Glomerulonephritis with Non-Randall-type, Non-Cryoglobulinaemic Monoclonal Immunoglobulin G Deposits (PGNMID and ITG).

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ORIGINAL ARTICLE

Glomerulonephritis with non-Randall-type, non-cryoglobulinaemic monoclonal immunoglobulin G deposits (PGNMID and ITG)

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ABSTRACT

Background. Glomerulonephritis (GN) with non-Randall-type, non-cryoglobulinaemic monoclonal immunoglobulin G deposits encompasses rare diseases [proliferative GN with non-organized deposits (PGNMID) and immunotactoid GN] that cannot be distinguished without ultrastructural analysis by electron microscopy (EM).
Methods. Here, we report and analyse the prognosis of 41 EM-proven (PGNMID for 39/41) and 22 non-EM-proven/DNAJB9-negative cases, diagnosed between 2001 and 2019 in 12 French nephrology centres.

Results. Median (interquartile range) serum creatinine (SCr) at presentation was 150 (92–256) µmol/L. The predominant histological pattern was membranoproliferative GN (79%), with IgG3 (74%) kappa (78%) deposits the most frequently observed. Disease presentation and patient management were similar between EM-proven and non-EM-proven cases. A serum monoclonal spike was detected for 21 patients and 10 had an underlying haematological malignancy. First-line therapy was mixed between clone-targeted therapy (n = 33), corticosteroids (n = 9) and RAAS inhibitors (n = 19). After 6 months, nine patients achieved complete and 23 partial renal recovery. In univariate analysis, renal recovery was associated with baseline SCr (odds ratio 0.70, P = 0.07). After a median follow-up of 52 (35–74) months, 38% of patients had progressed to end-stage kidney disease independently associated with baseline SCr [hazard ratio (HR) 1.41, P = 0.003] and glomerular crescentic proliferation (HR 4.38, P = 0.004).

Conclusions. Our results confirm that non-cryoglobulinaemic and non-Randall GN with monoclonal IgG deposits are rarely associated with haematological malignancy. The prognosis is uncertain but may be improved by early introduction of a specific therapy.

GRAPHICAL ABSTRACT
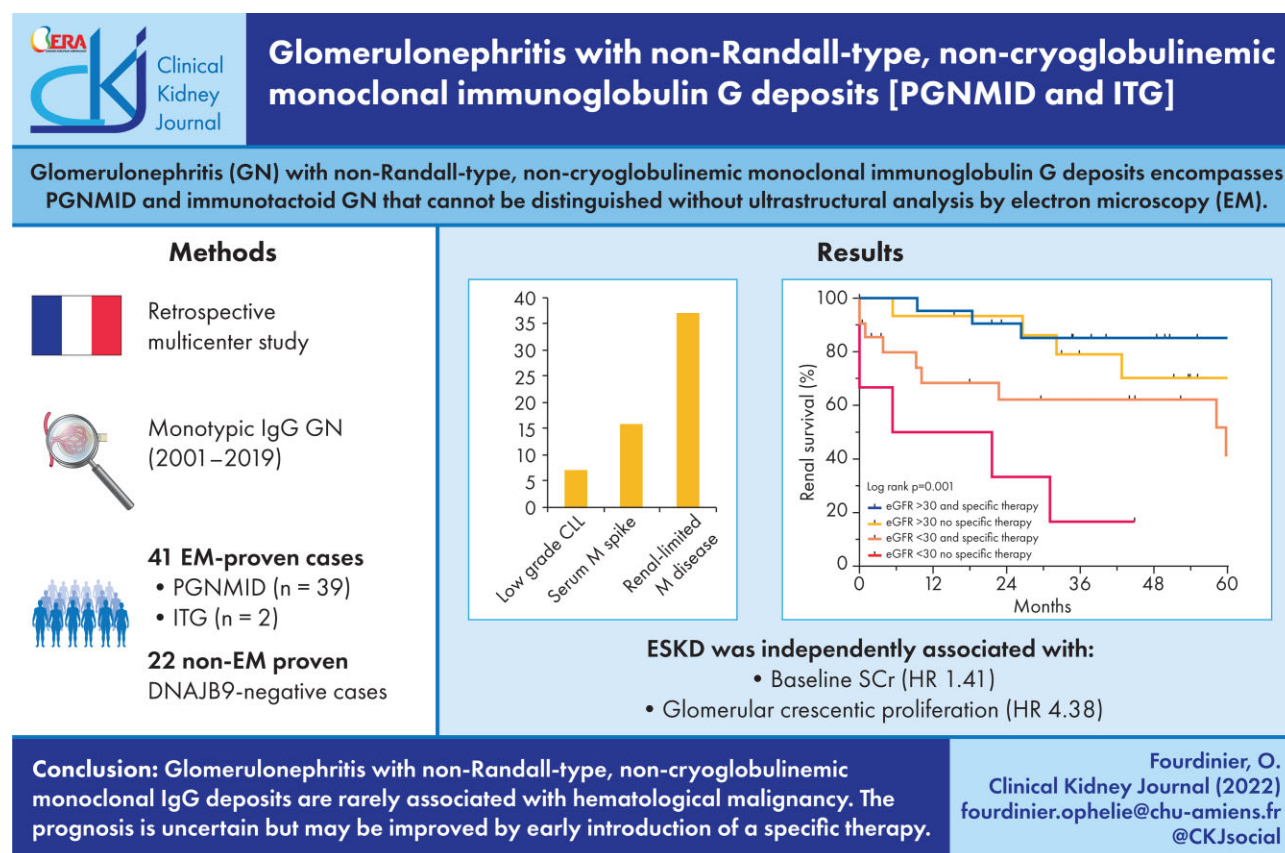
Keywords: DNAJB9, electron microscopy, monoclonal gammopathy of renal significance, monoclonal immunoglobulin G, PGNMID

INTRODUCTION

Introduced in 2012, the concept of monoclonal gammopathy of renal significance (MGRS) was recently redefined as B-cell or plasma-cell clonal proliferation with at least one renal lesion related to the produced monoclonal immunoglobulin (Ig) and without tumour complications or current haematological criteria for specific therapy [1].

MGRS is characterized by predominant glomerular involvement and can be categorized according to the ultrastructural characteristics of the deposits. These can contain isolated light or heavy Ig chains or intact Ig. The most common glomeru-

lar diseases are Randall-type monoclonal Ig deposition disease (MIDD) (non-organized deposits of light or heavy chains), AL amyloidosis (fibrillar deposits of light chains) and cryoglobuli-naemic glomerulonephritis (microtubular deposits of intact Ig).

