Kidney Medicine

Crystal-Induced Podocytopathy Producing Collapsing Focal Segmental Glomerulosclerosis in Monoclonal Gammopathy of Renal Significance: A Case Report

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Monoclonal gammopathy–associated crystalline podocytopathy causing collapsing focal segmental glomerulosclerosis (FSGS) is very rare and has been associated with pamidronate therapy. We present the case of a 53-year-old man with vision loss secondary to corneal crystals deposition, nephrotic-range proteinuria, and reduced glomerular filtration rate without associated comorbid conditions. Two kidney biopsies were initially reported as primary FSGS but the patient did not respond to high-dose corticosteroid immunosuppression therapy. Repeat review of biopsies with additional electron microscopy analysis revealed crystalline inclusions in podocytes leading to collapsing FSGS. Subsequent workup revealed an immunoglobulin G κ serum monoclonal protein. Bone marrow biopsy revealed 5% κ-restricted plasma cells with cytoplasmic crystalline inclusions. To our knowledge, this is the first case of monoclonal gammopathy of clinical significance manifesting as crystalline podocytopathy leading to collapsing FSGS and keratopathy leading to vision loss. Crystalline podocytopathy should be considered in the differential diagnosis of collapsing glomerulopathy, and careful ultrastructural examination of the kidney biopsy specimen is crucial to establish this diagnosis.

Complete author and article information provided before references.

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INTRODUCTION

Monoclonal gammopathies result from the excessive production of monoclonal immunoglobulin or subunits detectable in serum or urine resulting from clonal plasma cell or B-cell proliferation. The underlying hematologic conditions range from multiple myeloma to nonmalignant small clonal proliferations.[1] Kidney involvement is common.[2,3] In most cases, monoclonal immunoglobulin accumulates extracellularly as casts, fibrils, or finely granular "punctate" deposits, resulting in cast nephropathy, amyloidosis, or monoclonal immunoglobulin deposition disease, respectively.[2,3] Less commonly, monoclonal immunoglobulin precipitates as crystalline inclusions within the cytoplasm of tubular epithelial cells, producing light chain (LC) proximal tubulopathy, or even rarer within interstitial histiocytes, resulting in crystal-storing histiocytosis, or glomerular epithelial cells such as podocytes.[3,4] The terms monoclonal gammopathy of renal significance (MGRS) and monoclonal gammopathy of clinical significance were recently introduced to draw attention to kidney diseases related to monoclonal gammopathy in the absence of hematologic malignancy.[5,6]

Collapsing focal segmental glomerulosclerosis (FSGS) is a rare disease associated with viruses such as HIV and parvovirus or drugs like bisphosphonates, particularly pamidronate, used for treatment of multiple myeloma–associated hypercalcemia.[7-9] However, crystal-induced podocytopathy causing FSGS without the use of these drugs is extremely rare.

We present the case of a 53-year-old man with vision loss due to corneal crystal deposition, proteinuria, and reduced glomerular filtration rate without other comorbid conditions. Kidney biopsies were initially interpreted as primary collapsing FSGS but upon repeat review and additional electron microscopy (EM) evaluation, a diagnosis of collapsing FSGS secondary to crystalline podocytopathy was established. Further plasma cell dyscrasia workup confirmed the diagnosis of MGRS.

CASE REPORT

A 53-year old white man was evaluated for presumed bacterial keratitis in the left eye. During that examination, a diffuse crystalline keratopathy involving most of the central 9 mm of the right cornea and areas of the left cornea was noted. During follow-up 3 months later, the best corrected visual acuity in the left eye was limited to 20/300 by corneal scar and irregular astigmatism. Best corrected vision in the right eye was 20/25. Bilateral corneal anesthesia was also noted. A diagnosis of cystinosis was considered, but the genetic analysis was negative. The patient was treated with prednisolone drops twice daily in both eyes and had no recurrence of inflammation since stopping the use of contact lenses.

The patient was referred to nephrology 13 months after his original presentation for persisting proteinuria (protein excretion, 4-5 g/24 h) and increased serum creatinine levels (2 mg/dL) found during a routine examination. A kidney biopsy was performed and interpreted as collapsing FSGS with widespread foot-process effacement on EM examination, consistent with primary collapsing FSGS. The patient was started on treatment with lisinopril, 20 mg/d, orally, and prednisone, 80 mg/d, orally. Despite prednisone, proteinuria increased, and he underwent a repeat kidney biopsy that showed similar findings. Due to the uncertainty about the diagnosis of his kidney disease and recommendations regarding treatment, he was referred for further evaluation.

