Case Report

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Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits: A Case Report

Internal Medicine Section

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ABSTRACT

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID) is a relatively rare entity. Patient's usually present with proteinuria, elevated creatinine, and renal failure. The present case report details the clinical presentation, diagnostic assessments, and treatment outcomes of a 56-year-old female with a complex renal pathology. The patient, with a history of hypertension, presented with generalised anasarca and decreased appetite. Initial examinations revealed pedal oedema, low serum albumin, elevated Blood Urea Nitrogen (BUN), and markedly high serum creatinine levels, indicating impaired kidney function. Further investigations, including urine analysis and immunological tests, identified significant proteinuria and complement system involvement. Radiological studies demonstrated ascites and elevated renal cortical echogenicity. Renal biopsy revealed Proliferative Glomerulonephritis with conventional Monoclonal Immune Deposits-Immunoglobulin G3 (PGNMID-IgG3-kappa). Direct immunofluorescence analysis exhibited a specific staining pattern, confirming the diagnosis. Overall, the diagnostic impression suggested Proliferative Glomerulonephritis with Membranoproliferative Glomerulonephropathy (MPGN) injury pattern, emphasising the complexity of the renal pathology. Despite extensive medical interventions, including haemodialysis and immunosuppressive measures, the patient's condition deteriorated, leading to a fatal outcome on the 67th day of admission. The present case underscores the challenges in managing advanced renal diseases and emphasises the importance of precise diagnostic methods for guiding targeted therapeutic interventions in such complex cases.

Keywords: Electron microscopy, Immunoglobulin G3-kappa, Myeloproliferative glomerulonephritis

CASE REPORT

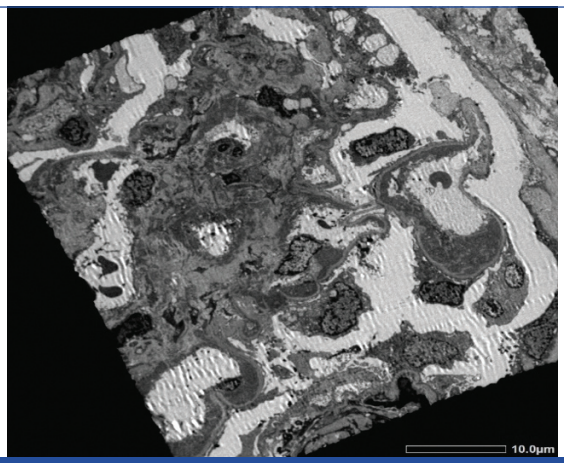
A 56-year-old female presented to the medicine Outpatient Department (OPD) with complaints of anasarca persisting for 3-4 days along with a recent decrease in appetite. The patient was a known case of hypertension spanning seven years on regular medication. Blood pressure was recorded at 140/90 mmHg, with a pulse rate of 90 beats per minute. Pallor and bilateral pedal pitting oedema were present, while icterus, cyanosis, clubbing, and lymphadenopathy were absent. Jugular venous pressure was not elevated. Mild abdominal distension, a non tender soft abdomen, and no organomegaly were present on palpation. On cardiovascular examination, both heart sounds were normal, and no murmur was heard. On the respiratory system examination, normal vesicular breath sounds were heard but decreased intensity at the basal region with no adventitious sounds. On the central nervous system examination, the patient was conscious, oriented to time, place, and person, had higher mental function, and both the motor system and sensory system were within normal limits. Laboratory investigations revealed a haemoglobin level of 9.2 g/dL, normal total cell count and platelet count. The serum albumin level was notably low at 2.4 g/dL, suggesting impaired protein synthesis or increased protein loss. The BUN was 65 mg/dL, and the serum creatinine level was 6.56 mg/dL, indicating impaired kidney function. Urine analysis demonstrated elevated protein levels (3+), a substantial presence of red blood cells (25-30 cells), and no pus cells. The serology profile was negative for Hepatitis C, Hepatitis B, and Human Immunodeficiency Virus (HIV) 1 and 2.

