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Pauci-immune Crescentic Glomerulonephritis Due to MGRS Crystalline Nephropathy

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INTRODUCTION

There are several known mechanisms by which monoclonal Igs (MIg) or their subunits can cause kidney disease: (i) deposition in 1 or more kidney compartments, resulting in distinct clinicopathologic lesions, such as Ig-related amyloidosis, monoclonal Ig deposition disease, and a variety of glomerulonephritides, including cryoglobulinemic glomerulonephritis type I and II, immunotactoid glomerulonephritis, and proliferative glomerulonephritis with monoclonal immunoglobulin deposits; (ii) precipitation in tubular lumina (e.g., myeloma cast nephropathy); (iii) activation of the alternative pathway of complement (e.g., C3 glomerulopathy associated with monoclonal gammopathy, thrombotic microangiopathy associated with monoclonal gammopathy); (iv) cytokine activation (e.g., POEMS syndrome); and (v) crystallization in the renal vasculature (e.g., crystalglobulin-induced nephropathy).[1,2] Here, we describe an unusual case of monoclonal gammopathy of renal significance (MGRS)–associated crystalline nephropathy that does not conform to any of the previously described patterns of kidney involvement by monoclonal gammopathy.

CASE PRESENTATION

A 59-year-old woman presented with severe anemia (hemoglobin 6.9 g/dl) and kidney injury (serum creatinine 3.06 mg/dl), which was up from 1.1 mg/dl 6 months before presentation. Past medical history included type 2 diabetes mellitus, essential hypertension, seropositive rheumatoid arthritis, and untreated IgG kappa monoclonal gammopathy diagnosed 13 months prior. Physical examination revealed mild peripheral edema; otherwise unrevealing.

Laboratory evaluation was notable for a proteinuria of 5.6 g/d, microscopic hematuria, a low serum albumin at 2.9 g/dl, and a hemoglobin A1C of 7.1%. Hepatitis B surface antigen, hepatitis C antibody, HIV antibody, antinuclear antibodies, anti-double-stranded DNA, anti-myeloperoxidase, anti-proteinase 3, and anti-glomerular basement membrane were all negative. Serum complement 3 was low and serum complement 4 was normal. Testing for serum cryoglobulin was positive (1%, type 1 cryoglobulin). Serum protein electrophoresis with immunofixation revealed a small IgG kappa MIg (0.32 g/dl). Serum free kappa and lambda light chains were elevated with a kappa:lambda ratio of 1.7. Renal sonography was negative for obstruction or masses. Computed tomography of chest, abdomen, and pelvis were negative for lymphadenopathy. Because of worsening kidney function and proteinuria, the patient was empirically treated with 3 days of pulse steroids and started on 60 mg of prednisone thereafter, and renal biopsy was performed.

Renal Biopsy Finding

Seventeen glomeruli were sampled for light microscopy, 5 of which were globally sclerotic. There was mild segmental mesangial sclerosis. Five glomeruli showed segmental cellular crescents, some of which were associated with fibrinoid necrosis with fibrin deposition and karyorrhexis (Figure 1a and b). Four glomeruli revealed large hypereosinophilic rod-shaped and irregular crystals within the urinary space and podocytes (Figure 1d), some of which were present in areas of fibrinoid necrosis and crescents (Supplementary Figure S1). Glomeruli

