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Dysproteinemia-Associated Kidney Diseases: Clinicopathological Correlations

Menezes MM[1]*, Costa LL[2], Soares E[3], Sousa H[1], Góis M[1] and Nolasco F[1]

[1]Department of Nephrology, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Lisboa, Portugal

[2]Department of Nephrology, Centro Hospitalar Tondela-Viseu, Viseu, Portugal

[3]Department of Nephrology, Centro Hospitalar de Setúbal, Setúbal, Portugal

***Corresponding author:** Menezes MM, Department of Nephrology, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central. Rua da Beneficiência, 8. 1050-099 Lisboa, Portugal

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Abstract

Introduction: Dysproteinemia-associated kidney diseases can have diverse clinical and histological presentation but not all patients with monoclonal gammopathy have Monoclonal Gammopathy of Renal Significance (MGRS) and some have other causes for kidney lesions. Therefore, kidney biopsy is essential to make this diagnosis.

We made a retrospective study, which aimed to: 1. Identify dysproteinemia-associated kidney lesions; 2. Establish clinicopathological correlations of patients with those lesions and 3. Identify kidney and patient survival predictors.

Methods: A retrospective, observational chart review of kidney biopsies performed, between January 2015 and February 2020, in three Portuguese Hospitals, to a total of 39 patients, with kidney lesions associated with monoclonal gammopathy, was undertaken.

Results: The three main dysproteinemic kidney diseases identified were cast nephropathy, AL amyloidosis and Monoclonal Immunoglobulin Deposition Disease (MIDD), with different features among them. Only three patients fulfilled the criteria to Monoclonal Gammopathy of Renal Significance (MGRS).

In regard to treatment, we verified that most of our patients were treated with chemotherapy. Unfortunately, only four recovered, either partially or completely. The mean kidney survival since kidney biopsy was 29,23 months and the mean patient survival since diagnosis was 24,46 months. Some clinical and pathologic features correlated to lowerkidney survival: acute tubular necrosis, cast nephropathy, Thrombotic Microangiopathy (TMA), haemoglobin and estimated Glomerular Filtration Rate (eGFR). Previous Nephrology follow-up correlated with higher kidney survival. Only eGFR was associated with lowerpatient survival.

Keywords: Dysproteinemia-associated kidney diseases; Monoclonal gammopathy of renal significanc; kidney survival

Abbreviations

AKI: Acute Kidney Injury; ATN: Acute Tubular Necrosis; CKD: Chronic Kidney Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CLL: Chronic Lymphocytic Leukemia; CN: Cast Nephropathy; eGFR: Estimated Glomerular Filtration Rate; ESKD: End Stage Kidney Disease; IFTA: Interstitial Fibrosis And Tubular Atrophy; MGRS: Monoclonal Gammopathy of Renal Significance; MIDD: Monoclonal Immunoglobulin Deposition Disease; MM: Multiple Myeloma; PGMID: Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposit; SD: Standard Deviation; TMA: Thrombotic Microangiopathy

Introduction

MGRS is an emerging concept that has been growing in documentation in the Nephrology practice. It is a challenging diagnosis that has been increasingly identified. According to the consensus report of the International Kidney and Monoclonal Gammopathy Research Group, the term MGRS applies specifically to any B cell or plasma cell clonal lymphoproliferation with both of the following characteristics: "One or more kidney lesions that are related to the produced monoclonal immunoglobulin or its components and the underlying B cell or plasma cell clone does not cause tumor complications or meet any current hematological criteria for specific therapy" [1,2]. If we take in consideration Cast Nephropathy (CN) which is considered a myeloma defining event, by the former definition, it is not a MGRS because it is almost always secondary to Multiple Myeloma (MM) due to a high tumor cell burden, [3]. However, to be more inclusive, in this paper we shall refer dysproteinemia-associated kidney diseases, instead of MGRS, [4].

The clinical presentation of these kidney diseases can be very variable. It can range from microscopic hematuria and sub-nephrotic proteinuria with preserved kidney function to a rapidly progressive renal dysfunction or a nephrotic syndrome. The monoclonal immunoglobulin can provoke damage in one or several kidney compartments - glomerulus, vessels, tubules and interstitium.