The serum N-terminal pro B-type Natriuretic Peptide (NT-proBNP) value was 268 pg/mL. The serum TSH was 2.03 mcIU/mL (0.35-4.94). The Erythrocyte Sedimentation Rate (ESR) was elevated at 45 mm/hr. Serum electrolytes showed sodium at 128 mmol/L and potassium at 4.6 mmol/L. Serum phosphorus was elevated at 7.9 mg/dL (2.6-4.7 mg/dL). Serum calcium was 7.6 mg/dL, and serum uric acid was 10.8 mg/dL. A 24-hour urinary protein was 15066 mg with a urine volume of 180 mL, emphasising significant proteinuria. The D-dimer was elevated at 978 ng/mL, indicating potential coagulation abnormalities. Immunological tests, including Perinuclear-antineutrophil Cytoplasmic Antibody and Cytoplasmic-antineutrophil Cytoplasmic Antibody, as well as Antinuclear Antibody (ANA) Blot and Immunoflourescece (IF), yielded negative results, suggesting an absence of specific autoimmune markers. However, the complement system assessment indicated a decreased C3 level of 62 ng/mL (normal range: 90-180 ng/mL) with a normal C4 level of 14 mg/dL, indicating possible complement system involvement.

Chest radiography revealed bilateral pleural effusion (right>left), and further pleural fluid diagnostic tapping was done, which was suggestive of transudative fluid. The Electrocardiograph (ECG) was suggestive of normal sinus rhythm with left ventricular hypertrophy. Additionally, echocardiography did not reveal any significant abnormality with an Ejection Fraction of 55% and no regional wall motion abnormality and grade 1 diastolic dysfunction. Ultrasonography of the abdomen and pelvis revealed moderate ascites along with mildly elevated bilateral renal cortical echogenicity. The right kidney measured 8.3×4.01 cm, while the left kidney measured 8.8×4.3 cm, both displaying normal size and shape. The corticomedullary junction was preserved. Protein electrophoresis revealed that alpha 1 Globulin was normal, Alpha 2 Globulin, Beta 1 Globulin, and Beta 2 Globulin levels were low. However, the Gamma Globulin level was significantly lower at 0.2 g/dL (normal range: 0.71-1.54 g/dL), indicating hypogammaglobulinemia. The Albumin to Globulin Ratio was 2.86, exceeding the upper limit of the reference range (normal range: 1.1-2.5), further emphasising the diminished gamma globulin levels relative to other proteins. Importantly, monoclonal bands were absent, suggesting a lack of abnormal protein bands associated with conditions like multiple

myeloma. However, hypogammaglobulinemia indicated a reduced concentration of immunoglobulins, which are crucial components of the immune system.

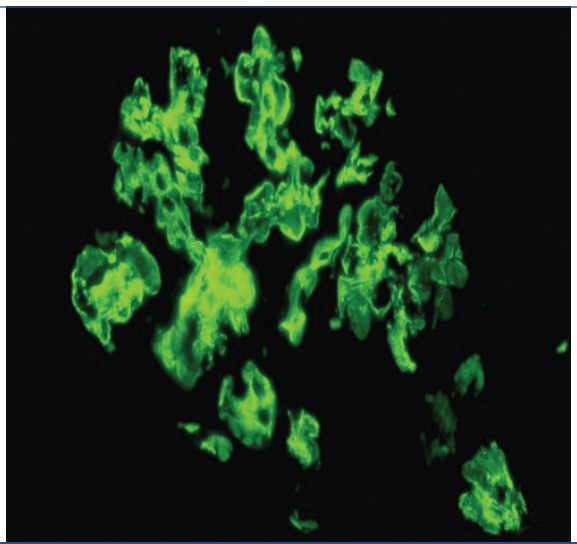
The Beta 2 microglobulin level was elevated at 9240 ng/mL. Hence, a nephrologist's opinion was taken and a renal biopsy was done, which showed normal findings under light microscopy. However, Electron Microscopy (EM) visualising two glomeruli revealed diffuse foot process flattening in one glomerulus and wrinkling of the capillary loops in another. Both glomeruli showed mesangial widening, with three to four cells per mesangial region, and a few loops revealing two endothelial cells. These features indicated Diffuse Proliferative Glomerulonephritis (DPGN) with copious Electron-dense Deposits (EDD) [Table/Fig-1]. The final diagnosis from the renal biopsy specifies proliferative glomerulonephritis with conventional monoclonal immune deposits (PGNMID-IgG3-kappa).



