Crystalglobulin-Induced Nephropathy

Vinay Gupta,* Mireille El Ters,† Kianoush Kashani,‡ Nelson Leung,*† and Samih H. Nasr§

Divisions of *Hematology, †Nephrology and Hypertension, ‡Pulmonary and Critical Care, and §Anatomic Pathology, Mayo Clinic, Rochester, Minnesota

ABSTRACT

Crystalline nephropathy refers to renal parenchymal deposition of crystals leading to kidney damage. The most common forms of crystalline nephropathy encountered in renal pathology are nephrocalcinosis and oxalate nephropathy. Less frequent types include urate nephropathy, cystinosis, dihydroxyadeninuria, and drug-induced crystalline nephropathy (e.g., caused by indinavir or triamterene). Monoclonal proteins can also deposit in the kidney as crystals and cause tissue damage. This occurs in conditions such as light chain proximal tubulopathy, crystal-storing histiocytosis, and crystalglobulinemia. The latter is a rare complication of multiple myeloma that results from crystallization of monoclonal proteins in the systemic vasculature, leading to vascular injury, thrombosis, and occlusion. In this report, we describe a case of crystalglobulin-induced nephropathy and discuss its pathophysiology and the differential diagnosis of paraprotein-induced crystalline nephropathy.


Renal dysfunction occurs in up to one-half of patients with multiple myeloma (MM). The classic clinicopathologic renal lesions related to MM are myeloma cast nephropathy, monoclonal Ig deposition disease, Ig-related amyloidosis, and acute tubular necrosis. Less frequent paraprotein-dependent lesions in MM include type 1 cryoglobulinemic GN, immunotactoid glomerulopathy, and proliferative GN with monoclonal IgG deposits. Rarely, the kidney damage is caused by crystallization of paraprotein within the kidney as occurs in light chain proximal tubulopathy, crystal-storing histiocytosis, and crystalglobulinemia. The latter is a rare complication of MM that manifests as polyarthralgias, skin rash or ulcers, and/or kidney insufficiency. This report describes a case of relapsed MM associated with crystalglobulinemia syndrome. We refer to the renal involvement in this syndrome as crystalglobulin-induced nephropathy.

CLINICAL HISTORY

A 61-year-old African-American woman presented to her local hospital in May 2013 with a 4-week history of worsening painful rash over bilateral distal upper and lower extremities, concurrent with subjective fevers, night sweats, nausea, and fatigue. She denied arthralgias, hives, or edema. She was found to have AKI with a creatinine of 4.8 mg/dl. Given her worsening renal function, she was transferred to our institution for a higher level of care. Her past medical history was significant for MM, and she was initiated on therapy with lenalidomide and dexamethasone with resolution of her skin rash and hypercalcemia. However, she developed elevated liver function tests attributed to bortezomib, leading to discontinuation of therapy.

On admission, the patient was noted to have a painful, purpuric nonblanching and nonpalpable rash involving her fingers, ankles, and soles bilaterally (Figure 1A). Vital signs were significant for hypertension and tachycardia. Her initial laboratory evaluation was notable for elevated serum creatinine of 5.2 mg/dl (baseline of 1.2 mg/dl 4 months prior), total calcium of 7.2 mg/dl, and mild anemia with a hemoglobin of 10.6 g/dl. Serum protein electrophoresis revealed monoclonal protein levels of 1.3 g/dl, which was IgG kappa on immunofixation. The serum free kappa/lambda ratio was 1.95 (normal range, 0.26–1.65). Urinalysis showed mild pyuria without hematuria. The 24-hour urine protein level was 1.1 g. Serological work-up including antinuclear antibody, rheumatoid factor, myeloperoxidase, proteinase-3, hepatitis B surface antigen, hepatitis C antibody, serum cryoglobulin, and plasma cryofibrinogen was negative. Renal ultrasonography showed that there was no evidence of hydronephrosis and the renal arteries and veins at the hilum were patent. A bone marrow biopsy performed at that time demonstrated 30% monotypic kappa plasma cells. A skin rash was also noted at this admission, but was not biopsied. The patient was reinitiated on a regimen of bortezomib and dexamethasone with resolution of her skin rash and hypercalcemia.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Samih H. Nasr, Division of Anatomic Pathology, Mayo Clinic, Hilton 10-20, 200 First Street SW, Rochester, MN 55905. Email: nasr.samih@mayo.edu

