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Randall-Type Light Chain Deposition Disease: Beyond Nephrotic Syndrome, the Importance of a Comprehensive Etiological Assessment

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Abstract **Case Report**

***Background*:** Randall-type light chain deposition disease (LCDD) is a rare complication of plasma cell dyscrasias, characterized by the deposition of monoclonal light chains in basement membranes, frequently leading to renal impairment. Extrarenal manifestations are also possible. Often associated with multiple myeloma (MM) or monoclonal gammopathy of renal significance (MGRS), its diagnosis relies on renal biopsy. Early diagnosis and targeted treatment are essential for improving outcomes. ***Case Presentation*:** We report the case of a 52-year-old man presenting with nephrotic syndrome, renal failure, and IgG Kappa monoclonal gammopathy, in whom a diagnosis of LCDD was confirmed by renal biopsy with symptomatic multiple myeloma. Subclinical cardiac and hepatic involvement were detected. ***Treatment*:** The patient was treated with VCD polychemotherapy (Velcade, Cyclophosphamide, Dexamethasone). Close monitoring of cardiac and hepatic involvement was implemented. ***Results*:** After one month of transient worsening of renal function, a significant improvement in renal function and a hematological response with a 66% reduction in the Kappa light chain was observed after two months of treatment. ***Conclusion*:** This case highlights the importance of considering Randall-type LCDD in the presence of renal failure and monoclonal gammopathy. The results suggest that VCD can be an effective treatment for Randall-type LCDD, emphasizing the importance of early diagnosis and rigorous therapeutic monitoring.

Keywords: Light Chain Deposition Disease, LCDD, Multiple Myeloma, Bortezomib, Case Report, Monoclonal Gammopathy.

INTRODUCTION

Randall-type light chain deposition disease (LCDD) is a rare complication of clonal B-cell disorders, characterized by the non-organized deposition of monoclonal immunoglobulins in basement membranes [1,2]. Primarily light chains (LCDD), but also heavy chains (HCDD) or both (LHCDD) can be deposited. Unlike AL amyloidosis, these deposits do not react with Congo red [1, 2].

LCDD frequently occurs in the context of multiple myeloma (MM) or monoclonal gammopathy of renal significance (MGRS) [3-5], the MGRS concept individualizing cases without MM. Its presentation, often with predominant renal involvement, can be variable, making diagnosis challenging and requiring renal biopsy.

LCDD is a systemic disease with predominant renal involvement [1], but its clinical presentation can be variable, ranging from rapidly progressive renal failure to minimal proteinuria. Extrarenal manifestations, particularly cardiac and hepatic, are possible [1-6], justifying a systemic evaluation. The pathogenic mechanisms involve specific physicochemical characteristics of light and heavy chains [7, 8]. The treatment of Randall-type LCDD aims to suppress the production of monoclonal light chains by the underlying plasma cell clone. Although bortezomib has improved prognosis [9], management remains a challenge.

Due to the rarity of this pathology, case reports remain essential. We report a case of Randall-type LCDD treated with VCD, illustrating the importance of early diagnosis and rigorous monitoring, and will discuss the diagnostic and therapeutic challenges in light of clinical and biological data.

CASE PRESENTATION

A 52-year-old man, former smoker (smoking cessation for one year), with no significant medical history, presented for consultation due to asthenia and involuntary weight loss of 16 kg in 3 months. These symptoms were associated with nausea, vomiting, pruritus, and the progressive onset of lower limb edema.

Clinical examination revealed the presence of lower limb edema extending up to the knees. Cardiovascular examination was unremarkable.

Investigations Revealed:

- Renal failure, with a serum creatinine level of 38 mg/L (N: 7-14 mg/L) and an estimated glomerular filtration rate (eGFR) of 18 ml/min/1.73m2 according to the CKD-EPI equation.
- Nephrotic syndrome with massive proteinuria at 11 g/24h and hypoalbuminemia at 16 g/L (N: 34-45 g/L).
- A narrow monoclonal peak in the gamma globulin region, quantified at 1.63 g/L on serum protein electrophoresis (SPEP).
- IgG Kappa type monoclonal gammopathy, confirmed by serum protein immunofixation (IFE). Quantitative immunoglobulin testing revealed: IgA: 1.67 g/L, IgG: 4.80 g/L (decreased), IgM: 0.86 g/L.
- Significant imbalance of serum free light chains (sFLC) (Kappa at 239mg/L, Lambda at 51 mg/L, Kappa/Lambda ratio at 4.68 (N: 0.37-3.10).
- Absence of Bence Jones protein in the urine.

Given the association of renal failure and a monoclonal immunoglobulin, a biopsy of the accessory salivary glands was performed, but histological examination revealed chronic lymphocytic sialadenitis, with negative Congo red staining.