At presentation at the Mayo Clinic, the patient looked healthy. On physical examination, blood pressure was 118/76 mm Hg with a pulse rate of 69 beats/min. Apart from trace edema on the lower extremities, the rest of the physical examination findings were unremarkable. Laboratory evaluation is presented in Table 1. Serum and urine immunoglobulin G (IgG) and κ monoclonal protein fractions were identified on immunofixation electrophoresis. Free κ and λ LC levels in serum were 3.27 and 1.48 mg/dL, respectively, and serum free LC ratio was 2.21. Fanconi syndrome was excluded by normal uric acid levels, no aminoaciduria, and no glycosuria. Ophthalmologic examination findings are presented in Fig 1A and C.

Light microscopy of the first biopsy specimen showed 22 glomeruli, of which 2 showed segmental sclerosis and 2 displayed segmental collapsing features. The second biopsy revealed a corticomedullary specimen containing 17 glomeruli, 7 of which were globally sclerotic, 2 showed segmental sclerosis with an increase in matrix material and adhesion to Bowman capsule, and 3 displayed segmental collapsing features (Fig 2A). There was moderate tubular atrophy and interstitial fibrosis, accompanied by mild chronic inflammation and mild focal acute tubular injury. Congo red staining was negative for amyloid deposition.

Immunofluorescence staining performed on frozen tissue on both biopsies revealed negative glomerular staining for IgG, IgM, IgA, C1q, κ, λ, or fibrinogen. There was weak segmental and focal staining for C3 corresponding to areas of sclerosis. Immunofluorescence staining for κ and λ on paraffin tissue after pronase digestion revealed 1+ diffuse glomerular and tubular basement membranes staining for κ (1+) with negative λ. Protein resorption droplets in tubular cells stained 1 to 2+ for κ with trace λ. No staining of glomerular or tubular crystals was observed.

Review of outside EM images and additional EM analysis was repeated at Mayo Clinic, which confirmed diffuse (≥80%) podocyte foot-process effacement. Additionally, there were abundant small needle and rhomboid-shaped electron-dense crystals within podocytes (Fig 2B and C) and tubular cells (Fig 2D), with few in mesangial cells. The crystals did not substructure on high-power examination. No interstitial histiocytes containing crystals were seen.

The patient subsequently underwent bone marrow biopsy that showed 5% κ-restricted plasma cells (Fig 3A). Needle-shaped intracytoplasmic crystals were seen within plasma cells (Fig 3B). Cytogenetics showed normal male karyotype. Full bone magnetic resonance imaging was performed and showed no abnormalities.

The patient had crystal-induced collapsing FSGS secondary to MGRS/monoclonal gammopathy of clinical significance diagnosed. Treatment was recommended with bortezomib, 1.3 mg/m^2, subcutaneous weekly; lenalidomide, 25 mg, 14 of 21 days; and dexamethasone, 40 mg, weekly.

Table 1. Laboratory Results of Blood and Urine Tests

Laboratory Test	Results	Reference Range
Complete blood cell count		
Hemoglobin, g/dL	12.2	13-17
Hematocrit, %	35.9	35-47
WBC count, 10^9/L	11.7 ×	4-10
Platelet count, 10^9/L	277	150-410
Blood chemistry		
Sodium, mmol/L	143	136-146
Potassium, mmol/L	4.1	3.5-5.1
Creatinine, mg/dL	2.2	0.7-1.2
Calcium, mg/dL	9.2	8.6-10.2
Phosphorus, mg/dL	3.0	2.5-4.8
Protein, g/dL	5.9	6.3-8.2
Albumin, g/dL	3.3	4.1-5.3
Uric acid, mg/dL	5.6	3.4-7
Immunoglobulins		
κ FLC, mg/L	3.27	3.3-19.4
λ FLC, mg/L	1.48	5.71-26.3
κ:λ FLC ratio	2.21	0.26-1.65
IgA, mg/dL	68	70-350
IgM, mg/dL	37	50-300
IgG, mg/dL	731	700-1,700
Serology test		
HBc IgM Ab	Negative	
HBs antigen	Negative	
HBs Ab	Negative	
HCV Ab	Negative	
HIV	Negative	
Urine studies		
Glucose	Negative	
Hemoglobin	Negative	
WBC	1-3 WBC/HPF	
Proteinuria, mg/24 h	10,280	0-300

