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ORIGINAL ARTICLE

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Epidemiological and clinical characteristics and outcome of monoclonal gammopathy of renal significance-related lesions in Latin America

Camila Peña[1] | Natalia P. Schutz[2] | Eloísa Riva[3,4] | Ricardo Valjalo[5] | Alejandro Majlis[6] | Hernán López-Vidal[7] | Vivianne Lois[7] | Daniela Zamora[8] | Paola Ochoa[9] | Claudia Shanley[10] | José Tomás Gonzalez[11] | Dorotea Fantl[2] | Gonzalo Correa[5] | Jhoanna Ramirez[12] | Paola Mur[13] | Guillermo Silva[14] | Verónica Verri[15] | Christine Rojas[16] | Karen Escobar[16] | Gustavo Glavic[17] | Gonzalo P. Méndez[18] On behalf of the Grupo de estudio latinoamericano de mieloma múltiple (GELAMM)

[1]Department of Hematology, Hospital del Salvador, Santiago de, Chile

[2]Department of Hematology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[3]Department of Hematology, Cátedra de Hematología, Hospital de Clínicas, Facultad de Medicina, Montevideo, Uruguay

[4]Department of Hematology, Hospital Británico, Montevideo, Uruguay

[5]Department of Nephrology, Hospital del Salvador, Santiago de, Chile

[6]Department of Hematology, Hemato-Oncology Department, Clínica Las Condes, Santiago de, Chile

[7]Department of Hematology, Hospital Barros Luco Trudeau, Santiago de, Chile

[8]Department of Nephrology, Hospital Barros Luco Trudeau, Santiago de, Chile

[9]Department of Hematology, Instituto Alexander Fleming, Buenos Aires, Argentina

[10]Department of Hematology, Hospital Británico, Buenos Aires, Argentina

[11]Department of Hematology, Hospital San Juan de Dios, Santiago de, Chile

[12]Department of Hematology, Hospital IEES, Guayaquil, Ecuador

[13]Department of Nephrology, Hospital San Juan de Dios, Santiago de, Chile

[14]Department of Hematology, FUSAT, Rancagua, Chile

[15]Department of Hematology, Instituto de Investigaciones Médicas Alfredo Lanari – UBA, Buenos Aires, Argentina

[16]Department of Hematology, Hospital Gustavo Fricke, Viña del Mar, Chile

[17]Department of Nephrology, Hospital Sótero del Río, Santiago de, Chile

[18]Department of Pathology, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago de, Chile

Correspondence
Camila Peña, Department of Hematology, Hospital del Salvador, Santiago de Chile, Avenida Salvador 364, Providencia, Santiago de, Chile.
Email: camipena@gmail.com

Abstract

Background: Monoclonal gammopathy of renal significance (MGRS)-related lesions are infrequent entities. There are no publications on these disorders in Latin America (LA). The aim of this study was to describe epidemiological and clinical characteristics of these patients in LA.

Methods: We performed a multicentre retrospective study. Patients with diagnosis of MGRS between 2012 and 2018 were included. Epidemiological and clinical data were collected from clinical records.

Results: Twenty-seven patients from Chile, Argentina, Ecuador and Uruguay were included. Half debuted with a nephrotic syndrome, and 32% required dialysis. Proliferative glomerulonephritis with monoclonal immunoglobulin deposits was found in 33%, amyloidosis in 26% and monoclonal immunoglobulin deposition disease also in 26%. The immunoglobulin most frequently found in renal biopsies was IgG kappa. In 67% a paraprotein was found. Twenty patients received an anti-plasma cell regimen, and 3 a rituximab-based regimen (IgM-MGRS). Renal response (RR) was achieved in 56%. Early treatment (≤3 months) was associated with higher RR (75% vs 43%). Three patients relapsed within 21.5 months, and 3 progressed: 1 to multiple myeloma, 1 to systemic amyloidosis and another to systemic light-chain deposition disease. Two patients died, both due to infection during induction treatment.

Conclusion: There was a higher than expected frequency of patients requiring dialysis. The most common MGRS-related lesion was PGNMD. Early treatment was associated with better response. As a rare disease, increasing awareness and promoting early diagnosis are necessary in LA to improve outcomes.

