Acute Kidney Injury in a Patient With Monoclonal Gammopathy

Janie Luong, Nicole Andeen, Robert Rope, Rebecca Silbermann, Mazdak Khalighi, and Rupali Avasare

Clinical Presentation

A man in his mid-50s presented with progressively worsening bilateral lower extremity rash (Fig 1), symmetric paresthesias of his lower extremities, and small-volume hemoptysis. Skin biopsy showed an occlusive vasculopathy with vasculitic changes. Hypercoagulability workup results were normal. Laboratory testing for antinuclear cytoplasmic antibody and lupus serologic tests for hepatitis B and C virus and HIV were negative. Complement levels were normal. Serum protein electrophoresis demonstrated an immunoglobulin G (IgG) κ light chain monoclonal protein at a concentration of 0.3 g/dL. Serum concentrations of light chains were 175.7 (κ) and 11.6 mg/L (λ), giving a κ:λ ratio of 15.1. Serum creatinine level was 0.97 mg/dL and complete blood cell count results were normal. Bone marrow biopsy specimen was normocellular, with a 5% monoclonal κ light chain–restricted plasma cell population. The patient received prednisone and rituximab for cutaneous vasculitis without significant improvement in symptoms. One year later, he developed hypertension, acute kidney injury with serum creatinine level of 1.38 mg/dL, proteinuria with protein excretion of 5 g/d, serum albumin level of 3.1 g/dL, and microscopic hematuria. Serum light chain concentrations were 453.2 (κ) and 15.2 mg/L (λ), giving a κ:λ ratio of 29.8. A kidney biopsy was performed (Fig 2).

Figure 1. Patient’s rash on initial presentation including erythematous to violaceous 2- to 4-mm macules and papules, blue toes, and livedo reticularis.

Figure 2. Type 1 cryoglobulinemic glomerulonephritis with (A) mesangial and endocapillary hypercellularity and massive eosinophilic immune deposits (Jones silver stain; original magnification, ×200); (B) segmental mesangial and peripheral capillary wall staining for immunoglobulin G1 (IgG1), IgG2, and κ light chain; and (C) semi-curved organized deposits (transmission electron microscopy; direct magnification, ×6,800).
What is the differential diagnosis?
Paraproteins, either whole immunoglobulins or components of an immunoglobulin (eg, light chains and heavy chains), may lead to many distinct patterns of injury on kidney biopsy. The most common paraprotein-related disease is multiple myeloma (MM)-associated cast nephropathy, usually in the setting of a high clonal burden. Other kidney diseases due to paraproteins include light-chain amyloidosis, glomerulonephritis (GN) including cryoglobulinemic GN, monoclonal immunoglobulin deposition disease, and light chain proximal tubulopathy. Monoclonal gammopathies that result in kidney disease but otherwise do not meet criteria for MM or lymphoma are termed monoclonal gammopathies of renal significance (MGRS).

What laboratory studies should be undertaken?
Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures less than 37°C.1 IgG and IgM are the most common pathogenic cryoglobulins, though other immunoglobulin classes have been implicated.2 When immunoglobulin class and clonality are known, the Brouet classification can guide the diagnostic evaluation of infection-related, autoimmune, and hematologic causes.2 In this patient, serum cryoglobulin and cryofibrinogen testing were completed and results were repeatedly negative. His kidney biopsy demonstrated a mesangial and endocapillary proliferative GN with large subendothelial immune deposits and ∼20% crescents. Immunofluorescence showed granular to chunky mesangial and capillary wall staining for IgG (3+), IgM (trace), κ light chain (2-3+), and C3 (1+). IgG subclass staining showed deposition of both IgG1 (2+) and IgG2 (2-3+). IgG3, IgG4, and all other immunoreactant results were negative. Electron microscopy showed organized immune deposits with straight to slightly curved coalescent rods measuring 10 to 17 nm in diameter, characteristic of cryoglobulinemic GN. The constellation of cryoglobulinemic GN and MGUS prompted further investigation with a repeat bone marrow biopsy. This demonstrated 20% monoclonal plasma cells, meeting minimal criteria for smoldering myeloma (>10% monoclonal plasma cells).

What is the likeliest diagnosis and how should the patient be treated?
After multidisciplinary review and taking into account diagnostic criteria,3 the patient’s presentation was believed to be most consistent with MM due to bone marrow involvement in the setting of reduced kidney function and anemia, rather than MGRS. MM-associated cryoglobulinemia usually involves a type I cryoglobulin and kidney involvement is exceedingly rare. A retrospective study by Sidana et al4 of patients with type I cryoglobulinemia and circulating or biopsy-proven cryoglobulin included 102 patients, of whom 20 had MM and 14 had kidney involvement. Clinical presentation is variable and the most commonly affected organs are skin, nerve, and kidney. Kidney involvement commonly presents with hematuria and proteinuria, and the most common finding on kidney biopsy is membranoproliferative GN.

