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Monoclonal gammopathy of renal significance; experience of a tertiary care hospital in India

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ABSTRACT

Introduction: Monoclonal gammopathy of renal significance (MGRS) disorders are indolent B-cell or plasma cell lymphoproliferative neoplasms which do not meet the hematological criteria for malignancy, however they cause renal dysfunction as a result of production of nephrotoxic monoclonal immunoglobulin (MIg).

Objectives: To study the clinical presentation, laboratory features, light microscopy and immunofluorescence (IF) characteristics of all cases of MGRS diagnosed at our hospital over a period of five years.

Patients and Methods: A record of all renal biopsies performed at our hospital between 2014-2019 was accessed from the database. Out of 1356 kidney biopsies, 68 had evidence of MIg deposition on immunofluorescence. Only six cases met the criteria of MGRS. Histopathological and immunofluorescence characteristics were studied to classify the lesions as per International Kidney and Monoclonal Gammopathy (IKMG) Research Group classification.

Results: All six cases presented with deranged renal function. Four had sub-nephrotic and one had nephrotic range proteinuria. MIg was identified in only one case on serum protein electrophoresis and free light chain assay. Using a conjunction of histomorphology of renal lesions, special stains and immunofluorescence all six cases of MGRS were categorized as per IKMG classification into monoclonal immunoglobulin deposition disease (two cases), AL amyloidosis, light chain cast nephropathy, proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) and light chain proximal tubulopathy (LCPT).

Conclusion: MGRS presents as renal failure and proteinuria. MIg may not be detected on protein electrophoresis due to low-secretion in serum. A kidney biopsy is essential to study the morphology of renal lesions and identify MIg deposition.

Case Series

Implication for health policy/practice/research/medical education:
An early kidney biopsy should be performed in all patients with progressively deteriorating renal function and proteinuria. Light microscopy and immunofluorescence is critical to identify morphology of renal lesions and establish monoclonality of deposited immunoglobulins.

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Introduction

Robert A Kyle was the first to publish a study in 1978 of 241 patients who had a monoclonal protein in serum but did not fulfil the clinical and hematologic criteria of multiple myeloma, Waldenström's macroglobulinemia, amyloidosis or lymphoma (1). He introduced the term monoclonal gammopathy of undetermined significance (MGUS) for a patient having <30 g/L serum MIg, <10% monoclonal bone marrow plasma cells and no evidence of any end-organ damage as a result of gammopathy. Patients diagnosed as MGUS do not qualify the criteria for overt B-cell malignancy. They are kept under close follow-up and do not require immediate treatment for B-cell disorder. Many patients, who are classified hematologically

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as MGUS, present with kidney disease as a result of MIg deposition in the kidney (2). Renal disease caused by MIg deposition is progressive and does not undergo spontaneous remission. These patients do not respond to conventional immunosuppression given for non-clonal gammopathies. Specific cytotoxic chemotherapy directed against the underlying B-cell clone is therefore needed (3). In order to differentiate monoclonal gammopathies of undetermined significance (MGUS) which cause renal manifestations, IKMG introduced the term monoclonal gammopathy of renal significance (MGRS) in 2012 (4). MGRS has been defined by IKMG as a clonal lymphoproliferative disorder of B-cell or plasma cell that does not meet any current hematological criteria for specific therapy, but produces nephrotoxicity as a result of production of monoclonal immunoglobulin (5).

Objectives

We present a case series of six cases diagnosed as MGRS at our institute over a period of five years. The clinical features, laboratory workup, hematological evaluation and renal biopsy findings are discussed to contribute to available literature and develop a better understanding of this relatively new and uncommon entity.

Patients and Methods

A laboratory database search was done for all kidney biopsies reported at our laboratory over a period of five years. Out of a total of 1356 kidney biopsies, MIg deposition on IF was present in 68 cases. Cases qualified as overt B-cell malignancy were excluded from the study. Only six cases met the clinical-hematologic and histopathologic criteria of MGRS. Formalin-fixed paraffin-embedded tissue blocks were retrieved and stained for hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) and silver stains using standard techniques. Immunofluorescence photographs of all six cases were retrieved from laboratory's image database. Clinical features, baseline renal function and haematological assessment were recorded for each case. A study of morphology and immunofluorescence characteristics was performed on renal biopsy to classify the renal lesions as per IKMG 2019 classification.

