An update of proliferative glomerulonephritis with monoclonal immunoglobulin deposits

Manna Li¹, Gaosi Xu¹

¹Department of Nephrology, the Second Affiliated Hospital of Nanchang University, China

Correspondence to: Gaosi Xu; E-mail: gaosixu@163.com

Running Title: Update of PGNMID
ABSTRACT

As aging increases, monoclonal gammopathy is becoming more common, and monoclonal gammopathy of renal significance (MGRS) is gaining attention due to frequent renal involvement. Among MGRS, proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a special category. The disease was first described in 2004, and the research history on it is relatively short. Compared with other MGRS, the detection rate of circulating clones is lower in patients with PGNMID, which is easy to be missed and misdiagnosed in clinical work. In this review, the etiology and clinical features of PGNMID are discussed. It is noted that PGNMID is not only associated with MGRS, but also with malignancy, infection, and other factors. PGNMID is not a disease exclusive to the elderly, young people can also develop this disease. Due to the low detection rate of circulating clones in most patients, confirmation of the disease needs to be combined with renal pathology, which emphasizes the importance of completing light and heavy chain subtype staining. Treatment options for patients with PGNMID differ by etiology. For MGRS-associated PGNMID, the current treatment is primarily empirical and more research evidence is needed to fill the treatment gap.

Keywords: etiology, proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID), treatment

1. Introduction

Monoclonal gammopathy is associated with an increase in “M protein” (entire monoclonal immunoglobulin or fragment thereof) secreted by plasma or B cells for various reasons [1,2]. The M proteins can be distributed in serum or urine, as well as in various organs (such as kidney, skin, liver, heart, bone marrow). When evaluating the tumor burden of patients, we need to consider all the M proteins, either in serum or deposited in organs. There is no doubt that a more aggressive treatment regimen, such as administering chemotherapy, will be pursued for patients who have clones detected in the serum or bone marrow and meet the diagnostic criteria for malignant diseases, such as symptomatic multiple myeloma or B-cell lymphoma. However, if
the clones detected in the serum or bone marrow do not meet the current diagnostic criteria for malignant hematological diseases, the patient's treatment is in a difficult situation. It depends on whether the M protein causes organ dysfunction or not (2,3). Naturally, the concept of monoclonal gammopathy of clinical significance (MGCS) was proposed, which encompasses all types of organ lesions induced by M proteins produced by non-malignant hematological tumors or asymptomatic small B-cell clones lacking chemotherapeutic criteria (4).

The kidney is the most important excretory organ and is often involved in hematologic disorders. To better understand and manage this type of disease, we introduced the concept of monoclonal gammopathy of renal significance (MGRS) (2), which connects the “grey area” between hematology and nephrology. In 2012, MGRS was first defined as a causal relationship between plasma or B-cell clones and kidney disease (2). The subsequent literature also reported the clinicopathological manifestations and treatment prognosis of MGRS (5-9). Unlike other types of MGRS, the positive detection rate of M protein in PGNMID is relatively low (about 30%) (10,11), which makes early diagnosis difficult. It is worth noting that a low positive detection rate for serum M protein does not mean that the renal damage is not severe. Among transplant-related MGRS, PGNMID is the more common type of transplanted kidney recurrence and has a poor prognosis (12,13). At present, there are still many problems worth exploring and solving for PGNMID. In this paper, we discuss PGNMID in terms of etiology, clinicopathological manifestations, and treatment.

2. Clinicopathologic features

In 2004, proliferative glomerulonephritis with monoclonal IgG deposition was first defined by Nasr et al. (14). The pathology is characterized by monoclonal IgG (a single IgG subclass) with a single light chain subtype deposited in the glomerulus. The clinical diagnosis of PGNMID also requires the exclusion of cryoglobulinemia and any known type of M protein-related glomerular diseases (such as light chain deposition disease, fibrillary glomerulonephritis, immunotactoid glomerulopathy, and the main points of identification are shown in Supplementary Table 1). This disease is uncommon, with an autologous kidney biopsy rate of 0.17-0.21%, as Nasr et al.
reported (10,14). Although the majority of patients are middle-aged, cases of adolescence have been reported in the literature (all showed heavy chain deposition of IgG3 subclass on glomerular immunofluorescence) (15,16). The patients often start with nephrotic syndrome, half of them have renal insufficiency and microscopic hematuria, and some have hypertension (38-67%) and hypocomplementemia (18-40%), a few patients present with gross hematuria. We have reviewed a series of case reports on PGNMID and summarized them in table 1 (10,14,17-19).