Copyright © 2015 by the American Society of Nephrology
Figure 1. Renal biopsy findings. (A) Photograph demonstrating nonblanchable, nonpalpable purpura of feet. The insert shows fingers with splinter hemorrhages. (B) Biopsy of the skin lesions shows occlusive vasculopathy. This small cutaneous arteriole shows intraluminal thrombosis without leukocytoclastic vasculitis (H&E). (C) This image of the kidney biopsy shows large extracapillary bright red crystals within glomerular capillaries (long arrows) and arterioles (short arrows) with secondary vascular thrombosis (arrowhead) (trichrome stain). (D) The glomerular and arteriolar crystals (arrows) are light pink on silver stain. The depicted interlobular artery (arrows) with secondary vascular thrombosis (arrowhead) (trichrome stain). (E) A large intraglomerular capillary electron dense crystal (electron microscopy) is shown. (F) On high magnification, the crystals exhibit a substructure characterized by parallel linear arrays (electron microscopy). (G and H) Large crystals in vessels and glomeruli stain brightly for IgG (G) and κ (H) by pronase immunofluorescence. H&E, hematoxylin and eosin. Original magnification, ×600 in B; ×400 in C; ×400 in D; ×13,000 in E; ×68,000 in F; ×200 in G and H.

showed slightly hypocellular bone marrow involved by a plasma cell proliferative disorder with 10%–20% monotypic κ plasma cells. A skin biopsy was performed showing occlusive vasculopathy without crystals (Figure 1B) with positive immunofluorescence staining on frozen tissue for fibrinogen in superficial vessels. Immunofluorescence on frozen tissue and pronase immunofluorescence were negative for IgG, IgA, IgM, κ, and λ. A kidney biopsy was performed.

KIDNEY BIOPSY

The sample submitted for light microscopy contained nine glomeruli, one of which was globally sclerotic. In three glomeruli, large hyperesinophilic fractured crystals with rounded or rod shapes were seen within glomerular capillaries, accompanied by abundant intracapillary infiltrating monocytes and neutrophils and focal fibrin deposition (Figure 1, C and D). The crystals stained periodic acid–Schiff–weak, trichrome-red, and silver light pink (Figure 1, C and D). Glomeruli without crystals did not exhibit intracapillary hypercellularity. Glomerular basement membranes appeared mildly thickened with normal texture and contour. No crescents were identified. There was diffuse acute tubular injury, mild tubular atrophy and interstitial fibrosis, and focal interstitial inflammation composed mainly of lymphocytes. Similar large crystals were seen in rare distal tubular lumina, without an associated cellular reaction. Several arterioles and small interlobular arteries exhibited similar large crystals, associated with intraluminal fibrin deposition and denudation of endothelial cells (Figure 1, C and D), without transmural arteritis.

Ultrastructurally, the crystals within glomerular capillaries and arteriolar lumina uniformly showed a substructure characterized by parallel linear arrays with a thickness of 6 nm and a periodicity of 14 nm (Figure 1, E and F). No subendothelial, mesangial, or subepithelial electron dense deposits were seen. Podocytes displayed moderate foot process effacement. No proximal tubular cytoplasmic crystals typical of light chain proximal tubulopathy were seen.

By immunofluorescence on frozen tissue and on pronase-digested, paraffin-embedded tissue, the crystalline deposits within glomeruli and vessels stained 2–3+ (on a scale of 0–3+) for IgG and κ (Figure 1, G and H) with trace IgM and trace λ. There was trace nonspecific diffuse linear glomerular and tubular basement membrane positivity for IgG, κ, and λ on pronase immunofluorescence. Glomeruli were negative for IgA, C1q, C3, and albumin and stained trace for IgM. Immunofluorescence staining for IgG subtypes showed 2+ staining of vascular crystals for IgG1 with negative staining for IgG2, IgG3, and IgG4. The final diagnosis was crystalglobulin-induced nephropathy.

CLINICAL FOLLOW-UP

The patient was initiated on hemodialysis due to development of hyperkalemia, hyperphosphatemia, and volume overload. She was initiated on prednisone empirically for management of the skin rash. In addition, she underwent a total of seven sessions of plasma-exchange and was started on cyclophosphamide and bortezomib. Her skin rash and pain improved significantly. She was discharged.
home with a regimen consisting of cyclophosphamide, bortezomib, and dexamethasone, and then transitioned to weekly bortezomib and dexamethasone. She was eventually able to recover renal function, and was transitioned off hemodialysis in October 2013 (5 months after presentation). Her serum creatinine was down to 2.4 mg/dl in December 2013. She is currently being evaluated for autologous stem cell transplantation.

