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Monoclonal Gammopathy with Renal Significance and a Normal Kappa Lambda Ratio: A Strange Duo

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Abstract

Background: Among the monoclonal gammopathies, monoclonal gammopathy of renal significance (MGRS) is a subtype that causes kidney damage. Kidney biopsy is considered to be the gold standard for diagnosis; however, several biomarkers may help to detect this disease. We aimed to evaluate the role of the κ/λ ratio in a cohort of monoclonal gammopathy patients who were followed by nephrologists.

Methods: We analysed 1,067 kidney biopsies from 2015 to 2020, and we only selected patients affected by monoclonal gammopathy of undetermined significance. We excluded kidney transplant recipients and patients with multiple myeloma, chronic lymphocytic leukemia or Waldenström's macroglobulinemia. Associations between the κ/λ ratio, clinical and laboratory parameters and the presence of MGRS were assessed.

Results: Of the 1,067 analysed patients, 46 had monoclonal gammopathy. Eight patients were excluded because they were not tested for the κ/λ ratio. Sixteen out of 38 (42.1%) reported a normal κ/λ ratio. The frequency of MGRS included 10 (62.5%) patients with a normal κ/λ ratio and 7 (31.8%) with an altered κ/λ ratio ($p = 0.060$). No significant differences were found between the other parameters. Immunoglobulin-related amyloidosis was the most represented histologic diagnosis (29%).

Conclusions: Among patients affected by monoclonal gammopathy of undetermined significance there was a high percentage of biopsies proving that MGRS with immunoglobulin-related amyloidosis was the most common diagnosis. The κ/λ ratio is not sufficient to predict MGRS or to guide the timing of kidney biopsy, which remains fundamental for diagnosis.

Keywords: Monoclonal Gammopathy; Monoclonal Gammopathy of Renal Significance; Kidney Biopsy; Kappa and Lambda Free Light Chains Ratio

Introduction

Monoclonal gammopathy (MG) is a group of hematological disorders characterized by the overproduction of monoclonal immunoglobulin (Ig) by clonal plasma cells or B lymphocytes that are detectable in plasma and/or urine [1]. According to specific laboratory findings and (most importantly) the tumour bulk, we can distinguish between monoclonal gammopathy of undetermined significance (MGUS) and related hematological malignancies that can be derived from MGUS, such as multiple myeloma (MM), chronic lymphocytic leukemia (CLL) and Waldenstrom's macroglobulinemia (WM). MGUS is a premalignant condition that is formally defined by the presence of < 30 g/L monoclonal serum immunoglobulin (Ig) and < 10% monoclonal plasma cells in the bone marrow without end-organ damage [2]. According to current hematological treatment criteria, as MGUS does not cause any end-organ damage, it does not require any type of therapy [1]. Monoclonal immunoglobulins can damage any renal compartment, such as the glomeruli, vessels and tubulointerstitium, via a wide variety of histological patterns [2]. The term monoclonal gammopathy of renal significance (MGRS) was introduced in 2012 to encompass all kidney lesions related to a nephrotoxic monoclonal immunoglobulin in the absence of hematologic malignancy and/or symptoms [2]. Kidney biopsy represents the only diagnostic tool for diagnosing MGRS. Light microscopy and immunofluorescence studies with a full panel of antibodies are invariably required to identify immunoglobulin deposits and to classify kidney lesions. Electronic microscopy must be performed when available [2]. Previous studies have reported that the MGRS is associated with an altered serum κ/λ ratio in patients with MGUS [3,4]. Herein, we performed a single-centre retrospective study analysing the prevalence of MGRS in our population of patients with MGUS who underwent kidney biopsy due to proteinuria and/or acute kidney injury (AKI) and/or micro haematuria. Moreover, we evaluated various histopathological patterns of kidney involvement in patients affected by MGUS and investigated the role of the κ/λ ratio in this population.

