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CASE REPORT

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A case of immunotactoid glomerulopathy in a patient with monoclonal gammopathy of renal significance

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ABSTRACT

Monoclonal gammopathy of renal significance is a relatively new diagnosis that attributes kidney disease to damage caused by a monoclonal protein. There is growing recognition of this disease in patients previously diagnosed with monoclonal gammopathy of undetermined significance, as they increasingly develop clinically significant renal impairment requiring treatment. We outline a case of a patient presenting with worsening renal function, found to have a circulating monoclonal protein and ultimately diagnosed with a subtype of monoclonal gammopathy of renal significance referred to as immunotactoid glomerulopathy.

Abbreviations: MGUS: Monoclonal gammopathy of undetermined significance; M-protein: Monoclonal protein; MM: Multiple myeloma; MGRS: Monoclonal gammopathy of renal significance; MGCS: Monoclonal gammopathy of clinical significance; CKD: Chronic kidney disease; C3 and C4: Complement 3 and complement 4, respectively; EF: Ejection fraction; CT: Computed tomography; IgG: Immunoglobulin G; GFR: Glomerular filtration rate; PET: Positron emission tomography; MRI: Magnetic Resonance Imaging.

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1. Introduction

Monoclonal gammopathy refers to the unhindered production of monoclonal immunoglobulins by plasma cells, B cells, or lymphoplasmacytic cells in the bone marrow [1]. The prevalence of monoclonal gammopathy increases with advancing age. A monoclonal protein is identified in about 3% of those over the age of 50 and in 5% of those over 70 [2]. Monoclonal gammopathy of undetermined significance (MGUS) is characterized by a monoclonal protein (M-protein) measuring <3 g/dL with <10% plasma cells in the bone marrow. When the M-protein rises above 3 g/dL and there are ≥10% plasma cells in the bone marrow, the patient is identified as having either smoldering multiple myeloma (if asymptomatic) or multiple myeloma (MM) (in the presence of end-organ damage) [3]. Formerly, a subset of patients previously diagnosed with MGUS, with clinically significant renal impairment, were deemed ineligible for treatment based on guidelines for the management of MGUS, which recommend surveillance for progression of disease. Hence, in 2012, the International Kidney and Monoclonal Gammopathy Research Group introduced the term monoclonal gammopathy of renal significance (MGRS) to identify individuals with kidney diseases secondary to M-protein production who do not have features of lymphoplasmacytic malignancy or myeloma-defining events, but notably often require treatment in order to prevent progression to end-stage renal disease [2,4]. The definition of MGRS was subsequently updated to include all plasma cell and B-cell proliferative disorders resulting in a nephrotoxic M-protein, such as smoldering Waldenstrom macroglobulinemia, smoldering MM, monoclonal B cell lymphocytosis, low-grade B cell lymphomas, and low-grade chronic lymphocytic leukemia [2].

In general, patients with MGRS may present with glomerular or tubulointerstitial disorders. Those with glomerular disorders present with renal impairment, proteinuria, hematuria, hypertension, and/or hypocomplementemia [1,3]. Those with tubulointerstitial disorders present with electrolyte derangements, proteinuria, renal impairment, and/or Fanconi syndrome [1]. Extrarenal manifestations have also been identified, such as involvement of the skin and peripheral nerves, hence the recent introduction of the entity referred to as monoclonal gammopathy of clinical significant (MGCS) [2]. Below we highlight a case of MGRS in a patient presenting with acute kidney injury superimposed on chronic kidney disease (CKD) stage III.