Dysproteinemia-associated kidney diseases may be related or not to immunoglobulin deposits. The deposits may be organized or non-organized, and the first ones can be further divided into fibrillar, microtubular and crystalline or inclusion deposits.

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Fibrillar deposits include Immunoglobulin related amyloidosis and monoclonal fibrillar glomerulonephritis. Microtubular deposits encompass immunotactoid glomerulonephritis and type I and II cryoglobulinemic glomerulonephritis. The last group includes light chain proximal tubulopathy, crystal storing histiocytosis and (Cryo) cristalglobulin glomerulonephritis. Non organized deposits include Monoclonal Immunoglobulin Deposition Disease (MIDD) and Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposit (PGMID). The absence of visible deposits may be the hallmark of C3 glomerulopathy with monoclonal gammopathy or TMA [5-7]. The description of these subtypes is beyond the scope of this article.

Without appropriate and timely treatment, most of these lesions will evolve to chronic kidney disease or end stage kidney disease (ESKD). Therefore, the high grade of suspicion is of utmost importance to prevent this course. However, not all patients with monoclonal gammopathy have MGRS and some patients have other causes for kidney lesions. So, the kidney biopsy plays an essential role to make this diagnosis.

Considering the aforementioned, the authors performed a retrospective study, which aimed to: 1. Identify dysproteinemia-associated kidney lesions, 2. Establish clinicopathological correlations of patients with those lesions and 3. Identify kidney and patient survival predictors.

Methods

A retrospective, observational chart review of kidney biopsies performed, between January 2015 and February 2020, in three Portuguese Hospitals, to a total of 39 patients with kidney lesions associated with monoclonal gammopathy, was undertaken. All patients with kidney lesions associated with monoclonal gammopathy were analyzed with a minimum of one-year follow-up. We reviewed pathology archives to identify these diagnoses. Standard processing of kidney biopsies included light microscopy and immunofluorescence analysis.

Light microscopy included hematoxylin and eosin, periodic acid-Schiff, Masson trichrome, Jones methenamine silver and Congo-red staining. Immunofluorescence contained antibodies to IgG, IgA, IgM, C3, C4, C1q, kappa and lambda light chain, albumin and fibrinogen.

Each biopsy was characterized regarding: number of glomerulus and percentage of those with sclerosis, Interstitial Fibrosis and Tubular Atrophy (IFTA) (score 0=0%; score 1=1-25%; 2=25-50%; 3=>50%); presence of Acute Tubular Necrosis (ATN); vascular involvement; interstitial inflammation (1=0-25%; 2=25-50%; 3=>50%); kidney lesion diagnosed (light chain cast nephropathy, Immunoglobulin-related amyloidosis, MIDD, PGMID, monoclonal fibrillary glomerulonephritis, cryoglobulinaemic glomerulonephritis and thrombotic microangiopathy).

Demographic information included age, sex and race at kidney biopsy date.

Laboratory data findings at the time of hematological diagnosis encompass hemoglobin and calcaemia. Physical symptoms linked to the former, like asthenia and bone pain, were also recorded. The main signs and symptoms related to amyloidosis were identified (hypotension if systolic blood pressure <120mmHg; macroglossia, neuropathy and purpura).

Immunologic data comprised: serum protein electrophoresis, serum immunofixation, free light chain assay, kappa/lambda ratio, involved/uninvolved ratio, number of plasma cells in bone marrow, cytogenetic study, beta-2 microglobulin.

All patients were screened about nephrology consultation prior to kidney diagnosis. Kidney findings at the time of kidney biopsy include: serum creatinine, clearance of creatinine eGFR according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, hematuria, proteinuria (24-hour protein excretion or in alternative protein/creatinine ratio), serum albumin, albuminuria (and it's percentage from total proteinuria) and presence of nephrotic syndrome. We divided in three main kidney presentations: Acute Kidney Injury (AKI), AKI on Chronic Kidney Disease (CKD) or kidney damage (the presence of structural changes namely proteinuria without changes in the eGFR), [8].

Finally, treatment performed was evaluated: chemotherapy, chemotherapy and hematopoietic stem cell transplantation or none. The kidney and patient survival were the last items to analyze. The first was defined as the time from kidney biopsy until renal replacement therapy was required and the second from the diagnosis until death occurred.Kidney function recovery implied an eGFR improvement from baseline.

