Clinical Presentation and Renal Histopathological Findings in Patients with Monoclonal Gammopathy and Kidney Disease

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Abstract

Monoclonal gammopathies have been widely associated with renal lesions. Nephrotoxicity of the secreted monoclonal (M)-protein relies on a complex interplay between biological characteristics and serum concentration. Little is known about the prevalence and renal manifestations of the different types of monoclonal gammopathies in patients with kidney disease.

We reviewed all renal biopsies in our Center during a 12-year period to characterize patients diagnosed with monoclonal gammopathy. Data about demographics, laboratory examinations, renal manifestations and histological lesions were collected retrospectively. Results were correlated with the different lymphoproliferative disorders to evaluate the relationship between renal involvement and monoclonal gammopathies.

Monoclonal gammopathy was detected in 179 (13.4%) patients. The circulating M-protein was secreted by monoclonal gammopathy of undetermined significance (MGUS) (51.9%), myeloma multiple (MM) (25.7%), primary amyloidosis (AL) (8.9%), smoldering MM (5%), non-Hodgkin lymphoma (NHL) (6.7%) and HL (1.7%). Documented renal involvement in benign disorders such as MGUS and SMM accounted for 7.5% and 11.1%, respectively. MM was associated with an increased risk of kidney involvement (adjusted odds ratio=36.4; P=<0.001) and manifested with higher serum creatinine compared to other disorders. AL amyloidosis was principally secondary to MGUS (75%) and presented with nephrotic proteinuria. NHL and HL patients had heterogeneous renal manifestations. MGRS manifested both with light chain deposition disease and membranoproliferative glomerulonephritis. Compared to the other lymphoproliferative disorders, MM and AL amyloidosis showed higher creatinine blood levels and proteinuria, respectively. MM was significantly associated with kidney disease in our cohort of patients.

Monoclonal gammopathy is a frequent diagnosis in patients with kidney disease. An accurate diagnostic process including lab tests and kidney biopsy is necessary to identify if the secreted M-protein is associated with renal involvement.
Introduction

Monoclonal gammopathy is a clinical condition characterized by the presence of an abnormal protein — known as monoclonal (M)-protein — in the blood.¹ M-protein is an intact antibody, or any chain fragment produced and secreted by a pathological clone. The ability of M-protein to disrupt cellular homeostasis is unpredictable and principally related to its physicochemical properties and blood concentration.²

Historically, renal toxicity of the M-protein has been associated with the malignancy of the underlying lymphoproliferative disorder. Myeloma multiple (MM), one of the most common hematologic malignancy³, has been widely associated with kidney disease.⁴,⁵ In this disease, renal injury relies principally on the overproduction of M-protein, which leads to the activation of tubulointerstitial inflammatory pathways and tubular obstruction. As a result, cast nephropathy is the classical renal presentation of MM.⁶ Other malignant lymphoproliferative diseases such as Waldenström macroglobulinemia (WM)⁷, lymphomas⁸,⁹ have been less frequently associated with renal injury and generally present with light-chain deposition disease, membranoproliferative glomerulonephritis and cryoglobulinemic vasculitis.⁹,¹⁰

However, even clones that have a low propensity to progress toward malignancy and secrete low amount of M-protein can be involved in tissue damage including neuropathy, autoimmune diseases as well as kidney disease.¹¹ In this setting, the deposition of M-protein or activation of the complement system may lead to renal lesions. Recently, the nephrological community has coined a new term: monoclonal gammopathy of renal significance (MGRS). The definition of MGRS includes all small B-cell or plasma cell clones that does need specific cytoreductive therapy but causes kidney lesions through the production of M-protein.¹² The most glaring example is monoclonal gammopathy of indeterminate signifycate (MGUS). It may be associated with renal lesions despite the low level of secreted paraprotein and the rare progression to MM.¹³

The growing interest in this new pathological entity has spurs nephrologists and hematologists to reevaluate the pathogenicity of these small, apparently indolent, clones. The enthusiasm to understand the impact of monoclonal gammopathy in patients with renal impairment has faced with the rarity of the phenomena and the fragmentary of the data. In light of these limits, we investigated the impact of all monoclonal gammopathies in a cohort of patients who underwent kidney biopsy for renal impairment. This study aimed to evaluate the prevalence and renal manifestations of monoclonal gammopathy as well as its association with renal histopathological findings.

