Monoclonal Gammopathy of Renal Significance: Histomorphological Spectrum at a Tertiary Care Center

Adarsh Barwad, Varun Bajaj, Geetika Singh, Amit Kumar Dinda, Ranjit Kumar Sahoo, Lalit Kumar, Sanjay Kumar Agarwal

Department of Pathology, All India Institute of Medical Sciences, New Delhi, India; Department of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India; Department of Nephrology, All India Institute of Medical Sciences, New Delhi, India

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Introduction
The term monoclonal gammopathy of renal significance (MGRS) has been described to include patients with renal manifestations associated with circulating monoclonal proteins with or without a clonal lymphoproliferation (B-cell or plasma cell) and not meeting diagnostic criteria for an overt hematological malignancy. A host of MGRS-associated lesions have been described that involve various renal compartments. Our study describes the histomorphological spectrum of MGRS cases at our center in the last 5 years and description as per the classification system of the International Kidney and Monoclonal Gammopathy Research Group (IKMG). Material and Methods: Retrospective analysis was carried out of all the renal biopsies with characteristic monoclonal immunoglobulin lesions for histopathological diagnosis between years 2015 and 2020 and reviewed by two independent pathologists. Results: Most patients in the study belonged to the fifth decade, with a median age of 50 years (mean 50.14 ± 10.43) range (24–68 years) with a male preponderance. Most patients presented with proteinuria as the sole manifestation (66.6%). Many of the patients (48%) had an M spike by serum protein electrophoresis or urinary protein electrophoresis with an abnormal serum free light chain assay (60.8%). AL amyloidosis was the most common diagnosis observed on histopathological evaluation (68.7%), followed by light chain deposition disease (10.4%). Conclusion: MGRS lesions are infrequently encountered in the practice of nephropathology and pose a diagnostic challenge due to the limitation of a congruent clinical or hematological picture. A thorough histological examination with immunofluorescence and electron microscopy often precipitates in the right diagnosis and prompts timely management.
teins found in "an illness hitherto undescribed" in 1847. Much insight has been gained since then, and association between multiple myeloma and resultant renal afflictions has been well established [2]. Plasma cell dyscrasia and monoclonal gammopathy of undetermined significance (MGUS) represent the share of cases with M protein spike without either clonal proliferation (MGUS) or clonal proliferation not enough to meet the diagnostic criteria for multiple myeloma [3]. The term monoclonal gammopathy of renal significance (MGRS) has been described to include patients with renal manifestations associated with circulating monoclonal proteins with or without a clonal lymphoproliferation (B-cell or plasma cell) and not meeting diagnostic criteria of an overt hematological malignancy [4]. The term was coined by the International Kidney and Monoclonal Gammopathy Research group (IKMG) in 2012 in recognition of the relationship between the absence of multiple myeloma (MM), Waldenström macroglobulinemia (WM) or cryoglobulinemia, and renal disease with the presence of a low-grade clonal disorder without additional organ involvement. The diseases tended to be progressive with higher recurrence rates and poorer responses to treatment than their non-monoclonal counterparts, prompting the need for revising the terminology from idiopathic to a more specific nomenclature [5]. The prevalence of MGUS has been described from 0.32% to 1.5% of MGUS patients and appears to be heavily age dependent [6, 7]. A host of MGRS-associated lesions have been described that involve the glomerular compartment, i.e., immunotactoid glomerulonephritis, C3 glomerulopathy, proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID); the tubular compartment, i.e., light-chain proximal tubulopathy (LCPT); and the multiple compartments, i.e., immunoglobulin-related amyloidosis, monoclonal immunoglobulin deposition disease, and thrombotic microangiopathy (TMA)-pattern as indirect paraprotein-mediated endothelial injury according to a consensus report [5]. Our study describes the histomorphological spectrum of MGRS cases encountered at our center in the last 5 years including immunofluorescence (IF) and electron microscopy (EM) features of the entities as per the classification system of the International Kidney and Monoclonal Gammopathy Research Group (IKMG) using a standardized reporting system proposed by the Mayo Clinic/Renal Pathology Society working group [5, 8].