Abbreviations: Ab = antibody; HBc, hepatitis B core; HBs, hepatitis B surface; HCV, hepatitis C; IgA, immunoglobulin A; FLC, free light chain; WBC, white blood cell.

DISCUSSION

The present case displays a not previously described combination of morphologic findings in MGRS, namely crystalline podocytopathy causing collapsing FSGS with crystalline keratopathy.

LC crystal deposition in the setting of a plasma cell dyscrasia is associated with a variety of clinical manifestations.[4,10] However, collapsing podocytopathy caused by crystalline inclusions is very rare. To date, only 17 cases in native kidneys have been reported in the English literature. Of these, 12 patients had multiple myelomas[7,11-21] and only 5 had MGRS[22-26] (Table S1). Interestingly, all cases (this case included) were associated with IgGκ serum paraprotein. However, 10 reports, including ours, were

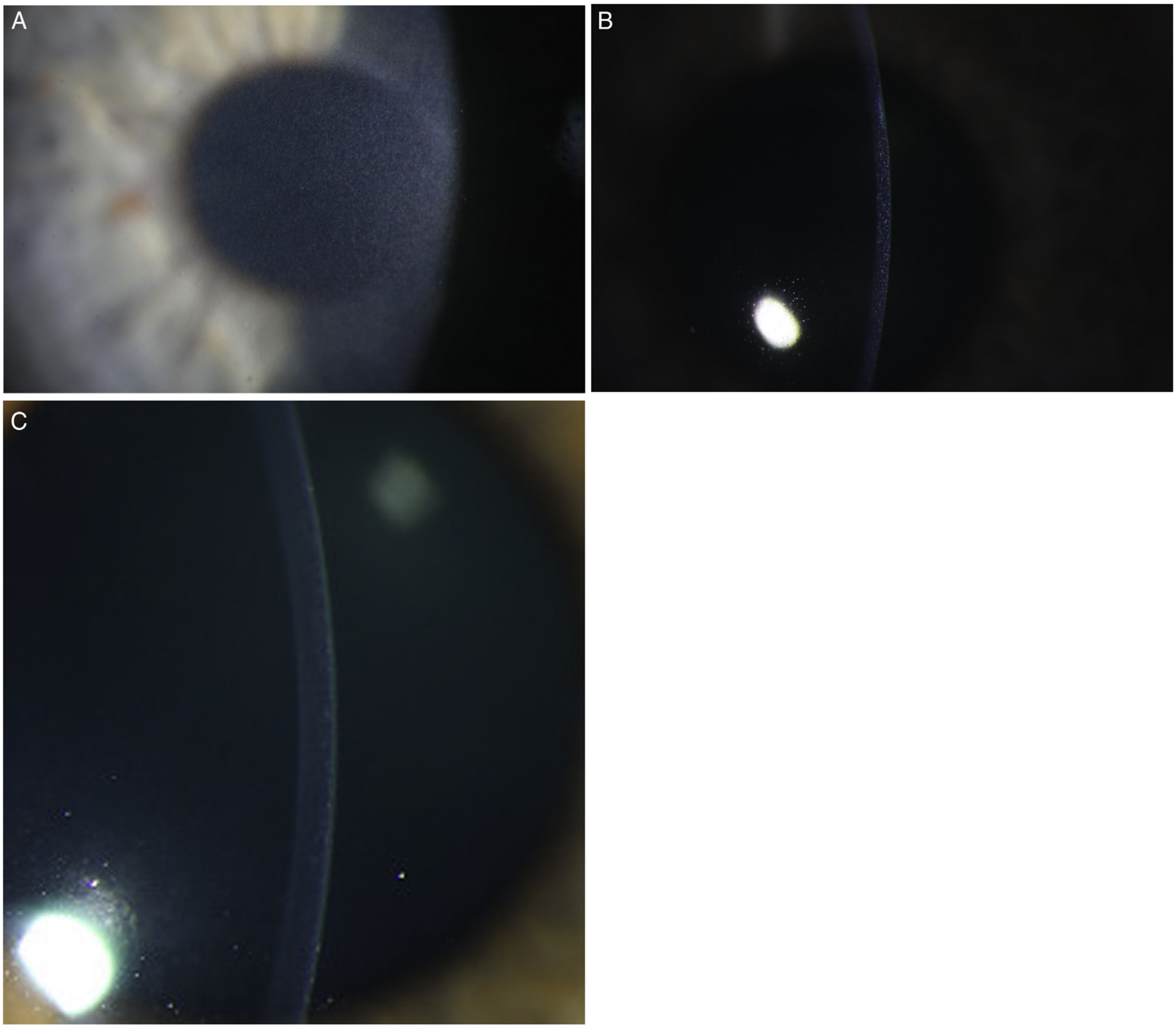

Figure 1. (A) Diffuse illumination of the right cornea shows semitransparent stromal haze without inflammation. The stromal opacity extends over most of the surface area of the cornea and is uniform in density throughout stromal depth. (B) Sagittal section of the corneal stroma of the right eye with slit beam shows small highly reflective stromal opacities evenly distributed throughout the depth of the cornea. (C) Sagittal section of normal cornea with slit beam for comparison.