[Table/Fig-1]: Electron Microscopy (EM) showing Diffuse Proliferative Glomerulonephritis (DPGN) with copious Electron-dense Deposits (EDD).

After obtaining a negative result for plasma cells in the renal biopsy, a bone marrow examination was performed to rule out multiple myeloma as a potential cause of DPGN. This additional investigation aimed to comprehensively assess any involvement of multiple myeloma in the patient's condition.

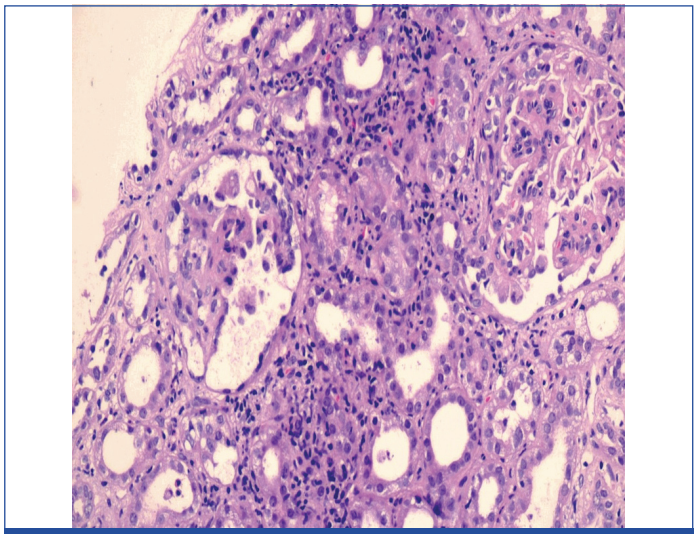
The direct immunofluorescence analysis of the renal cortical parenchyma, containing up to 5 glomeruli, revealed a specific immunostaining pattern. IgA and IgM were negative, while IgG exhibited a 3+ mesangial and capillary wall granular pattern, with elevated IgG3 levels. C1q demonstrated a 2+ mesangial and capillary wall granular staining. Kappa light chains exhibited a 3+ mesangial and capillary wall granular pattern, whereas Lambda light chains were negative [Table/Fig-2]. These immunofluorescence findings



[Table/Fig-2]: Direct immunofluorescence showing dominant mesangial and capillary wall staining for IgG and kappa light chain.

provided valuable information about the immune deposits present in the renal tissue, further supporting the diagnosis of proliferative glomerulonephritis with conventional monoclonal immune deposits (PGNMID-IgG3-kappa).

Haematoxylin and Eosin stain (H&E) staining of the renal biopsy revealed IgG3-kappa-associated proliferative glomerulonephritis with an MPGN pattern injury [Table/Fig-3]. The overall impression from the diagnostic assessments indicated a renal condition characterised by proliferative glomerulonephritis with an MPGN injury pattern. The direct immunofluorescence studies highlighted a dominant mesangial and capillary wall staining for IgG and Kappa light chain. Additionally, the biopsy revealed severe acute tubular injury with scattered coarse granular and beaded casts, along with sloughed cells in the tubular lamina, and multifocal lymphoplasmacytic interstitial inflammation mixed with focal neutrophilic infiltrate. The comprehensive analysis concluded that the biopsy findings aligned with IgG3-kappa-associated proliferative glomerulonephritis (PGNMID) with an MPGN pattern injury.



[Table/Fig-3]: IgG3-kappa associated proliferative glomerulonephritis (PGNMID) with an MPGN pattern injury. (H&E, 10x oil immersion field).