KEYWORDS

amyloidosis, monoclonal immune deposits, nephrotic syndrome, paraproteinemia, proliferative glomerulonephritis, renal failure

Renal failure is a common complication in multiple myeloma (MM) and other monoclonal gammopathies (MG).[1] The relationship between small B-cell clones and renal damage was described in the early 2000s.[2-5]

Monoclonal gammopathy of renal significance (MGRS) was first defined in 2012,[6] and the definition was updated in 2018 by the International Kidney and Monoclonal Gammopathy Research Group (IKMG).[7] MGRS is a clonal disorder that represents a group of renal lesions caused by a paraprotein secreted by a clone of mature B lymphocytes or plasma cells. This clone is generally small, and does not meet the criteria for treatment-requiring lymphoid or plasma cell neoplasm. However, the kidney damage induced by MGRS may be irreversible; thus, early recognition and management are necessary.[6-8]

The diagnosis of MGRS is based on renal biopsy findings, which must demonstrate that the nephropathy is caused by monoclonal deposits or an eventual indirect injury due to a paraprotein in the serum triggering a glomerular disorder secondary to alternative complement pathway interference and/or endothelial injury (thrombotic microangiopathy).

Histopathological analysis becomes particularly important in elderly patients with renal failure. These patients usually present with comorbidities that can cause renal failure, such as diabetes or hypertension. Conversely, the prevalence of MG of undetermined significance (MGUS) is relatively high among elderly patients.[9] However, unlike MGRS, MGUS does not require treatment.[10]

In summary, MGRS-associated lesions are infrequent but present as a complex clinical entity.

SUMMARY AT A GLANCE

A collection of 27 cases of MGRS from Latin America with information on epidemiology, clinical characteristics, treatment and outcome of patients diagnosed of MGRS-related renal lesions.

There are no large-scale studies to date on MGRS in the international literature; thus, our knowledge is based on the description of clinical cases or anatomopathological series.[11-13] In particular, there are no reports on this entity from Latin America (LA).

This study aimed to determine the epidemiological and clinical characteristics and outcomes of patients diagnosed with MGRS in LA.

1 | METHODS

This was an international multicentre retrospective case series study. All members of the Grupo de Estudio Latinoamericano de Mieloma Múltiple were invited to participate. Patients with MGRS diagnosed between 2012 and 2018 according to the current definition of IKMG were included. Epidemiological and clinical data were collected from clinical records on a standardized report form.

Inclusion criteria:

1. Diagnosis of MGRS from January 2012 to December 2018;
2. Renal biopsy studied with light and immunofluorescence microscopy, which included antibodies for immunoglobulins G, A and M, as well

as kappa and lambda light chains, C3 and C1q. Congo red was used as appropriate, and electron microscopy (EM) was desirable;
3. Bone marrow study (aspiration and/or biopsy);
4. Paraprotein study at diagnosis with at least protein electrophoresis (PEP) and immunofixation (IFE). A serum-free light chain assay was desirable;
5. Exclusion of an overt MG-associated neoplasm via computed tomography, positron emission tomography, lymph node biopsy or any analysis considered relevant according to suspicion; and
6. Only renal-limited light-chain (AL) amyloidosis was included, while systemic amyloidosis with renal involvement was not considered.

1.1 | Responses

Renal response (RR) in MGRS is not defined. Some use the International Myeloma Working Group (IMWG) RR criteria[14] for renal failure, and the criteria for renal amyloidosis for proteinuria.[15] We tried to look for the most appropriate response criteria, this means, criteria that cover both renal failure and proteinuria. Finally, we decided to use the RR criteria used by Chauvet et al, based on the KDIGO practice guideline on glomerulonephritis.[16,17] Complete renal response (CRR) was defined by proteinuria levels of 0.5 g/24 h or less, with albuminemia levels of 30 g/L or more and no more than 10% decrease in eGFR from baseline value. Partial renal response (PRR) was defined by post-treatment proteinuria between 0.5 and 2.5 g/24 h or by a 50% or more reduction from baseline value, with albuminemia levels of 25 g/L or more and no more than a 10% decrease in eGFR from baseline value.

A haematological (paraprotein) response was defined according to 2014 IMWG criteria.[18] This response was defined as NA if the clone could not be characterized at diagnosis (positive renal biopsy without paraprotein) or unknown if the HR was not properly measured.