Materials and Methods

This study is a retrospective analysis which was carried out of all the renal biopsies with characteristic lesions of monoclonal immunoglobulin (MiG)-associated renal injury received in our department for histopathological diagnosis between years 2015 and 2020. Stained slides comprising of hematoxylin and eosin (H&E), periodic acid Schiff (PAS), Jones’ silver methenamine (JSM), Masson’s trichrome (MT), and Congo red with immunohistochemistry slides for serum amyloid A (SAA, Dako monoclonal mouse antibody, clone MC1) and DNAJB9 (Sigma Aldrich, polyclonal rabbit antibody HPA040967, 1:200 in select cases) along with formalin fixed paraffin embedded tissue (FFPE) blocks of the cases were retrieved. The slides were reviewed independently along with IF panels comprising of IgG, IgA, IgM, C3, Clq, kappa, and lambda (Bio SB, rabbit polyclonal antibody 1:50) with IgG subclasses (Sigma Aldrich, monoclonal mouse antibody, 1:50) and KM-55(IBL, anti-human GdIgA1, Rat IgG MoAb) performed in one case, and EM (imaged on Talos F200S G2, ThermoFischer scientific) images from the database by two pathologists (VB and AB) for confirmation of diagnosis and classification according to the IKMG classification [5]. All cases were subjected to paraffin IF as per institutional protocol [9] to ensure accuracy and unmask any undiscovered polyclonal deposits, and only those cases where both the pathologists concurred unanimously and completely were included in the study. Cases with isolated C3 deposits and TMA were screened in detail by reviewing the clinical picture, microscopy, direct immunofluorescence, and repeated paraffin IF for light chain restriction. None of the cases qualified to be placed under the MGRS spectrum.

Cases with a confirmed diagnosis of overt hematolymphoid malignancy were subsequently excluded from the study. Data regarding age, sex, and clinical workup was obtained from request forms and records maintained by the department. Standard definitions and ranges for clinical parameters (plasma cell percentage, serum free light chain ratio, renal involvement by GFR, and creatinine criteria) given by the International Myeloma Working Group (IMWG) 2014 were used to include and exclude cases [10].

Results

Out of 4,763 renal biopsies obtained during the study period, a total of 66 suspected MGRS cases were encountered during our study period, out of which 18 cases were excluded post confirmation of overt multiple myeloma. The remaining 48 cases were assessed for diagnostic characterization.

Clinical Profile

Most patients in the study belonged to the fifth decade with a median age of 50 years (mean 50.14 ± 10.43) range (24–68 years) with a male preponderance and a male to female ratio of 2:1. Most patients (66.6%) presented with proteinuria as the sole manifestation (n = 32) followed by hematuria (31.2%), a combination of proteinuria and re-

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nal dysfunction \((n = 14)\) (29.16%), and only renal dysfunction was found in a minority \((n = 2)\) (4.16%) of the cases (Table 1).

**Investigations**
Investigation details of all the cases were obtained. Many of the patients were investigated after the renal lesions were identified in the biopsy.

The majority of the patients had abnormal serum free light chain ratio (60.8%). M spike by serum protein electrophoresis (SPEP) or urinary protein electrophoresis (UPEP) was seen in nearly half (48%) of the patients. At the time of analysis, none of the 48 patients were diagnosed with an overt hematolymphoid malignancy and continued to be on follow-up.

**Histopathology**
AL amyloidosis was the most common diagnosis observed on histopathological evaluation \((n = 33)\) followed by light chain deposition disease (LCDD) \((n = 5)\), LCPT \((n = 3)\), PGNMID \((n = 3)\), heavy chain deposition disease (HCDD) \((n = 1)\), fibrillary glomerulonephritis (FGN) \((n = 1)\), and immunotactoid glomerulonephritis \((n = 1)\) with 1 case being unclassifiable with the current schema (shown in Fig. 1).