Material and Methods

We conducted a retrospective study at the Nephrology Unit of the University Hospital of Modena. The charts of all patients with biopsy-proven kidney disease were evaluated from January 2005 to March 2017. The study protocol was approved by the Provincial Ethics Committee of the University Hospital of Modena (CE/1476).
Among all patients who underwent kidney biopsy, we enrolled only those with a diagnosis of serum M-protein that was detected by protein electrophoresis (SPEP) and subsequently characterized by serum or urine immunofixation. We excluded the patients with a diagnosis of kidney disease not proven by biopsy.

**Renal biopsy**

The diagnosis of kidney disease was provided histologically. Biopsy specimens were examined using light microscopy (LM) and immunofluorescence (IF). Kidney tissue sections have been evaluated by periodic acid-Schiff (PAS), periodic acid-methenamine silver (Jones), and Masson's trichrome stains. For immunofluorescence, cryostat sections were stained with fluorescein isothiocyanate-conjugated rabbit antihuman IgG, IgM, IgA, C3, C1q, kappa (k) light chain and lambda (λ) light chain. Staining with Congo red confirmed amyloid deposits. Primary amyloidosis or light chain amyloidosis (AL) was identified by light chain restriction using IF or immunohistochemistry performed in another Center. Renal biopsies were not routine processed by electron microscopy; it was principally performed to furnish additional information in nondiagnostic biopsies evaluated by LM and IF.

Monoclonal gammopathy was directly involved in the pathogenesis of renal lesions if histological evaluation revealed a diagnosis of cast nephropathy, M-immunoglobulin deposition, membranoproliferative glomerulonephritis with M-immunoglobulin restriction and primary amyloidosis or light chain amyloidosis (AL). Heavy or light chain restriction was determined by measuring fluorescence intensity.

**Study population**

Demographics and laboratory data were collected at the time of kidney biopsy. We evaluated data about complete blood count (leukocytes, erythrocytes, hemoglobin, platelets), serum calcium, creatinine, estimated glomerular filtration(eGFR) calculated using CKD-EPI equation\(^\text{14}\), proteinuria, serum and urine M-protein, serum M-protein concentration and serum free light chain (FLC). Proteinuria was principally estimated through the urine protein-to-creatinine ratio.

Nephrotic syndrome was defined as urine protein-to-creatinine ratio more 3 and serum albumin less than 3.5 gr/dl. We considered AL amyloidosis and light chain deposition disease associated with MM in the presence of lytic bone lesions and other sign of over MM or plasma cells count greater than 30% in the bone marrow.\(^\text{15}\)

Acute kidney injury (AKI) refers to an abrupt decrease in kidney function. The definition is based on one the following criteria: increase in serum creatinine by ≥0.3 mg/dL within 48 hours, or increase in serum creatinine to ≥1.5 times baseline or urine volume <0.5 mL/kg/hour for six hours.\(^\text{16}\)

Severe impairment of renal function refers to serum creatinine ≥3 mg/dL.
Statistical analysis

Continuous variables with normal distribution were presented as mean and standard deviation (SD). The difference between the means of two groups was performed with two-sample t-tests at. Kruskal-Wallis test (or one-way ANOVA on ranks) was used to perform multiple comparisons between groups. Dunn’s test determined whether there was a difference between the mean of all possible pairs. Logistic regression analyses were done to compute adjusted odds ratios (AOR), 95% confidence intervals (95% CI), and P-values to estimate the relationship between lymphoproliferative disorders and the occurrence of monoclonal gammopathy-associated renal lesions. Logistic regression was also used to evaluate the association between histological findings in MM patients and severe impairment of renal function. P-value <0.05 was considered to be statistically significant. All analyses were performed using SPSS version 23 (SPSS, Inc., Chicago, IL).