Here, we focussed on two particularly rare entities: proliferative glomerulonephritis with non-Randall type non-organized monoclonal Ig deposits (PGNMID) and glomerulonephritis with organized microtubular monoclonal Ig deposits, known as immunotactoid glomerulonephritis (ITG) [2], comprising 0.2% and 0.06% of native kidney biopsies, respectively [3–5]. In the literature, only one-third of these types of glomerulonephritis are associated with underlying haematological malignancies

[4, 6]. Most available data are essentially limited to electron microscopy (EM)-proven cases [3, 4, 6]. However, EM analyses are not routinely performed in most nephrology centres and a specific sample for EM is rarely collected in the absence of a known circulating serum or urinary paraprotein.

The aim of our study was to identify EM-proven and suspected cases of PGNMID and ITG with monoclonal IgG deposits to describe the pathological lesions and the haematological features of the patients and their therapeutic management and investigate renal recovery following various therapeutic approaches.

MATERIALS AND METHODS

Study population

We conducted a retrospective multicentre study in 12 French university hospital centres. All patients with glomerular deposits of monoclonal IgG in native kidney biopsies performed between January 2001 and January 2019 were included. In each centre, patients were identified from electronic medical registers, including pathological and clinical diagnosis databases. The inclusion criteria consisted of monotypic deposits of IgG isotype with only a single light chain (kappa or lambda), negative by Congo-red staining and strictly located in the glomerular area, confirmed by light microscopy (LM) and immunofluorescence (IF). Patients with cryoglobulinaemic glomerulonephritis, MIDD, or amyloidosis were excluded. An EM study was available for 41 cases. Otherwise, DNAJB9 immunohistochemical staining of glomerular deposits was performed to rule out fibrillary glomerulonephritis (FGN) [7, 8].

Consistent with French legislation on non-interventional studies, approval by an investigational review board was neither required nor sought. However, the study was registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, Paris, France; registration PI2021_843_0162). Patients were provided with information about the study and were free to refuse to participate.

Patient medical records

All demographic, clinical, biological, radiological and renal pathology data were collected from medical records.

The following definitions were applied: hypertension, blood pressure $\geq$140 mmHg systolic or $\geq$90 mmHg diastolic; nephrotic syndrome, proteinuria >3 g/g or 3 g/dL and albumin <30 g/L; microscopic haematuria, >10 red blood cells/mm^3 in urine. The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) equation. Chronic kidney disease (CKD) was staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification. Specific therapy was defined as the use of various immunosuppressive regimens, whether or not they were adapted to an underlying condition or hypothetical clone. Early intervention was defined as the initiation of a specific therapy within 6 months following the definitive diagnosis of kidney disease.

Pathology findings

All renal biopsies were processed for LM and IF. The degree of interstitial fibrosis was stratified into grade 0 (<5% of cortical surface area), grade 1 (6–25%), grade 2 (26–50%), or grade 3 (>50%). The degree of tubular atrophy was stratified into grade 0 (absence), grade 1 (<25%) grade 2 (26–50%) or grade 3 (>50%).

Renal outcomes

The following definitions were used as proposed by Nasr *et al.* [4]: (i) complete renal recovery (CR): proteinuria <0.5 g/g, with the recovery of renal function, or (ii) partial renal recovery (PR): reduction of proteinuria by at least 50% and <2 g/g, with stable renal function. Patients with initial proteinuria of <0.5 g/g and who experienced an improvement in the eGFR of >25% were considered to have a CR. Relapse was defined as proteinuria >3 g/g for patients who had previously attained CR or PR.

End-stage kidney disease (ESKD) was defined as the need for renal replacement therapy. Persistent renal impairment was defined as the absence of renal recovery without ESKD at the last follow-up. Renal survival was defined as survival without ESKD.

Statistical analyses

Patient characteristics are expressed as medians [interquartile ranges (IQRs)] for continuous variables or as numbers (frequencies) for binary variables. Intergroup comparisons between two groups were performed using Mann–Whitney tests for continuous variables and Pearson's chi-squared test or Fisher's exact test, as appropriate, for categorical variables. Intergroup comparisons between three groups were performed using Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical variables.

Univariate logistic regression was performed to determine parameters associated with renal recovery at 6 months. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported

The Kaplan–Meier method was used to assess renal survival. The log-rank test was used to compare survival curves. Univariate and multivariable analyses were performed by building a Cox proportional hazards model for renal survival. The multivariable analysis included all parameters with a P-value <0.05 in the univariate analysis, considering the number of events per variable of interest and the co-linearity between variables. Hazard ratios (HRs) with 95% CIs are reported when appropriate. The eGFR was dichotomized according to the best cut-off estimated on the receiver operating curves. The threshold for statistical significance was set to a P-value <0.05. Statistical analyses were performed using GraphPad Prism® software version 6 and SPSS® software version 21.

RESULTS

Characteristics of the study population

In total, 63 patients were included in the study. A total of 41 patients underwent ultrastructural analysis by EM (two ITG and 39 PGNMID). After the exclusion of eight patients without sufficient biological material for DNAJB9 staining and one with positive staining, 22 supplemental patients without EM analysis were included. The main characteristics of the population are presented in Table 1. The population was divided into two groups according to the availability of an EM study. Otherwise, baseline clinical and biological data were similar between the two groups. The median (IQR) age at diagnosis was 61 (46−71) years and the sex ratio was 1.0. The median (IQR) serum creatinine was 150 (92–256) µmol/L at diagnosis and eGFR was 43 (18–71) mL/min/1.73 m^2. A total of 27 patients had stage 4–5 CKD at the time of renal biopsy. The median proteinuria level was