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2. Case presentation

A 78-year-old male presented to his nephrologist with acute kidney injury. His medical history included a transient ischemic attack, atrial fibrillation on anticoagulation with warfarin, bladder cancer status post Bacillus Calmette-Guerin treatment currently under surveillance, chronic obstructive uropathy and subsequent CKD stage III, human papillomavirus positive head and neck squamous cell carcinoma status post radiation 4 years prior to presentation, hyperlipidemia, hypertension, and gout. Creatinine had increased to 1.7 mg/dL from a baseline of 1.2 mg/dL. The patient denied any hematuria, foamy urine, or worsening edema. Blood pressure was well controlled at 128/82 mm Hg on benazepril 10 mg daily and amlodipine 5 mg daily. Examination revealed chronic, stable 1+ pitting edema of the lower extremities. Otherwise, physical examination was unremarkable. Repeat creatinine on initial visit was 1.55 mg/dL with a protein/creatinine ratio of 1821.6 mg/G (see Table 1). Antineutrophil antibody (ANA) titer was elevated at 1:320. Complement 3 (C3) and complement 4 (C4) levels were within normal limits.

At 3-month follow-up, the patient complained of shortness of breath with exertion, generalized weakness, wheezing, and frothy urine with white sediment. Blood pressure was noted to be elevated at 144/90 mm Hg. Of note, benazepril had been discontinued one week prior by the patient's primary care physician. Physical exam was unchanged. Creatinine had increased to 1.79 mg/dL with a protein/creatinine ratio of 6975.1 mg/G. Furosemide 20 mg daily was initiated.

Three months later, he complained of worsening fatigue and had undergone a cardiac catheterization with his cardiologist, which revealed no significant obstructive coronary artery disease. This led to a diagnosis of nonischemic cardiomyopathy with a depressed left ventricular function with an ejection fraction (EF) of 35–40%. Metoprolol succinate 25 mg daily and isosorbide dinitrate 30 mg daily were initiated. Physical exam was notable for stable, pitting edema of the lower extremities and diminished breath sounds in the right lower lung. Creatinine rose to 2.37 mg/dL with a protein/creatinine ratio of 10039.0 mg/G. Urinalysis revealed proteinuria, hematuria, and trace amounts of leukocyte esterase. Microscopic evaluation of the urine showed 1–3 hyaline casts, 75–100 red blood cells, and >100 white blood cells. Blood pressure remained stable at 132/84 mm Hg. Subsequent serum immunofixation revealed a monoclonal immunoglobulin G (IgG) lambda protein measuring 0.71 g/dL. Urine immunofixation electrophoresis confirmed the presence of a monoclonal IgG lambda protein measuring 18.7 mg/dL. The patient was scheduled for computed tomography (CT)-guided left kidney biopsy. Pathology revealed immunotactoid glomerulonephritis with IgG1-lambda deposits.

Subsequently, the patient was referred to hematology/oncology and underwent a bone marrow biopsy, which showed normocellular bone marrow with trilineage hematopoiesis and approximately 15% plasma cell involvement. Microscopic examination via light microscopy revealed patchy moderate interstitial fibrosis (Figure 1) with tubular atrophy (Figure 2). Immunofluorescence revealed amorphous deposits within the glomeruli that stained positive for IgG (Figure 3) and lambda light chain (Figure 4). Congo red stain was negative for amyloid. Electron microscopy showed occlusion of capillary loops by large electron-dense microtubule deposits arranged in parallel arrays (Figure 5). Flow cytometry revealed a lambda restricted monoclonal population of plasma cells and 2.4% monoclonal kappa restricted B cells. Fluorescence in situ hybridization (FISH) study for myeloma was normal. Clonal B cells identified via flow cytometry were determined to most likely represent monoclonal B cell lymphocytosis. Repeat serum electrophoresis and serum immunofixation showed an IgG lambda monoclonal protein with a Monoclonal protein spike (M-spike) measuring 0.59 g/dL. Skeletal survey was unremarkable. Given worsening renal function with an estimated glomerular filtration rate (GFR) of <40 and a serum creatinine >3 mg/dL, as well as plasma cell involvement in the bone marrow, treatment was initiated with bortezomib, dexamethasone, and lenalidomide. Herpesvirus prophylaxis was initiated with acyclovir. Treatment was complicated by thrombocytopenia, requiring postponed treatment. One month following initiation of treatment, creatinine had improved to 1.8 mg/dL. Follow-up evaluation of M-spike showed a downtrend with a value of 0.29 g/dL.

