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Case Report

Usefulness of the Free Light Chains Ratio in the Diagnosis of Light Chain Deposition Disease (LCDD): A Case Report.

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Abstract

Background: Clinically Significant Monoclonal Gammopathies (MGCS) are a heterogeneous group of clinical pictures characterized by a clonal proliferation of B lymphocytes and/or plasma cells that produce a "toxic" monoclonal protein for some organs and tissues. Light Chain Deposition Disease (LCDD) is a clinical picture characterized by the deposition of monoclonal free light chains in the kidney, the main target organ, and in organs such as the liver and heart. In about 80% of cases the monoclonal free light chains are the kappa isotype, and form unorganized deposits at the level of the basement membranes of the glomeruli and renal tubules.

Case reports

A 64-year-old man with a clinical history of arterial hypertension, dependent edema, proteinuria, microhaematuria is admitted to the U.O. of Nephrology for the diagnostic classification of renal disease.

Results

The diagnostic work-up for plasma cell dyscrasias showed the presence of an altered kappa/lambda ratio without alterations of the serum protein electrophoretic tracing and without evidence of Monoclonal Immunoglobulin (MIg) at serum and urine immunofixation performed with High Resolution (HR) methods. Bone marrow biopsy showed < 10% plasmacytosis. Renal biopsy diagnosed Light Chian Deposition Disease (LCDD).

Conclusions

LCDD is a form of MGRS characterized by the deposition of monoclonal free light chains in the basement membranes of the glomerulus and renal tubule. The kappa/lamda ratio allowed to signal the presence of a small clone secreting monoclonal free light chains. In patients diagnosed with Monoclonal Gammopathies of Renal Significance (MGRS), timely therapy to eradicate the neoplastic clone can avoid the progression of irreversible renal organ damage.

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Key Words: Light Chain Deposition Disease; Free Light Chains Ratio; Glomerular Disease; MGRS; Renal Biopsy