As shown in table 1, the positive detection rate of M protein was lower for PGNMID than for monoclonal immunoglobulin deposition disease (MIDD) (30% vs. 100%) (3,20-22). Although it is challenging to detect M protein in serum, it does not mean that the tumor burden of PGNMID patients is low or the disease is not severe. To better evaluate PGNMID disease, various assay techniques can be used in clinical work to improve the detection rate of monoclonal immunoglobulin, including serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE), serum-free light chain (sFLC), and mass spectrometry (Supplementary Table 2). We can also use flow cytometry or immunohistochemistry and fluorescence in situ hybridization (FISH) on marrow specimens and extramedullary hematopoietic tissues to evaluate and identify traces of potential clones (3). Some patients have been diagnosed with PGNMID along with solid tumors, myelodysplastic syndrome (MDS), primary renal amyloidosis, MGUS, or autoimmune diseases (10,18,23) (Figure 2). However, based on current assays and evidence, no direct relationship between these concomitant diseases and PGNMID has been identified. Perhaps with further studies, an intrinsic link may be discovered.

Pathological evaluation of a kidney biopsy is essential for the diagnosis of PGNMID (Figure 1). Under light microscopy, the glomeruli were predominantly proliferative changes, including membranous proliferative glomerulonephritis (MPGN)-like, mesangial proliferative glomerulonephritis (MsPGN)-like, with a few presented membranous nephropathy (MN) changes (10,14), and glomerular crescent in 10-50% of patients (10,14,17-18). Initially, in the 10 cases of PGNMID reported by Nasr et al. (14), the type of heavy chain of M protein deposited in the glomeruli was
only IgG subclasses (e.g., IgG1, IgG2, or IgG3), and IgG3 heavy chain subclass was the most common type of deposition. It may be due to the considerable molecular weight of IgG3, which makes it difficult to pass through the glomerular filtration membrane. At the same time, IgG3 can self-aggregate through FC-FC interaction and may selectively accumulate in the glomerulus (10,14). From a retrospective study by Bhutani et al. (18), it seemed to be found that deposition of IgG3 subclass (IgG3-PGNMID) tended to show MPGN-like changes, whereas MN-like changes were common in IgG1-PGNMID, but this idea has not been confirmed. As studies progressed, PGNMID with heavy chain types of IgG4 subclass, IgA, IgM, and light chain (LC) only deposition were successively reported (10,12,18,24-28). Similarly, a few patients have been reported in the literature to show the deposition with focally variegated texture (10,13), which is different from the typical electron microscopic presentation (granular electron-dense deposits). And these atypical presentations further expanded the spectrum of pathological manifestations.

Immunofluorescence is an essential diagnostic tool for PGNMID, but in clinical work, the failure of further staining for IgG subclass or light chain subtypes is still encountered due to various reasons (e.g., no glomeruli to stain further), leading to diagnosis delay or misdiagnosis (29,30). To reduce the incidence of such events, adequate tissues should be taken at the time of renal biopsy, and staining for light and heavy chain subtypes should be perfected whenever possible. If necessary, special stains such as Congo red and serum amyloid P component (SAP) can also be used for differential diagnosis. Of note, the restriction of IgG subclass or light chain subtype is not sufficient to diagnose PGNMID. Fibrillary glomerulonephritis has been reported to show positive staining for a single IgG subclass usually, but light chain subtypes show double positivity (31). Similarly, in membranous-like glomerulopathy with masked IgG Kappa deposits (MGMID) showed IgG1-κ restricted deposits, but still not diagnostic of PGNMID. MGMID is mostly seen in autoantibody-positive young women with little or no Ig staining in routine immunofluorescence (IF) of renal tissue, but significantly brighter IF staining in paraffin tissue and positive SAP staining, which is distinct from PGNMID (32,33). Therefore, a combination of light
microscopy, immunofluorescence, electron microscopy findings and clinical manifestations is required for differential diagnosis in the diagnosis of PGNMID.