**Histomorphological Entities**

**AL Amyloidosis**
Majority of the cases that demonstrated AL amyloidosis \((69%)\) belonged to the fifth decade, with a median age of 50 years \((mean 51.63 ± 9.87)\) with a male predisposition \((M:F = 2:1)\). Majority of patients \((75.7%)\) in this group had proteinuria as the sole manifestation followed by microscopic hematuria \((27.3%)\), a combination of proteinuria and renal dysfunction \((21.2%)\) with only 1 patient presenting with pure renal dysfunction. An abnormal SFLC ratio was noted in most cases \((52.9%)\) with M spike seen in the fast gamma region in nearly a third of the cases \((35.29%)\). The bone marrow plasma cell percentage

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**Table 1.** Demographic profile and clinical parameters of MGRS cases \((n = 48)\)

| Cases, \(n (\%)\) | Proteinuria* | Renal dysfunction# | Overlap | Hematuria | Light chain/paraprotein predominance |
|-------------------|--------------|---------------------|---------|-----------|------------------------------------|
| Male \((n = 32)\)  | 32 (96.9)    | 8 (24.2)            | 7 (21.2) | 9 (27.3)  | Lambda (81.8)                      |
| Female \((n = 16)\)| 5 (100)      | 2 (40)              | 2 (40)  | 1 (20)    | Lambda (60)                        |
| Mean age ± SD, years | 50.5±10.5 | 48.5±11.85          | 49.5±12.35 | 48.8±12.9 | –                                  |

*ITG, immunotactoid glomerulonephritis. * Inclusive of concomitant renal dysfunction. # Inclusive of concomitant proteinuria.

![Frequency Chart](chart.png)

Fig. 1. Histomorphology spectrum of MGRS. The majority of the cases encountered at our center were AL amyloidosis, followed by LCDD.
was variable (mean 5%, range 3–12%). All cases were managed with bortezomib, cyclophosphamide, and dexamethasone (VCD) in 3–6 cycles with lenalidomide maintenance. Follow-up details were, however, limited and out of 9 patients whose follow-up was available, one case showed worsening, two showed no response, four showed a suboptimal response, and only two showed improvements in renal parameters.

Histologically, AL amyloidosis was characterized by the presence of PAS negative, silver negative Congophilic material in the glomerular, and the tubulointerstitial compartment, showing IF for one of the light chains. Lambda light chain restriction was most frequently encountered (81.8%). IHC for AA amyloidosis was negative. Electron microscopy showed randomly arranged fibrils ranging from 7 to 10 nm (shown in Fig. 2).

Light Chain Deposition Disease

LCDD was the second most common histological diagnosis (11%). Patients with LCDD in our study belonged to the fourth to sixth decade, with median age of 50 years (mean 49 ± 11.4 years) with a high male preponderance (M:F = 3:1). Most patients (60%) had proteinuria followed by a combination of proteinuria and renal dysfunction (40%), with microscopic hematuria seen in only 1 patient. An abnormal SFLC ratio was seen in all the cases, with M spike being present in a significant proportion (40%) of cases. Nearly half of the cases were managed with VCD regimen followed by lenalidomide maintenance, with the other half being treated with a bortezomib, lenalidomide, and dexamethasone (VRd) regime. Two of the cases underwent autologous stem cell transplantation (ASCT). Only one of the 5 cases showed improvement in proteinuria. Histologically, LCDD was characterized by presence of glomerular and tubulointerstitial deposits which were PAS positive, variably argyrophilic, and Congo red negative. IF showed lambda light chains in most cases (60%) with linear staining of glomerular capillary walls and tubular basement membranes. EM confirmed granular powdery electron dense deposits (EDD) (shown in Fig. 3). A case of a 65-year-old male with posttransplant LCDD from our center was previously published as a case report [11].