Results

Patient’s characteristics

We reviewed the charts of 1334 patients who underwent native kidney biopsy to investigate renal dysfunction. Monoclonal gammopathy was found in 179 patients (13.4%) with a mean age of 66.1±13.4 years (Table 1). Most of them (96.1%) were of Caucasian origin and males were predominant on females (63.7 vs. 36.3%). Compared to the entire study population, monoclonal gammopathy had a higher prevalence in the age range of 50-79 years (Table 2).

The hematologic disorders that presented with a circulating M-protein were MGUS (51.9%), MM (25.7%), amyloidosis (8.9%) smoldering MM (5%), non-Hodgkin lymphoma (NHL) (6.7%) and HL (1.7%). The detection of M-protein was associated with 57% to benign lymphoproliferative diseases and for 43% to malignant diseases). There were no differences (P=0.16) between the age of patients with benign (64.9±14.3) and malignant lymphoproliferative disease (67.6±12). (Figure)

MGUS

MGUS was the most common monoclonal gammopathy. Its prevalence was estimated to be 6.9% (93/1334) among patients who underwent kidney biopsy.

The mean age of patients was 64±14 years with a predominance of males 62.3% (Table 2). Laboratory tests showed that white cell count was 7.5±3.4 x 10^9/L, Hb 11.3±2.5 gr/dl, platelets 219.1±102.6 x 10^9/L, serum calcium 9.7 mg/dl and serum albumin 3.15±0.8 gr/dl.

Average serum creatinine was 2.68±2.1 mg/dl corresponding to an estimated glomerular filtration rate (eGFR) of 35.2±29.3 ml/min. Distribution of CKD stage was heterogeneous with a high prevalence of patients with later stages of CKD: 6.6% in CKD stage I, 9.9% in CKD stage II, 31.9% in CKD stage III, 20.4% in CKD stage IV and 30.8% in CKD stage V.
Urinary examination showed a urine protein-to-creatinine ratio of 5.1±6.5.

The serum concentration of M-protein oscillated between 0.2 and 2.3 gr/dl with a mean concentration of 0.6±0.5 gr/dl. IgG was the most common isotype (65.5%), followed by IgM (24.7%) and IgA (2.15%). Characterization of serum M-protein through immunofixation revealed a higher prevalence of k light chain. M-protein was biclonal in 7.5% of the cases.

Serum FLC k and λ were 302.3±177.8 and 172.5±159.3, respectively. Bence Jones proteinuria was detected in 26.8% of the subjects.

The most common kidney disease was membranoproliferative glomerulonephritis that occurred in 18 patients (19.3%); in four of them was secondary to viral hepatitis. Surprisingly, IgA glomerulonephritis was unrepresented in our group (1%,). In four (4%) patients MGUS was directly involved in the development of renal injury (MGRS) through deposition of light chains. In two out of 18 cases (11%) with a diagnosis of membranoproliferative glomerulonephritis, IF analysis showed intact immunoglobulin restriction. Overall, parenchymal lesions compatible with MGRS criteria accounted for 7.5% of all cases of MGUS.