Case 1

A 74-year-old non-diabetic male presented with pedal oedema and rash of two months duration. His serum creatinine was 1.8 mg/dL and urinary protein excretion was 1.8 g/24 hours. He incidentally also tested positive for hepatitis B. A kidney biopsy was performed to evaluate renal failure and proteinuria. Glomeruli showed obliteration of capillary lumina by fluffy, fibrillar material and mesangiolysis with formation of micro-aneurysms in glomerular capillaries. Nodular mesangial sclerosis was seen in a single glomerulus. In addition, the glomerular and tubular basement membranes were thickened which was confirmed as IgG deposits on immunofluorescence, with IgG3 subclass restriction. Kappa and lambda had equivocal staining pattern (Figure 1). Serum protein electrophoresis (SPEP) and serum free light chains (sFLC) assay could not identify a MIg and bone marrow aspirate revealed 20% plasma cells. Due to absence of CRAB (hypercalcemia, renal failure, anemia, and bone lesions) features and myeloma defining events, the patient did not meet the criteria for overt myeloma. As renal biopsy was suggestive of heavy chain deposition disease (HCDD) and associated thrombotic microangiopathy, a final diagnosis of MGRS was confirmed and chemotherapy was initiated.

Case 2

A 72-year-old hypertensive female presented with complaints of anasarca, dyspnea on exertion and reduced urine output. On examination, she had pallor, ascites, and bilateral pleural effusion. Laboratory workup revealed 6.6 gm/day urine protein excretion, hypoalbuminemia and serum creatinine of 2.8 mg/dL. Serum and urine protein electrophoresis did not show any M-band and sFLC ratio was 1.19. Bone marrow examination was unremarkable, serum calcium levels were normal and no lytic lesions were found on skeletal survey. Kidney biopsy showed diffuse glomerular capillary wall and mesangial deposition of an acellular, pale eosinophilic material which was Congo-red positive. On immunofluorescence (IF) study, the amyloid

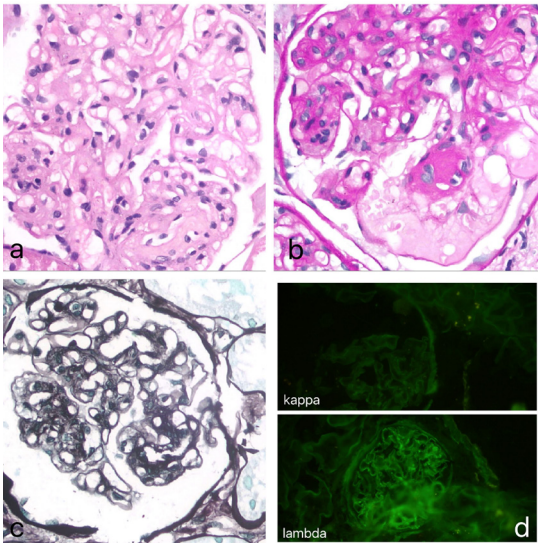

Figure 1. Obliteration of glomerular capillary lumina by fibrin thrombi giving the appearance of a blood-less glomerulus. Endothelial swelling is prominent; H&E 400x (**a**). Mesangiolysis and micro-aneurysm formation is seen. A single focus of nodular mesangiosclerosis is present; PAS 400x (**b**). Glomerular and tubular basement membranes are thickened; PASM 400x (**c**). Immunofluorescence microscopy shows linear positivity on the glomerular and tubular basement membranes for both kappa and lambda light chains (**d**).

deposits showed lambda restriction, thus establishing AL amyloidosis (Figure 2).