Table 1. Clinical and biological presentation at baseline

	Total (n = 63)	EM performed (n = 41)	No EM (n = 22)	P
Age, years	61 (46–71)	59 (41–69)	67 (56–74)	0.06
Male, n (%)	32 (50.8)	21 (51.2)	11 (50)	0.93
Hypertension, n (%)	33 (52.4)	19 (46.3)	14 (63.6)	0.19
Diabetes, n (%)	6 (9.5)	4 (9.8)	2 (9.1)	0.93
Hematological history, n (%)	10 (15.9)	5 (12.2)	5 (22.7)	0.27
Serum creatinine, µmol/L	150 (92–256)	134 (84–240)	172 (101–281)	0.21
eGFR, mL/min/1.73 m^2	43 (18–71)	47 (22–76)	29 (15–63)	0.12
CKD 1–2, n (%)	24 (38.1)	18 (43.9)	6 (27.3)	0.19
CKD 3, n (%)	12 (19.0)	7 (17.1)	5 (22.7)	0.59
CKD 4–5, n (%)	27 (42.9)	16 (39.0)	11 (50)	0.40
Proteinuria, g/g	3.6 (2.5–7.2)	3.8 (2.7–8.2)	3.4 (2.1–7.1)	0.69
Serum albumin, g/L	29 (23–35)	29 (23–34)	28 (26–36)	0.45
Nephrotic syndrome, n (%)	35 (55.6)	22 (53.7)	13 (59.1)	0.68
Haematuria, n (%)	47 (74.6)	30 (73.2)	17 (77.3)	0.72
Immunological findings				
C3 level, g/L	0.93 (0.8–1.1)	0.95 (0.8–1.1)	0.85 (0.8–1.1)	0.62
Low C3 level, n (%)	12/60 (20)	10/39 (26)	2/21 (9.5)	0.14
C4, g/L	0.24 (0.2–0.3)	0.24 (0.2–0.3)	0.24 (0.2–0.3)	0.94
Low C4 level, n (%)	5/60 (8)	4/39 (10)	1/21 (4.8)	0.46
Cryoglobulin negative, n (%)	52/52 (100)	35/35 (100)	17/17 (100)	>0.99
Haematological findings				
Haemoglobin, g/dL	11.6 (10.3–13)	11.8 (10.8–13.4)	11.1 (9.4–12.4)	0.06
Leukocyte count, ×10^3/mm^3	8.0 (6.2–10.2)	8.2 (6.7–10.5)	7.5 (6.0–9.3)	0.35
Platelet count, ×10^3/mm^3	247 (203–327)	259 (214–323)	245 (191–340)	0.83
Abnormal sFLC ratio, n (%)	2/50 (4.0)	1/35 (2.9)	1/15 (6.7)	0.53
Serum monoclonal Ig, n (%)	21 (33.3)	11 (27)	10 (45.4)	0.13

EM, electron microscopy; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; sFLC, serum free light chain; Ig, immunoglobulin.

3.6 g/g and 35 (56%) patients exhibited typical features of nephrotic syndrome. Fifty-two percent of the patients had a history of hypertension and 75% presented with microscopic haematuria. Serum cryoglobulinaemia testing was missing in 11 cases, including five patients without EM. The serum complement C3 and C4 fractions were low in 12 (20%) and 5 (8%) cases, respectively. These 14 patients all tested negative for cryoglobulin.

Renal pathology findings

The renal pathology findings are detailed in Supplementary data, Table S1. Membranoproliferative glomerulonephritis (MPGN) was the most frequent histological pattern, observed in 50 (79%) cases, followed by membranous nephropathy (MN) in 6 (10%) and mesangial glomerulonephritis (MesGN) in 6 (10%). One patient had no significant glomerular lesion by LM. Kappa light chains were the most common light chain, found in 49 (78%) cases. Staining for four subclasses of IgG1 was available for 57 (90%) patients and showed a marked predominance of IgG3 (74%), followed by IgG1 (19%). The distribution of IgG subclasses differed among histological patterns, with a predominance of IgG1 for patients with an MN pattern (3/5, 60%) and IgG3 (38/46, 83%) for those with an MPGN pattern. The pathology findings of two patients are presented in Figures 1 and 2.

Haematological findings

At baseline, 10 patients had a previously diagnosed clonal haematological disorder, including nine with an untreated low-grade B or plasma-cell proliferation [five with monoclonal gammopathy of undermined significance, four with low-grade chronic lymphocytic leukaemia (CLL)] and one with multiple myeloma who was receiving specific chemotherapy.

All haematological explorations performed at baseline are reported in Supplementary data, Table S2. Serum protein immunofixation was performed in 67 (93%) cases. Bone-marrow aspiration and/or biopsy were performed in 58 (81%) cases. A total of 59 (82%) patients had an imaging study [whole-body computed tomography (CT), with or without positron emission tomography (PET)].

A total of 16 additional clonal haematological disorders were diagnosed: 11 cases of serum monoclonal spikes, 3 of low-grade CLL, 1 of low-grade follicular lymphoma and 1 of smouldering Waldenström macroglobulinaemia. In all, 37 patients had a renal limited monoclonal disease (Figure 3).

In the overall population, a serum monoclonal spike was detected for 21 (33%) patients, most often at a low level (<5 g/L) at diagnosis. In 8/21 cases, the serum monoclonal spike differed from that of the renal IgG deposits. A monoclonal spike was subsequently detected by immunoelectrophoresis during follow-up for two other patients 20 and 32 months after the diagnosis.