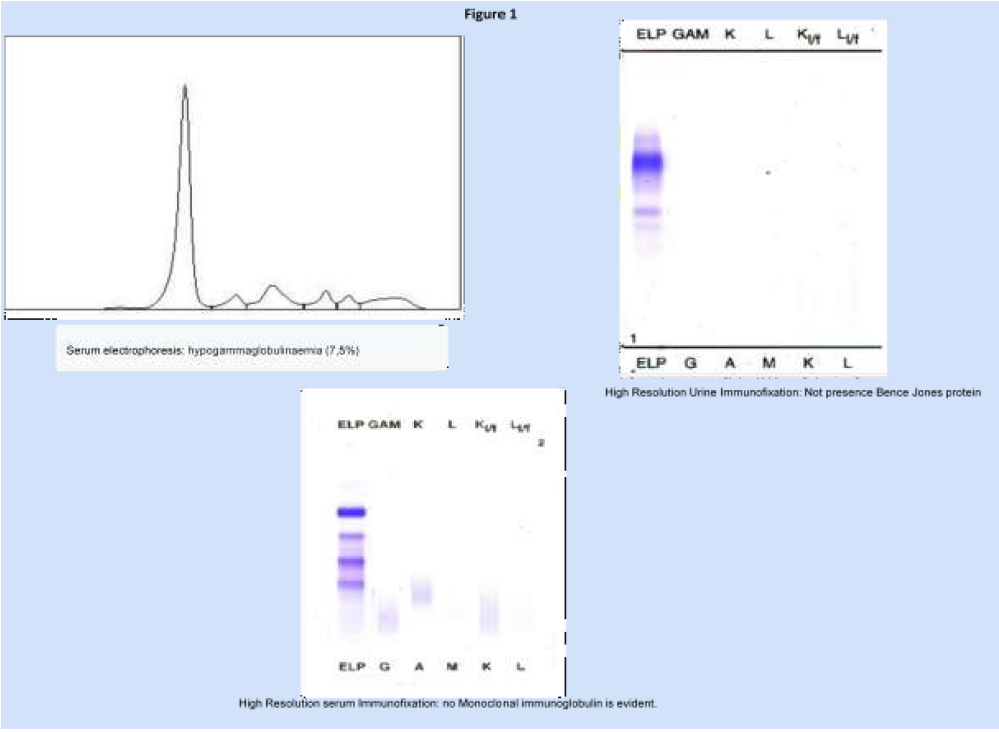
Introduction

The term Monoclonal Gammopathy of Renal Significance (MGRS) was introduced in 2012 by the International Kidney and Monoclonal Research Group (IKRG) to indicate renal pathologies caused by a complete nephrotoxic Monoclonal Immunoglobulin (MIg) or fragments thereof, kappa free light chains or lambda, produced by a neoplastic clone of B lymphocytes or plasma cells [1]. Monoclonal immunoglobulin deposition disease (MIDD) are divided into three subtypes: Light And Heavy Chain Deposition Disease (LHCDD), Heavy Chain Deposition Disease (HCDD), and Light Chains Deposition Disease (LCDD) depending on whether the deposits consist of complete immunoglobulin, heavy chains only (in particular of the IgG type) or more frequently kappa or lambda light chains only. [2-3]. MIg or fragments can deposit at the level of the glomerular and tubular basement membranes, can precipitate in the renal tubule or activate the alternative complement pathway by indirect mechanisms (C3 glomerulopathy; thrombotic microangiopathy). This explains the heterogeneity of the histopathological pictures of renal lesions [4].

We describe a clinical case of LCDD in which the alteration of the kappa/lambda ratio of Free Light Chians (sFLC) suggested the presence of a neoplastic clone secreting free light chains isotype kappa responsible of a rapid deterioration of renal function.

Case report

A 64-year-old man with a history of arterial hypertension under pharmacological treatment was admitted to the U.O. of Nephrology of the Policlinico Hospital of Bari for the appearance of sloping edema. The patient informed consent was obtained during the admission phase at the hospital. The first level laboratory investigations performed showed: WBC 5.76x10^ 3/µL (3.70-9.70), Neutrophilic Granulocytes 3.9 x10^ 3/µL (63.2%), Hemoglobin 10.2 g /dL (13.3-17.2 g/dL), s-creatinine 2.75 mg/dL (0.67-1.17 mg/dL), eGFR 23 mL/min/1.73m2) (> 90), blood glucose 95 mg/dL (< 100 mg/dL), total protein 4.7 g/dL (6.4 – 8.2 g/dL), albumin 2.3 g/dL (3.4-5. 0 g/dL), serum calcium 8.9 mg/dL (8.5-10.1 mg/dL), U-PCR (U-Protein/U-Creatinine Ratio) 6567 mg/g (<200), U- ACR (U-Albumin/U-Creatinine Ratio) 4310 mg/g (<30), 24h proteinuria (UTP) 6800 mg/24h (0-149), 24h albuminuria 3750 mg/24h (<30), beta2microglobulin 5.26 mg/L (1.09-2.53 mg/L); standard urine test microhematuria present. The plasma concentration of nT-ProBNP was 1595 pg/mL (0-77 pg/mL) and troponin I (hs method) was 18.2 pg/mL (0-74 pg/mL). Specialist cardiological evaluation with echocardiogram showed no signs of infiltrative cardiomyopathy. For a complete assessment of the renal damage, the following were performed: serum protein electrophoresis (CZE capillary method, SEBIA-France instrumentation) which highlighted hypogammaglobulinaemia (gamma zone 7.5%) Figure 1.



Serum (s-IFE) and urine (u-IFE) immunofixation, performed on agarose gel (Hydrasis Sebia France) with Hight Resolution (HR) method using standard antisera against IgG, IgA, IgM, kappa and lambda (Sebia; France) for the search for monoclonal immunoglobulin, did not detect the presence of monoclonal immunoglobulin in the serum and Bence Jones protein in the urine [5] (Fig.1). IgG, IgA and IgM assayed by immunonephelometric method on Dimension Vista 1500 analyzer (Siemens Healthineers) were 2.0 g/L, (7.0-16.0 g/L), 0.56 g/L (0.68 -3.79g/L) and 0.85g/L (0.40-2.30g/L) respectively, and the complement fractions C3 and C4 had concentrations within the reference limits. The laboratory diagnostic work-up was completed with the determination of s-Free Light Chains k (sFLCK) 217.2 mg/L (5.71-26.30 mg/L) and s-Free Light Chains λ (sFLCL) 26.7 mg/L (3.3-19.40 mg/L) (Freelite immunoturbidimetric method Optilite instrumentation The Binding Site, Birmingham, UK) with a k/λ ratio of 8.12 (0.25-1.65). The search for cryoproteins was negative. The Antineutrophil Cytoplasmic Antibodies (ANCA) test (Indirect Immunofluorescence (IFI), Antinuclear Antibody test (ANA) (Indirect Immunofluorescence (IFI)) and the anti-double stranded DNA (anti-dsDNA) (Indirect Immunofluorescence (IFI)) tests, were negative (Tab. 1).

