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Case Report

# Casts Nephropathy in a Patient with Chronic Kidney Disease

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## Abstract

We present the case of a patient with a previous diagnosis of chronic kidney disease (CKD) without an established etiological basis. The patient was admitted with criteria for urgent dialysis, prompting the initiation of renal replacement therapy. During hospitalization, there was a significant decrease in hemoglobin (Hb) associated with a positive direct Coombs test, leading to the consideration of autoimmune origin anemia. However, as the haptoglobin levels were normal, a false positive was determined. As part of the approach, flow cytometry was performed, revealing a phenotype compatible with clonal plasma cell neoplasia. A karyotype and renal biopsy were taken, establishing the diagnosis of multiple myeloma (MM) and nephropathy due to monoclonal spikes. A simple X-ray did not show evidence of osteolytic lesions, a definitive clinical manifestation of MM. The patient started treatment and underwent follow-up by nephrology and hematology. Timely diagnosis is imperative, especially in those with a rapid and atypical decline in renal function. It is essential to suspect primary or secondary associated glomerulopathies. In this patient's case, as previous described, in this diagnosis time of prompt treatment is directly proportional to the prognosis of renal function and overall survival.

**Keywords:** Renal biopsy; Monoclonal gammopathy; Acute kidney injury; Direct Coombs

## Abbreviations

Hemoglobin (Hb)

Acute kidney injury (AKI)

Multiple myeloma (MM)

Chronic kidney disease (CKD)

Disease-free survival (DFS)

Revised International Staging System for Multiple Myeloma (R-ISS)

Amyloidosis (AL)

## Introduction

MM is a malignant clonal disease of plasma cells. In Mexico, it ranks fourth among the most frequent hematologic neoplasms, with an incidence of 1 to 1.5% [1]. MM follows an evolution from an asymptomatic pre-malignant stage known as monoclonal gammopathy of uncertain significance, progressing to indolent MM and finally to symptomatic MM. AKI is one of the main complications of MM, being more frequently observed at diagnosis with an incidence of 16-31%. It is an important predictor of the prognosis of patients with symptomatic MM, especially those requiring dialysis support. The deterioration of renal function and even probable irreversible fibrosis is attributed to the combination of increased concentration and deposition of monoclonal light chains in the serum, which interact with uromodulin (Tamm-Horsfall) in the loop of Henle generating cylinders that obstruct the tubules and the well-known "MM kidney". The definitive diagnosis of cylinder nephropathy is made through renal biopsy, which reports diffuse tubular damage, with the presence of intratubular cylinders of eosinophilic staining, irregular, angled, and with fracture lines in the distal tubules. Regarding the MM approach, bone marrow aspiration and biopsy should be taken, establish the immunophenotype to assess treatment response, protein electrophoresis, and quantification of IgG-A and M immunoglobulins. Treatment consists of an immunomodulatory agent, a proteasome inhibitor in combination with steroids, and recently, a doubling in disease-free survival (DFS) has been observed by adding monoclonal antibodies (Anti-CD38 - Daratumumab) to the regimen [2-3].

## Objective

It is crucial to promptly undertake a comprehensive approach in every patient with declining renal function, especially in those exhibiting rapidly progressive behavior. The objective is to establish an etiological diagnosis that allows for targeted treatment. In the case of multiple myeloma (MM) and nephropathy due to monoclonal spikes, timely diagnosis can alter the course of the disease, delineating and in some cases, reversing renal damage. The ultimate goal is to enhance overall survival, impact prognosis and quality of life, while also considering the socioeconomic aspects of the disease.