Fig. 2. Histomorphological features of AL amyloidosis. a Acellular amorphous PAS negative material in the glomeruli (stain PAS, ×40). b Deposits were non-argyrophilic (stain Jones’ silver methenamine, ×40). c Congo red staining shows positivity in the deposits (stain Congo red, ×40). d Apple green birefringence seen on polarized light (stain Congo red, ×40). e Direct immunofluorescence shows restriction for a single (lambda in this case) light chain. f Electron microscopy shows organized fibrils of size 7–10 nm (200 kv, ×7,000).
Proliferative Glomerulonephritis with Monoclonal Immune Deposits

Three cases of PGNMID were encountered in our study and were found to be associated with a much younger age (median 39 years, mean 31.33 ± 18.71); all 3 cases were males and had proteinuria and renal dysfunction of variable degrees with 2 out of 3 cases (66.6%) showing microscopic hematuria. One case showed an abnormal SFLC ratio with another one case showing M spike. Bone marrow plasmacytosis was variable (6–7%). Cases were treated with bortezomib, thalidomide, and dexamethasone regimen (VTD). Follow-up details were limited and available only for a single patient who showed a worsening course and was subsequently lost to follow up.

Histologically, the diagnosis of PGNMID was made on a proliferative glomerular morphology wherein a predominant membranoproliferative pattern of injury was observed. The lesions exhibited a unique IF profile with 2
Fig. 5. Histomorphological features of PGNMID IgG type. a Diffuse mesangial and endocapillary proliferation with neutrophils (stain HE, ×40). b Mesangial and endocapillary hypercellularity with variable capillary wall thickening (stain, Jones’ silver methenamine, ×40). c Strong immunofluorescence for IgG and lambda light chain. d EM shows paramesangial and sub endothelial electron dense deposits (200 kv, ×2,550).

Fig. 6. Histomorphological features of monoclonal fibrillary glomerulonephritis. a PAS positive-mesangial deposits (stain PAS, ×40). b Capillary loop thickening with variable argyrophilia (stain Jones’ silver methenamine, ×40). c Non-Congophilic nature of the mesangial deposits (stain, Congo red, ×40). d Wooly capillary wall deposition of IgG and strong positivity for lambda light chain (inset). e DNAJB9 positivity in the deposits. f Randomly arranged fibrils identified in the mesangium and along glomerular basement membrane measuring 10–30 nm in diameter (200 kv, ×7,000).
cases showing monoclonal IgG positivity (IgG3 subclass) along with monoclonal lambda positivity and one case showing monoclonal IgA positivity with lambda restriction. In the latter case, KM55 was performed and was negative, thus excluding lambda-restricted IgA nephropathy. Small immune-type unorganized deposits were observed on EM (shown in Fig. 4, 5). Of the IgG type PGNMID, one case was encountered in a posttransplant setting. A case report on a 10-year-old male with PGNMID was published from our center [12].

Light-Chain Proximal Tubulopathy
Three cases of LCPT were seen with a median age of 58 years (mean 52.6 ± 11.9). LCPT showed an identical male preponderance to other MiG-related lesions (M:F = 2:1). Two of the patients presented with proteinuria (66.6%), whilst one (33.3%) presented with renal dysfunction. No hematuria was seen in the 3 cases. M spike was seen in one case, which was demonstrated to be G lambda by IFE. SFLC ratios were within the reference ranges, albeit close to the lower limits in 2 cases and upper limit in one. Cases were managed with VCD regimen. Follow-up of one case was available, who did not show any improvement in renal parameters.

Histologically, all 3 cases were noncrystalline type proximal tubulopathies with diffuse proximal tubular necrosis associated with interstitial inflammation with lymphomononuclear cells. IF revealed basolateral staining for lambda in one case, with one case showing epithelial cytoplasmic as well as basement membrane positivity for lambda light chain. The third case encountered showed kappa light chain restriction. EM showed loss of brush border, extensive tubular vacuolization with prominent lysosomes.