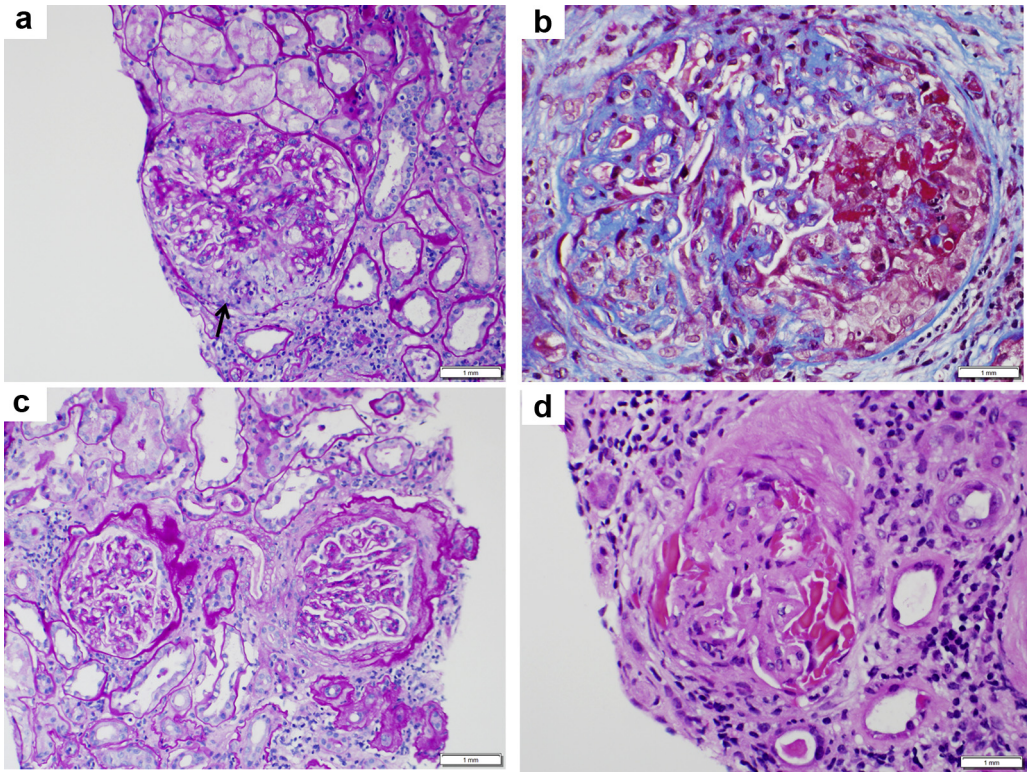

Figure 1. Light microscopic findings. (a) A glomerulus shows a segmental cellular crescent (arrow). The underlying glomerular tuft exhibits mild mesangial sclerosis (periodic acid–Schiff stain, original magnification ×200). (b) Another glomerulus shows a segmental cellular crescent with fibrinoid necrosis characterized by fibrin (dark red material) extravasation into the urinary space (trichrome stain, original magnification ×400). (c) Glomeruli without crescents or crystals do not show endocapillary hypercellularity or monocyte/macrophage infiltration (periodic acid–Schiff stain, original magnification ×100). (d) A glomerulus showing large hypereosinophilic crystals within the urinary space (hematoxylin and eosin, original magnification ×400).

without crescent formation did not show endocapillary hypercellularity or intracapillary infiltrating monocytes /macrophages, and no intracapillary pseudothrombi or crystals within the glomerular lumina were seen (Figure 1c). The glomerular basement membranes were mildly thickened with normal contour. There was moderate tubular atrophy and interstitial fibrosis with mild interstitial inflammation and acute tubular injury. One small interlobular artery showed luminal and intimal thrombosis and karyorrhexis, without arteritis or crystals. The remaining arteries were unremarkable.

On immunofluorescence, glomeruli were negative for IgA, C1q, and C3. There was linear diffuse glomerular and tubular basement membranes for albumin (3+) and IgG (1+), a common finding in diabetic nephropathy. Focal glomerular tuft staining for fibrinogen in areas of crescent formation was present. There was focal staining of protein resorption droplets within podocytes/urinary space for kappa with negative staining for lambda (Supplementary Figure S2). Staining for IgG, kappa, and lambda by immunofluorescence on pronase-digested, paraffin-embedded tissue and by the immunoperoxidase technique failed to stain the crystals.