Interestingly, M proteins (IgG2, IgG4, and Kappa deposits) have been reported to be detected in C3 glomerulopathy (C3G) patients treated with eculizumab (All 5 patients were found on procedural renal biopsy 1 year after treatment) (34). Combined with the electron microscopy results (punctate electron-dense deposited in GBM, TBM and vessels), the final diagnosis of MIDD was made (34). This situation is due to the structural characteristics of eculizumab. It is a recombinant intact immunoglobulin of human and murine origin in which CH2 and CH3 constant regions from IgG4 are fused to the IgG2 hinge region and CH1 domain and then paired with a Kappa light chain (35). It is an exogenous monoclonal immunoglobulin, and although immunofluorescence shows monoclonal immunoglobulin deposition, the deposition site is different. Therefore, careful differentiation is required in the diagnosis of PGNMID.

3. Exploration of the etiology and mechanisms of PGNMID

It is generally accepted that the pathogenesis of PGNMID is the deposition of M protein in the glomerulus, which activates the complement causing an inflammatory response that results in renal dysfunction (2,3,10). However, the upstream mechanism of this entity (M protein production) has been less studied. Based on the mechanism of immunoglobulin production and combined with the clinical manifestations of PGNMID, the following hypothesis can be made about its etiology (Figure 2A): a) Malignant B cells or plasma cells in the bone marrow or serum secrete large amounts of abnormal immunoglobulins. b) Normal B cells or plasma cells in the bone marrow or serum are affected by various factors, resulting in the secretion of abnormal immunoglobulins. The first condition is well understood. Consider a primary hematologic disorder with secreted M protein causing renal injury.

In the second condition, there is no primary disease of the hematological system, and abnormal immunoglobulins are secreted due to stimulation by various factors. Sirac et al. (36) have pointed out that changes in some amino acids, which may reduce the stability and folding of immunoglobulins, lead to oversecretion of unstable
immunoglobulins or immunoglobulin fragments. Similar cases have been reported in the literature that two patients with PGNMID (IgG3-κ) associated with parvovirus B19 infection (20). Scholars have speculated that PGNMID is mediated by IgG3κ-type monoclonal immunoglobulin after infection with the parvovirus B19, a process that occurs as part of the immune disorder associated with viral infection (20). Interestingly, the clinical manifestations and laboratory findings of PGNMID were transient in these two patients and returned to normal on their own after viral clearance. In addition, PGNMID has also been reported in association with HCV infection (37). Renal damage due to infection has been reported previously, but the type of renal damage varies (38-39). Combined with previous reports that no M protein was detected in the circulation, it is speculated that immune impairment after infection may be related to the pathogenesis of PGNMID.

In addition to being associated with viral infections, PGNMID has been related to solid tumors. The patient developed nephrotic syndrome three months after diagnosing squamous cell lung carcinoma (SCLC) (40). Laboratory results did not reveal hepatitis virus infection, autoimmune disease or hematologic tumors, and the final diagnosis of PGNMID (IgG1-λ) was made in combination with renal biopsy results. It has been mentioned that the presentation of nephrotic syndrome within 12 months after cancer diagnosis supported tumor-associated glomerulopathy (41). The patient treated with carboplatin and paclitaxel chemotherapy showed consistent improvement in tumor size and squamous cell carcinoma antigen (SCC) levels, reduced urinary protein, and improved renal function. All the above evidence supports the close association of PGNMID with lung cancer, emphasizing the possibility of paraneoplastic glomerulopathy, but the specific mechanisms behind it need further investigation. Therefore, not all PGNMID is associated with hematologic tumors. Infections and solid tumors can also be responsible for the disease (Figure 3).

4. Treatment of PGNMID

After reviewing the literature, the etiology of PGNMID is roughly divided into two categories: primary hematologic diseases and others. Based on the hematologic assessment, primary hematologic-related PGNMID can be further divided into
malignancy-related and MGRS-related PGNMID. In 2017, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) updated the definition of MGRS. It emphasizes that renal lesions caused by M proteins are considered MGRS when the underlying B-cell or plasma cell clones do not cause tumor complications or do not meet any current hematologic criteria for specific treatment. Just like low-grade chronic lymphocytic leukemia (CLL) and low-grade B-cell non-Hodgkin's lymphoma with renal lesions should be diagnosed as MGRS (3,42-44). Therefore, if a hematologic malignancy is found at the same time as the diagnosis of PGNMID, and there is a causal relationship between the two, the diagnosis of malignancy-associated PGNMID is more reasonable. PGNMID with monoclonal immunoglobulin light chain deposition only (LC-PGNMID) tended to be associated with malignancy (27). Other types of PGNMID include immune regulation disorders caused by infections, tumors, and other factors, and these types of PGNMID are relatively rare in clinical practice. The literature reports that PGNMID caused by the viral infection can recover spontaneously after viral clearance (20), and no specific treatment is needed for this type of PGNMID. Depending on the clinical situation, PGNMID can be classified in the manner of Figure 2B. Of these, unclassified PGNMID is considered MGRS-related PGNMID in clinical work (in the following, both of them will be collectively referred to as MGRS-related PGNMID).