A Renal Biopsy Was Performed, Revealing:

- The glomeruli show nodular matrix thickening with nearly constant flocculo-capsular synechiae and circumferential fibrosis. Tubular atrophy in the areas of fibrosis with a laminated appearance of the tubular basement membranes under light microscopy (**Figure 1**).
- Absence of Congo red staining.
- Linear deposits of IgG kappa light chains along the glomerular and tubular basement membranes by immunofluorescence (intensity 3+).

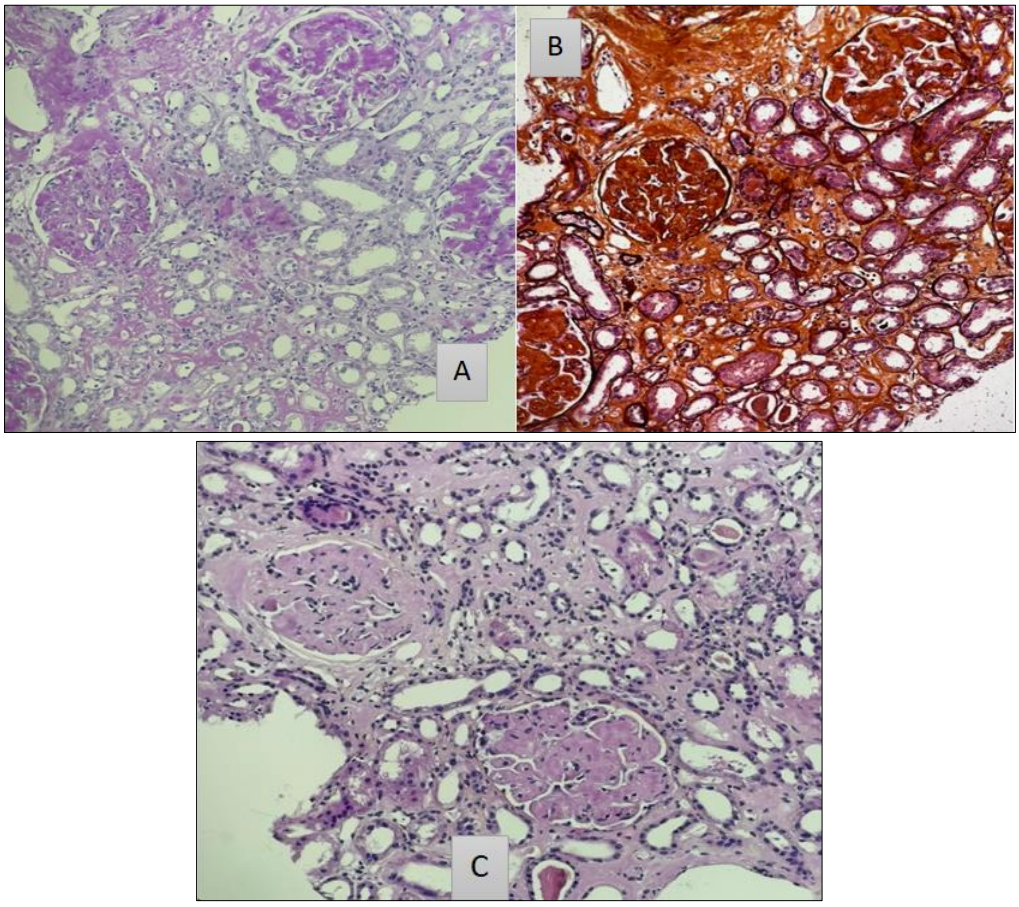

Figure 1: Histopathology of light chain immunoglobulin deposition disease (LCDD)

Light microscopy, stains:

- A (PAS: Periodic acid-Schiff)
- B (Reticulin)
- C (H&E: Hematoxylin and Eosin)

Bone marrow aspirate revealed 13% plasma cells.
The search for CRAB criteria (hypercalcemia, renal insufficiency, anemia, and bone lesions) showed:

- Corrected calcium at 105 mg/L (within the upper limits of normal).
- Renal function with creatinine at 38 mg/L, indicative of chronic renal failure.
- Hemoglobin at 16.5 g/dL.
- Absence of bone abnormalities on body scan.

Based on these findings, a diagnosis of symptomatic multiple myeloma with Randall-type renal involvement was made, according to the criteria of the International Myeloma Working Group (IMWG).