Therapeutic management and renal recovery

A total of 56 (89%) patients received the usual renal-protective measures, including renin-angiotensin system (RAAS) inhibitors [angiotensin-converting enzyme (ACE) inhibitor and angiotensin II receptor blocker (ARB)]. Specific therapy was started in 42 (67%) cases after a median (IQR) of 2.7 (0.6–10.5) months after diagnosis. In total, 9/10 patients with underlying low-grade B
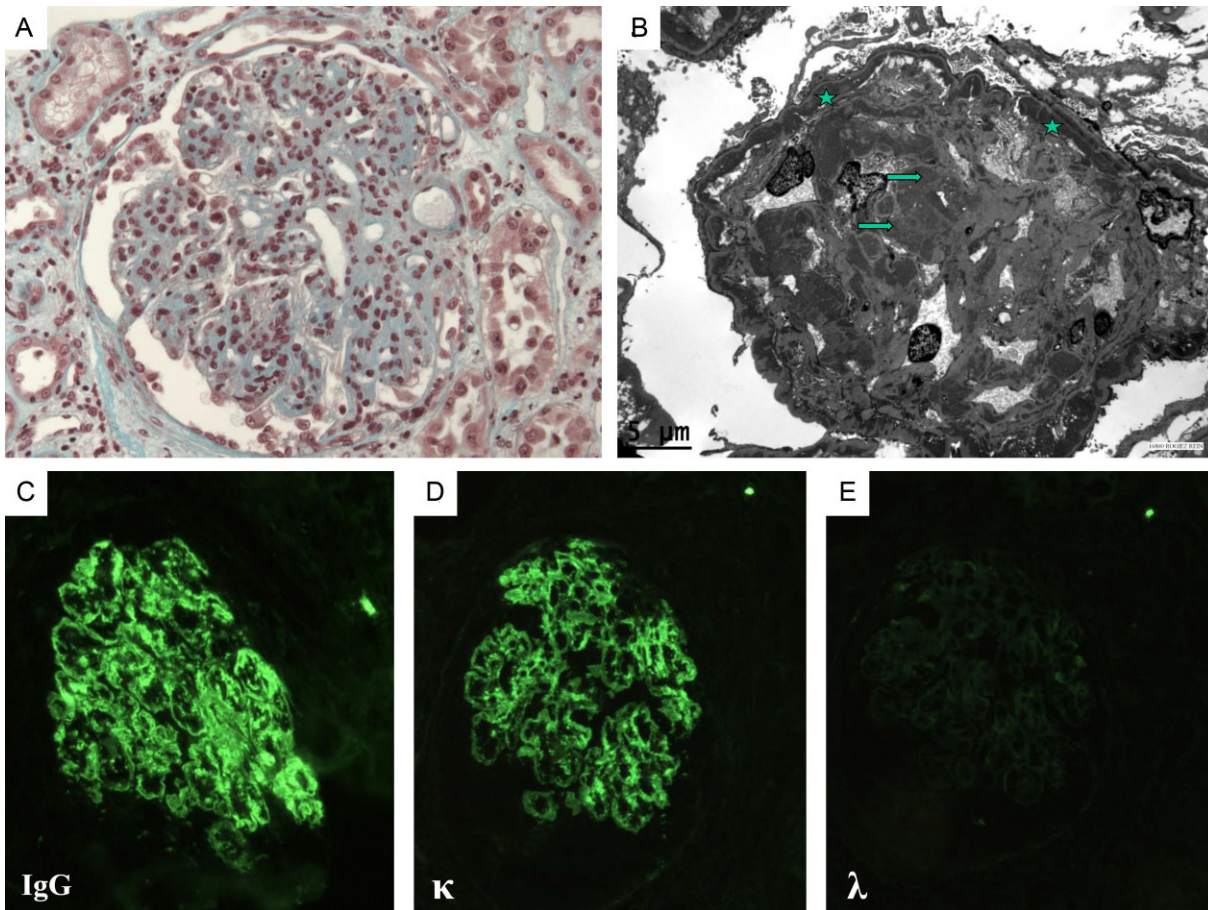
FIGURE 1: Proliferative glomerulonephritis with non-Randall type non-organized monoclonal Ig deposits (PGNMID). Membranoproliferative glomerulonephritis pattern. (**A**) Light microscopy findings (Masson trichrome; original magnification ×200) of lobular membrano-proliferative glomerulonephritis (MPGN). (**B**) Electron microscopy (original magnification ×4000). Numerous non-organized osmiophilic deposits are seen in subendothelial (*) and/or mesangial areas (arrows). (**C–E**) Immunofluorescence findings (original magnification ×200) with glomerular staining for monotypic immunoglobulin G kappa.

or plasma-cell proliferation received clone-targeted therapy and one was not actively treated. Among the remaining 53 patients without an identified haematological malignancy, 13 received an empirical plasma-cell clone-targeted therapy, 11 rituximab-based regimens, 9 corticosteroids only, 16 RAAS inhibitors only and 2 were not actively treated. Therapeutic regimens grouped by disease presentation are presented in Table 2.

In total, 11 patients (8 treated with chemotherapy and 3 with rituximab or prednisone only) experienced a severe adverse event during the treatment phase, including one cardiac arrest a few days post-introduction and five sepsis events requiring hospitalization.

Renal recovery 6 months after the introduction of specific therapy or symptomatic treatment is presented in Table 2. Among the 58 treated and evaluable patients, 9 (16%) showed a CR and 23 (40%) a PR. Three patients were not evaluable due to death or because they were lost to follow-up before 6 months. After the introduction of specific therapy, 7/39 (18%) patients showed a CR and 18/39 (46%) a PR. A total of 6 showed a PR relapsed after a median (IQR) of 19.4 (5.2–27.7) months and 14 (36%) patients did not respond to the initial specific therapy.

In the subgroup of patients without a haematological malignancy, the recovery rate was comparable between those who received empirical plasma cell clone-targeted therapy (7/12) and those who received a rituximab-based regimen (8/10), P = 0.28.

Among the 10 patients who had an eGFR <15 mL/min/1.73 m^2 at initial diagnosis, 3/7 receiving specific therapy showed a PR. Among the 19 patients who received the usual renal-protective measures only, 8 showed renal recovery (Table 2).

In univariate analysis, renal recovery at 6 months was associated with baseline serum creatinine levels [OR 0.70/100 µmol/L, 95% CI (0.48–1.00), P = 0.07] but was not statistically significant (Table 3). None of these parameters remained statistically significant when the analysis was restricted to the subgroup of patients with a diagnosis of PGNMID by EM (Supplementary data, Table S3).