unable to demonstrate LC restriction in crystalline inclusions by immunofluorescence staining on frozen tissue.[7,11,12,15,18-20,25,26] Some of these studies were able to identify monoclonal LC deposition in the crystals with immunofluorescence of paraffin-embedded sections after performing antigenic retrieval or immune EM.[7,12,15,20,25] However, Akilesh et al[19] and the present study failed to stain crystalline LC inclusions in kidney tissue for κ even with paraffin immunofluorescence. This could result from the extensive crystallization of the monoclonal protein, small crystal size, and intracellular localization, which could potentially prevent the LC antibodies from reaching their antigenic targets.[27] Almost all reported cases displayed additional intracellular crystalline deposition in other kidney compartments (Table S1).

Crystalline inclusions in glomerular cells are usually associated with a severe histologic manifestation of podocyte injury, with most patients (9/18) presenting with an FSGS pattern of injury (Table S1). However, only 3 cases (including ours) presented as collapsing FSGS,[7,19] a seldom described variant characterized by marked wrinkling and collapse of glomerular basement membranes plus hypertrophy and hyperplasia of overlying podocytes.[8,9] Nasr et al[7] and Akilesh et al[19] described 2 cases of crystalloid podocytopathy causing collapsing FSGS in a 54-year-old woman and a 45-year-old man, respectively. Both