Case 3

A 72-year-old female without co-morbidities presented with complaints of nausea, vomiting and weakness for two weeks. She was found to have anaemia (Hb; 10 g/dL) and a creatinine of 6.7 mg/dL. Urine examination was unremarkable. On kidney biopsy fractured renal tubular casts were seen, which were lambda restricted on immunofluorescence (Figure 3). Bone marrow examination showed 6% plasma cells. There were no bony lytic lesions and sFLC ratio was within range. Because of non-identification of a myeloma clone on bone marrow examination, absence of target organ damage, non-identification of sFLC and presence of myeloma casts with kappa restriction, she was diagnosed as MGRS manifesting as light chain cast nephropathy. The patient was treated with bortezomib based chemotherapy and plasmapheresis to lower sFLC levels. Her renal function and proteinuria improved after six cycles of chemotherapy.

Case 4

A 34-year-old male who underwent renal transplant fourteen years back for chronic tubulo-interstitial disease presented with asymptomatic graft dysfunction and fever of two weeks. His serum creatinine increased from a baseline of 1.5 mg/dL to 2.6 mg/dL. Anemia and sub-nephrotic proteinuria were also present. SPEP showed presence of MIg, which was identified as IgG-lambda on immuno-fixation. On sFLC assay, kappa: lambda ratio was 0.15 and bone marrow aspirate unfolded 30% plasma cells. Serum calcium was 8.8 mg/dL and no lytic lesion was identified on skeletal survey. On kidney biopsy, well-formed necrotizing granulomas with Langhans giant cells were seen in interstitium. Glomerular and tubular basement membrane thickening was noted on light microscopy which were confirmed to be due to IgG deposition with lambda restriction on IF (Figure 4). Based on renal biopsy findings, identification of MIg (IgG lambda-1.7 g/dL) and bone marrow plasmacytosis, a final diagnosis of MIDD with granulomatous interstitial nephritis was made. The patient became afebrile after two weeks of anti-tubercular therapy. He responded to bortezomib + dexamethasone + cyclophosphamide based chemotherapy and his serum creatinine reduced to 1.7 mg/dL after three months.

Case 5

A 55-year-old hypertensive and diabetic male presented with rapid rise of serum creatinine from 1.4 to 6 mg/dL over three months. Urine examination revealed sub-nephrotic proteinuria and microscopic hematuria. Kidney biopsy showed global sclerosis of 40% glomeruli. The remaining glomeruli were enlarged with an increased mesangial cellularity. Focal endocapillary proliferation was present. Glomerular basement membrane thickening and mesangial matrix expansion were noted. On IF, mesangial and glomerular capillary wall deposits exhibited strong granular positivity for IgG and C3 (3+). These deposits were kappa restricted. IF for IgG sub-classes showed positivity for IgG3 only (Figure 5). A complete haematological assessment done to identify an underlying

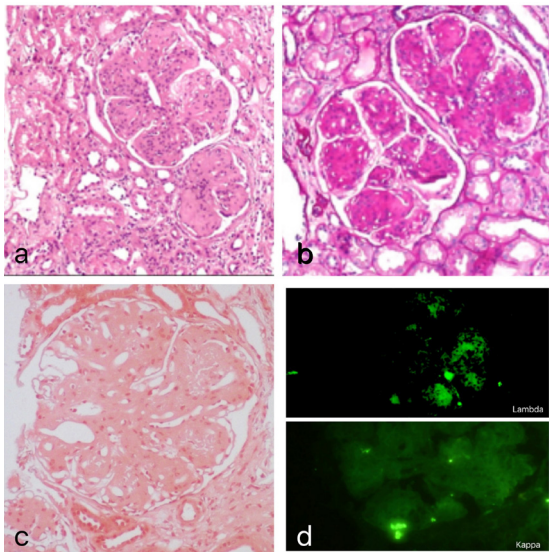

Figure 2. Two glomeruli with deposition of an acellular, pale eosinophilic material in mesangium and glomerular capillary walls; H&E 400x (**a**). The acellular glomerular deposits are PAS positive (**b**) and congophilic (**c**). Immunofluorescence shows kappa restriction (**d**).