Follow-up and outcomes

After a median (IQR) follow-up of 52 (35–74) months, 21 (33%) patients showed renal CR or PR, 18 (29%) had persistent renal impairment and 24 (38%) progressed to ESKD after a median (IQR) of 10 (5–35) months. In univariate analysis, the risk of progression to ESKD was associated with baseline serum creatinine levels [HR 1.58/100 µmol/L (95% CI 1.29–1.92), P < 0.001], the eGFR ≤38 mL/min/1.73 m^2 [HR 4.31 (95% CI 1.77–10.5), P = 0.001] and the presence of glomerular crescentic proliferation [HR 7.70 (95% CI 3.18–18.7), P < 0.001]. In multivariable analysis, baseline serum creatinine [HR 1.41/100 µmol/L (95% CI 1.12–1.78), P = 0.003] and
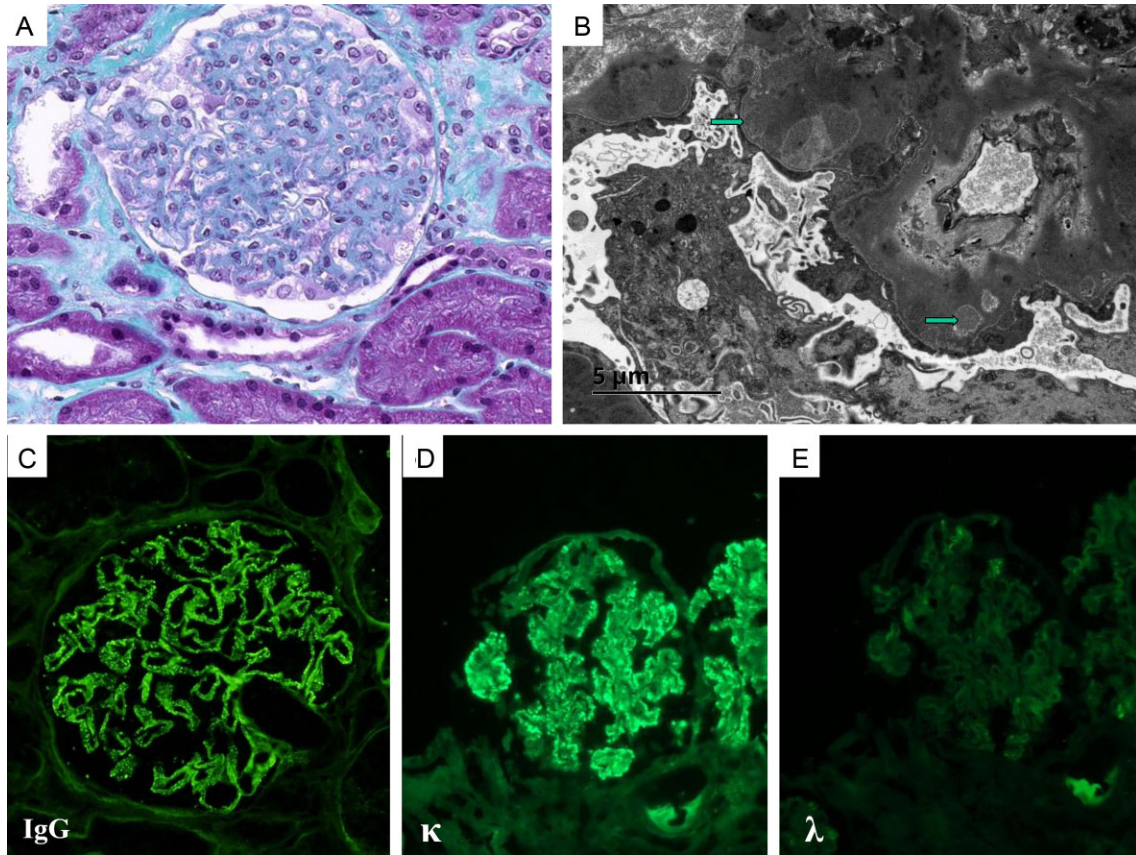
FIGURE 2: Proliferative glomerulonephritis with non-Randall type non-organized monoclonal Ig deposits (PGNMID). Membranous nephropathy pattern. (**A**) Light microscopy (Masson trichrome; original magnification ×200) showing variable degrees of alteration in the morphology of the glomerular basement membrane. (**B**) Electron microscopy (original magnification ×8000). Extensive subepithelial non-organized deposits are incorporated into a thickened glomerular basement membrane. Deposits lose their electron density until they disappear in this advanced stage IV (arrows). (**C–E**) Immunofluorescence (original magnification ×200) showing granular deposition of monotypic immunoglobulin G kappa along capillary walls.
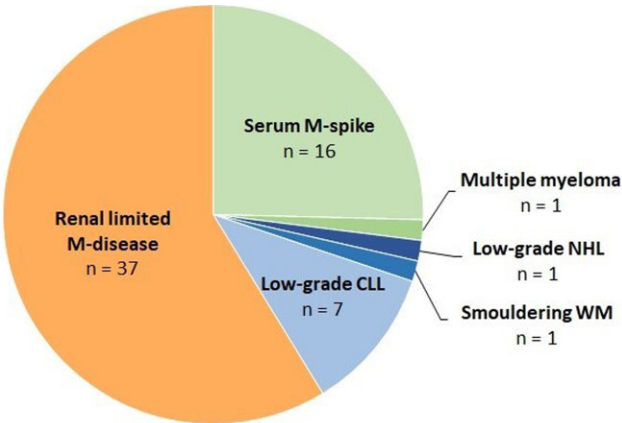
FIGURE 3: Distribution of clonal haematological disorders at baseline. CLL, chronic lymphocytic leukaemia; spike, monoclonal spike; NHL, non-Hodgkin lymphoma; WM, Waldenström macroglobulinaemia

the presence of glomerular crescentic proliferation [HR 4.38 (95% CI 1.59 –12.11), P = 0.004] remained independently associated with progression to ESKD (Table 4).

Renal survival following specific therapy and as a function of the eGFR (<30 or >30 mL/min/1.73 m^2) at diagnosis is presented in Figure 4. Renal survival was significantly different between the four groups (log-rank test, P = 0.001), with a lower survival rate for patients with an initial eGFR <30 mL/min/1.73 m^2 and not receiving specific therapy. There was no statistically significant difference in renal survival among patients with an eGFR >30 mL/min/1.73 m^2, whether or not they received specific therapy.

Overall, 12 (19%) patients died during follow-up, including 9 with ESKD. The main causes of death were sepsis (n = 5), cardiovascular events (n = 3) and cancer (n = 2). According to the Kaplan–Meier survival curve, overall survival rates at 1 and 3 years were 85.3% and 81.3%, respectively.

DISCUSSION

Here, we provide an extensive description of 63 cases of biopsy-proven glomerulonephritis with non-Randall-type, non-cryoglobulinaemic monoclonal IgG deposits. The predominant histological pattern was MPGN and IgG3 was the most frequent subclass involved in glomerular deposit formation. At the time of diagnosis, clonal haematological disorders or circulating monoclonal gammopathies were found in only 21 cases (33%), despite extensive exploration. A total of 42 (67%) patients received a specific therapy. Renal recovery was obtained for 55% of treated patients and appears to be closely related to the

Table 2. First-line therapy in the 61 treated patients and renal recovery 6 months after

	Haematological malignancy (n = 10)	Serum monoclonal spike (n = 16)	Renal-limited disease (n = 35)	P
Median time to introduction of a specific treatment, mos	2.6 (1.3–4.6)	2.1 (0.4–11.8)	2.8 (0.6–21.1)	0.35
Bortezomib-based regimen[a]	1 (10.0)	2 (12.5)	8 (22.9)	0.52
Cyclophosphamide-based regimen[b]	0 (0.0)	1 (6.2)	2 (5.7)	0.73
Rituximab-based regimen[c]	8 (80.0)	4 (25.0)	7 (20.0)	0.001
Corticosteroids only	0 (0.0)	3 (18.7)	6 (17.1)	0.35
RAAS inhibitors only	1 (10.0)	6 (37.5)	12 (34.3)	0.28
Renal recovery, n (%)	6/9 (66.7)	8/15 (53.3)	18/34 (52.9)	0.75
Bortezomib-based regimen	1/1	1/2	5/8	–
Cyclophosphamide-based regimen	0/0	1/1	0/1	–
Rituximab-based regimen	5/7	3/3	5/7	–
Corticosteroids only	0/0	2/3	2/6	–
RAAS inhibitors only	0/1	1/6	6/12	–
Relapse, n (%)	0/6 (0.0)	1/8 (12.5)	5/18 (27.8)	0.28

mos, months; RAAS, renin-angiotensin-aldosterone system.
[a]Bortezomib-dexamethasone or bortezomib-cyclophosphamide-dexamethasone.
[b]With thalidomide for one patient in the no-serum monoclonal spike group.
[c]Rituximab-bendamustine or rituximab-fludarabine-cyclophosphamide or rituximab-cyclophosphamide-dexamethasone or rituximab-dexamethasone for the B-cell or plasma proliferative disorders group and rituximab only or rituximab-prednisone for the two other groups.
A total of three patients were non-evaluable for renal recovery (two deaths before the sixth month and one lost to follow-up).

