

IgA nephropathy in IgG kappa multiple myeloma

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Abstract

Multiple myeloma (MM) frequently affects kidney function through multiple mechanisms. Nonetheless, some patients develop kidney injury due to other causes. A 54-year-old woman was diagnosed with IgG kappa MM developed IgA nephropathy without cast nephropathy. Further studies did not show criteria for MM progression or other causes. This case highlights the need for further investigation of kidney injury in MM patients (such as toxicity of previous drugs, infectious events, or immune-mediated disorders).

Keywords: acute kidney injury, corticosteroids, IgA nephropathy, multiple myeloma, purpura

To the Editor:

The kidney is one of the most commonly affected organs in multiple myeloma (MM), through multiple mechanisms: myeloma cast nephropathy, immunoglobulin light chain amyloidosis, light-chain deposition disease, light-chain proximal tubulopathy (LCPT), membranoproliferative glomerulonephritis (GN), among others.¹⁻³

Nowadays, renal dysfunction is not a diagnostic criterion for MM, so other causes should be excluded in first place, such as the effect of long-term chronic diseases (eg, diabetes mellitus), drug-related toxicity, secondary cancer, and infections.^{1,2}

Immunoglobulin A nephropathy (IgAN) associated with IgA lambda MM and mesangial proliferative GN has been reported.⁴ An interaction between mesangial cells and IgA as well as IgG immune complexes provides a possible mechanism for glomerular injury in IgAN.⁵ IgAN is an uncommon phenomenon (prevalence 2.5/100,000 people), but the most frequent GN.⁶⁻⁹ A defect in IgA1 *O-glycosylation* is the main underlying mechanism, contributing to glomerular inflammation and mesangial proliferation.⁶⁻⁹ To the best of our knowledge, there are only four case reports of IgAN in patients with IgG MM.^{6,10,11}

A 54-year-old woman was diagnosed with plasmacytoma on the left hip in 2002, and treated with local radiotherapy. In 2007,

she developed MM (IgG kappa type) ISS1 treated with idarubicin and dexamethasone, followed by an autologous stem cell transplant, achieving complete response. Meanwhile, a left parietal meningioma was identified in 2011 and a cervical HPV infection was disclosed in 2012. After 10 years (2017), the disease progressed with a cervical mass in the atlas vertebra, entailing treatment with thalidomide, cyclophosphamide, dexamethasone (stopped due to hematologic toxicity after 10 cycles), and radiotherapy.

While on bisphosphonate therapy, a progressive and persistent decline in kidney function happened (serum creatinine 1.5–2 mg/dL) with proximal tubular dysfunction, so zoledronic acid was suspended. A tubulo-interstitial nephritis caused by bisphosphonate toxicity or either LCPT were considered as possible causes. The patient refused kidney biopsy and remained in surveillance with a stable chronic kidney disease stage 3bA2.

In September 2019, the patient developed peripheral edema, abdominal pain, and low digestive tract bleeding. An abdominal CT scan showed signs of hemorrhagic colitis and 3 days later developed a rash in the lower limbs. Laboratory results were unremarkable. Prednisolone 40 mg was prescribed for 5 days, improving the cutaneous lesions.

In October 2019, the patient developed severe and disseminated osseous pain, arthralgia, anorexia, dysphagia, constipation, vomits, oliguria, “port wine” color urine, worsening fatigue, hypertension, edema leading to complete immobilization in bed for 1 week. Two weeks before, she had been medicated for acute medium otitis with amoxicillin clavulanate. On examination, the patient was pale and edematous, with regular vital signs. The analytic study revealed a hemoglobin of 7.7 g/dL, platelets of $58 \times 10^9/L$, urea of 157 mg/dL, creatinine of 4.62 mg/dL, ionized calcium of 0.79 mmol/L, other ions within normal range, albumin 30 g/L, and C-reactive protein of 15 mg/L. Estimated creatinine clearance was less than 10 mL/min (by chronic kidney disease epidemiology collaboration, CKD-EPI), urine protein-creatinine ratio was 7.2 g/g, and erythrocyturia was present. Arterial blood gases documented metabolic acidosis. Urinary immunoglobulin light chain quantification was negative. The patient was then hospitalized due to non-oliguric acute/rapidly progressive kidney insufficiency requiring emergent hemodialysis.

