Case Report

Monoclonal gammopathy of renal significance: case report

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Introduction

Monoclonal gammopathies result from the activation of clonal B cells/plasma cells that secrete a particular type of immunoglobulin, called monoclonal protein or M protein and whose levels may remain stable or progress over time.1 Monoclonal gammopathy of undetermined significance is the most common form and is considered a non-malignant or pre-malignant condition. It is more prevalent in advanced ages affecting about 3% of the over 50-year-old population. It is defined as the presence of M protein in serum of less than 3.0 g/dL and/or in urine of less than 1 g in a 24-h urine sample, plasma cell infiltration of the bone marrow corresponding to less than 10% of the total nucleated cells and the absence of lesions in target organs and tissues.2

The term monoclonal gammopathy of renal significance, proposed in 2012 by the International Kidney and Monoclonal Gammopathy Research Group, is relatively recent. It applies to cases that do not meet the diagnostic criteria for multiple myeloma and the renal damage secondary to M protein (both by direct and indirect mechanisms) and do not allow a diagnosis of monoclonal gammopathy of undetermined significance.3

Case report

This is the case of a 77-year-old woman, hospitalized in the Nephrology Unit in February 2017 due to renal insufficiency lasting for one year, with progressive worsening. She waited for about six months before being attended by the specialty. The patient presented arterial hypertension and malleolar edema with, at the time of admission, emergency renal replacement therapy being indicated due to hypervolemia. Besides the renal condition, she presented bicytopenia (anemia and thrombocytopenia) and despite negative serum protein electrophoresis and negative immunofixation of serum proteins, immunofixation of urinary proteins showed a pattern suggestive of immunoglobulin G (IgG)/Kappa restriction. The term ‘suggestive’ was used by the laboratory to describe a monoclonal band of tenuous limits but able to
Figure 1 – (A–D) Glomeruli with increased volume, lobulated aspect, endocapillary hypercellularity with reduced capillary lumen and increased mesangial matrix. In addition, there are double contours in some capillary loops. (A) Hematoxylin eosin; (B) Sirius Red; (C) Periodic acid silver methenamine stain (PAMS); (D) Masson Trichrome – magnification: 20×. (E) Immunofluorescence for immunoglobulin G showing accentuated deposition in capillary loops, subendothelial glomerulus. (F and G) Enlargement of subendothelial space with randomly distributed fibrils and mesangial interposition (transmission electron microscopy: F – 7000×; G – 12,000×) and (H) detail of the deposit of fibrillary material (transmission electron microscopy: 30,000×).

maintain its meaning, proving the presence of clonality in this case. The free light chain assay was not performed due to the unavailability of this exam in the service where the patient was treated. However, it was possible to define clonality through immunofixation of urinary proteins.

Considering the possibility of a disease in the spectrum of monoclonal gammopathies, a myelogram with a representative sample and a bone marrow biopsy with morphological and immunohistochemical evaluations were performed but showed no evidence of plasma cell infiltra-
tion (which excluded multiple myeloma). A renal biopsy revealed a membrano proliferative pattern at light microscopy (Figure 1A–D) and an investigation of β-fibrillose by Congo red staining was negative. Subendothelial deposits of IgG (Figure 1E), Kappa, Lambda, C3 and C1q were identified in glomeruli by immunofluorescence. Electron microscopy showed mesangial and subendothelial fibrillary deposits (Figure 1F–H). A diagnosis of monoclonal gammopathy of renal significance was reached after excluding other etiologies for renal failure. In this case, there was no benefit in chemotherapeutic treatment as it was already an end-stage renal disease and there was no perspective of renal transplantation.

**Discussion**

In the present case, a patient with nephrotic syndrome, progressive renal failure and bicytopenia (moderate anemia and mild to moderate thrombocytopenia) had immuno fixation of urinary proteins suggestive of IgG/Kappa restriction; a renal biopsy was compatible with fibrillary glomerulonephritis – membranoproliferative pattern with IgG deposits. An additional investigative propaedeutic provided the diagnosis of monoclonal gammopathy of renal significance. A membranoproliferative pattern is one of the possible renal lesions described in this medical entity. However, it is important to note that histological changes by themselves are not sufficient to establish the diagnosis, which requires an investigation of the clinical context and exclusion of multiple myeloma as an etiological mechanism.