Table 3. Univariate analyses of renal recovery 6 months after the introduction of specific or symptomatic treatment (logistic regression)

	Univariate analysis	
Events n = 32/58 patients	OR (95% CI)	P
Age, by year	1.00 (0.97–1.03)	0.78
Sex (ref: female)	1.32 (0.47–3.73)	0.60
Serum creatinine, per 100 μmol/L	0.70 (0.48–1.00)	0.07
eGFR, per 1 mL/min/1.73 m^2	1.01 (0.996–1.03)	0.13
CKD stage 1–3 (versus stage 4–5)	1.43 (0.51–4.09)	0.51
Proteinuria, per g/g	1.08 (0.92–1.25)	0.35
Clonal haematological disorder	1.24 (0.43–3.57)	0.68
B-cell clone (versus plasma cell clone)	1.30 (0.23–7.38)	0.77
IF grade 0–1 (versus 2–3)	1.70 (0.60–4.85)	0.32
TA grade 0–1 (versus 2–3)	2.00 (0.64–6.20)	0.23
Sclerotic glomeruli (%)	0.98 (0.94–1.00)	0.13
MPGN (versus MN and MesGN)	0.54 (0.14–2.07)	0.54
Glomerular crescentic proliferation	0.35 (0.08–1.54)	0.16
EM-proven cases (versus EM not-performed)	2.19 (0.74–6.52)	0.16
Specific therapy (versus symptomatic)	2.20 (0.72–6.72)	0.17
Early intervention (versus late intervention)	2.62 (0.67–10.35)	0.17
Clone-targeted therapy (versus IS therapy)	1.03 (0.28–3.77)	0.96

OR, odds ratio; 95% CI, 95% confidence interval; ref, reference; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; IF, interstitial fibrosis; IS, immunosuppressive; TA, tubular atrophy; MPGN, membranoproliferative glomerulonephritis; MN, membranous nephropathy; MesGN, mesangial glomerulonephritis; EM, electron microscopy.
Five patients who died before month 6 or did not receive any treatment were excluded from the analysis.

early initiation of specific therapy. Over one-third of the study population progressed to ESKD, with no significant relationship to a specific therapy.

Patients without ultrastructural analysis were included, as they represent a large proportion of patients in the clinical setting. Despite the absence of a precise ultrastructural diagnosis, these patients were managed similarly to those with EM-based diagnoses and were comparable for all studied variables. The patient characteristics and pathology findings from our cohort are highly similar to those of other studies [2, 4]. The two largest cohorts have been published by Nasr *et al.,* with 54 patients having PGNMID and 49 patients with ITG [4, 9, 10]. As observed in other studies, IgG3 was the most common Ig heavy-chain subclass, frequently associated with MPGN and predominant in PGNMID. This was followed by IgG1, which was preferentially associated with an MN pattern and frequent in ITG [6, 11, 12]. Among IgG subclasses, IgG3 is the most nephritogenic, due to its ability to self-aggregate and activate the complement pathway [13, 14]. IgG3 deposits may activate downstream inflammatory mediators, thus inducing glomerular cell proliferation [13, 15]. IgG1 is the second strongest complement activating IgG and is, in this specific context, the most common subtype found in membranous nephropathy [16]. The rate of low C3 or C4 observed in our cohort is quite similar to that reported in a recent literature review [17].

Ultrastructural analysis revealed non-organized deposits in 95% of the 41 cases, suggesting a large predominance of PGNMID in the global population. Consistent with our findings, Guiard *et al*. [12] found that 11/14 patients with EM in a study involving 26 patients had non-organized deposits. In another recent study reporting the results of 160 kidney biopsies of patients with monoclonal gammopathy of undetermined significance, 12 had PGNMID and only one exhibited ITG [18].

A consensus statement concerning patients with MGRS recommends starting therapy directed against the underlying clone [19, 20]. However, similar to previous studies [4, 10, 12, 19, 21], documentation was limited to a monoclonal spike in 33% of cases and 58% of the patients had no detected underlying haematological disorders. Monoclonal protein may be difficult to detect by conventional techniques [10] and may disappear spontaneously when present, without any detectable monoclonal spike [22, 23]. The use of highly sensitive methods, such as immunoblot- or mass spectrometry-based techniques, may be beneficial in certain cases [24, 25]. Flow cytometry on bone-marrow aspirates for the minimal residual disease could also increase sensitivity in detecting a micro-clone [1, 26], but its cost-effectiveness is yet to be determined [27]. Strikingly, circulating paraproteins were different from those of the glomerular deposits in one-third of cases, as described in other studies [6, 27].

Table 4. Univariate and multivariate analyses of risk of progression to end-stage kidney disease at the end of follow-up (Cox proportional hazards model)

Events n = 24	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, by year	1.02 (0.99–1.05)	0.12		
Sex (ref: female)	0.48 (0.20–1.13)	0.09		
Serum creatinine, per 100 µmol/L	1.58 (1.29–1.92)	<0.001	1.41 (1.12–1.78)	0.003
eGFR ≤38 mL/min/1.73 m^2	4.31 (1.77–10.5)	0.001		
Proteinuria, per g/g	0.98 (0.88–1.10)	0.76		
Clonal haematological disorder	0.80 (0.34–1.84)	0.59		
B-cell clone (versus plasma cell clone)	0.44 (0.09–2.18)	0.32		
IF grade 0–1 (versus 2–3)	1.28 (0.56–2.91)	0.55		
TA grade 0–1 (versus 2–3)	0.96 (0.39–2.33)	0.92		
Sclerotic glomeruli (%)	1.01 (0.99–1.03)	0.39		
MPGN (versus MN and MesGN)	7.20 (0.97–53.4)	0.054		
Glomerular crescentic proliferation	7.7 (3.18–18.7)	<0.001	4.38 (1.59–12.11)	0.004
EM-proven cases (versus likely)	0.61 (0.27–1.37)	0.23		
Specific therapy (versus symptomatic)	0.61 (0.27–1.40)	0.24		