Table 1. Timeline of laboratory results.

	7 June 2019 (initial visit)	25 September 2019	31 December 2019	24 March 2020 (1 month following initiation of treatment)
Serum creatinine (mg/dL)	1.55	1.79	2.37	1.8
Protein/creatinine ratio (mg/G)	1821.6	6975.1	10,039.0	

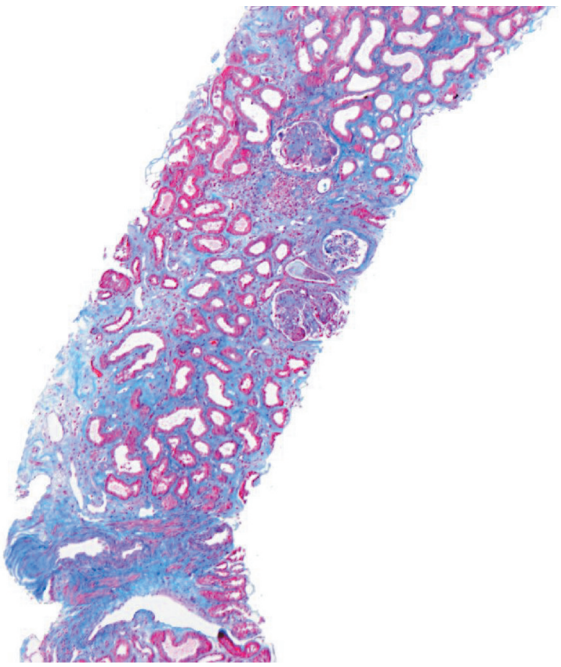

Figure 1. Moderate interstitial fibrosis on light microscopy.

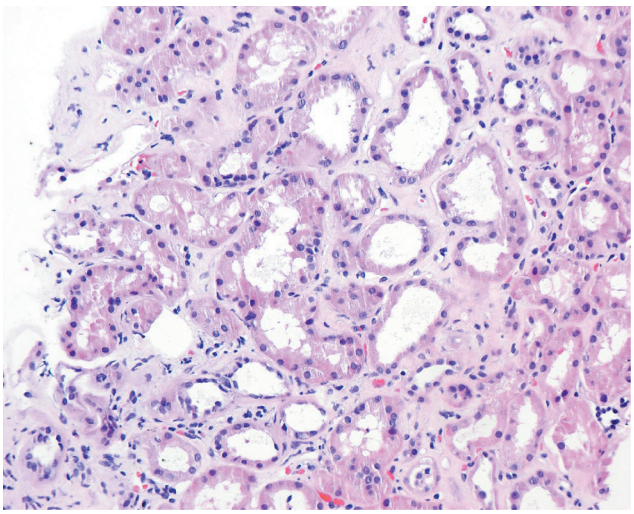

Figure 2. Tubular injury on light microscopy.

3. Discussion

Kidney diseases associated with a monoclonal gammopathy are being increasingly recognized. MGRS has a prevalence of 0.32% in patients over the age of 50 and 0.53% in those over 70. It has been estimated to account for 10% of cases of MGUS [1]. Clonal populations may be small as seen with MGUS, however unlike in patients with MGUS, patients with MGRS-related diseases have organ damage, including cardiomyopathy, neuropathy, dermopathy, hepatic dysfunction, and renal injury [4]. Kidney damage can occur via direct mechanisms, in which intact immunoglobulin molecules are trapped in the glomerulus and are unable to be internalized and degraded by lysosomes, as well as via indirect mechanisms when the monoclonal protein acts as an autoantibody resulting in complement activation. Glomerular and tubulointerstitial injury can occur via activation of inflammatory pathways and reactive oxygen species with resultant tissue injury [1].