All clinical data were obtained from patient's medical records.

Data analysis

Data was characterized considering mean and Standard Deviation (SD) and minimum and maximum values in the case of continuous variables. For categorical variables, the characterization was made determining absolute and relative frequency.

Survival analysis was considered to analyzekidney and patient survival. The Kaplan-Meier estimator was used to estimate the survival function of all patients and in each group of patients, log rank test was applied to compared survival between two or more groups. The mean survival was also reported.

A cut-off was determined for continuous variables, using ROC curves, in order to transform those continuous variables in binary variables. The Kaplan-Meier estimator and the log rank test were then applied.

When comparing groups, we used Fisher's exact test in case of categorical variables and or Kruskal-Wallis test in case of continuous variables.

Data analysis was performed with the IBM SPSS Statistics software (v. 26), considering a minimum significance level of 0.05.

Results

The baseline clinical and laboratory characteristics of patients can be observed in Table 1.

Five patients had no visible spike in serum protein electrophoresis but four of them had a monoclonal gammopathy identified by serum immunofixation. Only one had both negative and the biopsy revealed a fibrillary glomerulonephritis.

Table 1: Patient's baseline clinical and laboratory characteristics.

Patient's baseline clinical and laboratory characteristics	
Age (years-old), mean (minimum - maximum), (SD)	68,26 (28-86); (38,86)
Male, n (%)	21 (53,8)
Race, n (%)	
Caucasian	31 (79,5)
Black	1 (2,6)
Not mentioned	7 (17,9)
General symptoms, n (%)	
Asthenia	11 (28)
Weight loss	1 (2,6)
Absent	24 (61,5)
Specific signs, n (%)	
Bone pain/fracture	5 (12,8)
Hypotension	5 (12,8)
Neuropathy	1 (2,6)
Macroglossia	2 (5,1)
Purpura	1 (2,6)
Haemoglobin (g/L), mean (minimum - maximum); SD	11,1 (6,9 - 15,3); 2,4
Calcemia (mg/dL), mean (minimum - maximum); SD	8,2 (6,8 - 11,5); 1,0
Serum monoclonal protein heavy chain, n (%)	
IgG kappa	7 (17,9)
IgG lambda	8 (20,5)
IgA kappa	4 (10,3)
IgA lambda	3 (7,7)
IgD lambda	1 (2,6)
IgM kappa	2 (5,1)
IgM lambda	1 (2,6)
Serum monoclonal protein light chain, n (%)	
Free kappa light chain	7 (17,9)
Free lambda light chain	17 (43,6)
Free kappa light chain (mg/dL), mean (minimum - maximum); SD	2139 (7,68 – 50800); 8759,2
Free lambda light chain (mg/dL), mean (minimum - maximum); SD	846,0 (4,0 – 12800); 2256,4
Ratio kappa/lambda, mean (minimum - maximum); SD	122,0 (0,0 – 2490); 440,5
Ratio involved/uninvolved, mean (minimum - maximum); SD	226,0 (0,3 – 2490); 560,6
Plasma cells in bone marrow (%), mean (minimum - maximum); SD	
Myelogram	12 (0 - 60); 15
Bone biopsy	20 (0 - 90); 26
Cytogenetic study results, n (%)	
t (4;14)	1 (2,6)
Negative	11 (28,2)

SD: Standard Deviation; n: Number

Next, in Table 2 and 3, we can observe the kidney characteristics at presentation as well as kidney biopsies results.

Half of our sample was previously followed in Nephrology.

The main finding of kidney presentation was AKI on CKD with 22 cases (56%) and the mean serum creatinine was 3,7mg/dL. Few had hematuria and the majority had proteinuria [21 patients in the nephrotic range (53,8%) but only 10 patients had the full nephrotic syndrome (25,6%)].

The dysproteinemic kidney diseases encountered include: CN, MIDD, AL amyloidosis, membranoproliferative glomerulonephritis with monoclonal immunoglobulin deposits, fibrillary glomerulonephritis, thrombotic microangiopathy and cryoglobulinaemic glomerulonephritis. Also, CN was associated with either MIDD, TMA and AL amyloidosis in the same biopsy in four patients.