DISCUSSION

Renal involvement is common in MM and is frequently the first manifestation of disease. The most common clinical renal presentation in MM is kidney impairment, which is an independent factor for poor patient survival.6 Kidney involvement may also manifest as subnephrotic proteinuria, nephrotic syndrome, or tubular function defects. The spectrum of pathologic lesions caused by MM is wide. In the largest study to date of renal biopsy findings in MM, the three most common paraprotein-dependent lesions found were myeloma cast nephropathy (33%), monoclonal Ig deposition disease (22%), and amyloidosis (21%), although many other rarer lesions were encountered such as direct interstitial infiltration by malignant plasma cells (1%), fibrillary GN (1%), immunotactoid glomerulopathy (0.5%), and light chain proximal tubulopathy (0.5%).1

The term crystalglobulinemia refers to crystallization of monoclonal proteins in the systemic microvasculature leading to vascular injury. The term cryocrystalglobulinemia is occasionally used for cases in which the crystalized monoclonal protein has cryoprecipitating properties. These two terms, however, have been used interchangeably in some prior publications.5,7,8 Crystalglobulinemia has been described mainly in patients with MM2,5,10 but may rarely occur in patients with monoclonal gammopathy of renal significance.9 The biochemical basis for the phenomenon of crystallization of monoclonal protein is still unknown. Anecdotal evidence suggests that it occurs due to Fc–Fc interactions of IgG-type monoclonal protein,11 possibly owing to abnormal glycosylation of the light chain portion of monoclonal protein, or through interactions with albumin (Figure 2).12 These interactions may be enhanced by cooling and/or stasis in the systemic microvasculature.2,4 Crystalglobulins lead to vascular endothelial injury and activation of coagulation cascade predisposing to thrombosis, occlusive changes, and subsequent ischemic injury (Figure 2). The involvement of renal vessels manifests with acute worsening of kidney function and rarely bilateral renal arterial thrombosis,2,5,9 necessitating RRT and frequently leading to ESRD. Cutaneous vasculature injury leads to ulcerated and purpuric lesions, commonly in distal extremities. Other findings include peripheral neuropathy and polyarthropathy, which clinically mimics rheumatologic conditions such as polyarteritis nodosa, but without active inflammatory changes.8 Corneal and bone marrow deposition have also been described.13,14

No clear risk factors for crystalglobulinemia have been identified thus far.2 Systemic crystalglobulin deposition is associated with rapid progression and worse outcomes in patients in MM.5 It may be the initial manifestation of hitherto undiagnosed MM in a small subset of patients.2 Demonstration of crystal deposition in renal vasculature remains the mainstay of diagnosis. Renal biopsy should be considered in patients with unexplained cutaneous presentation and worsening serum creatinine despite appropriate management. Initiation of MM-directed therapy is essential in the management of these patients. Plasmapheresis and corticosteroids serve as

Figure 2. The pathomechanisms of crystalglobulinemia are still unclear. Crystallization of monoclonal protein potentially occurs due to Fc–Fc interactions of IgG-type monoclonal protein possibly owing to abnormal glycosylation of the light chain portion of monoclonal protein or through interactions with albumin. These interactions may be enhanced by cooling and/or stasis in the systemic microvasculature. Crystalglobulins may induce vascular endothelial injury and activation of coagulation cascade predisposing to thrombosis, occlusive changes and ischemic injury to kidney, skin, and other organs. LC, light chain; RBC, red blood cell.

bridging therapy until response to treatment of underlying MM is seen. Multiple sessions of plasmapheresis may be necessary to reduce monoclonal paraproteinemia and prevent further crystallization into vascular tissues.\textsuperscript{2,5} The rarity of crystalglobulinemia precludes objective assessment of response to therapy. However, therapy with chemotherapeutic regimens comprising cyclophosphamide or melphalan is rarely associated with clinical response.\textsuperscript{5} In the modern era, regimens comprising immunomodulatory drugs or proteasome inhibitors have shown improvement of renal function.\textsuperscript{4} RRT is often required at presentation. However, the likelihood of restoration of renal function remains low and patients often remain dialysis dependent, reflecting sustained ischemic injury before diagnosis.\textsuperscript{5}

Paraprotein-induced crystalline nephropathy can be divided into two categories based on whether the crystals in the kidney are intracellular or extracellular (Table 1). The former tends to present with slowly worsening kidney dysfunction and generally has a good prognosis, whereas the latter usually presents with rapidly progressive renal failure and is associated with poor renal outcome. Paraprotein-induced crystalline nephropathy with predominantly intracellular crystals include light chain proximal tubulopathy with crystals “light chain Fanconi syndrome” and crystals storing histiocytosis. In light chain proximal tubulopathy, the light chain crystals are typically located within proximal tubular cytoplasm, usually freely (non-membrane bound).\textsuperscript{15,16} In renal involvement by crystal-storing histiocytosis, the crystals are mainly seen within interstitial histiocytes\textsuperscript{17} but occasional crystals can be seen in proximal tubular cells and glomerular cells particularly podocytes.\textsuperscript{18–20} Paraprotein-induced crystalline nephropathy with predominantly extracellular crystals include the crystalline variant of myeloma cast nephropathy and crystalglobulin-induced nephropathy. Myeloma cast nephropathy is characterized histologically by diffuse acute tubular injury and distinctive distal tubular casts that appear large and fractured with sharp edges. A rare distinctive

