of minority of PGNMID cases have documented paraprotein or hematological malignancies, it is possible that abnormal clone arises secondary to normal immune response. The small quantity of this monoclonal IgG may escape detection by serum or urine protein electrophoresis because of its high avidity for the glomeruli favored by its intrinsic physical properties & glomerular sieving itself [2]. IgG3, the most common IgG subtype in PGNMID is thought to be particularly nephritogenic resulting in influx of inflammatory cells and subsequent proliferative GN.

The clinical presentation of PGNMID is non specific and may present as nephrotic syndrome with or without renal insufficiency, nephritic-nephrotic syndrome, RPGN or chronic GN.

The prognosis too is variable with some reports showing complete remission while few cases progressing to ESRD. Most of the reported cases are above 50 years of age and PGNMID may recur after kidney transplant despite lack of detectable circulating monoclonal proteins [6]. Management of this disorder remains controversial with few advocating therapy targeting IgG production that may result in decreased deposition and improvement in renal diseases.

Renal EMH, another rare histopathologoical finding recognized in ante mortem setting, led to the diagnosis of underlying hematological malignancy (PMF) in this case. Although in majority of published cases, hematological disorders antedate the diagnosis of renal EMH, it is not the rule. EMH is defined as the development and growth of hematopoietic tissue outside the bone marrow. It most commonly occurs in PMF and thalassemia but may be associated with number of other disorders where normal functioning of bone marrow is compromised [7]. EMH is mostly seen in reticuloendothelial system (liver, spleen & lymph nodes). Renal EMH has been recognized only in sporadic case reports or small series particularly on post-mortem specimens [8].

Ante mortem diagnosis of renal EMH is challenging. Renal involvement can be parenchymal, intrapelvic or perirenal. Many times it is misdiagnosed as tubule-interstitial nephritis because of the presence of eosinophilic precursors that may be interpreted as eosinophils seen in allergic interstitial nephritis or sometimes overlooked as non specific inflammation [9]. By light microscopy, the biopsy in our case showed trilineage hematopoiesis in area affected by renal EMH (Figure 2).

The pathophysiology of renal localization of EMH is not fully understood. It has been speculated that hematopoietic cells are derived from resident mesenchymal pluripotent cells that could proliferate as

a response to a disease related stimulating factor [9] or may arise from migration of stem cells from bone marrow driven by intrarenal erythropoietin excess.

Glomerulopathy associated with PMF has rarely been described and defined as myeloproliferative neoplasm (MPN) related glomerulopathy [10]. However, most biopsies with EMH show concurrent glomerular diseases like fibrillary like GN, chonic thrombotic microangiopathy, focal segmental glomerulosclerosis or nodular diabetic glomerulosclerosis [9] but PGNMID has never been described.

Conclusion

Increased awareness for recently described entity of PGNMID is required for better understanding of this disorder and its associations with other diseases. Renal EMH should be considered in the differential diagnosis of interstitial infiltrates particularly in the presence of a glomerulopathy and hematological malignancy. Under recognition might explain the lack of such publications. In published literature this could be the first reported case of PGNMID associated with underlying PMF and EMH.

Declarations

Conflicts of interest: The authors declare that they have no conflicting interests.

Ethical considerations: Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the author.

Informed consent: Written informed consent for publishing this report was obtained from the patient's son as patient is not alive, in accordance with the guidelines of the ethical committee of our hospital.

Authors' contribution: PA wrote the manuscript, investigated, treated, followed and revisited the case.BB performed the histological investigations and VP investigated and followed the case. All authors read and signed the final paper.

References

1. Nasr SH, Markowitz GS, Stokes MB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. Kidney Int. 2004; 65: 85-96.

2. Nasr SH, Satoskar A, Markowitz GS, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol. 2009; 20: 2055-2064.

3. Lusco MA, Fogo AB, Najafian B, Alpers CE. AJKD Atlas of Renal Pathology: Proliferative Glomerulonephritis With Monoclonal Immunoglobulin Deposits. Am J Kidney Dis. 2016; 67: e13-e15.

4. Barbour SJ, Beaulieu MC, Zalunardo NY, Magil AB. Proliferative glomerulonephritis with monoclonal IgG deposits secondary to chronic lymphocytic leukemia. Report of two cases. Nephrol Dial Transplant. 2011; 26: 2712-2714.

5. Fujita E, Shimizu A, Kaneko T, et al. Proliferative glomerulonephritis with monoclonal immunoglobulin G3κ deposits in association with parvovirus B19 infection. Hum Pathol. 2012; 43: 2326-2333.

6. Nasr SH, Sethi S, Cornell LD, et al. Proliferative glomerulonephritis with monoclonal IgG deposits recurs in the allograft. Clin J Am Soc Nephrol. 2011; 6: 122-132.

7. Koch CA, Li CY, Mesa RA, Tefferi A. Nonhepatosplenic extramedullary hematopoiesis: associated diseases, pathology, clinical course, and treatment. Mayo Clin Proc. 2003; 78: 1223-1233.

8. Gibbins J, Pankhurst T, Murray J, et al. Extramedullary haematopoiesis in the kidney: a case report and review of literature. Clin Lab Haematol. 2005; 27: 391-394.

9. Alexander MP, Nasr SH, Kurtin PJ, et al. Renal extramedullary hematopoiesis: interstitial and glomerular pathology. Mod Pathol. 2015; 28: 1574-1583.

10. Said SM, Leung N, Sethi S, et al. Myeloproliferative neoplasms cause glomerulopathy. Kidney Int. 2011; 80: 753-759.

Manuscript Information: Received: August 01, 2021; Accepted: September 24, 2021; Published: September 30, 2021

Authors Information: Puneet Arora[1]*; Bhawna Bansal[2]; Vimal Pandita[3]
[1]Department of Nephrology, Max Super Specialty Hospital, Dehradun, India.
[2]Department of Histopathology, Max Super Specialty Hospital, Saket, New Delhi, India.
[3]Department of Oncology, Max Super Specialty Hospital, Dehradun, India.

Citation: Arora P, Bansal B, Pandita V. Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) associated with underlying haematological malignancy (primary myelofibrosis) with renal extra-medullary haematopoesis. Open J Clin Med Case Rep. 2021; 1796.