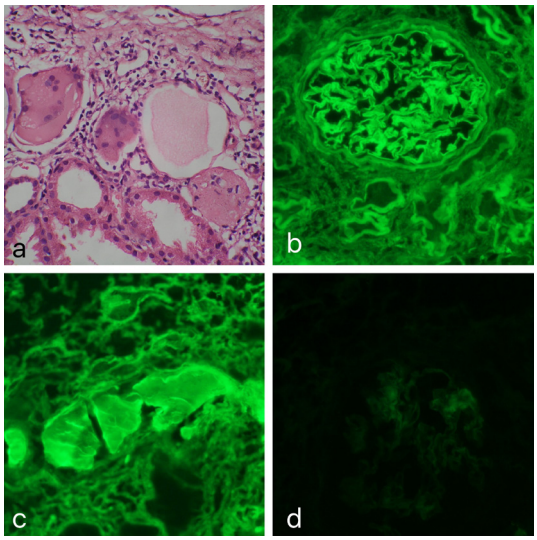

Figure 3. Image shows presence of eosinophilic casts in renal tubules; H&E 100x (a). Immunofluorescence shows deposition of lambda light chains along glomerular and tubular basement membranes (b). Presence of intra-tubular fractured casts with lambda restriction are highlighted (c). IF for kappa light chain is negative (d).

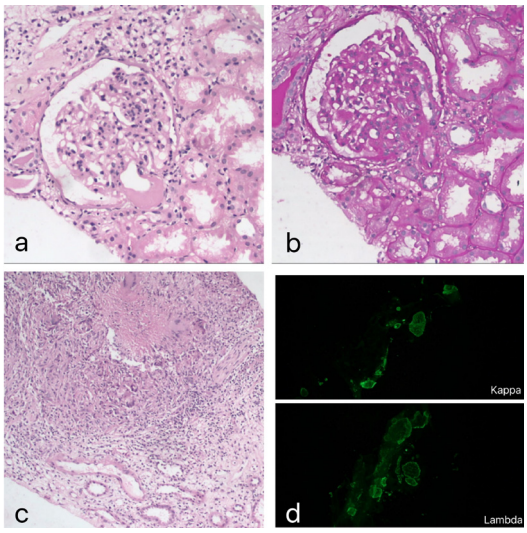

Figure 4. Image show a single glomerulus with conspicuously thickened vascular basement membrane; H&E 100x (**a**). On PAS stain thickening of glomerular and tubular basement membranes can be appreciated; PAS 100x (**b**). Presence of well formed granulomas in interstitium with central necrosis and Langhans type of giant cells are seen; H&E 100x (**c**). IF shows linear deposition of immunoglobulin along tubular basement membranes. Staining for lambda is more intense than kappa (**d**).

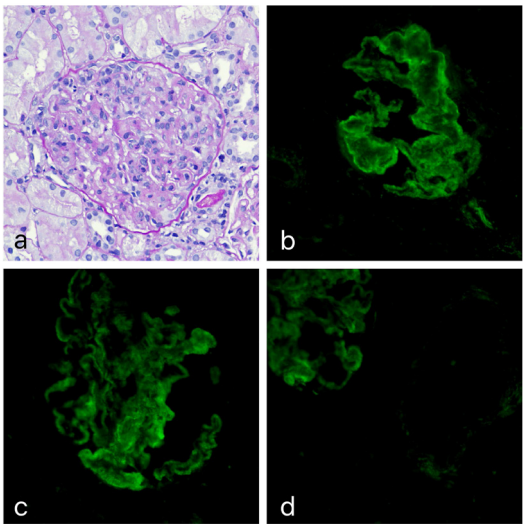

Figure 5. Glomerular enlargement with an increase in mesangial cellularity is conspicuous. Focal endocapillary proliferation, mesangial matrix expansion and glomerular basement membrane thickening is present; PAS 400x (**a**). Immunofluorescence shows intense global mesangial and glomerular capillary wall staining for IgG (**c**) with IgG3 subclass (**b**) and kappa restriction (**d**).

B-cell malignancy was unremarkable. A diagnosis of MGRS manifesting as Proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID) was established.