Materials and Methods

We analysed a total of 1,067 kidney biopsies performed in the Nephrology Department of Sant'Orsola Hospital between 2015 and 2020. We included all patients with a monoclonal peak on serum electrophoresis and positive serum and/or urinary immunofixation. Patients with MM, CLL and WM were excluded from the study, as were patients with chronic kidney disease (CKD) and kidney transplant recipients. Proteinuria and/or AKI and/or microhematuria were the clinical indications for kidney biopsy. Monoclonal Ig was detected by using immunosubtraction as an alternative to serum immunofixation. A turbidimetric method was used to analyse serum free light chains. We used the "conventional" κ/λ ratio range (from 0.26 to 1.65) without adjusting for renal kidney impairment because we did not have patients affected by CKD. At the baseline visit, demographic, clinical and laboratory characteristics were recorded. All of the biopsies were examined via light microscopy and immunofluorescence. Due to the fact that they are not always available, electronic microscopy was not reported. MGRS-associated diseases were classified according to the International Kidney and Monoclonal Gammopathy (IKMG) Research Group consensus of 2018 [3].

Statistical analysis

Continuous variables are reported as either the mean ± standard deviation (SD) or median and interquartile range (IQR) based on their distribution. Categorical variables are reported as percentages (%). Comparisons among κ/λ ratio categories were assessed via one-way unpaired t tests or Kruskal–Wallis tests. Categorical variables were analysed by using the chi-square test. To assess the associations between clinical, laboratory and histologic variables and the MGRS, we first tested the univariate associations between the main variables and the MGRS. Afterwards, a backward variable selection method with an elimination criterion of $p < 0.10$ was performed to fit a multivariate logistic regression model. To avoid model overfitting, we chose to add one predictor for each of the ten patients who were enrolled. A two-tailed p value < 0.05 was considered to be statistically significant for all of the analyses. The data were analysed by using STATA version 14 (Stata Corp. College Station, TX, USA).

Results

Among the 1,067 analyzed patients, 46 were diagnosed with monoclonal gammopathy (4.3%), 8 of whom were excluded for not having the κ/λ ratio evaluated (Figure 1). When considering the 38 patients who were eligible for our analysis, the average age was 70.5 years (SD: 12.3 years). Twenty-seven out of 38 (71%) patients were male (Table 1). Proteinuria was the most frequent indication for kidney biopsy (23 out of 38, 60.5%), with 14 patients having nephrotic-range proteinuria (36.8%). Ten patients (26.3%) who underwent kidney biopsy for AKI were considered to have increased serum creatinine from the historical baseline, and 5 (13.2%) had isolated microscopic hematuria. Sixteen out of 38 patients (42.1%) had a normal κ/λ ratio, 10 of whom had MGRS (62.5%), with immunoglobulin-related amyloidosis as the most frequent diagnosis (6 out of 16 patients, 37.5%). The second most frequent histopathological lesion was thrombotic microangiopathy (TMA), which was found in 2 of the 10 patients. The other identified lesions are reported in Supplementary Table 1. Among the remaining 22 patients with an abnormal κ/λ ratio (57.9%), only