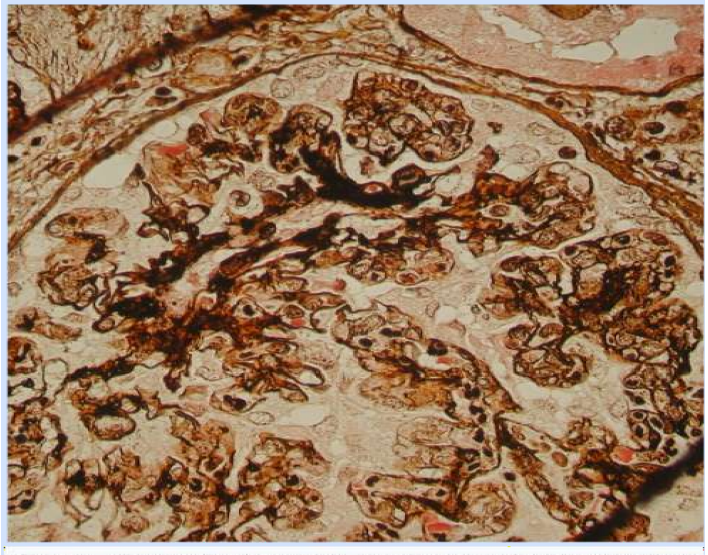
Tests	Patient Value	Reference Value
Haemoglobin (g/L)	10.2	13,3-17,2
WBC (10^3/µL)	5,76	(3,70-9,70)
NG (%)	73,6	(42,9-78,4)
s-creatinine (mg/dL)	2,75	0,67-1,17
e-GFR (mL/min/1,73m^2)	23	>90 (CKD-EPI)
glicemia (mg/dL)	95	<100
calcemia (mg/dL)	8.9	8,5-10,1
albumin (g/dL)	2.3	3,4-5,0
FLC kappa (mg/L)	217.2	3.3 ÷ 19.40
FLC lambda (mg/L)	26.7	5.71 ÷ 26.30
k/λ ratio	8.13	0.26-1.65
IgG (g/L)	2.0	7.0 ÷ 16
IgA (g/L)	0.85	0.68 ÷ 3.79
IgM (g/L)	0.56	0.40 ÷ 2.30
C3 (g/L)	0.94	0.9 ÷ 1.8
C4 (g/L)	0,25	0.10 ÷ 0,40
Total Protein (g/dL)	4,7	6,4 ÷ 8,2
β^2 microglobulin (g/dL)	8.12	1.09 ÷ 2.53
U-PCR (mg/g)	6567	<200
U-ACR (mg/g)	4310	<30
dU-Total Protein (mg/24h)	6800	0 ÷ 149
dU- Albumin (mg/24h)	3750	< 30
nT-proBNP (pg/mL)	769	5.0-125
Troponina I (ng/mL)	<0.015	0.015-0.045
ANCA (IFI)	negative	negative
ANA (IFI)	negative	negative
Anti dsDNA (IFI)	negative	negative

Table1: Laboratory values admission to the patient's hospital

Based on laboratory data a kidney biopsy was performed for the suspected of having MGRS and to maximize the chance of correct diagnosis. Immunoflorescence (IF) studies of the kidney biopsy showed pseudolinear parietal deposits of kappa isotype light chains along the glomerular basement membranes At electron microscopy, the ultrastructural morphological picture showed an increase in the mesangial matrix, with a nodular appearance, thickening of the glomerular and tubular basement membranes due to mainly parietal deposition, in the subendothelial space and in the lamina densa and mesangial, of material of variable structure and electronic density compatible with organised deposits monoclonal immunoglobulins isotype k. Bone marrow biopsy performed to identify the

lymphoproliferative clone revealed < 10% infiltration of plasma cell elements CD138, MUM1 and positive kappa chains. The patient's bone marrow plasma cells analyzed by flow cytometry confirmed the presence of a small monoclonal plasma cells with clonality of the kappa isotype light chains. Additional genetic tests and fluorescent in situ hybridization studies have not proved useful for clonal identification.Furthermore, PET-CT was performed, which did not highlight areas of hypermetabolism. The laboratory investigations associated with the renal biopsy allowed the diagnosis of LCDD isotype kappa. The patient underwent drug therapy with three cycles of bortezomib, cyclophosphamide and dexamethasone, followed by three cycles of thalidomide, cyclophosphamide and dexamethasone. The follow-up showed a "partial" haematological response with a progressive reduction of FLCk 137.88 mg/L, to FLCλ 76.38 mg/L, normalization of the ratio 1.80 k/λ [6] and a stabilization of renal disease.

Figure 2: Renal biopsy



Glomerulus with endocapillary hypercellularity presenting aspects of double contour of the basement membranes associated with cellular interposition ("proliferative membrane" pattern). (Silver-Methenamine, x400).