Concerning treatment (Table 4) we verified that most of our patients were treated with chemotherapy (71,8%). Twenty-nine patients performed a bortezomib based treatment. The more common schemes were bortezomib+cyclophosphamide+dexamethasone (n=15) followed by bortezomib+melphalan+prednisolone (n=6) and thalidomide+bortezomib+dexamethasone (n=3). Unfortunately, kidney function was either partially or fully recovered by only four patients.

Table 2: Patient's kidney characteristics at presentation.

Kidney characteristics at presentation	
Previous follow up in Nephrology (n, %)	20 (51)
Kidney presentation, n (%)	
AKI	11 (28)
AKI on CKD	22 (56)
Kidney damage	6 (15)
Serum creatinine (mg/dL), mean (minimum, maximum), SD	3,7 (0,6 - 12,6); 5,2
Estimated GFR (ml/min/1,73m^2), mean, (minimum, maximum), SD	30,8 (3 -106); 27,8
Hematuria, n (%)	9 (23)
24-h urine protein (g) or protein/creatinine ratio (g/g), mean, (minimum; maximum), SD	5,8 (0,1 - 23,4); 5,3
Urine protein category, n (%)	
<1gr	3 (7,7)
1-3,5 g	12 (30,8)
>3,5 g	21 (53,8)
Bence Jones protein, n (%)	
Present	6 (15,4)
Absent	3 (7,7)
Missing data	30 (76,9)
Albuminuria (% of proteinuria), mean (minimum, maximum); SD	53 (2 - 95); 31
Serum albumin (g/dL), mean (minimum, maximum); SD	4,2 (0,7 - 25,3); 4,7
Nephrotic syndrome, n (%)	10 (25,6)
Beta-2 microglobulin (mg/dL), mean, (minimum, maximum); SD	10,2 (1,5 - 46,9); 9,9

AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; n: Number; SD: Standard Deviation

The mean kidney survival since kidney biopsy was 29, 23 months and the mean patient survival since hematologic diagnosis was 24,46 months (median 33 months).

Some clinical and pathologic features wereassociated to lowerkidney survival: acute tubular necrosis (p=0.013), cast nephropathy (p=0.015), TMA (p=0.008), hemoglobin <10g/dL (p=0.036), serum creatinine>2mg/dL (p=0.003) and eGFR <50ml/min/1.73m^2 (p=0.026). Previous Nephrology follow-up associated to higher kidney survival (p=0.018).

Only eGFR <50ml/min/1,73m^2 was associated toworst patient survival (p=0.042).

MGRS

Most of our patients analyzed had MM. Nevertheless, 12 patients had less than 10% plasma cells in bone marrow andno biopsy-proven bony or extramedullary plasmacytoma. Of these, one had a to Chronic Lymphocytic Leukemia (CLL) and two Waldenstrom Macroglobulinemia.

We highlight that most of these patients only had myelogram results, but no bone biopsy. As a result, MGRS' interpretation had to be made with caution. We only considered patients with both myelogram and bone biopsy results. Of our total sample of 39 patients, only three had MGRS. These patients' kidney diseases were:

Table 3: Kidney biopsies characteristics.

Kidney characteristics	
General characteristics of kidney biopsies	
Number glomerulus, mean (minimum - maximum), SD	13,5 (2 - 34); 7,8
% sclerotic glomerulus, mean (minimum - maximum), SD	11,4 (0 - 50); 14,2
IFTA, n (%)	
0	11 (28,2)
1-25%	12 (30,8)
25-50%	2 (5,1)
>50%	14 (35,9)
ATN, n (%)	14 (35,9)
Vascular involvement	
Amyloid deposition	6 (15,4)
Endotheliosis	2 (5,1)
Arteriolar hyalinosis	1 (2,6)
Fibrotic hypertrophy of the intima	8 (20,5)
Trombi	1 (2,6)
No changes	15 (38,5)
Inflammatory infiltrate, n (%)	
0-25%	32 (82,0)
25-50%	4 (10,3)
> 50%	3 (7,7)
Dysproteinemic kidney diseases, n (%)	
Cast nephropathy	14 (35,8)
Monoclonal immunoglobulin deposition disease	7 (17,9)
Glomerular involvement	7 (17,9)
Vascular involvement	4 (10,3)
Interstitial involvement	2 (5,1)
AL amyloidosis	15 (38,5)
Glomerular involvement	15 (38,5)
Vascular involvement	14 (35,9)
Interstitial involvement	9 (23,1)
Membranoproliferative glomerulonephritis with monoclonal immunoglobulin deposits	3 (7,7)
Fibrillary glomerulonephritis	1 (2,6)
Thrombotic microangiopathy	2 (5,1)
Cryoglobulinaemic glomerulonephritis	1 (2,6)

IFTA: Interstitial Fibrosis and Tubular Atrophy; ATN: Acute Tubular Necrosis; n: Number; SD: Standard Deviation

Table 4: Treatment and outcome.