Despite recent advances in MM therapy with US Food and Drug Administration approval of several new therapies since 2015, myeloma remains incurable. Autologous stem cell transplant as consolidation therapy remains the standard of care for the appropriate patient populations. In our case, 1 week after kidney biopsy, the patient’s serum creatinine level increased to 2.33 mg/dL and he had new-onset hypertension. He was admitted and started on intravenous methylprednisolone, plasma exchange, intravenous cyclophosphamide, and carfilzomib due to pre-existing neuropathy. Although the role of plasma exchange is debated in the new era of highly effective MM therapies, in our case the goal was to remove cryoglobulins in a patient with rapidly progressive GN and crescents on kidney biopsy. The American Society of Apheresis rates plasma exchange therapy for severe/symptomatic cryoglobulinemia as category II (acceptable second-line stand-alone or adjunctive therapy), grade 2A.5 The patient later underwent melphalan-conditioned autologous stem cell transplantation and achieved a very good partial hematologic response, with trace detectable monoclonal protein in serum and no monoclonal plasma cells on bone marrow biopsy. One year after kidney biopsy, serum creatinine level was 0.9 mg/dL, protein excretion was < 500 mg/dL, and he did not have microscopic hematuria.
Final Diagnosis
Cryoglobulinemic glomerulonephritis associated with multiple myeloma.

Article Information
Authors’ Full Names and Academic Degrees: Janie Luong, DO, Nicole Andeen, MD, Robert Rope, MD, Rebecca Silbermann, MD, Mazdak Khalighi, MD, and Rupali Avasare, MD.

Authors’ Affiliations: Division of Nephrology, Department of Medicine (JL, RR, RA), and Department of Pathology (NA), Oregon Health & Science University; Department of Medicine, Knight Cancer Institute, Oregon Health & Science University, Portland, OR (RS); and Department of Dermatology, University of Utah Health, Salt Lake City, UT (MK).

Address for Correspondence: Janie Luong, DO, Oregon Health & Science University, Department of Medicine, Division of Nephrology, 3181 SW Sam Jackson Park Rd, Mail code: L113, Portland, OR 97239.

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Patient Protections: The authors declare that they have obtained consent from the patient reported in this article for publication of the information about him that appears within this article.

Peer Review: Received January 16, 2020. Direct editorial input from the Education Editor and a Deputy Editor. Accepted in revised form May 23, 2020.

Publication Information: © 2020 by the National Kidney Foundation, Inc. doi:10.1053/j.ajkd.2020.05.033

References

FELLOWSHIP PROGRAM HIGHLIGHT

Note from editors: To recognize fellowship programs’ educational mission, AJKD is using its popular Quiz feature to highlight Nephrology Fellowship programs when an author is a Nephrology Fellow. To participate, Fellowship Program Directors mentor fellows in submitting prospective Quizzes; those that are selected for publication include a brief description of the fellowship program from the Director. For “Acute Kidney Injury in a Patient With Monoclonal Gammapathy,” the corresponding author is Janie Luong, a Nephrology Fellow at Oregon Health and Science University.

Program: Oregon Health and Science University Nephrology Fellowship Training Program (https://www.ohsu.edu/school-of-medicine/nephrology-and-hypertension/fellowship-training-programs)

Program Director: Jessica Weiss, M.D., M.C.R.

Program Description from program leadership: OHSU Nephrology has been training physicians to become outstanding nephrology providers since 1972. We offer a flexible program, tailored to the goals of our fellows, including clinical and research tracks. Optional pathways in glomerulonephritis, transplant, hypertension, palliative care, and critical care offer additional support for individual interests. Fellows master core nephrology care in both the inpatient and outpatient setting including hemodialysis, peritoneal dialysis, and CRRT. In addition, senior fellows have a continuity dialysis experience at the Portland VA. All training takes place in Portland, Oregon, so trainees can experience all that Portland and the Pacific Northwest have to offer!

Submitting a Manuscript for Consideration: Prospective Quizzes should be submitted through AJKD’s Editorial Manager system (www.editorialmanager.com/ajkd). Information on the Quiz format is available in the AJKD Information for Authors (www.ajkd.org/content/authorinfo) and by reviewing previously published Quizzes (all freely available) at www.ajkd.org/content/quizpages.