HR, hazard ratio; 95% CI, 95% confidence interval; ref, reference; eGFR, estimated glomerular filtration rate; IF, interstitial fibrosis; TA, tubular atrophy; MPGN, membranoproliferative glomerulonephritis; MN, membranous nephropathy; MesGN, mesangial glomerulonephritis; EM, electron microscopy.
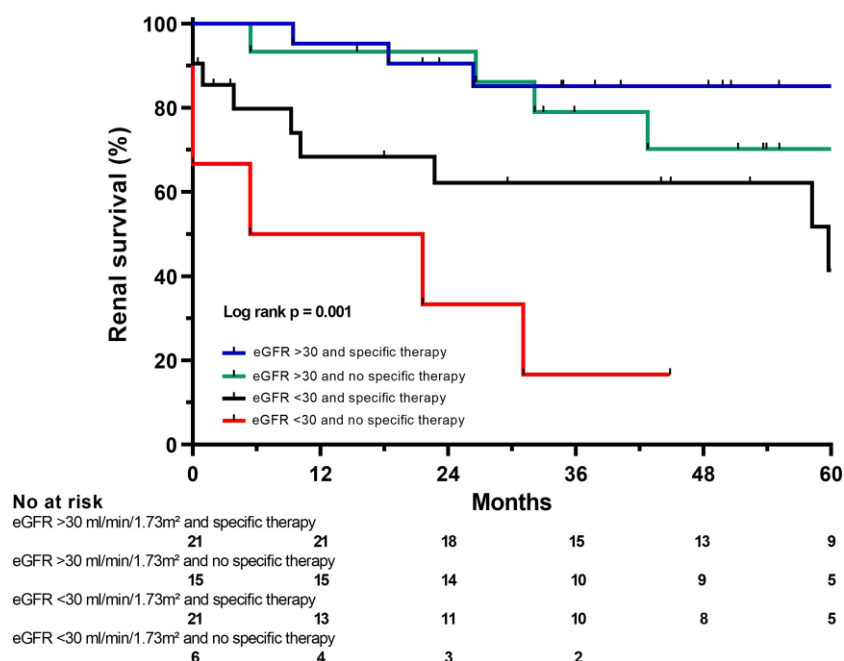

FIGURE 4: Renal survival as a function of use or non-use of specific therapy and estimated glomerular filtration rate (eGFR). The Kaplan–Meier survival curves were constructed to estimate renal survival. The log-rank test was used to compare survival curves.

Our findings suggest that the renal prognosis of glomerulonephritis with non-Randall-type, non-cryoglobulinaemic monoclonal IgG deposits is poor, as only 33% of patients were in renal recovery and 38% had progressed to ESKD by the end of follow-up. The prevalence of ESKD was more marked than in other studies, but this difference could be explained by a longer follow-up [4, 11, 12]. In accordance with previous studies [4, 6], we failed to demonstrate a clear relationship between the use of specific therapies, including clone-targeted therapy, and renal recovery. However, as observed by others [11, 28], a non-significant trend toward improvement of renal recovery appears to be associated with early intervention.

Gumber *et al*. reported a series of 16 PGNMID with a renal recovery rate of 76% (CR 35%) after the initiation of specific therapy, allowing most of the treated patients to be free of dialysis after a median follow-up of 1.9 years [19]. Interestingly, we and others found that general renal-protective measures achieved a renal recovery rate similar to that of the specific treatment group in our study, suggesting that spontaneous renal recovery may occur in certain cases [4, 19, 21, 29]. The benefit–risk balance of clone-targeted therapy without any definitive identification of the underlying haematological disorder is yet to be determined, given the lack of strong evidence of efficacy in renal survival. In this context, certain authors have recommended reserving clone-targeted therapy for CKD stages 3 and 4

or proteinuria >1 g/dL after the initiation of RAAS inhibitors [20]. Rituximab should be exclusively given in the presence of a CD20 B-cell clone [30]. However, in our cohort, rituximab was administered alone or in association with steroids in a large proportion of patients, and some data suggest its successful use, even in the absence of a B-cell clone [12, 27, 31].

Our study had several limitations. Retrospective studies suffer from limitations inherent to this type of approach, inducing a selection bias, missing data and patients lost to follow-up. The follow-up period and treatment regimens were heterogeneous and may limit the interpretability of the results. We focused on glomerular injury directly related to monotypic IgG deposition diseases, but some have described PGNMID or ITG in association with monoclonal IgM, IgA or light chain deposits [2, 6, 10, 32]. Nevertheless, the profile of IgG-deposit diseases appears to be different, with less documentation of clones or paraproteins and a possibly poorer response to treatment. Definitive diagnoses of renal pathologies were based on interpretations by pathologists and there was no centralized review. Although light microscopy and immunofluorescence findings were highly suggestive of these diagnoses, alternate pathologies, such as atypical monotypic anti-glomerular basement membrane disease [33], or a false negative cryoglobulin assay cannot be altogether ruled out. However, patients with FGN were not included, given that it is nearly always a polyclonal disease, even when associated with a monoclonal gammapathy [8, 34, 35].

In our study, patients with PGNMID and ITG by EM were considered together, as these diseases could not be differentiated in the subgroup of patients without EM. We recognize that these two diseases present differences, notably in the rate of association with haematological disease and histological presentation.

Despite its limitations, our study is one of the largest to-date to report glomerulonephritis with non-Randall-type, noncryoglobulinaemic with monoclonal IgG deposits with a detailed description of clinical, biological and pathological characteristics and outcomes, with or without specific treatment. Among these patients, the most common presentation in the renal biopsy examination was an MGPN pattern, with predominant IgG3κ glomerular deposits, whereas EM demonstrated a large predominance of PGNMID (95%). The accurate origin of the underlying clone involved in MGRS was not determined in 58% of our cases. The renal recovery rate tended to be higher for patients receiving early specific therapy, but without any significant influence on renal survival.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

V.A. received consulting fees from Addmedica outside of the submitted work. The other authors all declare no competing interests.