Treatment and outcome	
Treatment performed, n (%)	
Chemotherapy	28 (71,8)
Chemotherapy and Hematopoietic stem cell transplantation	2 (5,1)
None	5 (12,8)
Kidney function recovery, n (%)	
Yes	4 (10,3)
No	26 (66,7)
NA	5 (12,8)
Mean kidney survival since kidney biopsy (months), (SE), [95% CI]	29,23 (3,16); [23,03; 35,43]
Mean patient survival since diagnosis (months) (SE), [95% CI]	24,46 (2,94); [18,70; 30,27]

n: Number; SE: Standard Error; CI: Confidence Interval

PGMID, AL amyloidosis and MIDD. Only the latter was treated with chemotherapy (cyclophosphamide, bortezomib and dexamethasone) but died three months later. The first remains on conservative treatment (hypertension and proteinuria control) and is dialysis independent, while the second patients dialysis dependent since biopsy performance.

Comparison of CN, MIDD and AL amyloidosis

Taking into consideration the three more prevalent dysproteinemic kidney diseases CN, MIDD and AL amyloidosis we decided to compare these groups (excluding those with more than one kidney phenotype). We present the statistically significant differences between them, as well as mean kidney and patient survivalin Table 5.

CN patients had the worst renal impairment (compared to other kidney lesions). MIDD group had no hemodialysis requirement during the follow-up period.

The highest protein excretion (mainly due to albuminuria) was found in AL amyloidosis patients as well as nephrotic syndrome.

Discussion

This study's main goal wasto describe and characterize clinical and histological features of patients with dysproteinemic kidney diseases. As reported in other studies [4,9], CN, MIDD and AL amyloidosis were the most prevalent, comprising 87.2% of our sample. Therefore, we were able to compare these groups and their main characteristics. MIDD and amyloidosis were more associated with males, as described in the literature [3]. Regarding clinical features, mean haemoglobin was lower in CN group considering the number of MM patients. General symptoms and specific signs were poorly reported but hypotension and neuropathy were mainly found in AL amyloidosis as expected.

We found a great difference between mean bone marrow plasma cells from myelogram and bone biopsy. The latter is more specific because sometimes plasma cells are fixed in the bone. Insome patients assuming bone biopsy results instead of myelogram alone allowed a MM diagnosis rather than MGRS. Therefore, we could only identifythree patients with MGRS in our sample of 39 patients.

We would like to highlight one CN case. Clinical presentation, with elevated serum free light chains, AKI and a compatible kidney biopsy, was typical of a cast nephropathy. A severe T lymphocytic infiltrate associated with the remaining hematologic evaluation precluded a MM diagnosis making it possible to assume a CLL. Unfortunately, the patient died during treatment. Despite being a MM defining event, CN is not MM exclusive and rarely appears in other hematologic neoplasia, namely CLL [10,11].

Patients with no spike in serum protein electrophoresis had AL amyloidosis, MIDD and fibrillar GN, which are usually associated with small clones. Serum free light chain assay and kidney biopsy were hereby central to diagnosis [12]. According to literature, IgG monoclonal was the most frequent heavy chain observed [13]. Concerning free light chain, lambda type was the mostoften found. Thismay be justified by the elevated number of AL amyloidosis patients present, where they are more common. The mean ratio involved/uninvolved free light chain reveals a number compatible to a myeloma defining event as confirmed by the number of Multiple Myeloma diagnosis. Unfortunately, in most of the patients, cytogenetic studies were not performed (sometimes due to insufficient material collected to perform analysis), which is not compliant with MM management recommendations.