For the acute or rapidly progressive kidney injury, AKI/RPKI, methylprednisolone pulses were started in day 2 of hospitalization (500 mg IV for 3 days, 1 mg/kg/daily for 8 days and 0.75 mg/kg/daily afterwards). A cyclophosphamide pulse of 500 mg

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intravenously was prescribed on day 5. On day 6, the patient referred a progressive improvement of the articular pain and edema.

At this time there were no criteria for MM progression (urine analysis, protein electrophoresis, skeleton X-ray, positron emission tomography (PET CT) scan, and bone marrow aspirate were performed). The immunologic study was unremarkable for several antibodies (antineutrophil cytoplasmic, antinuclear, double stranded DNA, myeloperoxidase, proteinase 3, rheumatoid factor, SS-A, SS-B, anti-Smith, ribonucleoprotein, topoisomerase I, centromere, basal membrane, histone, ribosome, and cryoglobulins). Serologies for human immunodeficiency virus, hepatitis B and C were negative. Serum complement levels were normal. The patient finally agreed to undergo a kidney biopsy on day 8 and histology confirmed an IgAN (mesangial proliferative GN with IgA deposits in mesangium, regions with acute pyelonephritis, acute interstitial nephritis, and significant tubular and interstitial atrophy probably caused by previous exposure of bisphosphonate and/or LCPT). It became clear that the patient previously had signs of IgA vasculitis (Henoch-Schonlein purpura), with hemorrhagic colitis, arthritis, and purpura. The electron-microscopy examination did not disclose crystal deposition in the PT. Hence, the most likely diagnosis is IgA vasculitis.

Nonimmunosuppressive measures were followed with strict blood pressure control, removal of extra volume, and control of cholesterol levels. Patient was discharged with oral prednisolone (40 mg/day tapered down until discontinuation). Later, at nephrology clinic, an angiotensin-converting enzyme inhibitor, ACE inhibitor, was introduced.

The fatigue, osseous pain, arthralgia, anorexia, and peripheral edema improved and the patient regained autonomy at day 22. Unfortunately, kidney function only recovered partially to a chronic kidney disease, CKD, stage 5 and 3 months after being discharged she was in the process of starting renal replacement therapy.

MM progression is a frequent cause of kidney dysfunction in MM patients, but other etiologies must be ruled out.^{3,9,12,13} In our case a definitive diagnosis of IgAN was only confirmed after the kidney biopsy results, the gold standard method.¹² Crystal deposition was not seen in the PT of this patient (which would be more suggestive of LCPT, commonly found in some patients with kappa light chain disease, that we cannot exclude) (Figs. 1 and 2). Laboratory studies (virology and immunology) are frequently unhelpful. Due to a previous IgG kappa MM, it is unlikely that IgAN was caused by increased production or secretion of IgA by plasma cells. IgAN is a commonly manageable (and sometimes reversible) cause of acute kidney injury in the general population. A fast and adequate treatment is extremely important.⁷ Treatment options for IgAN vary according to the severity of kidney dysfunction and the presence of proteinuria and hematuria, but include both immunosuppressive therapy and nonimmunosuppressive interventions to slow disease progression.^{8,14} This patient was treated with high-dose glucocorticoids, tapered down after 2 months. Cyclophosphamide was added due to the rapid presentation of the AKI/RPKI and for its action upon MM cells. However, it cannot reverse a chronic kidney lesion and also has cumulative toxicity. A blood pressure control was ensured with ACE-inhibitor therapy, protein intake reduction to moderate ingestion, and salt consumption limited to 3g daily.