REFERENCES

1. Leung N, Bridoux F, Batuman V *et al.* The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol* 2019; **15**: 45–59
2. Bridoux F, Hugue V, Coldefy O *et al.* Fibrillary glomerulonephritis and immunotactoid (microtubular) glomerulopathy are associated with distinct immunologic features. *Kidney Int* 2002; **62**: 1764–1775
3. Nasr SH, Markowitz GS, Stokes MB *et al.* Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. *Kidney Int* 2004; **65**: 85–96
4. Nasr SH, Satoskar A, Markowitz GS *et al.* Proliferative glomerulonephritis with monoclonal IgG deposits. *J Am Soc Nephrol* 2009; **20**: 2055–2064
5. Rosenstock JL, Markowitz GS, Valeri AM *et al.* Fibrillary and immunotactoid glomerulonephritis: distinct entities with different clinical and pathologic features. *Kidney Int* 2003; **63**: 1450–1461
6. Nasr SH, Fidler ME, Cornell LD *et al.* Immunotactoid glomerulopathy: clinicopathologic and proteomic study. *Nephrol Dial Transplant* 2012; **27**: 4137–4146
7. Nasr SH, Vrana JA, Dasari S *et al.* DNAJB9 is a specific immunohistochemical marker for fibrillary glomerulonephritis. *Kidney Int Rep* 2018; **3**: 56–64
8. Rosenstock JL, Markowitz GS. Fibrillary glomerulonephritis: an update. *Kidney Int Rep* 2019; **4**: 917–922
9. Nasr SH, Kudose SS, Said SM *et al.* Immunotactoid glomerulopathy is a rare entity with monoclonal and polyclonal variants. *Kidney Int* 2021; **99**: 410–420
10. Bhutani G, Nasr SH, Said SM *et al.* Hematologic characteristics of proliferative glomerulonephritides with nonorganized monoclonal immunoglobulin deposits. *Mayo Clinic Proc* 2015; **90**: 587–596
11. Javaugue V, Dufour-Nourigat L, Desport E *et al.* Results of a nation-wide cohort study suggest favorable long-term outcomes of clone-targeted chemotherapy in immunotactoid glomerulopathy. *Kidney Int* 2021; **99**: 421–430
12. Guiard E, Karras A, Plaisier E *et al.* Patterns of noncryoglobulinemic glomerulonephritis with monoclonal Ig deposits: correlation with IgG subclass and response to rituximab. *Clin J Am Soc Nephrol* 2011; **6**: 1609–1616
13. Grey HM, Hirst JW, Cohn M. A new mouse immunoglobulin: IgG3. *J Exp Med* 1971; **133**: 289–304
14. Capra JD, Kunkel HG. Aggregation of gamma-G3 proteins: relevance to the hyperviscosity syndrome. *J Clin Invest* 1970; **49**: 610–621
15. Irani V, Guy AJ, Andrew D *et al.* Molecular properties of human IgG subclasses and their implications for designing therapeutic monoclonal antibodies against infectious diseases. *Mol Immunol* 2015; **67**: 171–182
16. Aucouturier P, Mounir S, Preud'homme JL. Distribution of IgG subclass levels in normal adult sera as determined by a competitive enzyme immunoassay using monoclonal antibodies. *Diagn Immunol* 1985; **3**: 191–196
17. Bridoux F, Javaugue V, Nasr SH *et al.* Proliferative glomerulonephritis with monoclonal immunoglobulin deposits: a nephrologist perspective. *Nephrol Dial Transplant* 2021; **36**: 208–215
18. Klomjit N, Leung N, Fervenza F *et al.* Rate and predictors of finding Monoclonal Gammopathy of Renal Significance (MGRS) lesions on kidney biopsy in patients with monoclonal gammopathy. *J Am Soc Nephrol* 2020; **31**: 2400–2411

19. Gumber R, Cohen JB, Palmer MB *et al.* A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Kidney Int* 2018; **94**: 199–205

20. Fermand JP, Bridoux F, Kyle RA *et al.* How I treat monoclonal gammopathy of renal significance (MGRS). *Blood* 2013; **122**: 3583–3590

21. Kousios A, Duncan N, Tam FWK *et al.* Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID): diagnostic and treatment challenges for the nephrologist! *Kidney Int* 2019; **95**: 467–468

22. Kyle RA, Therneau TM, Rajkumar SV *et al.* A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med* 2002; **346**: 564–569

23. Murray DL, Seningen JL, Dispenzieri A *et al.* Laboratory persistence and clinical progression of small monoclonal abnormalities. *Am J Clin Pathol* 2012; **138**: 609–613

24. Bridoux F, Javaugue V, Bender S *et al.* Unravelling the immunopathological mechanisms of heavy chain deposition disease with implications for clinical management. *Kidney Int* 2017; **91**: 423–434

25. Mills JR, Barnidge DR, Dispenzieri A *et al.* High sensitivity blood-based M-protein detection in sCR patients with multiple myeloma. *Blood Cancer J* 2017; **7**: e590

26. Flores-Montero J, Sanoja-Flores L, Paiva B *et al.* Next generation flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. *Leukemia* 2017; **31**: 2094–2103

27. Sethi S, Zand L, Leung N *et al.* Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. *Clin J Am Soc Nephrol* 2010; **5**: 770–782

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

29. van Kruijsdijk RCM, Abrahams AC, Nguyen TQ *et al.* Clone-directed therapy for proliferative glomerulonephritis with monoclonal immunoglobulin depositions: is it always necessary?: Two case reports and literature review. *J Nephrol* 2020; **33**: 611–617

30. Barbour SJ, Beaulieu MC, Zalunardo NY *et al.* Proliferative glomerulonephritis with monoclonal IgG deposits secondary to chronic lymphocytic leukemia. Report of two cases. *Nephrol Dial Transplant* 2011; **26**: 2712–2714

31. Bhat P, Weiss S, Appel GB *et al.* Rituximab treatment of dysproteinemias affecting the kidney: A review of three cases. *Am J Kidney Dis* 2007; **50**: 641–644

32. Nasr SH, Larsen CP, Sirac C *et al.* Light chain only variant of proliferative glomerulonephritis with monoclonal immunoglobulin deposits is associated with a high detection rate of the pathogenic plasma cell clone. *Kidney Int* 2020; **97**: 589–601

33. Nasr SH, Collins AB, Alexander MP *et al.* The clinicopathologic characteristics and outcome of atypical anti-glomerular basement membrane nephritis. *Kidney Int* 2016; **89**: 897–908

34. Kudose S, Canetta P, Andeen NK *et al.* Diagnostic approach to glomerulonephritis with fibrillar IgG deposits and light chain restriction. *Kidney Int Rep* 2021; **6**: 936–945

35. Andeen NK, Troxell ML, Riazy M *et al.* Fibrillary glomerulonephritis: clinicopathologic features and atypical cases from a multi-institutional cohort. *Clin J Am Soc Nephrol* 2019; **14**: 1741–1750