7 patients (31.8%) had histological features of MGRS. In particular, 5 of them (22.7%) had immunoglobulin-related amyloidosis, and 2 had cryoglobulinemic type II glomerulonephritis. The histopathological lesions of the remaining non-MGRS patients in this group are recorded in Supplementary Table 1. Among the 16 patients showing a normal κ/λ ratio (42.1%), 11 (68.7%) had a slight prevalence of λ light chain that did not produce a lambda dominant κ/λ ratio, 3 had a slight prevalence of κ chains (18.7%), and in 2 patients, sFLC was not detectable. Conversely, when considering the 22 patients with an altered κ/λ ratio, 14 had a slight prevalence of κ light chains (63.6%), and 7 had a slight prevalence of λ light chains (31.8%). In 1 patient, the sFLC was not detectable. Overall, MGRS was diagnosed in 17 patients (44.7% of patients with MGUS), and immunoglobulin-related amyloidosis represented the most common histological pattern (64.7%). When comparisons between the normal and altered κ/λ ratio groups were tested (Table 1), we found no statistically significant associations between clinical or laboratory variables and the κ/λ ratio. Additionally, the presence of MGRS was not significantly associated with the serum κ/λ ratio (p = 0.060). When we tested the adjusted risk for MGRS, we found no association between the κ/λ ratio and MGRS (odds ratio [OR]: 0.29, 95% CI: 0.06-1.36, p = 0.119), even after adjusting for the main confounders, including age, sex and proteinuria. We found a borderline association between proteinuria and MGRS (OR: 1.01, 95% CI: 0.99-1.01, p = 0.056) and no association between proteinuria and age (OR: 1.05, 95% CI: 0.98-1.13, p =0.185) or sex (OR: 0.37, 95% CI: 0.07-2.05, p = 0.256; Table 2). To further investigate the association between κ and λ chain levels and MGRS, we also stratified the analysis by κ or λ predominance categories and the presence or absence of MGRS. No significant association between κ or λ predominance and the MGRS was found (p = 0.059, not shown). However, when the analysis was stratified by proteinuria and κ or λ predominance, we found that a greater number of patients with MGRS had proteinuria greater than or equal to 1 g/day and a greater λ predominance (p value of chi squared test= 0.030, Table 3).

	Overall (n=38)	Normal κ/λ ratio(n=16)	Altered κ/λ ratio (n=22)	p
Age, years	70.5±12.3	72.8±11.7	68.9±12.8	0.337
Male gender, n (%)	27 (71.1)	12 (75.0)	15 (68.2)	0.647
eGFR, mL/min	44.2±27.0	45.0±31.8	43.6±23.6	0.877
Uprot, g/24 h	2.22 [0.51-4.36]	3.26 [0.70-7.34]	1.89 [0.37-4.18]	0.344
Indication for kidney biopsy				0.84
Uprot, n (%)	23 (60.53)	9 (56.25)	14 (63.64)	
AKI, n (%)	10 (26.32)	5 (31.25)	5 (22.73)	
Microhematuria, n (%)	5 (13.16)	2 (12.50)	3 (13.64)	
Diabetes, n (%)	9 (23.7)	3 (18.8)	6 (27.3)	0.542
Hypertension, n (%)	22 (61.1)	8 (50.0)	14 (70.0)	0.221
Ig related amyloidosis, n (%)	11 (29.0)	6 (37.5)	5 (22.7)	0.321
MGRS, n (%)	17 (44.7)	10 (62.5)	7 (31.8)	0.06

eGFR, estimated glomerular filtration rate; Uprot, 24-h proteinuria; AKI, acute kidney injury; Ig, immunoglobulin MGRS, Monoclonal Gammopathy of Renal Significance.

Table 1: Baseline characteristics of patients: overall and by κ/λ ratio category.

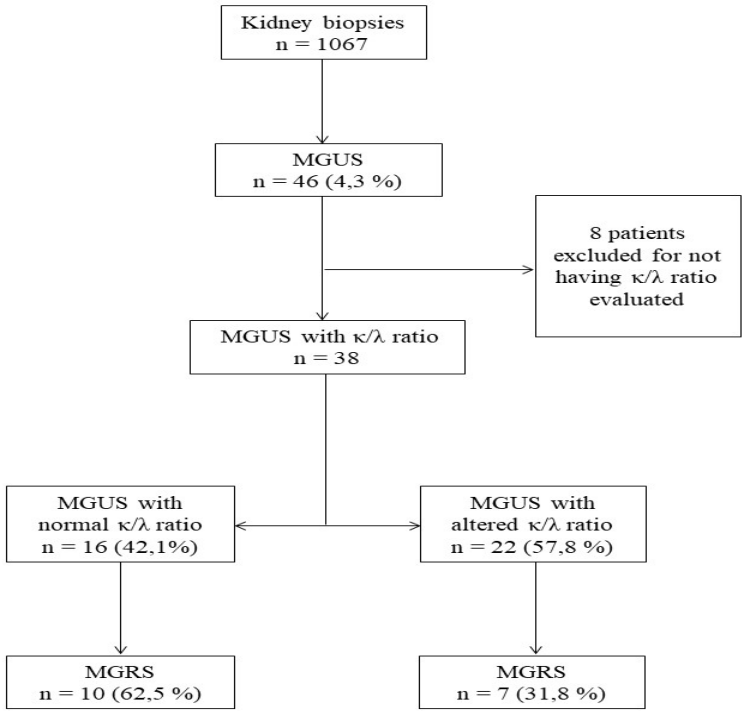
	OR	95% CI	*p*
Age	1.05	[0.98-1.13]	0.185
Male gender	0.37	[0.07-2.05]	0.256
Uprot, *mg/die*	1.01	[0.99-1.01]	0.056
κ/λ ratio	0.29	[0.06-1.36]	0.119
OR, odds ratio; CI, confidence interval; Uprot, 24-h proteinuria.			