Case 6

A 54-year-old lady investigated for anorexia and tiredness was found to have sub-nephrotic proteinuria and deranged renal function (serum creatinine; 2.5 mg/dL). Bone marrow examination, SPEP and sFLC assay were within range. On kidney biopsy, glomerular morphology was unremarkable. However, tubular epithelial cells showed diffuse apical cytoplasmic blebbing and vacuolation. No well-defined crystalline structures were seen. On IF, intra-cytoplasmic positivity for light chains with lambda restriction was seen in proximal tubular epithelial cells (Figure 6). On account of a normal glomerular morphology, degenerative changes in proximal tubular epithelial cells, absence of intra-cytoplasmic crystals and deposition of lambda light chains on IF, a diagnosis of light chain proximal tubulopathy (LCPT) without crystals was confirmed.

Results

All six cases in our study had clinical and laboratory evidence of renal failure. Five cases had proteinuria at presentation. Monoclonal protein was found in only one case on SPEP and sFLC assay whereas; all six cases had evidence of monoclonal immunoglobulin deposition on immunofluorescence. Indication for kidney biopsy in all cases was renal dysfunction.

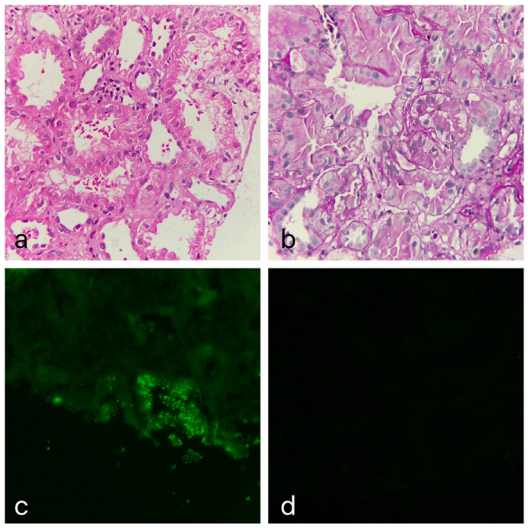

Figure 6. H&E 400x (**a**) and PAS 400x (**b**) stained sections show intact brush border of proximal tubular epithelial cells and diffuse apical cytoplasmic blebbing. Degenerative changes are present in the form of diffuse cytoplasmic vacuolation. Immunofluorescence microscopy shows presence of intra-cytoplasmic positive staining for lambda (**c**) and negative kappa staining in proximal tubular epithelial cells (**d**).

The clinical, laboratory, haematological and renal biopsy findings of all six cases are summarized in Table 1.

Discussion

Renal involvement due to monoclonal gammopathy in low grade clonal lymphoproliferative neoplasms is known (2). These low-grade neoplasms were initially classified as MGUS by Kyle et al (1). Patients diagnosed

as MGUS were earlier kept on follow-up, but not offered treatment. However, due to production of nephrotoxic immunoglobulin by dangerous B-cell clones, therapy is needed to prevent end-stage renal disease (6). IKMG consequently introduced the term MGRS for a B cell/plasma cell proliferative disorder which does not meet hematological criteria for malignancy but produces nephropathy as a result of production of nephrotoxic MIg (5). IKMG has classified MGRS-associated lesions based on light microscopy, immunofluorescence and ultrastructural characteristics of deposits on electron microscopy. Deposits in MGRS associated lesions have been classified as organized, non-organized and non-immunoglobulin. Organized MIg deposition is subdivided into fibrillar, micro-tubular and crystalline type based on thickness and structure of immunoglobulins on EM. Fibrillar subtype includes light-chain, heavy-chain and light and heavy chain immunoglobulin-related amyloidosis (AL, AH and AHL) (7).