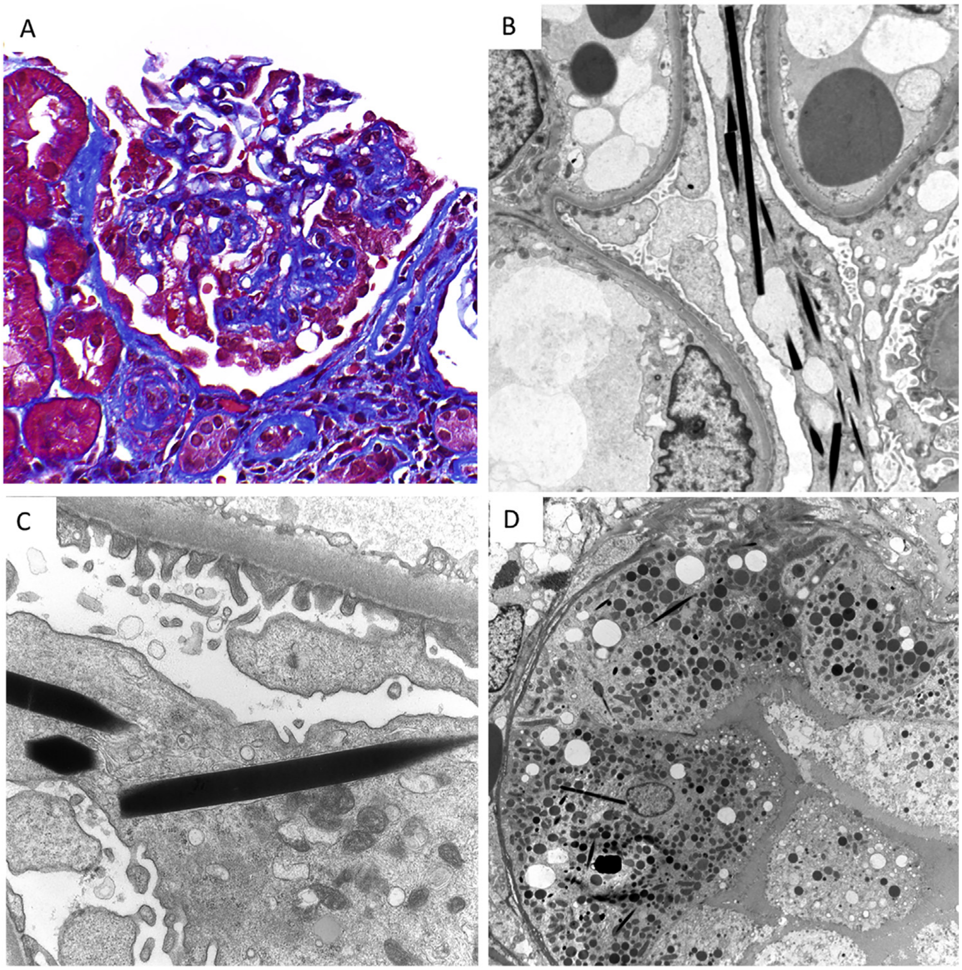

Figure 2. (A) A glomerulus from the second biopsy shows collapsing features characterized by podocyte hypertrophy and hyperplasia with intracytoplasmic protein resorption droplets and collapse of the underlying glomerular tuft (trichrome stain; original magnification, ×400). (B) A low-power electron microscopy image shows needle and rod-shaped highly electron-dense crystals within podocyte cytoplasm. Podocytes show marked foot-process effacement (original magnification, ×2,200). (C) A higher magnification electron microscopy image shows crystals with needle and rhomboid shapes, without substructure, within podocyte cytoplasm (original magnification, ×18,500). (D) Similar crystals were also observed in proximal and distal tubular cells. The figure depicts crystalline inclusions in proximal tubular cells. Proximal tubular cells also show protein reabsorption droplets (original magnification, ×2,900).

had IgGκ multiple myelomas and presented with nephrotic-range proteinuria and acute kidney injury.

Collapsing FSGS was first described in patients with HIV-associated nephropathy in African American patients. However, there has been increasing recognition of collapsing FSGS associated with patients with multiple myeloma treated with pamidronate,[7-9] which used to be widely prescribed for the treatment of multiple myeloma–associated hypercalcemia.[7-9] Interestingly, crystalloid podocytopathy causing collapsing FSGS in the absence of pamidronate, viral infection, or toxins has only been described by Akilesh et al[19] and our present case. This prompted us to consider that collapsing FSGS manifestations were caused by the paraproteinemia itself because no other causative factors were involved. Some studies have reported ultrastructural examination in favor of crystals coming from the urinary space after backflowing from the tubules because of proximal tubule obstruction by apoptotic epithelial cells.[13] Monoclonal proteins could be also endocytosed by podocytes and crystallize inside lysosomes, causing podocyte dysfunction due to accumulation of light chains. Relatedly, Eyre et al[28] quantified the capacity in vitro of podocytes to endocytose albumin and presumably other proteins. Monoclonal proteins are also considered to be processed in the same manner. Nevertheless, if any of these monoclonal proteins are resistant to proteolysis, this may result in crystal formation and subsequent accumulation within the podocyte, producing injury that leads to collapsing FSGS. Supporting this theory, membranous endocytic receptors of proximal tubular epithelial cells, such as megalin, cubilin, and C1C-5, that play a key role in the proximal tubular uptake of filtrated albumin and other low-molecular-weight proteins, have also been found in human podocytes.[29]