Table 2: Logistic regression for the clinical correlates of MGRS.

	Overall (n=35)	MGRS-no (n=19)	MGRS-yes (n=16)	*p*
κ or λ prevalence, *n (%)*				0.030
λ prevalence & Uprot ≥ 1 g/die	15 (42.86)	4 (21.05)	11 (68.75)	
λ prevalence & Uprot < 1 g/die	3 (8.57)	3 (15.79)	0 (0.00)	
κ prevalence & Uprot ≥1 g/die	7 (20.00)	5 (26.32)	2 (12.50)	
κ prevalence & Uprot < 1 g/die	10 (28.57)	7 (36.84)	3 (18.75)	
OR, odds ratio; Uprot, 24-h proteinuria.				

Table 3: MGRS risk according to proteinuria and the predominance of κ and λ.

Figure 1. Study flowchart



Normal κ/λ ratio	MGRS-no	MGRS-yes
	3 Membranous glomerulonephritis	6 Immunoglobulin related amyloidosis
	1 Renal oxalosis	2 Thrombotic microangiopathy
	1 Focal segmental glomerulo-sclerosis	1 Light Chain Deposition Disease lambda
	1 IgA nephropathy	1 Monoclonal fibrillary glomerulonephritis
Altered κ/λ ratio	MGRS-no	MGRS-yes
	1 minimal change disease	5 Immunoglobulin related amyloidosis
	1 IgG 4 related disease	2 cryoglobulinemic type II glomerulonephritis
	1 cryoglobulinemic type II membranoproliferative glomerulonephritis HCV related	
	1 lupus-like IgG dominant polyclonal glomerulonephritis 1 diabetic nephropathy 1 membranous nephropathy	
	5 chronic lesions	
	4 minor histological lesions	

Supplementary Table 1: Histologic diagnosis by the MGRS and κ/λ ratio.

Discussion

In 2012, for the first time, kidney diseases related to MG were referred to as "monoclonal gammopathy of renal significance" (MGRS); since then, the attention given to MG as being a potentially significant cause of kidney injury has progressively increased [5]. The epidemiology of MGRS is still a topic of discussion, and there is a high discordance between prevalence rates according to various studies. In general, the likelihood of finding an MGRS disorder in patients affected by MG ranges from 6% to 40-45% [6-8]. Our study is in conjunction with the data recorded by Kyle and colleagues, who reported a 44.7% prevalence of MGRS in patients affected by MGUS [7]. Kidney biopsy represents the cornerstone for the diagnosis of MGRS because it permits the identification of Ig deposits and the classification of histological lesions. In the majority of cases, the histological evidence of a monoclonal deposit and its correspondence with the Ig found in serum and/or urine are the keys to establishing a diagnosis [2,9]. C3 glomerulopathy and thrombotic microangiopathy (TMA) are exceptions because they are not always characterized by the deposition of monoclonal immunoglobulin, even though monoclonal Ig can act through indirect mechanisms, such as the activation of the complement system [2]. The main indications for kidney biopsy in patients with MG are at least one of the following conditions: AKI, eGFR < 60 ml/min/1.73 m2, urinary albumin creatinine ratio (UACR) between 3 and 30 mg/mmol if eGFR > 60 ml/min, hematuria if eGFR < 60 ml/min and/or evidence of light chain proteinuria [2]. However, established guidelines on this topic are still unavailable. Our Center applies these indications to identify all patients who require kidney biopsy at earlier times among the cohort of MG patients proposed by hematologists. The aim of this strategy was to diagnose MGRS early in patients with a recent diagnosis of MG. From a hematological standpoint, the acknowledged gold standard for the diagnosis of MG is serum and urine protein electrophoresis and immunofixation, whereas serum immunofixation helps to confirm the presence of monoclonal Ig [10,11, p. 3]. In those cases in which monoclonal Ig is not detectable via electrophoretic methods, a urine sample should be analysed because its positivity for monoclonal light chain is diagnostic for MG [10,12]. However, routine employment of urine protein electrophoresis and immunofixation is not always performed due to its increased costs [13,14]. The International Myeloma Workshop Consensus Panel 3 recommends routine testing of serum free light chain (SFLC) for the screening of MG [10], [11]. However, abnormal SFLC and κ/λ ratios taken alone are not sufficient to prove the presence of MG and need to be confirmed by using electrophoretic methods and/or bone marrow biopsy [12]. Singh compared the diagnostic performance of SFLC, serum and urine protein electrophoresis and immunofixation with the objective of assessing their relative diagnostic contributions. He observed that protein electrophoresis was concordant with the