## Case

A 56-year-old male with a history of type 2 Diabetes. The current condition began in July 2023 with paraclinical evidence of serum creatinine of 2.6 mg/dL, so treatment with telmisartan was started. Within a month, kidney damage was exacerbated, reaching present creatinine of 26 mg/dL, with a marked decrease in uresis, asthenia, adynamia, oral intolerance, chills and generalized fasciculations. He went to the emergency room of our hospital because he was drowsy

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and had difficulty breathing. Laboratories were requested where Hb: 9.2 g/dL, BUN: 128 mg/dL, UREA: 273.9 mg/dL, Cr: 23.53 mg/dL, Total proteins: 12.4 g/dL, Albumin: 2.60 g/dL, Globulins: 9.8 g/dl, K: 6.7 mmol/L, Ca: 12.3 mmol/L, P: 12.0 mmol/L and metabolic acidosis with anion GAP. Dialysis therapy and a diagnostic approach for MM were initiated due to clinical and paraclinical suspicion. Radiographs performed without evidence of osteolytic lesions, results were obtained for B2 microglobulin: 17.35, total serum proteins 9.60, gamma 5.56, albumin/globulin ratio 0.32, monoclonal peak 4.01 g/dL, IgG 3699 g/dL. Flow cytometry reports a phenotype compatible with clonal plasma cell neoplasia, abnormal CD28 and CD56 expression, and identification of kappa light chains. The bone marrow aspirate with bone biopsy reported positive CD138, KAPPA, and CD56; in the bone marrow karyotype, a clone with 45 chromosomes, loss of chromosome 14 and the normal line was found. In addition, the ultrasound-guided percutaneous renal biopsy reported cast nephropathy, predominantly lambda positive, with marked regenerative changes of the tubular epithelium, focal mesangiosclerosis and interstitial fibrosis with grade III tubular atrophy. It was decided to start treatment with dexamethasone, carfilzomib and daratumumab without obtaining an adequate renal response. During his hospitalization, jaundice was noted with Hb: 5 g/dL, with a sudden drop of 5 mg/dL in a period of approximately 24 hours. This was ruled out as a probable cause of hemorrhage, so a direct Coombs was requested, which was reactive for IgG, hemolytic anemia was ruled out with normal haptoglobin levels (109 g/L), and a false positive secondary to hyperproteinemia was established.

Currently the patient is being monitored by hematology, who will perform a new bone marrow aspiration to determine response to treatment, and by nephrology to continue hemodialysis.

## Discussion

This patient, prior to admission, had a recent diagnosis of CKD managed by a private physician; apparently, the etiological cause was never identified. Within a month, there was a sudden and severe deterioration in renal function, prompting an investigative approach to rule out associated etiologies. In this scenario, primary or secondary glomerulopathies may account for these clinical presentations. MM is classified as a cause of AKI, present in 16-31% of patients at the time of diagnosis.

The approach to a patient with sudden deterioration in renal function requires ruling out causes such as primary and/or secondary glomerulopathies, drug-induced nephritis, and complications inherent to chronic degenerative diseases. In this patient's case, the hypercalcemia and hyperproteinemia upon admission raised suspicion for diagnostic investigation, having ruled out secondary causes (Table 1).

In MM, diagnosis is possible if it meets any of the following criteria:

| Bone marrow aspirate with plasma cells > 10% + a component of the CRAB mnemonic: | Bone marrow aspirate with plasma cells >10% + ones of the following components: |
|---|---|
| C. Hypercalcemia >11 mg/dL o >1 mg/dL above the maximum limit. | Bone marrow biopsy with >/= 60% plasma cells. |
| R. AKI with serum creatinine >2 mg/dL or glomerular filtration rate <40 mL/min/1.73m2. | Free serum light chain ratio >100 mg/dL. |
| A. Anemia with hemoglobin >2 g/dL below the lower limit or <10 g/dL. | >1 lesion on MRI >/= 5mm |
| B. Bone lesions >/=1 on radiography, tomography or PET-CT. | |

**Table 1:** Diagnostic Criteria [4] MM is Diagnosed by Fulfilling Column 1 and/or Column 2.

The osteolytic lesions are present in 70% of patients, being evident when there is erosion of the cortex by 30-50% [4], which was not identified in this case, probably due to a lower percentage of erosion. Therefore, current recommendations suggest magnetic resonance imaging or computed tomography. The suspicion of hemolytic anemia arose due to the sudden decrease in hemoglobin, in addition to alterations in other biomarkers. However, it was ultimately ruled out due to normal haptoglobin levels, indicating a false-positive direct Coombs test, a condition likely and commonly described in gammaglobulinemias [5].