In clinical work, 65%-100% of PGNMID is associated with MGRS (10,14,17-19,27). The goals of managing these patients include preserving renal function, restoring renal graft eligibility, improving life expectancy, and minimizing adverse effects of treatment (45). In 2012, IKMG (7) gave several treatment recommendations, summarized in Figure 4, which emphasizes the need to consider the patient's renal function, urinary protein and drug tolerance when treating PGNMID. In a series by Nasr et al. (10,14), some MGRS-related PGNMID patients had stable renal function at last follow-up after treatment with renin-angiotensin system (RAS) inhibitors or prednisone alone, even when they had nephrotic range proteinuria or stages 3-4 CKD at renal biopsy. It seems that PGNMID is relatively easy to control. The same question has been raised (46): is clone-directed therapy...
always necessary for MGRS-related PGNMID? There is no clear answer yet. Recently, Gumber et al. (19) mentioned that the principle of treating MGRS-related PGNMID is targeted the potential clones. In patients without detectable clones, who received treatment targeting a hypothetical potential clone (i.e., antilymphoma regimen for B-cell clone, antmyeloma regimen for plasma cell clone, and most patients treated continuously for about 6 months), there was no end-stage renal disease at the last follow-up (median 23 months after diagnosis), and the treatment was well tolerated. Further analysis of the study by Gumber et al. showed that all patients were in stage 3-5 CKD, and some patients also had large amounts of proteinuria. Both studies suggest that MGRS-related PGNMID patients at a late stage of chronic kidney disease can achieve stable conditions either with conservative treatment or by targeting potential clones. Therefore, the need to target potential clones in patients with MGRS-related PGNMID is inconclusive.

Another important and controversial issue is the choice of chemotherapy regimen when patients with MGRS-associated PGNMID clearly need chemotherapy. This is a good clue if circulating clonal cells consistent with renal tissue deposition can be detected in MGRS-associated PGNMID patients so that we can target chemotherapy (rituximab-based regimens for potential B-cell clones and bortezomib-based regimens for potential plasma cell clones). For MGRS-associated PGNMID patients who fail to detect clonal cells in the circulation consistent with renal deposition, empirical chemotherapy is currently the mainstay. Some scholars (18,27) have noted that the clones of PGNMID were most often related to plasma cell clones (60%-100%). Based on this view, a bortezomib-based regimen is recommended. Many cases of bortezomib-based therapy have been reported in the literature, with most patients showing improvement (47-49). It has been reported that two patients did not respond to the initial regimen of rituximab and were subsequently relieved by bortezomib (19). Of course, there are also empirical chemotherapies based on rituximab that have good efficacy (17,50), thalidomide or lenalidomide (immunomodulation) (17). While empirical chemotherapy is given, the efficacy of the treatment needs to be closely evaluated and the regimen changed if necessary. With the current study results, it is
not easy to choose a specific treatment, and large samples of evidence-based evidence are still needed.

5. Conclusions

PGNMID, as a histopathological entity, was identified as monoclonal-related nephropathy when it was first proposed in 2004 (14). As research progressed, scholars gradually realized that not all PGNMID was associated with hematological tumors and that infections and solid tumors could also cause the disease (20,37,40). The detection rate of circulating clones in PGNMID patients is low, and the diagnosis of the disease is based mainly on renal pathology. Restriction of IgG subclasses or light chain subtypes is not sufficient to diagnose PGNMID, and it is necessary to complete the staining of light and heavy chain isoforms for comprehensive analysis and careful differentiation. For patients with PGNMID associated with malignant hematologic neoplasms, early chemotherapy is emphasized. Immune disorder-associated PGNMID can be treated for the etiology of the disease. Moreover, treatment of MGRS-associated PGNMID is mostly administered empirically based on the patient's condition.

While the interest in PGNMID is on the rise, the knowledge of it remains limited. The pathogenic mechanisms of PGNMID are unclear and effective treatment remains challenging. Further research is necessary to find biomarkers, describe their mechanisms, improve detection sensitivity, and identify clones to guide treatment.