Discussion

Light Chain Deposition Disease (LCDD) is a form of Monoclonal Gammopathy of Renal Significance (MGRS) characterized by the deposition of free monoclonal light chains, at the level of various organs and tissues and in particular of the kidney. Renal involvement can be attributed to the fact that the light chains are filtered by the renal glomeruli and reabsorbed in the proximal tubules through the cubulin-megalinpathway and catabolized by lysosomal enzymes [7]. Kidney damage is closely related to their ability to interact with different types of cells and renal districts. Some of them exert their toxicity on the proximal tubules, while others interact with the mesangial cells of the glomerulus causing glomerular dysfunction. In fact, the circulating monoclonal light chains, depending on the physicochemical and structural characteristics, interact in different ways with the mesangium causing LCDD or AL amyloidosis [8]. In LCDD, nephrotoxic light chains form unordered amorphous aggregates that trigger mechanisms responsible for mesangial expansion with an increase in the extracellular matrix forming nodules along the mesangium. On the contrary in AL amyloidosis instead, the amyloid substance is deposited in the form of fibrils in the mesangial space causing the destruction of the matrix [9]. The monoclonal light chains in LCDD are in about 80% of the kappa isotype cases unlike in AL amyloidosis in which the light chains are mainly of the lambda type. LCDD differs from Amyloidosis AL in its lack of affinity for Congo red and in its lack of fibrillar organization [9-10]. In 2019 the International Kidney and Monoclonal Research Group (IKMG) determined that kidney biopsy is the gold standard for diagnosing MGRS; but an appropriate laboratory and haematological diagnostic workup, to identify the B-cell or plasma-cell clone responsible for the production of nephrotoxic monoclonal immunoglobulin (MIg), is important to steer for the diagnosis, therapy and patient prognosis [11]. LCDD predominantly affects subjects between the ages of 50 and 60 and presents clinically with renal insufficiency, microhematuria and proteinuria often accompanied by nephrotic syndrome and arterial hypertension, as in the case reported by us [12]. Laboratory diagnostic tests of serum and urine electrophoresis and immunofixation have a diagnostic sensitivity of 25-76% in cases of LCDD. As shown in the case presented, MIg is not always detected in serum and urine; this is determined not only by the small size of the secreting neoplastic clone, but also by the physical-chemical characteristics of MIg which favor aggregation and deposition in the mesangium and along the basal membranes of the tubule and glomerulus [13]. In the case we evaluated, the sFLC dosage and the k/λ ratio proved to have high diagnostic sensitivity as they were the only serum markers of clonality capable of early starting the haematological evaluation and to direct of the renal biopsy. A correct haematological diagnosis and a therapy useful for eliminating the lymphocytic and/or plasmacytic clone allow to reduce the renal damage, improving the patient's outcome. Besides the laboratory diagnostics becomes of fundamental importance to differentiate the renal dysfunction of LCDD from other forms of renal damage of different aetiology of new onset or arising in the context of known pathology [14-15]. Renal biopsy performed according to the recommendations of the IKMG, allowed to evaluate in a precise and accurate way the histopathological lesions of the kidney, the type of nephropathy and its impact on renal function. Immunoflorescence and electron microscopy studies have been crucial both to evaluate the composition of the deposits and their organization and for the differential diagnosis with other MIg deposit pathologies such as AL amyloidosis, proliferative glomerulonephritis with monoclonal IgG deposits,

glomerulonephritis from type [16] I. Studies have shown that in subjects with chronic kidney disease (CKD) in the absence of clonal disease (MM CLL etc.) the ratio k/l is 0.34–3.10 [17]. The case presented by us, despite an important renal dysfunction (eGFR of 23 ml/min/1.73m2) (CKD stage IV), the ratio was 8.12 predictive of LCDD [18].

Conclusion

If renal biopsy is the recognized diagnostic tool for the diagnosis of MGRS, the k/λ ratio of sFLC is a marker strongly predictive of the presence of clonal disease, therefore useful for directing the diagnosis and for starting treatment aimed at eliminating the clone neoplastic. Timely diagnosis and appropriate therapy reduces the likelihood of progression of renal damage, often irreversible, improving the patient's outcome, especially for patients ineligible for renal biopsy Data availability statement the original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written Informed Consent was obtained for the publication of any potentially identifiable images or data included in this article.

Author contributions

Author Contributions: Conceptualization, TT and VB; methodology, LDM and BG; Software, VB and RL; validation, FDS and TT; formal analysis, VB; investigation, LDM and PP; resources, VM; data curation, RL and VM; writing—original draft preparation, TT; writing—review and editing, TT and VB; visualization, BG and LDM; supervision, TT; project administration, FDS; funding acquisition, VM. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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