It seems reasonable to consider that the predisposing cause for the acute onset of IgA vasculitis was the previous acute medium otitis, however there was a continuous kidney dysfunction

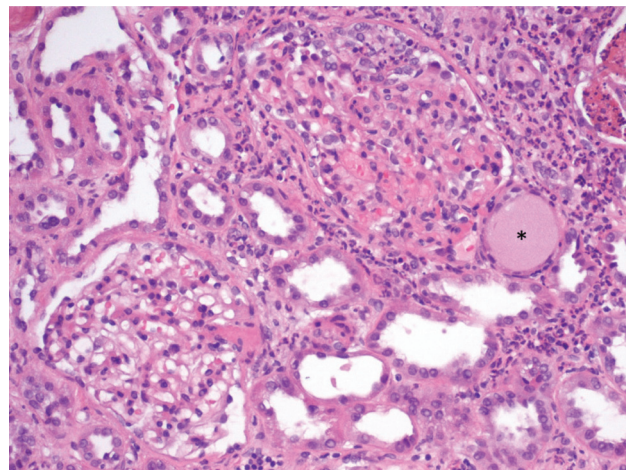


Figure 1. Light microscopy (hematoxylin & eosin, staining $\times 20$) of the renal biopsy: glomeruli show mesangial hypercellularity, there is a cellular cast within a tubule (*) and significant polymorphonuclear-predominant interstitial infiltrate.

presented for many months before the abrupt clinical presentation of AKI/RPKI with decreased creatinine clearance, tubular dysfunction, and hematuria. Because the patient had been exposed recently to thalidomide/cyclophosphamide/dexamethasone, there is a possibility that the immunosuppression might have caused an attenuation of the clinical signs related to kidney disease ongoing.

The patient progressively improved and was discharged with regular surveillance by nephrology and hematology. However, patient's kidney function only recovered partially for 3 months and is currently on hemodialysis.

Finally, our unique case highlights the need for regular surveillance of kidney function in patients with MM and the need for further studies when there is a change in kidney function, as other etiologies can be found. To the best of our knowledge this is the fifth reported case of the unusual association between IgG MM and IgA nephropathy, emphasizing the need for an accurate

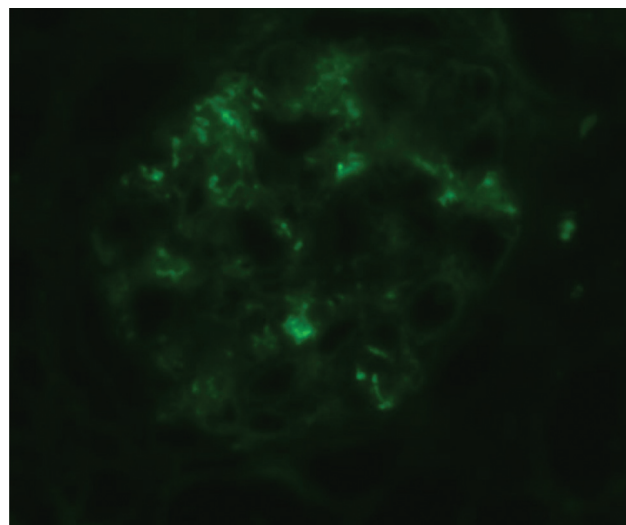


Figure 2. Immunofluorescence image of the kidney biopsy: IgA ++ in the mesangium. Crystals were not found in the cytoplasm of proximal tubule cells, however, light-chain proximal tubulopathy cannot be excluded.

diagnosis and a multidisciplinary approach to MM patients, especially when renal dysfunction develops.^{6,7,10,11}

Author contributions

Acquisition of data, clinical and imaging data review, literature review and final manuscript writing: Couto, Sousa, Tavares.

Important intellectual contribution and final manuscript writing: Couto, Sousa, Ferreira, Oliveira, Domingues, Tavares, Paiva, Chuva, Maximino, Henrique and Mariz.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of interest

The authors have no conflicts of interest to declare.

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