<table>
<thead>
<tr>
<th>Table 1. Differential diagnosis of paraprotein-induced crystalline nephropathy</th>
<th>Composed of</th>
<th>Distribution of Crystals</th>
<th>Extranodal Involvement</th>
<th>Renal Clinical Manifestations</th>
<th>Hematologic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light chain proximal tubulopathy with crystals</td>
<td>Light chain (almost always k)</td>
<td>Intracellular, proximal tubular cells, rarely glomerular cells</td>
<td>Bone marrow</td>
<td>Chronic renal insufficiency</td>
<td>MGRS, MM</td>
</tr>
<tr>
<td>Light chain proximal tubulopathy with crystals</td>
<td>Light chain (usually k)</td>
<td>Intracellular, histiocytes (in the interstitium and perirenal fat, occasionally in tubular and glomerular cells)</td>
<td>Bone marrow</td>
<td>Tubular proteinuria</td>
<td>MGRS, MM</td>
</tr>
<tr>
<td>Crystal-storing histiocytosis</td>
<td>Light chain (k &gt; A)</td>
<td>Extracellular, distal tubular lumen</td>
<td>Bone marrow</td>
<td>AKI</td>
<td>MM</td>
</tr>
<tr>
<td>Crystal-storing histiocytosis</td>
<td>Light chain (k &gt; A)</td>
<td>Extracellular, arteries, arterioles, glomerular capillaries, rarely glomerular lumen and Bowman’s space</td>
<td>Bone marrow</td>
<td>Overflow proteinuria</td>
<td>MGRS, MM</td>
</tr>
<tr>
<td>Crystalline variant of light chain cast nephropathy</td>
<td>Light chain only (l, k)</td>
<td>Extracellular: arteries, arterioles, glomerular capillaries, rarely glomerular lumen and Bowman’s space</td>
<td>Bone marrow</td>
<td>Infarction of kidney</td>
<td>MGRS (rare)</td>
</tr>
<tr>
<td>Crystalglobulinemia</td>
<td>Heavy and light chains (IgG k or IgG l)</td>
<td>Extracellular: arteries, arterioles, glomerular capillaries, rarely distal tubular lumen and Bowman’s space</td>
<td>Bone marrow</td>
<td>AKI</td>
<td>MM</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Immunofluorescence on pronase-digested, paraffin-embedded tissue is much more sensitive than standard immunofluorescence to establish the composition of crystals in all of these entities.
morphic and myeloma cast nephropathy exists in which the casts in distal tubular lumina are composed entirely of small needle- or rod-shaped electron dense crystals. Occasionally, the crystals rupture the tubular basement membranes and extravasate into the interstitium, leading to florid inflammatory reaction including abundant histiocytes that histologically may mimic crystal-storing histiocytosis. Patients with the crystalline variant of myeloma cast nephropathy may show similar large extracellular crystals in the bone marrow.\textsuperscript{13,21} Crystalglobulin-induced nephropathy is characterized by large extracellular crystals within the lumen of arteries, arterioles, and/or glomerular capillaries with or without secondary vascular thrombosis. Rare crystals may also be seen within Bowman’s capsule and tubular lumina.\textsuperscript{3,22} Different from myeloma cast nephropathy, light chain proximal tubulopathy with crystals, and crystal-storing histiocytosis in which the paraprotein crystals are generally composed of monoclonal light chains (almost always k), the crystals in crystalglobulin-induced nephropathy can be composed of both Ig heavy and light chains (Table 1).\textsuperscript{2,23} As in the current case. In our case, serum cryoglobulin was negative, the intraglomerular infiltrating monocytes and neutrophils were restricted to glomeruli with crystals, there were no mesangial or subendothelial electron dense deposits, and there was no evidence of cutaneous leukocytoclastic vasculitis or renal endo-vasculitis. Therefore, this case is better designated as crystalglobulin-induced nephropathy and not cryocrystalglobulin-induced nephropathy, although underlying covert cryoglobulinemia remains a remote possibility considering the known relatively high false negativity rate of the serum cryoglobulin test.

This case exemplifies the importance of awareness of crystalglobulinemia as a clinical entity and appropriate diagnostic testing including serum protein electrophoresis and renal and skin biopsies for confirmation. The histologic finding of large hypereosinophilic extracellular crystals within the lumina of arteries, arterioles, or glomeruli should raise a suspicion for crystalglobulinemia. Early therapeutic intervention is imperative to minimize morbidity and mortality.

DISCLOSURES
None.

REFERENCES