**Myeloma multiple**

MM was the second most common gammopathy in our study population. The disorder was detected in 46 subjects with a mean age of 66.84±13 years. MM was more frequent in males than in females (69.6 vs 30.4%). In relation to the criteria CRAB (calcemia, renal disease, anemia and bone disease), laboratory tests at presentation revealed serum calcium of 9±1.2 mg/dl, hemoglobin of 10.3±1.6 gr/dl, myeloma bone lesions in 71.7% of patients and an average serum creatinine of 4.8±2.8 mg/dl, corresponding to an eGFR of 20.7±23.5 ml/min. White cell count was 6.2±1.9 x 10⁹/L, platelet count 226±145.7 x 10⁹/L and serum albumin of 3.3±0.7 gr/dl. Plasma cells infiltrates in bone marrow biopsy accounted for 50% of the cells. The majority of patients was admitted with severe renal impairment (82.6%) and 12 patients (26%) required urgent hemodialysis for the development of oliguric AKI due to cast nephropathy. In seven patients (15.2%) clinical manifestation of kidney disease was a nephrotic syndrome with average urine protein-to-creatinine ratio ranging from 4.2 to 18.5 associated with a wide variability of renal function (serum creatinine ranged from 1.01 to 6 mg/dl).

Measurement of serum M-protein concentration was 1.47±0.98 gr/dl and three patients had biclonal isotype. Light chain MM accounted for 32.6% of the cases and, as expected, kappa light chain MM resulted more prevalent compared to λ light-chain MM (60 vs.40%). Immunoglobulin isotype were IgGk (23.2%); IgGl(16.2%); IgAk(6.9%). IgA (13.9%) and IgMk(4.6%). Dosage of serum FLC showed chain k of 419.5±158.9 and a chain λ of 158.9±191.1 mg/dl. Bence Jones was detected in 93.7% of the tested patients.

Histological evaluation of kidney biopsy specimen showed cast nephropathy (71.7%), multiple myeloma-associated AL amyloidosis (15.2%), multiple myeloma-associated-light chain deposition disease (4.3%) and interstitial nephritis (8.7%). Cast nephropathy was the only histological lesion associated with severe renal
impairment identified with a serum creatine ≥ 3 mg/dl (supplemental Table 1). Lastly, all patients with histological diagnosis different from cast nephropathy had bone osteolytic lesions compatible with myeloma bone disease.

**MM smoldering**

Nine (5%) patients had a diagnosis of smoldering MM. The disorder manifested at a mean age of 69.2±10.8 years and showed a slightly higher prevalence in men than women (55.5 vs 44.5%). According to the definition of MM smoldering, bone lytic lesions were absent in all patients. Hemoglobin and serum calcium were in the normal range, 12.4±2.3 gr/dl and 9.8±0.4 mg/dl, respectively. Further lab examinations reported a white cell count of 6±1.5 x 10⁹/L, platelets count of 196.2±50.8 x10⁹/L and a serum albumin level of 3.8±0.67 gr/dl. At presentation, mean serum creatinine was 2.31±2.6 mg/dl (eGFR of 41.3±25 ml/min) with proteinuria of 1.2±1.1.

Immunofixation of the serum M-protein detected the following isotypes: IgGλ (33.3%), IgGk (0.22%) IgMk (11.1%), IgAλ (11.1%) and k light chain (11.1%). Bence Jones was found in 66.6% of the patients. Bone marrow biopsy revealed a mean plasma cell count of 18%.

Evaluation of renal biopsies showed different patterns of glomerular diseases including interstitial nephritis (33%), membranoproliferative glomerulonephritis (22%), acute tubular necrosis (ATN) (11%), vasculitis ANCA-negative (11%) and membranous glomerulonephritis (11%). Light chain restriction was diagnosed only in one patient (11.1%) affected by membranoproliferative glomerulonephritis.

**Hodgkin Lymphoma**

Three patients (1.12%) had a diagnosis of Hodgkin's lymphoma at an average age of 69.04±5.3 years. At presentation, complete blood count showed white blood cell of 14.1±16 x 10⁹/L, platelets of 188.7±52.6 x10⁹/L, hemoglobin 13.3±0.9 x10⁹/L and albumin of 3.7±0.7 gr/dl. All patients had a normal renal function manifesting with a mean creatinine of 0.93±0.07 mg/dl corresponding to an eGFR of 62.7±7.4 ml/min. Mean urine protein-to-creatinine ratio was of 0.3±0.2. Mild proteinuria was present only in one patient (urine protein/creatinine ratio of 0.5). Serum immunofixation identified isotype IgMk in two cases and isotype IgGk in only one case. Mean FLC k was and free light chain lambda were 254±173.1 and 140.8±117.9 mg/dl, respectively. Bence Jones protein was present in only one patient. Cryoglobulinemic glomerulonephritis was found in two-thirds of the patients and hypertensive nephrosclerosis in one.