Evaluation of extrarenal involvement revealed:

- Troponin at 0.043 µg/L (43 ng/L). NT-proBNP level was elevated at 569 pg/ml (normal values < 175 pg/ml). Echocardiography revealed normal cardiac chamber dimensions, good left ventricular function (LVEF 55%), as well as a minimal circumferential pericardial effusion (3-4 mm) without hemodynamic compromise.
- Cholestatic syndrome, with elevated Gamma GT at 933 IU/L (N: 10-66 IU/L) and alkaline phosphatase at 349 IU/L (N: 40-129 IU/L). Liver ultrasound was unremarkable.
- Hemoglobin at 16.4 g/dL, platelets at 511,000/µL, neutrophil count at 4020/µL. The white blood cell differential was confirmed on blood smear.
- Electromyogram (EMG) borderline normal.

Prognostic assessment showed:

- Beta-2-microglobulin in progress.
- Albumin at 16 g/L.
- R-ISS in progress (pending cytogenetic results).
- Lactate dehydrogenase (LDH) normal at 286 IU/L.
- Bone marrow cytogenetics not performed.

Pre-therapeutic assessment revealed:

- Negative viral serologies for HBV, HCV, and HIV.
- Renal function with creatinine at 38 mg/L and GFR at 18 ml/min/1.75m2.
- Liver tests with alkaline phosphatase at 349 IU/L, Gamma GT at 933 IU/L, normal total and direct bilirubin and normal transaminases.
- Normal oral-dental assessment and panoramic dental X-ray.

Treatment

Following discussion in a multidisciplinary consultation meeting (MCM), VCD polychemotherapy (Velcade, Cyclophosphamide, Dexamethasone), followed by possible autologous stem cell transplantation (ASCT) was decided upon.

The protocol included:

- Bortezomib: 1.3 mg/m² subcutaneously, initially twice weekly, then adapted to weekly administration after initial toxicity.
- Dexamethasone: 40 mg orally, administered according to the standard protocol.
- Cyclophosphamide: 500 mg orally, administered continuously. The dose was adjusted based on tolerance.

Supportive care:

- Folic acid: for prevention of macrocytosis due to cyclophosphamide.
- Cotrimoxazole: for anti-infectious prophylaxis against *Pneumocystis jirovecii*.
- Valaciclovir: for anti-viral prophylaxis against shingles (Herpes zoster).
- Enoxaparin sodium 0.4 ml subcutaneously

This protocol was chosen due to its demonstrated efficacy in the treatment of multiple myeloma, particularly in cases of renal involvement [6]. The goal was to achieve a deep hematologic response and improvement in renal function.

Evolution and Follow-Up

The evolution at one month of treatment was marked by a transient worsening of renal function, with urea at 1.47 g/L and creatinine at 51 mg/L (eGFR at 12 ml/min/1.73m²). This deterioration was attributed to dehydration secondary to vomiting and post-chemotherapy diarrhea, leading to hemodynamic impact and hypotension. Management consisted of intravenous rehydration and symptomatic treatment. Due to this toxicity, the rate of administration of VCD was changed to weekly administration, and the doses of bortezomib and cyclophosphamide were reduced to 1 mg/m² and 400 mg, respectively.

At two months, an improvement in renal function was observed (urea at 0.70 g/L, creatinine at 39 mg/L, eGFR at 19 ml/min/1.73m²), as well as a decrease in kappa free light chains to 81 mg/L (compared to 239 mg/L initially) and lambda light chains to 12 mg/L (compared to 51mg/l), with a Kappa/Lambda ratio of 6.75 (normal values: 0.37 to 3.10), a 66% reduction from the initial Kappa light chain level.

At three months, the improvement in renal function continued: urea 0.40 g/L, creatinine 24 mg/L

(GFR at 30 ml/min/1.73m²), proteinuria 6 g/24h, albumin 23 g/L.

In total, after 3 cycles of VCD, the patient presented a partial response, with:

- Partial hematologic response: Decrease in kappa light chains to 80.76 mg/L (before treatment: 238 mg/L). Kappa/Lambda ratio at 6.75. No complete normalization of the ratio.
- Partial renal response: Decrease in proteinuria to 6 g/24h (before treatment: 11 g/24h). Stabilization of creatinine at 24 mg/L (GFR at 30 ml/min/1.73m²).

Table 1: Evolution of key biological parameters at the time of diagnosis, at 1 month, 2 months, and 3 months

Biological Parameters	At Diagnosis	At 1 Month	At 2 Months	At 3 Months
Kappa Light Chains (mg/L)	239	N/A	81	N/A
Lambda Light Chains (mg/L)	51	N/A	12	N/A
Kappa/Lambda Ratio	4.68	N/A	6.75	N/A
Proteinuria (g/24h)	11	N/A	N/A	6
Serum Creatinine (mg/L)	38	51	39	24
eGFR (ml/min/1.73m2)	18	12	18	30

Regular follow-up is planned to evaluate the long-term hematologic and renal response, as well as tolerance to treatment, with a view to possible therapeutic intensification by autologous stem cell transplantation.