Based on the previously described findings, this case meets the criteria with a hemoglobin level of 9.2 g/dL, hypercalcemia with 12.3 mmol/L, AKI with a serum creatinine of 23.53 mg/dL, and flow cytometry with a phenotype compatible with clonal plasma cell neoplasia, abnormal expression of CD28 and CD56, and identification of kappa light chains along with the bone marrow aspirate showing CD138, KAPPA, CD56. Due to the acute deterioration in renal function, a renal biopsy was performed, revealing tubular cast nephropathy. Tubular cast nephropathy is objectively defined as a serum glomerular filtration rate less than 40 ml/min/1.73m2 or serum creatinine >2mg/dl [3], although it is not a mandatory condition, considering that creatinine depends on previous baseline levels, malnutrition, and associated comorbidities. Tubular cast nephropathy is the most common cause of sudden glomerular filtration decrease in MM, therefore, the clinical expression depends on the site of deposition in the nephron [6].

However, there are other forms of morphological alterations at the nephron level that may cause MM, such as monoclonal gammopathy of renal significance with elevated albuminuria due to glomerular involvement, disorganized fibrillar deposition (fibrils with a diameter of 7-12 nm) leading to immunoglobulin λ-related amyloidosis (AL), with deposition at the glomerular basement membrane, explaining the presence of nephrotic syndrome in these patients. Another type of involvement in MM is proliferative glomerulonephritis (mesangioproliferative, membranoproliferative, or endocapillary) with deposition of monoclonal immunoglobulins, resulting in a nephritic syndrome behavior. Finally, there are Type I cryoglobulinemic glomerulonephritis, monoclonal gammopathy associated with C3, and immunotactoid glomerulopathy with variable nephrological expression, with subnephrotic proteinuria and gradual deterioration in renal function. (reference).

As there is a greater deposition of chains at the capillary, mesangial, tubular, or interstitial level, mechanisms of nuclear factor κB activation have been described, stimulating the transcription of genes, encoding macrophage and monocyte chemotactic proteins, interleukin 6, interleukin 8, transforming growth factor B (TGF-B). If this inflammatory response is not corrected, it will lead to tubulointerstitial fibrosis and subsequently glomerulosclerosis, resulting in a bleak prognosis for renal function and patient survival.

The renal biopsy of this patient (gold standard) [3] showed deposits of predominantly lambda chains at the tubular level and ruled out light chain involvement at the glomerular level due to the absence of immune complex deposition, absence of arteriolar damage, and no associated morphological pattern, although grade 3 tubulointerstitial fibrosis and glomerular sclerosis were identified, which condition a poor prognosis for residual renal function.

After diagnosis, it is necessary to classify patients with the Revised International Staging System for Multiple Myeloma (R-ISS), which includes: B2 microglobulin levels, albumin, lactate dehydrogenase, and high-risk chromosomal mutations: del(17p), t(4;14), t(14;16), classifying patients as stage 1, 2, 3 risk with a 5-year survival rate of 77%, 62%, and 47%, respectively. In this patient, although high-risk mutations were not identified, the levels of the other parameters give a 5-year survival rate of 47% [7].