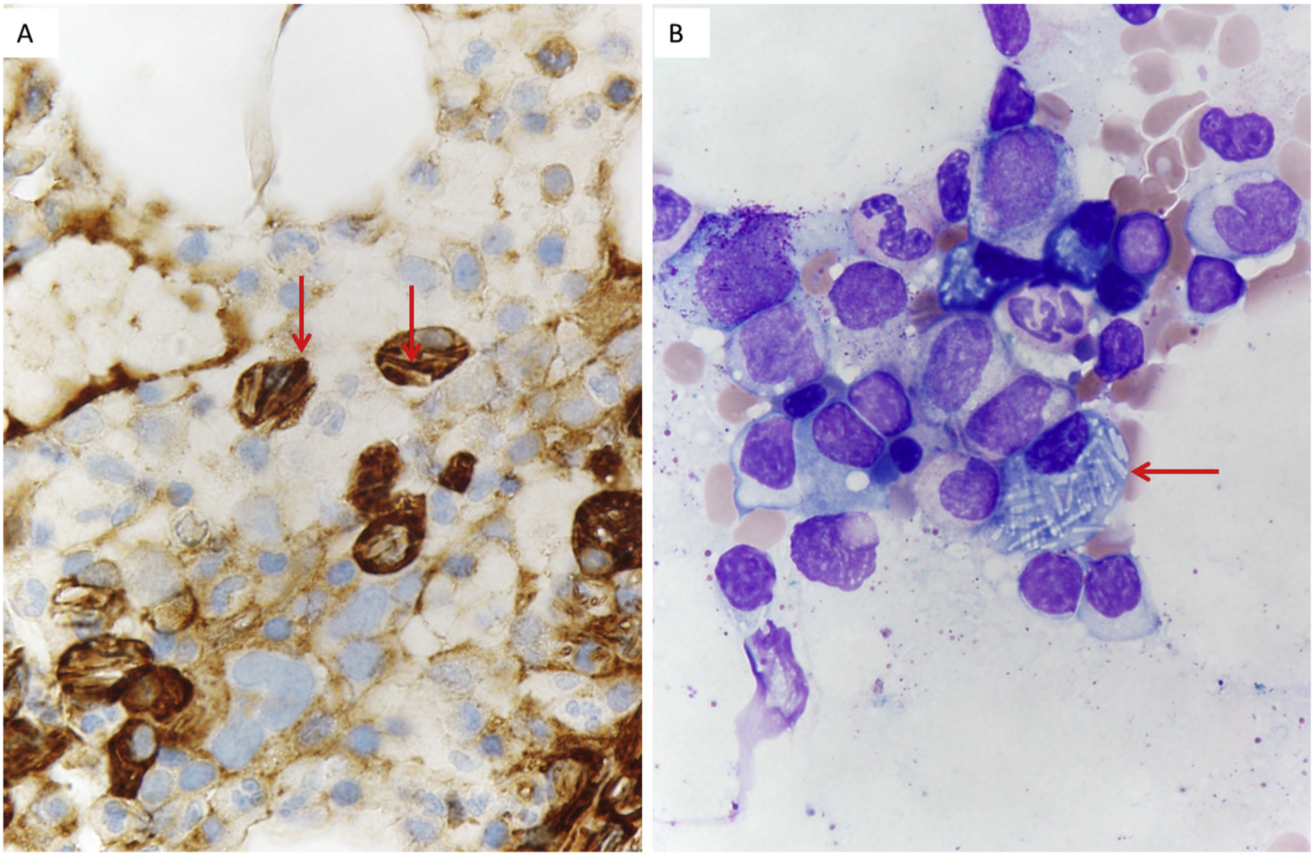

Figure 3. Bone marrow biopsy findings. (A) Plasma cells show intense cytoplasmic staining for κ immunohistochemical stain though crystals (red arrows) do not stain (original magnification, ×1,000). Plasma cells including the intracytoplasmic crystals were negative for λ (not shown). (B) On Giemsa stain of bone marrow smear, needle-shaped crystals (red arrow) were seen within plasma cells (original magnification, ×1,000).

Crystalloid podocytopathy is a rare cause of collapsing FSGS in the setting of MGRS. The present case illustrates the importance of ruling out a monoclonal gammopathy, including free LC quantification, as well as thorough EM examination of the kidney biopsy specimen, in evaluating patients with proteinuria and collapsing FSGS.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Main features of previously reported cases of crystalloid inclusions in podocytes associated with plasma cell dyscrasia.

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