1.2 | Statistical analysis

The statistical analysis was performed using descriptive and analytic statistics. All analyses were performed using Stata 13.

The present study was approved by the local research ethics committee.

2 | RESULTS

We received data from 27 patients from centres in Chile, Argentina, Ecuador and Uruguay. The median follow-up period was 24.3 months.

The patients' characteristics are shown in Tables 1 and 2. Median patient age was 58 (range, 25-78 years) with a male-to-female ratio of 1:1.25. Sixteen patients had a history of hypertension, while one had a history of diabetes and hypertension. One patient underwent a prior renal transplantation, one had a history of MGUS and one had a history of smoldering Waldenström macroglobulinemia. Anaemia was present in 74% of cases, hypoalbuminemia in 63%, and renal failure in 70%, with 30% of them (8 patients) requiring renal replacement therapy (RRT). All patients presented with some kind of proteinuria. Lactate dehydrogenase (LDH) level was high in two patients, and calcemia was normal in all cases.

In all patients, the diagnosis of an overt MG-related neoplasm was discarded based on a bone marrow study and ad hoc images. In 22 patients, EM was performed.

Half of the patients presented with nephrotic syndrome and three with non-nephrotic proteinuria (Figure 1). Regarding the histological subtypes of renal involvement, the most frequent diagnosis was PGNMID (9 patients [33%]), followed by AL amyloidosis in 7 (26%) and light-chain deposition disease (LCDD) in 5 (19%). Two patients had light- and heavy-chain deposition disease. The main characteristics of these three groups are shown in Table 3. IgG kappa was the most frequently identified immunoglobulin through renal biopsies (in 48%).

In 18 cases (67%), a serum or urine paraprotein was detected. Interestingly, three cases of paraproteinemia (11%) were biclonal. Serum protein electrophoresis (sPEP) was performed in all cases. Fourteen of 27 patients underwent urine PEP. Urine and serum IFE were performed in 81%, while serum free light-chain (sFLC) assays were performed in 78% of patients. The most sensitive panels used to detect the paraprotein were sPEP, sIFE and sFLC, with a 70% sensitivity (Figure 2).

TABLE 1 Epidemiological and clinical characteristics of the whole cohort according to renal responses (mean ± SD)

	All patients (N = 27)	CR (n = 10)	PR + NR (n = 17)
Median age	58	60	57
Male sex	44%	50%	41%
Hb (g/dL)	10.7 ± 2.1	11.4 ± 2.3	10.2 ± 2.2
LDH (UI/L)	243 ± 149	230 ± 65	252 ± 176
Creatinine (mg/dL)	3.2 ± 2.8	2.5 ± 2.2	5.1 ± 5.2
Proteinuria (g/24 h)	5.3 ± 4.9	6.4 ± 5.7	4.6 ± 5.0
Albumin (g/dL)	2.8 ± 0.8	2.8 ± 0.8	2.9 ± 0.9
Time to treatment (months)	2.6	2.1	2.9

Abbreviations: Hb, haemoglobin; LDH, lactate dehydrogenase; NR, no response; PR, partial response; RR, renal response.