The biopsies analyzed were slightly below the limit of the glomeruli determined necessary to be considered a significant sample. Even so, we believe that it hasn't significantly influenced the obtained results. All patients with M and AL amyloidosis had glomerular involvement, as it is the main site of monoclonal Ig deposition and therefore a higher proteinuria. Regarding some features observed

Table 5: Comparison between CN, AL amyloidosis and MIDD patients.

Variables	CN (n=10)	MIDD (n=6)	AL amyloidosis (n=14)	*p* value
Mean Haemoglobin (g/L)	9,7	11,2	12,8	0.02
Mean free kappa light chain (mg/dL)	7308	213	30	0.046
Mean ratio involved/uninvolved free light chain	565	418	39	0.05
Mean serum creatinine (mg/dL)	5,0	2,8	2,3	0.01
Mean eGFR (ml/min/1.73m^2)	14,5	25,0	49,0	0.009
Mean protein excretion (g/day)	2,39	0,96	9,44	0.001
Nephrotic syndrome n (%)	0	0	7 (53,8)	0.008
Serum albumin (g/dL)	5,76	3,26	3,64	0.04
Mean kidney survival (months), (SE); [95% CI]	20,56 (6,43); [8,00; 35,15]	NA	29,36 (4,39); [20,75; 38,00]	0.027
Hemodialysis free survival (%)	48	100	75	-
Mean patient survival (months), (SE); [95% CI]	28,77 (4,69); [19,57; 37,96]	21,00 (7,22); [6,85; 35,15]	21,57 (4,37); [12,99; 30,14]	0.81

CN: Cast Nephropathy; MIDD: Monoclonal Immunoglobulin Deposition Disease; eGFR: Estimated Glomerular Filtration Rate; SE: Standard Error; CI: Confidence Interval

in the vascular portion, as fibrotic hypertrophy of the intima, we cannot despise the contribution of other causes of kidney disease, like hypertension. Consistent with what is described in the literature, vascular involvement was more common in AL amyloidosis.

Still regarding histological characteristics, ATN and cast nephropathy related to poorest kidney survival [14]. All of them imply an interstitial involvement, which, if severe, (in CN with high free light chain level) requires renal replacement therapy as well as TMA, another serious condition, but on the glomerular side.

As expected, a lower eGFR and a higher serum creatinine wereassociated to worst kidney survival. This can be explained by the loss of nephrons.

Interestingly, previous Nephrology follow-up imply a better kidney survival, possibly due to nephroprotective measures applied as well as early management of complications.

Nevertheless, despite acute kidney injury being associated with a lower patient survival, in one study, patients with lower eGFR at baseline had a superior estimated kidney survival [15]. In our study the lower patient survival related to AL amyloidosis, as well as MIDD, may be justified by the poor prognosis of cardiac involvement in these patients.

The superior mean kidney survival compared to that of patient survival, is justified by the simultaneous diagnosis of kidney and hematological disease in many cases and also because many patients died with a functioning kidney.

Novel therapies have significantly improved the survival of patients with kidney disease, especially in patients with severe dysfunction. However, our patients' mean overall survival is lower than the 30 months described in the literature [16]. Whether this difference is related to indolent presentation, delayed diagnosis, or time of therapy initiation, we cannot know due to the lack of data reported. According to recent recommendations, most MGRS must be treated to prevent further kidney damage [17,18] and the absence of some registered data precludes more conclusions.

There are five clearly identified limitations in this work. The first one is its retrospective nature. The second is the limited number of patients and the number of variables that may preclude a significant statistical analysis. The third one, is the incomplete data from medical records which didn't allow us to uniformize the investigation. Also, some patients' had a 24 hour protein excretion evaluation while others had a protein/creatinine ratio inan occasional sample. This is considered this work's fourth limitation. Finally, the absence of electron microscopy in most of our biopsies limited the diagnosis of some rare kidney lesions like Ligh chain proximal tubulopathy, for example. Nevertheless, despite of all limitations, the authors consider this work an add-on research on this evolving field.

Conclusion

Dysproteinemia-associated kidney diseases can have diverse clinical and histological presentation and the kidney biopsy is essential to make this diagnosis. Despite this is not a novel theme, to our knowledge this is the first Portuguese retrospective study of kidney biopsies analyzing this subject and can be a starting point for new and larger studies.

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