**AL Amyloidosis**

Amyloidosis, defined as primary amyloidosis or AL amyloidosis AL was diagnosed in 16 patients (8.9%). Amyloidosis was secondary to MGUS (75%) and smoldering MM (25%). The mean age of the affected subject was 66.34 ±11.38 years and females were slightly more prevalent than males (53 vs 46%). Mean
white cell and platelets count were 7.1 ± 2.5 x 10^9/L and 306.6 ± 154.8 x 10^9/L, respectively. The measurement of serum Hb revealed a value of 12.7 ± 2 gr/dl and that of albumin a value of 2.8 ± 0.8 gr/dl. Serum creatinine ranged from 0.5 to 4.5 mg/dl with a mean serum creatinine of 1.4 gr/dl, corresponding to 56.5 ml/min of eGFR. At presentation, the average urine protein-to-creatinine ratio was 8.33 ± 3.2 associated to hypoalbuminemia (2.74 ± 0.84 gr/dl).

Serum creatinine ranged from 0.5 to 4.5 mg/dl with a mean serum creatinine of 1.4 gr/dl, corresponding to 56.5 ml/min of eGFR. At presentation, the average urine protein-to-creatinine ratio was 8.33 ± 3.2 associated to hypoalbuminemia (2.74 ± 0.84 gr/dl).

Serum immunofixation revealed the following isotypes: IgGλ (56%), IgGκ (13%), IgAλ (13%), IgMκ (13%) and IgMλ (6%). Serum M-protein concentration was 0.67 ± 0.46 gr/dl. Mean FLC κ and λ were 140 ± 101.5 and 200.4 ± 208.7 mg/dl, respectively. Detection of urinary light chain occurred in 81.2% of the patients. The diagnosis of amyloidosis was performed by the detection of deposit of amorphous material in the mesangium and capillary loops of glomeruli. Congo red stain confirmed the diagnosis of amyloidosis and further studies identified the etiologic trigger of amyloidosis.

**Non-Hodgkin's lymphoma**

Twelve patients (6.7%) with monoclonal gammapathy had a diagnosis of NHL, which term includes several heterogeneous lymphoproliferative disorders. According to the WHO classification\(^\text{17}\) lymphoplasmacytic lymphoma accounted for 41.6%, Waldenstrom's macroglobulinemia for 30.7%, marginal zone lymphoma for 15.2%, diffuse large B-cell lymphoma for 7.6% and anaplastic large cell lymphoma for 7.6%. Male gender was fully associated (100%) with NHL in our cohort of patients. The average age of subjects was 72.6 ± 9.6 years. White cell measured 7.66 ± 3.08 x 10^9/L, Hb = 11.37 ± 2.03 gr/L, platelets 245 ± 39.2 x 10^9/L. Serum calcium was 10.2 ± 0.38 mg/dl. Renal function was extremely variable at presentation. Serum creatinine ranged between 0.85 and 6.35 mg/dl; mean creatinine was 2.4 ± 1.6 mg/dl corresponding at an eGFR of 30.4 ± 22.7 ml/min. Five out of 12 patients had nephrotic syndrome at admission. Daily proteinuria ranged from 0.7 to 8.2 gr/day. Average proteinuria was 4.36 ± 3.36 gr/24 hour. IgMκ (66.6%) was the most common monoclonal protein whereas IgA lambda, IgG κ, IgM λ accounted for 8.33%, respectively. A patient with marginal zone lymphoma had a circulating biclonal M-protein represented by IgMκ and IgM λ.