TABLE 2 Clinical characteristics and outcomes of the 27 patients

Sex	Age at dg	Paraprotein (blood or urine)	Renal biopsy (monoclonal immunoglobulin deposit)	Main Clinical presentation	Creatinine at dg (mg/dL)	Treatment	n° cycles	Renal response	Haematologic response
F	70	Not found	Anti-GBM disease (IgG lambda)	Acute renal failure	3.5	CTD	2	CR	NA
F	72	IgG kappa + kappa	Proximal tubulopathy (kappa)	Acute renal failure	3.3	CyBorD	6	PR	VGPR
M	67	IgG kappa	PGNMID (IgG kappa)	Nephrotic syndrome	3.8	CyBorD	2	CR	ND
M	52	Kappa	PGNMID (IgA kappa)	Acute renal failure	1.2	CTD	6	CR	sCR
F	42	Not found	PGNMID (IgG kappa)	Acute renal failure	2.6	CTD	6	CR	NA
M	42	Not found	PGNMID (IgG kappa)	Acute renal failure	4.3	CyBorD	4	NR	NA
F	53	Kappa	PGNMID (IgG kappa)	Acute renal failure	4.8	CD	10	NR	sCR
F	72	Kappa	PGNMID (IgG kappa)	NN proteinuria	3.3	CTD	6	CR	sCR
M	39	Not found	PGNMID (IgG kappa)	Nephrotic syndrome	0.8	CyBorD	3	CR	NA
F	63	Kappa	PGNMID (IgG Kappa)	Nephrotic syndrome	3.9	CTD	3	NR	ND
M	78	IgM kappa	PGNMID (IgM kappa)	Nephrotic syndrome	8.0	RCHOP	6	CR	ND
M	60	IgG kappa	Type 1 cryoglobulinemic GN (IgG kappa)	NN proteinuria	1.4	CD	1	NR	PR
F	36	Not found	AH amyloidosis (IgM)	Nephrotic syndrome	0.5	RCD	3	NR	NA
F	77	IgM kappa	AL amyloidosis (IgM kappa)	NN proteinuria	0.8	RCD	3	PR	ND
F	58	IgG lambda	AL amyloidosis (lambda)	Nephrotic syndrome	0.6	CyBorD	3	NR	ND
M	62	IgA lambda	AL amyloidosis (lambda)	Nephrotic syndrome	0.6	CyBorD	6	CR	sCR
F	77	IgA lambda	AL amyloidosis (lambda)	Nephrotic syndrome	0.5	CyBorD	2	NR	PR
F	71	Not found	AL amyloidosis (lambda)	Nephrotic syndrome	2.5	CyBorD	1	NR	NA
M	71	Lambda	AL Amyloidosis (Lambda)	Nephrotic syndrome	3.2	CTD	3	NR	ND
F	25	Not found	Fibrillary glomerulonephritis (IgG kappa)	Nephrotic syndrome	3.1	Enalapril	NA	NR	NA
M	62	Not found	LHCDD (IgG kappa)	Acute renal failure	3.2	MelDex	8	NR	NA
M	68	Kappa	LHCDD (IgG kappa)	Nephrotic syndrome	8.0	CyBorD	5	CR	ND
M	48	Kappa	LCDD (kappa)	Acute renal failure	13.0	CTD	3	NR	sCR
M	59	Not found	LCDD (kappa)	Acute renal failure	6.0	CyBorD	2	PR	NA
F	45	IgM kappa + IgG kappa	LCDD (kappa) + TMA	Acute renal failure	1.6	VD + rituximab	6	CR	PR
F	68	IgG lambda	LCDD (lambda)	Nephrotic syndrome	1.2	CyBorD	5	CR	PR
F	50	IgG kappa + lambda	LCDD (lambda) + immunotactoid GP (IgG kappa)	Nephrotic syndrome	1.6	CyBorD	4	CR	CR

Abbreviations: CD, cyclophosphamide and dexamethasone; CR, complete response; CTD, Cyclophosphamide, thalidomide, dexamethasone; CyBorD, cyclophosphamide bortezomib and dexamethasone; Dg, diagnosis; GN, glomerulonephritis; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; MelDex, melphalan and dexamethasone; NA, not applicable; ND, no data; NN, non-nephrotic; NR, no response; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits; PR, partial response; RCD, rituximab, cyclophosphamide, and dexamethasone; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TMA, thrombotic microangiopathy; VD, velcade (bortezomib) dexamethasone; VGPR, very good partial response.

Twenty patients received an anti-plasma cell drug (a thalidomide-based regimen in 7 and a bortezomib-based regimen in 13). Three patients with IgM MGRS were treated with a rituximab-based regimen (Table 2). The mean number of cycles was 4.2. One patient underwent an autologous stem cell transplantation. None of our patients underwent a kidney transplantation.

Fifteen patients achieved RR, and 12 of them achieved complete RR. No patient among those who did not receive clone-based therapy achieved RR. The RR of the 23 patients treated with a clone-directed approach according to time to induction treatment are shown in Table 4.

Four of 8 (50%) patients became RRT-independent.

Three patients relapsed at a median 21.5 (range, 8-34) months; three patients progressed in a median 11.3 months: one to MM, one to systemic amyloidosis and one to systemic LCDD.

Two patients, both being treated with cyclophosphamide, bortezomib and dexamethasone (CyBorD), died of an infection during treatment.