DISCUSSION

This case report highlights the presentation of Randall-type LCDD in a 52-year-old patient with symptomatic multiple myeloma, initially manifesting as severe renal involvement. It emphasizes the importance of considering this diagnosis in the presence of unexplained renal failure associated with monoclonal gammopathy. The diagnosis was confirmed by renal biopsy.

Randall-type LCDD is a rare entity, representing approximately 0.1% of renal biopsies [1]. It is characterized by the deposition of monoclonal light chains in the basement membranes of various organs, leading to organ dysfunction.

The pathogenic mechanisms of LCDD involve specific physicochemical characteristics of light and heavy chains, promoting their aggregation and deposition [2-8]. It has been shown that some lambda light chains have substitutions in their primary sequences that promote their aggregation and deposition [8]. Similarly, heavy chains may have a deletion of the first constant domain, contributing to their tissue deposition [2]. These structural and physicochemical abnormalities explain the formation of deposits in the basement membranes.

Renal involvement is almost constant, generally manifesting as nephrotic syndrome and renal failure [1]. Our patient's clinical presentation is consistent with this description. However, LCDD can manifest variably, making diagnosis sometimes difficult [10].

The diagnosis of LCDD relies on renal biopsy [1-8], which reveals linear deposits of kappa or lambda light chains along the glomerular and tubular basement membranes. The absence of Congo red staining distinguishes LCDD from AL amyloidosis [1-11]. In our case, renal biopsy was essential to confirm the diagnosis.

LCDD frequently occurs in the context of malignant plasma cell proliferation, most often in the context of a plasma cell disorder meeting the criteria for multiple myeloma (MM) in nearly 50% of cases, and for monoclonal gammopathy of renal significance (MGRS) in the remaining patients [3-5]. In our case, the diagnosis of multiple myeloma was retained because of the presence of 13% plasma cells on bone marrow aspirate and renal involvement justifying CRAB criteria. Although the patient did not present other CRAB criteria, the presence of renal involvement with chronic renal failure was sufficient to retain the diagnosis of symptomatic multiple myeloma, thus influencing the therapeutic strategy.

The concept of MGRS has been recently introduced to individualize small clones of B lymphocytes that do not meet the criteria for symptomatic disease but secrete a pathogenic monoclonal immunoglobulin directly or indirectly responsible for renal disease [12, 13]. Renal lesions in MGRS do not depend on the clonal load but on the physicochemical characteristics of the monoclonal immunoglobulin [12]. Previous studies have suggested an overrepresentation of the Vk4 LC variability subgroup in LCDD [14]. But the mechanisms governing immunoglobulin tissue deposition remain unknown.

Although renal involvement is predominant, LCDD is a systemic disease, and extrarenal manifestations are frequent, particularly cardiac and hepatic [1-6], emphasizing the need for a complete systemic evaluation. In our case, the patient presented subclinical signs of cardiac and hepatic involvement. These findings highlight the importance of a complete systemic evaluation in patients with LCDD [1]. Cardiac involvement in LCDD can manifest as restrictive

hypertrophic cardiomyopathy, similar to that observed in AL amyloidosis, with rhythm or conduction disorders [6].

The treatment of Randall-type LCDD aims to suppress the production of monoclonal light chains by the underlying plasma cell clone. Bortezomib, often used as first-line therapy, has demonstrated efficacy, inducing favorable hematologic and renal responses [9], but management remains a challenge, especially in patients with severe renal involvement and comorbidities. In our case, the patient received VCD, a protocol that has demonstrated its effectiveness in multiple myeloma, particularly in cases of renal involvement [9]. The evolution at one month was marked by a transient worsening of renal function, attributed to dehydration due to chemo-induced vomiting and diarrhea. However, after two months of treatment, a significant improvement in renal function and a hematologic response with a 66% reduction in the Kappa light chain level were observed.

This case illustrates the importance of considering Randall-type LCDD in the presence of renal failure and monoclonal gammopathy. Early recognition, accurate diagnosis, and targeted treatment, as well as careful monitoring of extrarenal involvement, are essential to improve the prognosis and quality of life of patients with this rare pathology.

CONCLUSION

Randall-type monoclonal immunoglobulin deposition disease remains a rare and complex entity, often underdiagnosed due to its polymorphic clinical presentation. The case we presented illustrates this complexity, highlighting the importance of a rigorous diagnostic approach in the face of multi-organ involvement. This case highlights the importance of renal biopsy for definitive diagnosis and recalls the need for careful differential diagnosis with AL amyloidosis. Although the initial response to the VCD protocol is encouraging, it also underscores the need for close monitoring and individualized therapeutic adaptation. Ultimately, this case report contributes to enriching the literature on Randall-type LCDD and argues for further research to improve the understanding, early diagnosis, and optimal management of this rare but potentially severe pathology, involving nephrologists and hematologists.

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