AL-amyloidosis presents as chronic kidney disease and nephrotic range proteinuria. Neuropathy, cardiac manifestations and liver failure are frequently seen. Our case of AL amyloidosis (case 2) presented with nephrotic range proteinuria, severe anemia, hypoalbuminemia and deranged kidney function. PEP and sFLC assay could not detect M protein (monoclonal proteins) or FLC excretion. Amyloid appears as acellular, amorphous and pale eosinophilic deposits on H&E stain around glomerular capillaries, arterioles and interstitium. Congo-red stain gives an orange-red colour under light microscopy and produces apple-green birefringence under polarized light (8). In our case, amyloid deposition was confirmed by glomerular capillary wall and mesangial deposition of congophilic substance.

Micro-tubular immunoglobulin deposition is seen in type I /II cryoglobulinemic and immunotactoid glomerulonephritis. Microtubules have a hollow centre and a diameter of 17-52 nm. Cryoglobulinemic glomerulonephritis is associated with systemic manifestations like vasculitic rash, arthralgia, peripheral neuropathy and presence of glomerular protein thrombi. In contrast, immunotactoid glomerulonephritis is a limited to the kidney (9).

The third subtype of organized deposits are crystalline deposits and include LCPT, crystal storing histiocytosis and crystalglobulinemic glomerulonephritis (6). Patients of LCPT with crystals have intra-cytoplasmic rod or rhomboid-shaped hyper-eosinophilic kappa restricted

Table 1. Clinical, biochemical, hematological and renal biopsy findings of six cases of MGRS

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	74	72	72	34	55	54
Gender	Male	Female	Female	Male	Male	Female
Co-morbidities	Hepatitis B	Hypertension	Nil	Renal transplant recipient, pulmonary TB	Diabetes mellitus, hypertension	Nil
Clinical presentation	Bilateral ankle oedema	Anasarca, dyspnea, oliguria	Nausea, vomiting & weakness	Asymptomatic graft dysfunction	Deteriorating renal function, haematuria	Loss of appetite and weakness
Proteinuria	Sub-nephrotic	Nephrotic	Nil	Sub-nephrotic	Sub-nephrotic	Sub-nephrotic
M band on SPEP	Not detected	Not detected	Not detected	Detected – IgG lambda	Not detected	Not detected
sFLC ratio (κ: λ)	Not done	Within range (1.19)	Within range	0.15	Not done	Within range
Bone marrow plasma cells	20%	Not available	Not available	30%	Not available	Not available
Light microscopy	Diffuse GBM and TBM thickening, Nodular mesangial sclerosis, TMA	Mesangial and glomerular capillary wall amyloid deposition	Fractured casts in renal tubules	Vascular and tubular basement membrane thickening. Interstitial granulomas	Increased mesangial cellularity and matrix expansion. Thickening of GBM	Diffuse proximal tubular cell blebbing and vacuolation
Direct IF	Linear IgG deposits along GBM and TBM, Equivocal κ: λ	λ restricted	λ restricted	λ restricted Ig deposits along TBM, GBM and arterioles	IgG and C3 – granular +++ IgG3 subclass & κ restricted	λ light chain deposition in cytoplasm of proximal tubular cells
Diagnosis	MIDD, likely HCDD	AL amyloidosis	Light chain cast nephropathy	MIDD with interstitial granulomatous nephritis	PGNMID	LCPT without crystals

Abbreviations: GBM, Glomerular basement membrane; TBM, Tubular basement membrane; TMA, Thrombotic microangiopathy; MIDD, Monoclonal immunoglobulin deposition disease; HCDD, Heavy chain deposition disease; AL, Amyloid light chain; PGNMID, Proliferative glomerulonephritis with monoclonal immunoglobulin deposition; LCPT, Light chain proximal tubulopathy.

crystals in proximal tubular cells. It is often associated with Fanconi syndrome (10). Cases of LCPT without crystals have deposition of monoclonal light chains in proximal tubular cells, but no crystal formation. Renal morphology shows cytoplasmic swelling, vacuolation and apical blebbing of proximal tubular epithelial cells. IF confirms the presence of intra-cytoplasmic light chains with kappa/lambda restriction in tubular epithelial cells (11). Our case of LCPT without crystal formation, a 54-year-old lady underwent kidney biopsy for proteinuria and deranged renal function (case 6). Glomerular morphology was unremarkable, however renal tubules showed cytoplasmic swelling, apical blebbing and vacuolation. Intra-cytoplasmic light chain deposition with lambda restriction in tubular epithelial cells was confirmed on IF.