3 | DISCUSSION

To the best of our knowledge, this is the largest clinical study on this topic in LA. We collected 27 cases from 4 LA countries. A significant effort, although there were fewer cases than expected at the beginning of this study. This could be explained due to the shortage of haematologists in some countries, difficulty in performing renal biopsies, unavailability of immunofluorescence for the histological studies and lack of experienced renal pathologists. Nevertheless, we believe that we obtained relevant information to establish initial conclusions about this pathology in our region.

Our cohort included rather young patients. It is important to remember that patients with MG-related diseases in LA are younger than those in other geographical areas,[19,20] which could in part explain our "young" cohort. However, this finding could also be related to the fact that renal biopsies are performed less frequently in elderly patients, due to comorbidities and possible complications. Considering that the incidence of MGRS, like that with MGUS, increases with age, this entity may be underdiagnosed in elderly patients. To minimize this problem, the last update of the IKMG Group[7] recommended that a renal biopsy should be performed for all patients, regardless of age, who, despite having a disease that causes chronic kidney disease (eg, diabetes, hypertension), have an atypical clinical course.

Special attention should be paid to diabetic patients. Despite the high prevalence of diabetes in the general population, our cohort had a very low incidence of this disease. One possible explanation for this result is that proteinuria and renal failure in these patients are attributed to diabetic nephropathy; thus, there may be a sub-diagnosis in this sub-group of patients. Therefore, clinical observation is crucial for evaluating an atypical course of this disease.

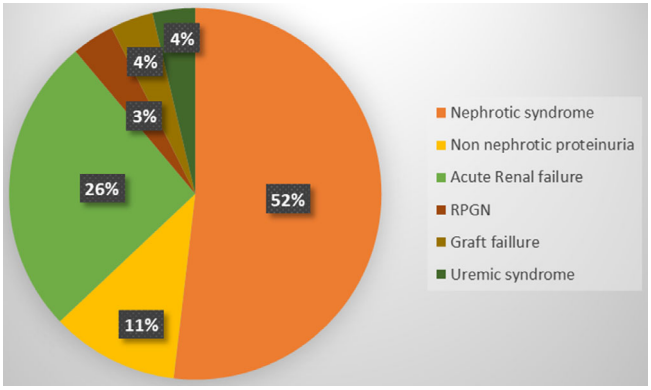

FIGURE 1 Clinical presentation at diagnosis. RPGN, rapidly progressive glomerulonephritis

Of the 27 patients evaluated in this study, only 1 had a history of prior MGUS and 1 had smoldering Waldenström macroglobulinemia. This result means that the vast majority of patients were diagnosed because a renal biopsy was performed for other indications, without the suspicion of MGRS-related lesions. Haematologists and nephrologists in LA must be aware of this "new" entity to diagnose it; more relevant education should thus be provided.

Anaemia as a myeloma-defining event was ruled out in all cases. Therefore, its high prevalence in our series can be attributed to "renal" anaemia or chronic anaemia due to other cause.

Although not statistically significant, there was a trend of less severe anaemia, lower LDH, lower creatinine and less time to treatment among patients who achieved CRR. These data should be corroborated with larger studies.

Among MM patients, approximately 10% eventually require RRT.[21] In a recent series of MGRS-related lesions, 9.8% of patients needed dialysis.[22] In our cohort, a high prevalence of RRT was noted, perhaps reflecting a late diagnosis. However, in this regard, the fact that 50% of the patients who required haemodialysis eventually became independent of it should be highlighted. This means that patients have a strong possibility of recovering kidney function with appropriate treatment.

A wide spectrum of renal lesions is associated with MGRS, and it is thus important to understand that MGRS is not a diagnosis by itself, but that it encompasses many renal pathologies with different physiopathology and clinical behaviours.[23] All renal biopsies should be accompanied by appropriate complementary studies, and therefore, a complete immunofluorescence panel is crucial.

The three most frequent lesion types found were those involving the glomerulus.