This diagnosis underscores the complex nature of the renal pathology, involving both proliferative glomerular changes and features characteristic of MPGN. The identified immunostaining patterns provide critical insights for targeted therapeutic considerations and the ongoing management of the patient's renal condition.

Following an elevated 24-hour protein report, the patient's management plan included initiating treatment with Tablet Prednisolone 60 mg. This approach is commonly employed to address conditions involving immune system dysregulation, such as certain glomerulonephritis disorders, to mitigate inflammation and manage the underlying pathology.

An oncologist's opinion was taken for starting bortezomib and dexamethasone. Subsequently, the patient underwent a bone marrow examination as advised, which turned out to be negative for the presence of plasma cells.

Despite extensive medical interventions, the patient's condition remained challenging. The treatment included 20 doses of intravenously administered injection human albumin 20% and 18 sessions of haemodialysis. Various anti-hypertensive medications were administered to manage blood pressure. During the hospital stay, the patient used to have fever spike intermittently and was started on broad-spectrum antibiotics but on the 42nd day of admission, the patient suddenly desaturated and was shifted to the intensive care unit and intubated. After a week, she developed ventilator-associated pneumonia. The organism detected was *Acinetobacter baumannii*, which was sensitive to minocycline. Unfortunately, despite these concerted efforts, the patient succumbed to the illness on the 67th day of admission.

DISCUSSION

The natural progression and renal prognosis of PGNMID remain relatively obscure. According to a study by Hussain SM and Sureshkumar KK, the incidence ranges between 0.17-3.7% [1]. However, a comprehensive understanding of its pathology has been eloquently outlined by Nasr SH et al., [2]. PGNMID typically exhibits a predominant histologic pattern resembling endocapillary proliferative glomerulonephritis. The characteristic immunofluorescence pattern is granular, with glomerular capillary walls and mesangial deposits. Notably, IgG3 deposits are the most frequently encountered immunoglobulin deposits and are typically restricted to kappa (κ)-light chains [2].

Electron Microscopy reveals granular EDD confined solely to the glomerular compartment. These deposits are primarily localised in the subendothelial and mesangial areas, often associated with foot process effacement [2,3]. This intricate description of PGNMID pathology provides valuable insights into its histological and immunofluorescent characteristics, aiding in the diagnostic understanding and potentially guiding therapeutic approaches for patients with this renal condition.

The majority of PGNMID cases are characterised by the absence of underlying diseases, and patients typically do not have a background of pre-existing medical conditions. However, it is noteworthy that a minority of PGNMID cases may be associated with underlying diseases. This includes potential connections to haematologic neoplasms or viral infections [4-7].

The varied associations observed in a subset of PGNMID cases underscore the heterogeneity of this condition and highlight the need for comprehensive clinical evaluation and investigations to elucidate potential contributing factors. The clinical presentation of PGNMID manifests in various ways, including nephrotic syndrome, nephritic-nephrotic syndrome, rapidly progressive renal failure, or chronic glomerulonephritis. Extra-renal manifestations are rare, and the condition frequently results in Chronic Kidney Disease (CKD). Prognosis in PGNMID is variable, with some reported cases showing complete remission [8]. The prognosis of PGNMID is often reported to be poor, with a significant number of patients ultimately progressing to End-stage Renal Disease (ESRD) [2,9]. This suggests that PGNMID can have a severe impact on renal function, leading to the advanced stage of kidney disease where renal replacement therapy may be required for survival.

The poor prognosis underscores the challenges in managing this condition. The variability in prognosis among different cases emphasises the importance of individualised care and further research to better understand the factors influencing the course of PGNMID [10,11].

CONCLUSION(S)

The present case underscores the complex nature of renal disorders, emphasising the challenges in managing conditions like proliferative glomerulonephritis. It also highlights the critical need for ongoing research and advancements in the field to improve outcomes for such patients. Every proteinuria should be evaluated, as there is a specific cause and treatment for every glomerular pathology.

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