Fibrillary Glomerulonephritis
One case of FGN was encountered in a 47-year-old female with proteinuria and microscopic hematuria. SFLC was within normal range and no M spike was seen in the case.
Histologically, PAS-positive, variably argyrophilic, and fuchsinophilic deposits which were negative for Congo red were observed in the mesangium. IF showed a wooly deposition for IgG with lambda restriction. Immunohistochemistry for DNAJB9 was positive confirming the diagnosis of FGN (shown in Fig. 6).

Immunotactoid Glomerulonephritis
One case of immunotactoid nephropathy was seen in a 59-year-old male with proteinuria and microscopic hematuria. The SFLC ratio was deranged (0.19) with the presence of M spike in urine protein electrophoresis, which was found to be lambda only by immunofixation. Histologically, there were eosinophilic, weakly PAS-positive, fuchsinophilic, and silver-negative nodules seen in the glomeruli. IF showed only lambda positivity with all other heavy chains and complement being negative. EM showed the nodules to be composed of microtubules in parallel arrays in the mesangium and glomerular basement membrane of size 42–51 nm length (shown in Fig. 7).

Heavy Chain Deposition Disease
One case of HCDD was seen of a 37-year-old female who presented with a combination of proteinuria and renal dysfunction with microscopic hematuria. M spike was seen and demonstrated to be IgG by immunofixation. Bone marrow showed 6% plasma cells.

Histologically, the biopsy demonstrated PAS-positive glomerulosclerosis with variable argyrophilia. IF showed a linear deposition of IgG and negativity for all other immunoglobulins and complement. Ultrastructurally powdery dense deposits were observed in the glomerular basement membranes (shown in Fig. 8). We described a similar case of HCDD in a 42-year-old male in 2012, but the same was not included the study as it predated the inclusion criteria [13].

Discussion
Current classification of MGRS lesions relies on histomorphology, IF, and EM. However, due to EM not being widely available to the pathologist, it necessitates a full panel of IF and a robust correlation with the clinicopathological profile [5]. The IKMG consensus classification along with recent additions of miscellaneous subcategory to the nonorganized deposit diseases and TMA to the non-immunoglobulin diseases is summarized in Figure 9.

Renal lesions in MGRS are attributed to inappropriate production of larger amounts of immunoglobulin molecules or paraproteins by the marrow, which can be of light and/or heavy chain excess. Biochemical analysis of these proteins showed a predominance of light chains followed by light and heavy chain fragments regardless of M band...

Fig. 8. Histomorphological features of heavy chain deposition disease. a Nodular PAS-positive deposits (stain PAS, ×40). b Nodules were variably argyrophilic (stain, Jones’ methenamine silver, ×40). c Linear deposition of IgG noted in the capillary walls and tubular basement membranes. d Powdery electron dense deposits in the glomerular basement membranes.
in serum or urine [14]. Additionally, these molecules may be produced with abnormal physicochemical properties like increased size, polymeric forms, fragments, and abnormal glycosylation [15, 16]. Earlier studies by Buxbaum [17] attribute this to presence of inherent peptides, which on isolation from their molecular environment desist or undergo limited proteolysis and get deposited at various sites. Renal injury patterns with paraproteins can be attributed to the fact that light chain polymers and heavy chains remain unfiltered and hence affect the glomeruli preferentially; whereas, the light chains are filtered freely and affect the tubulointerstitial compartment as well by exceeding the resorption capacity of the proximal tubular cubulin-megalin receptors [18, 19]. Further, the capacity to form pathogenic deposits may exist in a spectrum with amorphous, non-fibrillar deposits at one end and amyloidosis on the other [20].

Our study demonstrated many MGRS lesions to be AL amyloidosis with a median age of 50 years. AL amyloidosis is a common histologic presentation in older adults (>85 years) with nephrotic range proteinuria [21] and is the most common type of amyloid associated with a plasma cell dyscrasia in the USA and Europe [22].