Interestingly, the most common MGRS-related lesion was PGNMID, a rather rare entity. These data must be corroborated with larger prospective studies. The co-occurrence between MG and PGNMID was first described as an entity in 2004,[24] when 10 cases of monoclonal immunoglobulin deposits were reported but could not be classified according to any previously described pattern. In 2010, Sethi et al presented a study of 68 patients with membranoproliferative glomerulonephritis, with some of them being PGNMID. However, it is not clear what specific renal lesions these patients had.[25] In 2009, Nasr et al reported 37 patients with PGNMID, with only one having MM.[12] In 2015, Bhutani

TABLE 3 Characteristics of the main MGRS-related lesions

	Median age (years)	Male (%)	Proteinuria (%)	Renal failure (%)	Paraprotein detection (%)	Main renal MIg detection (%)
PGNMID	56.4	56	56	44	66	IgG kappa (78%)
Amyloidosis	64.5	22	100	0	78	Lambda (71%)
LCDD/LHCDD	57.1	57	43	57	72	Kappa (43%)

Abbreviations: LCDD, light-chain disease; LHCDD, light- and heavy-chain deposition disease; MGRS, monoclonal gammopathy of renal significance; MIg, monoclonal immunoglobulin; PGNMID, proliferative glomerulonephritis associated with monoclonal immune deposits.

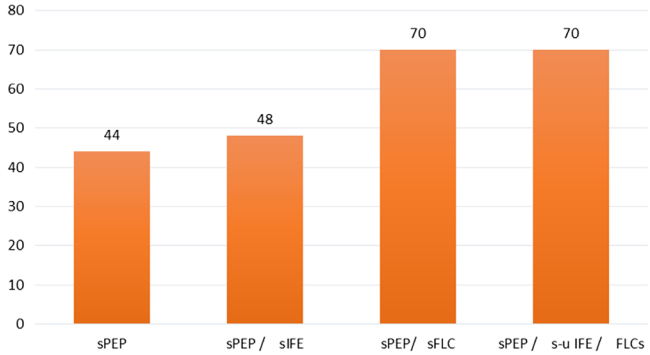

FIGURE 2 Sensitivity among different paraprotein screening panels. sFLC, serum free light-chain; sPEP: serum protein electrophoresis; s-u IFE, urine and serum immunofixation

TABLE 4 Renal responses according to time between diagnosis and treatment, in patients who received clone-directed treatment

TTT in months	Total n°	NR	PR + R
0–3	16	25%	75%
≥4	7	57%	43%

Abbreviations: NR, no response; PR: partial response; R, complete response; TTT, time to initiation of treatment.

et al reported 60 patients from the Mayo Clinic,[26] all of them PGNMID. In these articles, the most frequently associated MG was MGRS, the median age was 56 years, and the majority (90%) of cases were due to IgG deposits, similar to the results of this study. In our cohort, the majority of patients presented with renal failure or a nephrotic syndrome. The internationally accepted detectable monoclonal immunoglobulin rate is 30%,[12,26] lower than the 66% found in the present study. These results might be related to the fact that PGNMID could be underdiagnosed in LA since not all kidney biopsy specimens with membranoproliferative glomerulonephritis undergo immunofluorescence staining.

This entity has also been described in patients with kidney transplantation, with a recurrence rate in the grafted kidney of up to 70%.[27-29] The deposits usually comprise IgG3 kappa; in two-thirds of the cases, no paraproteins are detected in the blood or urine. In our cohort, one such case was of a woman who had undergone renal transplantation, in whom no paraproteins were detected in the blood or urine. She achieved CRR with cyclophosphamide, dexamethasone, and thalidomide administration; however, recurrence was noted after 2 years. She was treated with the same regimen, reaching CRR again.

Conversely, as expected, nephropathies frequently associated with MM were also found in this cohort: AL amyloidosis and LCDD.[30-33]

Disregarding the cases of cast nephropathy, AL amyloidosis is the most frequent renal lesion associated with any MG,[34] and it is best identified by mass spectrometry, which is not available in most centres in LA. We only considered renal localized AL amyloidosis as MGRS-related lesion. This strict inclusion criterion might be one reason it was not the most frequent lesion detected, as we expected. The majority of cases of proteinuria or nephrotic syndrome appeared in the seventh decade of life. We found slight female predominance in our study.