already established diagnosis of MG significantly more often than the κ/λ ratio [12]. From a nephrological standpoint, the evaluation of SFLC is not included among the criteria for performing kidney biopsy in patients with MG. In one Mayo clinic study, the authors reported that younger age, elevated serum creatinine and higher levels of proteinuria were the clinical and laboratory factors that increased the likelihood of receiving a kidney biopsy, and an altered κ/λ ratio did not seem to influence this odd discordance. This may suggest that nephrologists should not consider an abnormal κ/λ ratio when deciding whether to perform kidney biopsy, although it is considered a predictor of MGRS [4]. In our study, the κ/λ ratio was neither diagnostic nor exclusionary for the MGRS. Only 18.4% of patients with MGUS had both an altered κ/λ ratio and MGRS-associated disease, whereas the majority of patients (26.3%) had MGRSs in the context of a normal κ/λ ratio. However, we adopted the "conventional κ/λ ratio", while for patients with an eGFR < 60 ml/min, other authors used the "renal κ/λ ratio", which is greater than the conventional κ/λ ratio. These data reinforce the association that we found between a normal κ/λ ratio and MGRS lesions, even if it was not statistically significant ($p = 0.06$). Concerning the possibility of an elevated κ/λ ratio in our patients who were diagnosed with MGRS, we could propose a different hypothesis. First, we cannot exclude that MGRS has been detected in an early stage of the disease in which the κ/λ ratio is still normal, whereas in advanced stages, it may become altered as a consequence of the increased production of SFLC. This hypothesis reflects our attempt to make an early diagnosis.