The type of monoclonal protein in MGRS, referred to as a nephrotoxic monoclonal immunoglobulin, dictates the type of renal lesion produced and plays a direct role in renal injury despite the absence of high tumor burden [2,4]. Several disease entities exist under the umbrella of MGRS, each with a specific type of M-protein resulting in renal injury. These include light and heavy chain amyloidosis, monoclonal immunoglobulin deposition disease, monoclonal gammopathy-associated C3 glomerulopathy, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, cryoglobulinemia-associated glomerulonephritis, immunotactoid

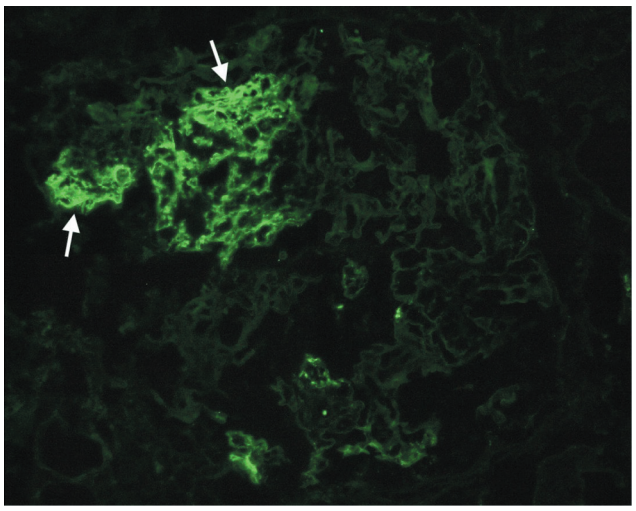

Figure 3. IgG positive immunofluorescence.

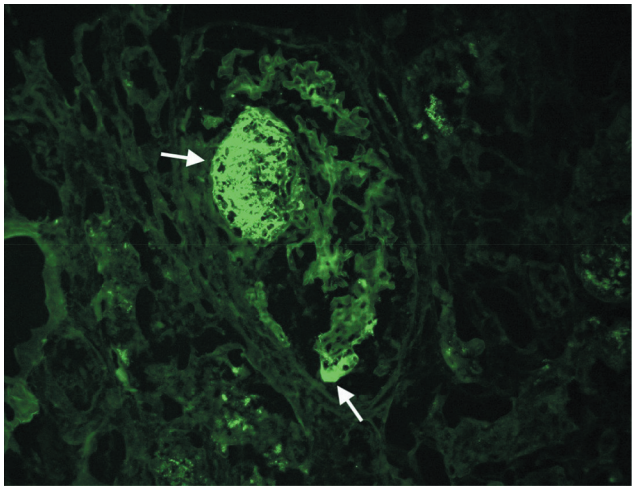

Figure 4. Lambda light chain positive immunofluorescence.

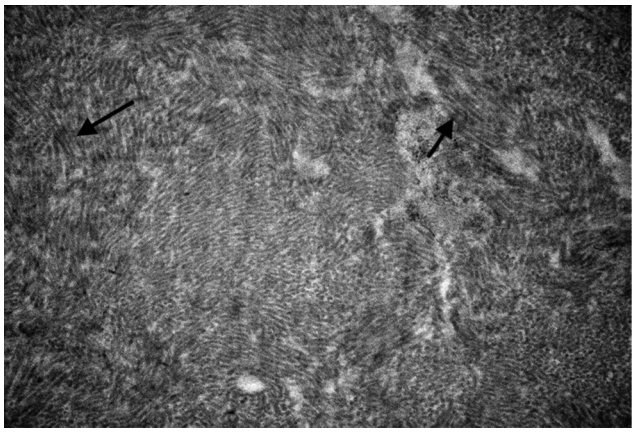

Figure 5. Immunotactoid (microtubular) deposits arranged in parallel arrays on electron microscopy.

glomerulopathy, paraprotein-associated fibrillary glomerulonephritis, monoclonal gammopathy-associated thrombotic microangiopathy, light chain proximal tubulopathy, and crystal-storing histiocytosis [2]. The patient in our case was ultimately diagnosed with immunotactoid glomerulopathy, which is characterized by glomerular deposits of organized, parallel microtubules with hollow centers predominantly within the subepithelium and subendothelium. These deposits stain for immunoglobulins, commonly IgG, and C3 on immunofluorescence [2,5]. Histopathology is most similar to membranous or membranoproliferative glomerulonephritis. Interestingly, about 50% of patients with immunotactoid glomerulopathy have an underlying

lymphoma, most commonly chronic lymphocytic leukemia (CLL) [5].