NHL subjects had a circulating M-protein of 0.6 ± 0.4 gr/dl. Serum FLC κ and λ were 319.3 ± 178.1 and 148.8 ± 115.2 mg/dl, respectively. Urine monoclonal component was found in 68.7% of patients. Histological evaluation of biopsy specimen revealed amyloidosis (25%), membranoproliferative glomerulonephritis (25%), LCDD (25%), ANCA-associated vasculitis (8.3%), cast-nephropathy (8.3%), and hypertensive nephrosclerosis (8.3%). In a case (8.3%) of membranoproliferative glomerulonephritis, Ig deposits were restricted for the same serum M-protein.

**Comparison between groups.**
Kruskal-Wallis test showed that mean serum creatinine levels (P < 0.0001) and mean proteinuria (P < 0.0001) were statistically different between the groups. A higher value of serum creatinine and urine protein excretion was found in MM and AL amyloidosis patients, respectively. Lymphoproliferative diseases were variably associated with renal lesions due to M-protein. Documented renal involvement in patients with NHL, MGUS, MM, SMM and AL amyloidosis accounted for 58.3%, 6.4%, 91.3%, 22.2% and 100%, respectively. Regression analysis excluding amyloidosis, which diagnosis necessarily required demonstration of tissue damage, showed that MM was significantly associated with renal damage (P < 0.001). MM patients had a 36.4-fold increased risk of renal lesions (95% CI, 12.63 to 110.15) (Table 4).

**Discussion**

The recent literature has placed great emphasis on the pathogenic role of monoclonal gammopathy as a potential cause of kidney disease. Our study showed that monoclonal gammopathy was a frequent diagnosis (13.4%) in patients with renal impairment who underwent kidney biopsy. Monoclonal gammopathy occurred predominantly in subjects over 65 years of age and presented with a wide spectrum of renal manifestations. The lymphoproliferative disorders that we recognized as monoclonal gammopathies were MGUS, SMM, NHL, LH, MM and AL amyloidosis. MGUS was found to be the most common disorder. It accounted for more than half (51.9%) of all cases of monoclonal gammopathies. However, despite the predominance of this indolent form, the prevalence rate of malignant lymphoproliferative disorders was surprisingly high in our cohort of patients. Aberrant cellular proliferation of neoplastic clones accounted for 43% and included MM, HL and NHL.

Besides the malignancy of these disorders, the nephrotoxicity of M-protein should be considered when evaluating monoclonal gammopathy. M-protein, even if it is produced by an indolent clone with a low propensity to progress toward uncontrolled proliferation, may be extremely harmful to renal parenchyma. Etiological mechanisms of M-protein nephrotoxicity are strictly dependent on the idiosyncratic properties of the secreted paraprotein. Deposition of M-protein and activation of complement are the leading pathological processes underlying the onset of monoclonal gammopathy-associated renal lesions.

According to the recent definition of MGRS, renal lesions due to the interplay with circulating M-protein were detected in 6.4% and 11.1% of our MGRS and SMM patients, respectively. Histological lesions compatible with MGRS included light chain deposition diseases and membranoproliferative glomerulonephritis with Ig-restriction. While light chain deposition disease is known to be associated with the deposition of circulation of M-protein, little is known on the causative factors of membranoproliferative glomerulonephritis. This latter has been frequently encountered in patients with MGUS, but it is not uncommon in chronic lymphocytic leukemia, lymphomas and MM. Deposition of secreted monotypic immunoglobulin protein along the capillary walls and the activation of the complement...
system (both classical and alternative pathway) are believed to be the trigger for the development of the membranoproliferative pattern of glomerular damage.\textsuperscript{22}

It is worth noting that the histological detection of membranoproliferative glomerulonephritis is not sufficient to meet the diagnosis of MGRS. The identification of the restricted circulating immunoglobulin in renal parenchyma by immunofluorescence (or immunoperoxidase) and transmission electron microscopy is a practical and effective way to demonstrate M-protein nephrotoxicity\textsuperscript{20}. Although membranoproliferative glomerulonephritis was the predominant histopathological diagnosis in MGUS and SMM, patients, we found only few cases with this histological pattern of injury fulfilling MGRS criteria. Ig-restriction involved only a minority (about one-tenth) of patients with membranoproliferative glomerulonephritis.