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AUTHORS’ CONTRIBUTIONS

Manna Li contributed the idea of the article, performed the literature search and data analysis, and drafted the article. Professor Gaosi Xu critically revised the work.
CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

ETHICAL APPROVAL
This article does not contain any studies with human participants or animals performed by any of the authors.

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### Table 1. Comparison of clinical data in review literature

| Year   | Nasr et al. (14) | Nasr et al. (10) | Guiard et al. (17) | Bhutani et al. (18) | Gumber et al. (19) | Nasr et al. (27) |
|--------|------------------|------------------|--------------------|---------------------|--------------------|------------------|
| 2004   | 0.21%            | 0.17%            | NA                 | NA                  | NA                 | NA               |
| 2009   |                   |                  |                    |                     |                    |                  |
| 2011   |                   |                  |                    |                     |                    |                  |
| 2015   |                   |                  |                    |                     |                    |                  |
| 2018   |                   |                  |                    |                     |                    |                  |
| 2020   |                   |                  |                    |                     |                    |                  |
| N. of studies | 10               | 37               | 26                 | 60                  | 19                 | 17               |
| Male / Female | 5/5             | 23/14            | 10/16              | 32/28               | 12/7               | 13/4             |
| Renal biopsy age | 58              | 55               | 52                 | 56<sup>st</sup>      | 58                 | 62               |
| (Y, mean [range]) | (44-78)         | (20-81)          | (29-77)            | (47, 62)            | (25-83)            | (44-84)          |
| Nephrotic syndrome, n (%) | 4/9 (44%)       | 17/35 (49%)      | 22 (85%)           | NA                  | NA                 | 9/16 (56%)       |
| Hypertension, n (%) | NA              | 14 (38%)         | 16/24 (67%)        | NA                  | NA                 | 15 (88%)         |
| Renal insufficiency, n (%) | 80%             | 68%              | 54%                | NA                  | 100%               | 94%              |
| Scr (mg/dL, mean [range]) | 2.8             | 2.8              | 2.4                | NA                  | 1.7                | 2.3              |
| Microscopic hematuria, n (%) | 6 (60%)         | 27/35 (77%)      | 24/24 (88%)        | NA                  | NA                 | 16 (94%)         |
| 24-hour urine protein (g, mean [range]) | 5.8             | 5.7              | 5.3                | 3.6<sup>st</sup>     | 3.6<sup>st</sup>    | 5.7              |
| Glomerular crescent, n (%) | 1 (10%)         | 12 (32%)         | 13 (50%)           | 11 (18%)            | NA                 | 1 (6%)           |
| Complement IF staining in Glomerular, n (%) | NA              | NA               | NA                 | NA                  | NA                 | NA               |
| C3     | 9 (90%)          | 36 (97%)         | -                  | 52/56 (93%)         | -                  | 17/17            |
| C1q    | 3 (30%)          | 23/36 (64%)      | -                  | 29/54 (54%)         | -                  | 2/17 (12%)       |
| Underlying clone and M protein evaluation |                    |                  |                    |                     |                    |                  |
| SIFE<sup>+</sup>, n (%) | 5 (50%)         | 10 (27%)         | 8/26 (31%)         | 12/59 (20%)         | 4 (21%)            | 11 (65%)         |
| sFLC<sup>+</sup>, n (%) | NA              | 1/4 (25%)        | NA                 | 12/56 (21%)         | 3 (16%)            | 10/12 (83%)      |
| PBFCM<sup>+</sup>, n (%) | NA              | NA               | NA                 | 1/9 (11%)           | NA                 | NA               |
| BM<sup>+</sup>, n (%) | 0/8 (0%)        | 2/22 (9%)        | 9/22 (41%)         | 10/40 (25%)         | 6/17 (35%)         | 14/16 (38%)      |
| Cloned cell types |                    |                  |                    |                     |                    |                  |
| PC     | PC (1),          | PC (2),          | PC (6), BC         | PC (3), BC          | PC (14)            |                  |
| BC     | BC (1)           | BC (7), LPC (1)  | BC (2)             |                    |                    |                  |

<sup>+</sup> PC: plasma cell, BC: B cell, LPC: lymphoid PCR, BM: bone marrow.
## Extrarenal Disease

| Extrarenal Disease | Non | MM (1), AL (1), solid tumor (4), autoimmune hemolytic anemia (1) | CLL (3), MDS (1), MGUS (4), solid tumor (9), Autoimmune hemolytic anemia (1) | MMUS (5), MGUS (1) |
|--------------------|-----|---------------------------------------------------------------|--------------------------------------------------------------------------------|------------------|