Monoclonal immunoglobulin deposition disease (MIDD) and PGNMID are MGRS-associated lesions with non-organized deposits. MIDD is characterised by linear deposition of monoclonal light chains (LCDD), heavy chains (HCDD) or both light and heavy chains (LHCDD) along glomerular and tubular basement membranes. In contrast to amyloidosis, the deposits in MIDD are non-fibrillar and Congo-red negative. Patients commonly present with renal insufficiency, proteinuria, microscopic hematuria and hypertension (12). Our cases of MIDD (case 1and 4) presented with renal failure, proteinuria and hypoalbuminemia. Monoclonal protein and sFLC excretion was seen in one case. The characteristic histopathologic features of MIDD on renal biopsy are nodular sclerosing glomerulopathy and thickening of tubular basement membrane and vessel walls. Diffuse linear staining of glomerular and tubular basement membranes for a single light or heavy chain is seen. Both cases reported in this series had thickened tubular basement membrane and vascular walls. Nodular sclerosing glomerulopathy was seen in case 1. On IF, basement membrane deposition of IgG (IgG3 subclass) was seen in case 1 (HCDD). Case 4 had similar pattern of IgG deposition with lambda restriction (LCDD).

Clinical presentation of PGNMID is proteinuria, chronic kidney disease, microscopic hematuria and hypertension. Histopathologic pattern is predominantly membranoproliferative or endocapillary proliferative with membranous features. Mesangial and sub-endothelial deposition of intact immunoglobulins, most commonly IgG3 is present (13). Our case (case 5) presented with rapid deterioration of renal function, proteinuria and microscopic haematuria. A proliferative glomerulonephritis pattern, strong and granular IgG expression with kappa restriction in the mesangium and glomerular capillary walls was seen. The sub-class of immunoglobulin was confirmed as IgG3.

The third category of MGRS-associated lesions in IKMG classification are lesions without deposits. It includes C3 glomerulopathy with monoclonal gammopathy. In these patients of C3 glomerulopathy, renal immunoglobulin deposits are absent but monoclonal immunoglobulin is present in serum (14). Lastly, thrombotic microangiopathy and microangiopathic hemolytic anaemia with concurrent monoclonal gammopathy have also been reported as an MGRS-related lesion in some studies (15).

Conclusion

MGRS should be suspected when a patient with clinical and laboratory features of renal dysfunction has evidence of presence of MIg. MIg and FLC secretion can be identified using protein electrophoresis and sFLC assay. However, in cases where the underlying B-cell clone is very small or the MIg has increased affinity for tissues, protein electrophoresis and sFLC assay may be non-contributory. In such cases, MIg may be demonstrated on kidney biopsy by immunofluorescence. In our series, MIg could be identified in only one case on protein electrophoresis and sFLC assay. Whereas, all six cases had MIg deposition on IF of kidney biopsy. Study of morphology of renal lesions on kidney biopsy of an MGRS-associated lesion is essential to identify the renal lesion and classify it as per IKMG recommendations.

Limitations of the study

Though this study includes all renal biopsies which were performed at our institute over a period of five years, the number of cases which fulfilled the criteria for MGRS is small. A larger study would be beneficial in understanding the clinical presentation, laboratory evaluation and histopathological characteristics of this diverse but uncommon entity.

Authors' contribution

The principal investigators for this study were SHM, RT and TC. SP, AK and VS helped in the preparation, concept and design of study. RT and SHM revised and critically evaluated the intellectual content of the manuscript. All authors were involved in preparation of the final draft of the manuscript, revision of the manuscript and critical evaluation of the intellectual contents. The content of the manuscript has been read and approved by all authors.

Conflicts of interest

The authors declare that they do not have any competing interests.

Ethical considerations

Required consent has been taken for publication of cases from the patients. All ethical issues concerning plagiarism, data fabrication and duplicate publication have been

observed by the authors. Patients gave their consent to publish as a case report.

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