MM was the only lymphoproliferative disease significantly associated with kidney diseases in our cohort study (P=<0.0001). Subjects with MM presented with higher average serum creatinine compared with other monoclonal gammopathies. The majority of patients (89.1\%) was admitted with a severe and acute worsening of renal function that required renal replacement treatment in about a third of cases. In line with previous native renal biopsy studies\textsuperscript{24,25}, cast nephropathy was the most prevalent histopathological finding (71.7\%), significantly associated with severe renal impairment. Further paraprotein-associated lesions included light-chain deposition disease and AL amyloidosis. Overall these histological lesions accounted for 91.3\%, whereas in the remaining patients presented with tubulointerstitial nephritis, a rare renal manifestation of MM\textsuperscript{26}.

Lymphoma is well-associated with renal involvement and presents with a wide spectrum of renal manifestations. Lymphocytic infiltration of the parenchyma is the most prevalent finding in the largest case series of autopsies\textsuperscript{27}. Further renal manifestations rely on several distinct malignancy-related mechanisms and include minimal change disease, amyloidosis, membranoproliferative glomerulonephritis, immuntatoid glomerulopathy and M-protein deposition disease. In the setting of HL, presentation of renal involvement was normal renal function and mild proteinuria, but the limited number of cases does not allow us to generalize this data. On the other hand, renal function was extremely variable in NHL patients; it ranges from normal renal function to acute kidney failure. Glomerulonephritis with membranoproliferative-like patterns and M-immunoglobulin deposition disease was the most common histological findings in this group of patients. Similar to the literature, glomerular involvement with membranoproliferative glomerulonephritis\textsuperscript{28,28,29} and M-protein deposition disease\textsuperscript{30–32} was common in patients with NHL\textsuperscript{33,34}.

AL amyloidosis represented only a small percentage (8.9\%) of all monoclonal gammopathies. The leading cause of this low rate is due to the exclusion from this group of all cases of amyloidosis coexistent with lymphoma and MM. AL amyloidosis was secondary to the proliferation of a benign clone of MGUS in two-third of the cases and to smoldering MM in the remaining one third. AL amyloidosis was characterized by the
deposition of light-chain deposition in the renal parenchyma of all renal biopsy specimens. We observed that our results confirmed the high prevalence of light chain isotype and urine M-protein in subject with renal amyloidosis. AL amyloidosis manifested with a nephrotic syndrome characterized by a significantly higher level of proteinuria than other gammopathies. Renal function was not severely impaired and showed only a slight increase in serum creatinine.

The results of this study point out the close and variable interplay between monoclonal gammopathy and renal injury; it ranges from an established causality in MM and MGRS to an unrelated mechanism in the majority of cases of MGUS and smoldering MM. The workflow process for the assessment of monoclonal gammopathy-associated renal lesion is based on the identification of the hematological disorder and underlying nephropathy. Once M-protein has been identified and characterized, exclusion of a malignant disorder should remain a high priority among nephrologists, as the outcome of the patient is associated with a poor prognosis if left untreated. Diagnostic tests such as flow cytometry, bone marrow biopsy, radiological examinations should be have a low threshold if there is a high suspicion index. Evaluation of renal function trajectory and urinary abnormalities is essential to assess renal function. The main limit of this approach is the overlapping pattern of renal manifestations in the setting of monoclonal gammopathies. Although, MM and AL amyloidosis manifest with a significantly higher level of serum creatinine and proteinuria, respectively, evaluation of renal function by kidney biopsy has a crucial role in the diagnosis of the underlying hematological disorder and renal injuries driven by M-protein. Lastly, kidney biopsy carries important therapeutic and prognostic implications in subjects with MGRS, as this condition is associated with a concerning poor renal outcome and with a high rate of recurrence after renal transplantation and appropriate chemotherapy.