LCDD was the second most common diagnosis in our study with a median age of 50 years with a male predilection. We report a slightly higher rate of renal dysfunction (40%) than available studies on the subject [23]. A significant number of patients with LCDD as the underlying lesion do not have overt plasmacytosis at presentation [24]. Our cases demonstrated classical histomorphology findings, prompting further diagnostic ingress into the etiology.

Our cases showed features similar to findings presented in the largest case series by Larson et al. [25]. In the absence of crystals, a definitive diagnosis of LCPT is a difficult one; however, the available literature does not confer specific diagnostic criteria for noncrystalline type of LCPT, which has been described to be a commoner occurrence compared to its crystalline counterpart. Only, lambda light chain restriction with light chain on IF and inclusions in the lysosomes have been described on EM, of which the latter are difficult to demonstrate and sometimes not seen altogether [25]. One case of fibrillary glomerulonephritis was identified in the study, which is currently considered under the umbrella of MiG-related lesions. However, of late a considerable number of cases

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**Fig. 9.** The IKMG consensus classification for lesions of MGRS.
with FGN have been reported to have masked polyclonal deposits [26]. Our case did not show the unmasking effect described by repeating paraffin IF and was consistently IgGλ positive.

We report one case of immunotactoid glomerulopathy in a 59-year-old male with proteinuria. Immunotactoid glomerulopathy is rare in literature and the largest study is of 73 cases [27]. Our case showed a lambda restriction and was unique in terms of IF being negative for all heavy chains and complement. The EM had a characteristic microtubular arrangement and a diagnosis was made after excluding other differentials of microtubular deposits (cryoglobulinemia type I and II) based on clinical (absence of vasculitic features, arthralgias, neuropathy, and hyper viscosity syndromes) and light microscopic features (absence of glomerular protein thrombi and vasculitis).

One case of heavy chain deposition disease was reported at our center in a 37-year-old female presenting with a combination of renal symptoms. HCDD is a rarely encountered condition with only about 70 reported cases characterized by the presence of deposits of truncated monoclonal immunoglobulin heavy chains, most frequently with heavy chain from immunoglobulin G (IgG; g-HCDD) [28].

Limitations of the Study
Our study, being aimed at a histomorphology spectrum, highlights the spectrum of MGRS lesions, which should be suspected and appropriately diagnosed by the nephropathologist. The study is limited by relatively lesser number of cases in all histomorphological groups with the exception of AL amyloidosis. Thus, their behavior and presentations cannot be generalized in the context of local population. Also, being a referral center complete follow-up details of some cases were limited. Since, the incidence of these lesions is also low, continuing work in diagnosing and following up these cases will strengthen our initiative.

Conclusion
MGRS lesions are infrequently encountered in the practice of nephropathology, and many a times pose a diagnostic challenge due to limitation of a congruent clinical or hematological picture and can even initiate a diagnostic thought process in a previously unconsidered direction. Nevertheless, a thorough histological examination with IF and EM often precipitates in the right diagnosis and prompts timely management.

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Statement of Ethics
The study was reviewed and approved by the Institutional Ethical Committee (Institute Ethics Committee, All India Institute of Medical Sciences, IEC -71/January 14, 2022) Written informed consent was obtained from all the patients to use the diagnostic material for publication and all investigations performed were a part of the patient investigations and diagnosis and were provided to the patients, and no additional diagnostic material was obtained for research purposes.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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Author Contributions
Conception and design of the work and drafting the article: Adarsh Barwad and Varun Bajaj. Data collection and imaging: Varun Bajaj, Lalit Kumar, and Ranjit Kumar Sahoo. Data analysis and interpretation: Geetika Singh, Adarsh Barwad, and Varun Bajaj. Critical revision of the article: Geetika Singh, Sanjay Kumar Agarwal, and Amit Kumar Dinda. Final approval of the version to be published: Geetika Singh, Adarsh Barwad, Ranjit Kumar Sahoo, and Sanjay Kumar Agarwal.

Data Availability Statement
All data pertaining to the cases has been included in the study. However, if needed, the authors are willing to share the xls files on demand. Further inquiries can be directed to the corresponding author.
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