Regarding treatment, according to the Clinical Practice Guidelines in Oncology (NCCN), the initial treatment may vary depending on the patient's eligibility for stem cell transplantation and other clinical factors. It is important to apply the most effective treatment combinations early in the course of the disease to achieve deep and lasting remissions. New therapies focus on overcoming disease refractoriness. According to this, the first-line treatment for newly diagnosed patients eligible for transplantation is with a proteasome inhibitor (bortezomib), an immunomodulator (lenalidomide), and a steroid (dexamethasone) (VTd). The quadruple regimen is reserved for those with aggressive disease, which consists of adding the monoclonal antibody Anti-CD38 (Daratumumab) to the VTd regimen (D-VTd). The addition of daratumumab is supported by the CASSIOPEIA study, in which it was found to be associated with high rates of minimal residual disease negativity and favorable progression-free survival rates versus VTd alone in eligible transplant candidates with newly diagnosed multiple myeloma. Therefore, this quadruple regimen was selected, in our case, lenalidomide was omitted due to severe renal impairment, which is a contraindication for its use. The preference for carfilzomib over bortezomib was made with the support of increased treatment tolerability according to NCCN guidelines. Once a treatment response is achieved, consolidation with transplantation is recommended. The patient remains on hemodialysis with high cut-off (HCO) filters. High-flow hemodialysis (hemodiafiltration) can remove molecules of 10-20 kDa, however, the weight of lambda chains is approximately 45 kDa, so it is necessary to use HCO, which have the ability to remove chains of higher molecular weight [2]. Rapid clearance of light chains can be achieved by intensive hemodialysis using HCO dialyzers and very high protein permeability (Figures 1 & 2).

Two randomized trials (MYRE and EuLite) evaluated HCO hemodialysis versus hemodiafiltration; in the HCO groups of both studies, dialysis independence rates at 6 months were 60%, considering no previous associated fibrosis. Currently, based on evidence, combining effective chemotherapy with HCO hemodialysis and/or hemodiafiltration remains a relevant therapeutic option in patients with light chain deposition [8].

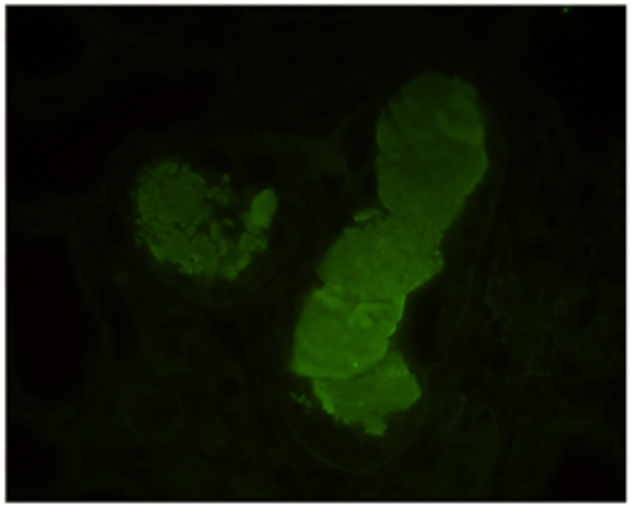

**Figure 1:** Immunofluorescence Technique. Kappa Chain.

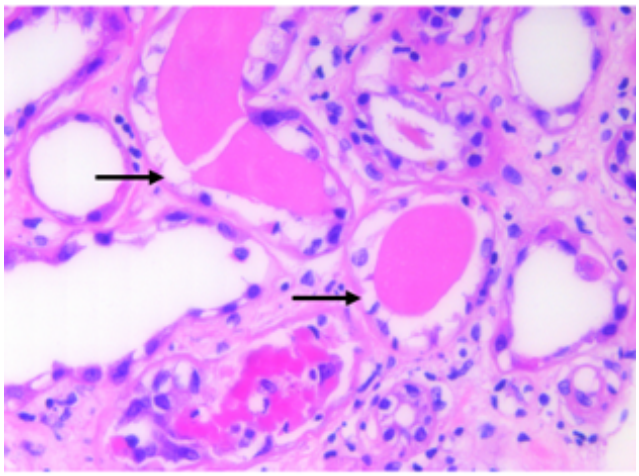

**Figure 2:** Hematoxylin and Eosin Staining. Fragmented Tubular Cylinders (Arrows).

## Conclusion

In the scenario of a patient with acute renal deterioration, it is important to consider associated pathologies beyond chronic degenerative diseases. In this case, a comprehensive approach allowed the identification of MM and tubular cast nephropathy, the most common histological involvement in this pathology. Having tools such as karyotype and renal biopsy allows the identification of risk mutations and therefore the selection of the most appropriate therapeutic strategies, in order to modify the progression of the disease, increase disease-free survival, decrease associated complications, and achieve recovery of dialysis-free renal function.

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