The principal strength of our study is the detailed description of renal manifestations in patients with monoclonal gammopathy. It is the first study that provides an overview of the prevalence of all monoclonal gammopathy and MGRS in a cohort of patients with renal impairment. In all subjects, all M-proteins has been diagnosed and characterized by electrophoresis and immunofixation and renal pathology has been confirmed by kidney biopsy. The main limitations of the study are the retrospective analysis and the small sample size of certain groups of patients with monoclonal gammopathy that do not allow to properly identify and characterize renal involvement. Likely, the not routine use of electron microscopy has led to the underestimation of some cases of MGRS, and point out an unintentional bias frequently present in the current literature. The prognosis of patients is unreported but it is beyond the scope of this article. Knowing the prognosis of renal involvement in the context of monoclonal gammopathy may serve as a stimulus to enhance efforts to conduct prospective studies among centers.

In conclusion
Lymphoproliferative disorders secreting M-protein carry a different potential for renal involvement. MGUS is the most frequent monoclonal gammopathy among patients who undergo kidney biopsy. Although MGUS has a low propensity to progress toward malignant disease, it is related to the development of specific renal lesions. MM is significantly associated with renal impairment and commonly manifesting with severe impairment of renal function. Patients diagnosed with AL amyloidosis has a higher level of proteinuria compared to the other monoclonal gammopathies. Careful evaluation is mandatory to identify malignant disorders and MGRS because both conditions require specific chemotherapy treatment.

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Table 1. Demographics and clinical characteristics of patients with monoclonal gammpopathy
| Characteristic            | All patients |
|--------------------------|--------------|
| Age – yr                 | 66.1±13.4    |
| Mean (±SD)               |              |
| Male – n. (%)            | 114 (63.7%)  |
| Ethnic group – n. (%)    |              |
| Caucasian                | 172 (96)     |
| Hispanica                | 1 (0.5)      |
| Asiatic                  | 3 (1.6)      |
| African                  | 3 (1.6)      |
| Monoclonal gammopathy    |              |
| MGUS – n. (%)            | 93 (51.9)    |
| MM – n. (%)              | 46 (25.7)    |
| AL amyloidosis – n. (%)  | 16 (8.9)     |
| NHL – n. (%)             | 12 (6.7)     |
| Smoldering MM – n. (%)   | 9 (5)        |
| HL – n. (%)              | 3 (1.7)      |

Table 2. Range of age of patients with monoclonal gammopathy

| Range of age | Study population – n. | Patients with MG – n. (%) | MG patients/study population –% |
|--------------|-----------------------|---------------------------|---------------------------------|
| ≤50          | 572                   | 25 (14)                   | 4.4                             |
| 50-59        | 63                    | 23 (12.8)                 | 36.5                            |
| 60-69        | 232                   | 51 (28.5)                 | 22.0                            |
| 70-79        | 241                   | 64 (35.7)                 | 26.6                            |
| ≥80          | 226                   | 16 (8.9)                  | 7.1                             |
| TOT.         | 1334                  | 179 (100)                 |                                 |

Table 3. Laboratory test results in patients with monoclonal gammopathy
### Table 4. Association between monoclonal gammopathy and renal involvement

| Variable | Adjusted odds ratio (95% CI)* | P value |
|----------|-------------------------------|---------|
| MM       | 36.4 (12.03-110.15)           | <0.001  |
| NHL      | 2.1 (0.63-7.12)               | 0.21    |
| SMM      | 0.4 (0.82-2.01)               | 0.27    |
| MGUS     | 0.18 (0.006-0.05)             | <0.001  |
| HL       | /                             | 0.99    |

Although this analysis shows that MGUS had a protective effect for direct renal injuries compared to the other gammopathies, the result was not considered clinically significant.