Second, according to the Consensus Statement, the definition of MGRS does not include any mention of an overproduction of the immunoglobulin, which better reflects the tumour burden rather than kidney involvement. In this context, the nephrotoxicity of immunoglobulin in MGRS seems not to result from the amount of immunoglobulin itself but rather from its intrinsic pathogenic properties [15,16]. Proteomic studies, which permit the investigation of the intrinsic characteristics of pathological immunoglobulin to identify possible common aspects, are potentially useful in the treatment of MGRS. In this context, urinary exosomes are a potentially powerful tool for studying cellular proteomics in the urinary tract. In patients with amyloidosis, urinary exosomes contained monotypic light chains in vesicles, which later disappeared in patients who achieved complete remission. This suggests that urinary exosomes could be an excellent alternative biomarker to the κ/λ ratio for the diagnosis and monitoring of kidney responses in patients with MGRS-associated disorders. The disadvantages are the excessive costs and the nonavailability on a large scale [17,18]. When referring to our study, we subsequently conducted a sub analysis assessing the burden of the predominant light chain (κ or λ) in MGRS patients, and we did not find a statistically significant association between the prevalence of a single light chain and the presence of MGRS ($p = 0.059$, not shown). However, we observed that the concomitant presence of λ predominance and proteinuria ≥ 1 g/day were strongly associated with MGRS lesions (p value of the chi-square test= 0.030). Moreover, we found that the highest level of proteinuria (3.89 g/day, $p = 0.027$) was significantly associated with MGRS lesions. In contrast to our results, some authors have shown that the κ/λ ratio is greater in lesions with λ chains [12]. When considering the longer half-life of λ chains than that of κ chains, a lambda-dominant κ/λ ratio is expected to be more prevalent. However, λ chain lesions have a greater false-negative rate for the κ/λ ratio than κ chain lesions, and approximately 90% of MGUS patients with λ light chain evidence have a normal κ/λ ratio [19]. This effect could be explained by the greater tendency of λ light chains to polymerize and consequently possibly hide the epitopes that are normally detected by the antibodies that are used in the laboratory assay [12]. Another potential explanation for the high false-negative rate of the κ/λ ratio for λ chain lesions could be the overproduction of polyclonal κ chains and the underproduction of excess free λ light chains in patients with neoplastic monoclonal gammopathies with λ chain lesions [20,21]. It is important to correctly interpret the κ/λ ratio when considering the clinical context. In fact, there are many conditions that can possibly alter the κ/λ ratio, such as primary antibody deficiency and polyclonal gammopathy [18]. The latter condition is typical of inflammatory states and is characterized by the overproduction of κ light chain, which interferes with the interpretation of the κ/λ ratio if an underlying MG is suspected [19]. In our study, a review of clinical data did not suggest the presence of concomitant diseases that could influence the production of free light chains. All of these data raise questions about the clinical usefulness of SFLC in routine testing as a predictor for the diagnosis of MGRS. Making a correct diagnosis of MGRS is fundamental due to its impact on kidney function and survival. A combined hematological and nephrological approach is crucial. These results highlight the complexity of making a correct diagnosis of this family of clonal proliferative disorders and the need to evaluate both the laboratory findings and the histological data. A high risk of progression of MG to a related hematological malignancy, a low response to immunosuppressive therapies and a 90% risk of recurrence on kidney grafts are recognized if MG is not correctly treated during the perioperative period. From a "tumoral" viewpoint (i.e., their bulk and proliferative rate), even patients with MGRS should not require treatment. However, the prevention of renal deterioration makes therapy mandatory and sometimes urgent. In the MGRS, the normalization of the SFLC is included among the factors predicting a complete response to treatment [21]. The principal limitation of our study is the limited sample size. In addition, in contrast with other authors, we used the conventional κ/λ ratio, which limits the possibility of comparison. Our study has the strength of possessing a nephrological perspective, as it

was conducted at a single Center, thus mirroring the daily practice of kidney biopsy decision-making. Our study also demonstrated that collaboration may allow for an early and optimal diagnosis of the disease. In conclusion, our single-Center experience revealed a high percentage of biopsies demonstrating MGRS among patients affected by MGUS. Immunoglobulin-related amyloidosis is the most common pattern of renal involvement. Serum-free light chain assays and altered κ/λ ratios are not sufficient for detecting MGRS, and kidney biopsy remains fundamental for diagnosis. Accurate monitoring of patients affected by MGUS is key for the early diagnosis of MGRS. Increased proteinuria is the main factor predictive of kidney involvement.

Declarations

Conflict of interest: All of the authors confirm that they have contributed to the intellectual content of this paper and that they have no competing interests.

Ethical approval: This study was approved by the local Ethics Committee and was performed according to the Declaration of Helsinki. The participants received an explanatory statement and provided written informed consent to participate in the study (Protocol number 204/2020/Oss/AOUBo).

Author contributions: Conceptualization: GV, Data curation, Formal analysis: GP, AC, MP, Investigation, Project administration, Supervision: GV, GP, AC, MP, OB, GC, EZ, GLM, Writing–original draft: GV, GP, AC. All of the authors have read and approved the final manuscript. AC and GP participated equally.

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