In the context of monoclonal gammopathies, the presence of cytopenia should always raise a suspicion of possible multiple myeloma/lymphoproliferation. However, in the present case, this hypothesis was ruled out as described. Anemia and thrombocytopenia were of mild to moderate intensity (mean hemoglobin: 8.9 g/dL; platelet count: 100–130 × 10⁹/L). They were investigated and attributed to a multifactorial process such as hematopoiesis deficiency (vitamin B12 deficiency of disabsortive etiology) with a chronic disease component, acute inflammatory context due to urinary infection during hospitalization and inadequate production of erythropoietin due to renal impairment. Peripheral blood immunophenotyping was performed and showed no evidence of clonality in lymphocytes.

Monoclonal gammopathy of undetermined significance is considered a non-malignant or pre-malignant lesion that does not induce lesions in target organs. Important intraclonal heterogeneities have been observed but the detection of predictive factors of malignancy remains a challenge as both cytogenetic factors (point mutations such as N-Ras, K-Ras, MYC upregulation and gain/loss of chromosome 1q or 1p function) and aspects of bone marrow microenvironment (angiogenesis, RANKL upregulation and interaction between clonal cells and the stromal population) seem to be involved. The follow-up of patients with monoclonal gammopathy of undetermined significance has identified some cases in which there is renal damage as a consequence of renal deposition of clonal components or due to alternative mechanisms resulting from the action of clonal B cells and bone marrow that does not present enough plasma cell infiltration to characterize multiple myeloma. Therefore, in 2012, the International Kidney and Monoclonal Gammopathy Research Group defined a new entity named monoclonal gammopathy of renal significance.

In monoclonal gammopathy of renal significance, the effector component corresponds to a small B cell clone whose determination of clonality can be challenging. Thus, renal biopsy with electron microscopy and immunohistochecvry is fundamental in the investigation and diagnosis; this strategy allows the identification of the pattern of renal deposits (which, by electron microscopy, can be organized/structured or not).

Different mechanisms have been described for renal failure in monoclonal gammopathies, such as deposition and precipitation of M proteins in different renal compartments such as glomeruli, vessels and the interstitium, dysregulation of alternative pathways of complements and immunological mechanisms. Similar renal lesions can also occur in lymphoproliferative diseases with the prevalence of lesions changing according to the disease. Among small cell lymphomas/chronic lymphocytic leukemia there is a predominance of membranoproliferative glomerulonephritis, followed by minimal change disease and amyloid light-chain amyloidosis. In lymphoplasmyctic lymphoma, non-Hodgkin’s lymphoma and mantle cell lymphoma, there is predominance of renal amyloid light-chain amyloidosis, followed by membranoproliferative glomerulonephritis.

The goal of treatment of patients with monoclonal gammopathy of renal significance is to stop the natural evolution of the disease to prevent progress to end-stage renal disease. It is important to emphasize that renal transplantation without previous treatment might have a significant risk of graft loss, since the mechanism of injury remains in full activity. Thus, the great benefits of early recognition of possible cases with this diagnosis can be implied.

**Conclusions**

As a new entity whose diagnosis and treatment in early stages has a great impact on prognosis, this case report aims to emphasize the heterogeneity of clinical and histological presentations of monoclonal gammopathy of renal significance. It is crucial to consider this possibility in cases of patients with monoclonal gammopathy and renal dysfunction of ill-defined etiology. In this investigative process, a detailed histopathological analysis is fundamental. In the present case, there was no benefit in starting specific treatment as the patient was already on renal replacement therapy without prospect of renal transplant.

**Conflicts of interest**

The authors declare no conflicts of interest.
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