### Malignancy-Associated PG NMID

| Malignancy-Associate PG NMID | 0/10 | 1/37 | 9/26 | 1/60 \(^c\) | 0/19 | 5/17 |
|------------------------------|------|------|------|----------|------|------|
| MGRS-related PG NMID \(^b\)   | 10/10 (100%) | 36/37 (97%) | 17/26 (65%) | 59/60 (98%) | 19/19 | 12/17 |
| Follow-up time (M, mean [range]) | 12 (2-52) | 30 (1-114) | 68 (2-216) | 21 \(^M\) | 23 \(^M\) | 72 |

### Outcomes, n (%)

| Kidney function | ESRD (2/9, 22%) | ESRD (7/32, 22%) | ESRD (6/25, 24%) | NA | ESRD (8/15, 53%) |
|-----------------|-----------------|-----------------|-----------------|----|-----------------|
| Hematological evaluation | PD (0, 0%) | new M protein | MM protein (3) | 5% | PD (0, 0%) |
| Death | 0 (0%) | 5/32 (16%) | 1/25 (4%) | NA | 1 (5%) |

\(^a\): The clone detected in bone marrow are consistent with renal deposition;

\(^b\): Contains MGRS-related and unclassified PG NMID;

\(^c\): All three patients had Low-grade CLL (Rai stage 0) without treatment, but one patient at the time of presentation with kidney disease was found to have 80% BM involvement and renal parenchyma involvement with CLL;

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NA: Not Applicable, the upper right M: Median (interquartile range), SIFE: Serum Immunofixation Electrophoresis, sFLC R: Serum Free Light Chain Ratio, BM: Bone marrow, MM: Multiple myeloma, LPC: lymphoplasmacytic clone, PC: Plasma cell clone, BC: B-cell clone, PBFCM: peripheral blood flow cytometry, PD: progressive disease, AL: Amyloidosis, CLL: Chronic lymphocytic leukemia, NHL: Non-Hodgkin lymphoma, MDS: Myelodysplastic Syndromes, MGUS: Monoclonal Gammopathy of Undetermined Significance, ESRD: End Stage Renal Disease.
Figure 1: An example of PGNMID (IgG3-κ) renal biopsy image.

(A) Under light microscope, the glomerulus shows membranoproliferative pattern characterized by endocapillary and mesangial hypercellularity with lobular configuration and basement membrane double contours (Periodic acid-Schiff stain, magnification ×400); (B) Electron microscopy showed subendothelial (green arrow), mesangial (yellow arrow) and subepithelial (red arrow) granular electron-dense deposits. (C-H) Under immunofluorescence, IgG3, κ, C3 and C1q were deposited in mesangial area and vascular loops, whereas λ staining was negative (magnification ×400). The IgM, IgA and other IgG subclasses were negative and are not shown in the figure.
Figure 2A: M protein pathogenic mechanism hypothesis.

a: Abnormal B/plasma cells in bone marrow or/and blood secrete M protein.
b: Normal B/plasma cells in bone marrow or/and blood secrete M protein.

The M protein can be in the circulating blood or deposited in the kidneys, skin or other organs, which is determined by the M protein load and physicochemical properties.

Figure 2B: Clinical classification combined with the etiology and laboratory findings of PGNMID.

Unclassified PGNMID is considered as MGRS-related PGNMID.
Figure 3: Possible causes and accompanying diseases of PGNMID.
A: Malignant tumor of hematology system: multiple myeloma (MM), chronic lymphatic leukemia (CLL), non-Hodgkin lymphoma (NHL), etc.
B: Not meeting the criteria for hematologic malignancy: monoclonal gammopathy of renal significance (MGUS), MGRS, solid tumor, autoimmune disease. More patients with PGNMID are due to these types of causes.
Figure 4: International Kidney and Monoclonal Gammopathy Research Group (IKMG) recommended the treatment of PGNMID in 2012.

I: Patients with proteinuria of less than 1 g/day and no evidence of progressive disease.

II: Patients with proteinuria >1 g/day or progressive disease.

III: Candidate for renal transplantation (with detectable clones).

IV: Patients who are ineligible for renal transplantation.

Blank represents symptomatic measures and careful surveillance. Gray represents chemotherapy.

In stage III, when the patient is a kidney transplant candidate and the clones can be detected, the treatment is shown in the figure. However, when the patient fails to detect clones, there is no consensus on the treatment prior to kidney transplantation.