Light-chain deposition disease is infrequent and characterized by unorganized (non-fibrillar), coarse granular and monoclonal light chain deposits along the glomerular and tubular basement membranes. Light-chain deposition disease is always associated with MG, but MGRS is only considered if it is not related to an overt treatment-requiring MM or lymphoma. A cohort of 64 patients with monoclonal deposit disease was studied in 2012.[35] In this article, unlike in PGNMID, a paraprotein was detected in the blood or urine of 97% of patients, but the percentage corresponding to MGRS was not described. Cohen et al[36] studied 49 patients with monoclonal immunoglobulin deposition disease. Thirty-eight percent were MGRS related. Our cohort showed similar characteristics.

The lack of cases of C3 glomerulonephritis could be explained by the apparently low biopsy rate and incomplete pathological studies performed in some countries in LA.

From the haematological point of view, it is necessary to test for paraproteins in the blood and urine. In the present study, the most sensitive panels for its recognition were sPEP, sIFE and sFLC as described in other MGs.[37] Although, paraproteins may not be detected in certain cases, its non-detection does not exclude the diagnosis. Tests to detect paraprotein are key to monitoring and measuring the treatment response.

The sFLC assay is highly recommended to be part of the initial MGRS study work up. It might be important even in predicting renal disease in MGUS patients.[38-40] Therefore, although this assay has high costs in our region, physicians should make an effort to incorporate it into daily practice.

3.1 | Treatment

Although the clone is often small, it can cause irreversible kidney damage. It is crucial to protect kidney function by reducing the toxic monoclonal protein level. In general, if the paraprotein is of the IgM type, it is more related to mature B lymphocyte clones, and its treatment should include rituximab. Conversely, if the clone is of a non-IgM type, it is related to plasma cell clones; therefore, treatment should incorporate proteasome inhibitors or immunomodulators.[41] This is the so-called clone-directed approach. Interestingly, none of the patients treated with non-specific regimens achieved RR in this study. The time to treatment initiation was also an important parameter in our cohort, and a delay in therapy initiation was associated with worse renal outcomes.

Two patients in our cohort died during induction. Infections should be carefully considered when choosing a therapy. This is especially important for MGRS-related lesions, in which the disease itself is not life-threatening. Therefore, the risk vs benefit of the chosen regimen must be carefully analysed.

Only one patient underwent autologous stem cell transplantation, while none underwent a kidney transplantation; hence, no conclusion can be made in this regard based on the results of this study.

3.2 | Responses

Sometimes, the glomerular filtration rate and proteinuria can be the only parameters used to assess disease activity, because cases of an

undetectable or difficult to measure M-protein. Nevertheless there is no international consensus regarding the evaluation of haematologic or RR in these patients. The response criteria used by the IMWG in MM or amyloidosis were used in other studies.[22,42] We used criteria based on the KDIGO criteria[16,17] although it must be emphasized that there is a need to create specific MGRS-related lesion response criteria.

More than half of our patients achieved a PRR or CRR. A RR was more likely in patients treated within 3 months of diagnosis. Therefore, prompt initiation of treatment is apparently crucial.

We did not observe a direct correlation between renal and haematological responses as described in other studies.[43] Some patients showed haematological responses but not RR. In these patients, it is hypothesized that the toxicity of paraproteins may have permanently damaged the renal function, most likely due to a late diagnosis.

3.3 | Relapse and progression

Despite the short follow-up period, three relapses occurred in our patients at a median of 25 months. Two patients achieved RR again with the same treatment regimen.

Like MGUS, MGRS is thought to have a higher risk of progression to plasma cell neoplasms or mature B lymphoid neoplasms. We reported three cases of progression: one to MM, one to systemic amyloidosis and one to systemic LCDD. A recent study addressed this aspect[44] and showed a risk of progression to MM of 30.6/1000 patients/year in MGRS vs 8.8 in MGUS. Based on these results, follow-up of these patients is recommended from the haematological and nephrological points of view.

4 | CONCLUSIONS

In our series, PGNMID was the most frequent MGRS-related lesion. More than half of our patients achieved RR, especially those who received early treatment, which reinforces the need for prompt haematological evaluation and renal biopsy analysis. A higher-than-expected proportion of patients required dialysis. As a rare disease, increasing the awareness and promoting an early diagnosis of MGRS are necessary in LA to improve the associated outcomes. Despite the retrospective nature and small number of patients in our series, we believe that our results make a significant and initial contribution to the knowledge regarding this entity in our region.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Camila Peña https://orcid.org/0000-0002-8076-2077

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