The diagnosis of MGRS requires renal biopsy and identification of the monoclonal protein in the serum and/or urine, as well as identification of the clonal population of cells that secrete said protein [1]. Kidney biopsy is performed with immunofluorescence (IF) and electron microscopic (EM) studies, which allow for identification of the type of MGRS lesion and the severity of renal disease [3]. Serum protein electrophoresis (SPE) and urine protein electrophoresis confirm the presence of a circulating monoclonal protein that corresponds to that identified via renal biopsy. Unfortunately, serum protein electrophoresis may not detect low levels of M-protein. Hence, serum immunofixation electrophoresis (IFE), urine IFE, and/or serum free light chain assay are performed due to their increased sensitivity [2]. Clonal cell population is identified via bone marrow aspiration and biopsy with identification of atypical lymphoid or lymphoplasmacytic cells or percentage of plasma cells [4]. In cases where a clonal cell population is not identified with bone marrow evaluation, imaging studies, such as CT, positron emission tomography (PET)-CT, or magnetic resonance imagining (MRI), can be performed to assess for lymphadenopathy or bone lesions, which should be biopsied [4].

Though there are no guidelines regarding the appropriate time to start therapy in patients with MGRS, initiation of chemotherapy is indicated in patients with CKD stages I to III and in patients with CKD IV or end-stage renal disease (ESRD) in the setting of extrarenal involvement or plans for renal transplant [1]. Treatment is directed at the underlying plasma cell or B-cell clone with a primary goal of improvement or stabilization of renal function [1,6]. Though no strict guidelines exist for treatment regimens, anti-myeloma agents are often utilized [2]. Commonly used regimens include bortezomib-dexamethasone, bortezomib-dexamethasone-cyclophosphamide, and thalidomide-dexamethasone-cyclophosphamide. However, therapy varies depending on the nature of the clonal cells, either plasmacytic or lymphocytic [4]. For instance, in CD20-expressing B-cell clones and lymphoplasmacytic clones, rituximab-based therapy is considered first-line treatment [2]. Autologous stem cell transplant is considered in patients that meet eligibility criteria as follows: under 70 years of age, adequate pulmonary and cardiac function with an EF greater than 45%, a World Health Organization performance score under 2, systolic blood pressure over 90 mmHg, and New York Heart Association scores I to II [2].

Baseline GFR is prognostic in terms of renal outcome following therapy [3]. A retrospective study conducted by Khera et al. investigated patients treated between 2004 and 2017 and showed that patients with CKD stages II to IIIb had improved renal survival (defined as the time from diagnosis until requirement of renal replacement therapy) at 24 months compared to those with CKD IV to V at diagnosis, 100% compared to 80.7%, respectively [6]. Achievement of a hematologic response, assessed via measurement of M-protein, correlates with renal response [1]. Proteinuria, renal function (creatinine, GFR), or repeated bone marrow biopsy can be used to assess response to treatment in patients who do not have a detectable M-protein at the time of diagnosis [1,2]. Of note, renal response may be delayed, with one study demonstrating evidence of renal response 12 months following hematologic response [2].

4. Conclusion

MGRS is a relatively new diagnosis, and as such, it is underdiagnosed. Our case calls for the consideration of this diagnosis in patients presenting with renal insufficiency. Given that baseline renal function at diagnosis is prognostic for renal outcome, it is vital that this diagnosis be considered in patients presenting with worsening renal function and even in those with newly diagnosed renal insufficiency in order to initiate treatment in a timely manner and improve the chance of renal recovery.

Disclosure statement

No potential conflict of interest was reported by the authors.

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