On electron microscopy, some podocytes contained large intracytoplasmic rod-shaped electron-dense crystals (Figure 2a and b). On high power, the crystals showed a lamellated substructure characterized by parallel linear arrays (Figure 2c). No crystals were seen within mesangial, endothelial, or proximal tubular epithelial cells, or within glomerular or interstitial inflammatory cells or histiocytes. Podocytes showed segmental foot process effacement. Glomeruli also showed moderate global mesangial sclerosis and thickening of glomerular basement membranes, and were devoid of immune complex type granular electron-dense deposits, punctate deposits, or fibrillary deposits. The final clinicopathologic diagnosis was crescentic and necrotizing glomerulonephritis secondary to monoclonal gammopathy–associated crystalline nephropathy, concurrent with diffuse diabetic glomerulosclerosis and focal arterial thrombosis.

Follow-up

Bone marrow biopsy revealed 3 very small foci of kappa-restricted plasma cells, without evidence of crystals. The patient received 7 sessions of plasmapheresis for her crescentic glomerulonephritis but renal function failed to improve and hemodialysis was started for severe azotemia and uremic symptoms. She then received a dose of i.v. 500 mg of cyclophosphamide and was started on Bortezomib 1.3 mg/m^2 therapy with

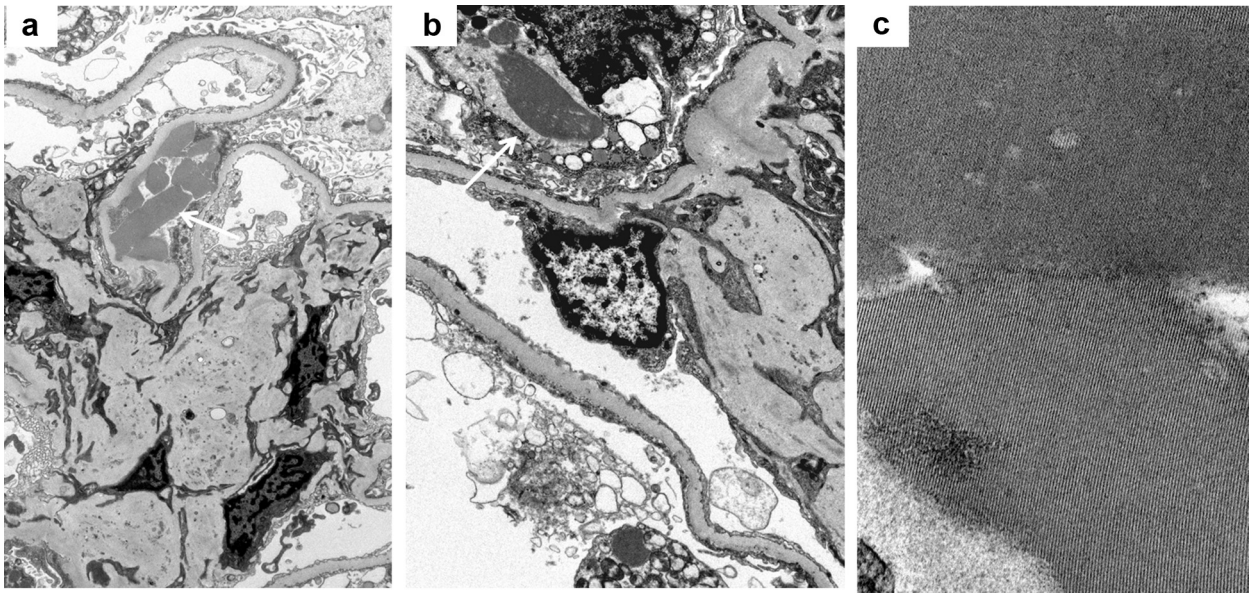

Figure 2. Electron microscopic findings. (a,b) Electron-dense crystals are seen within podocytes (arrows). The underlying glomerular tuft shows features of diabetic nephropathy with mesangial sclerosis and thickening of the glomerular basement membranes (original magnification ×6000 for a, b). On high power, the crystals show a lamellated substructure characterized by parallel linear arrays (original magnification ×80,000).

plan to continue therapy on a schedule of 2.2 mg on days 1, 8, and 15 of each 28-day cycle for 6 cycles. The patient developed palpable rash coinciding with an increase in cryocrit to 5%. She completed 3 cycles of therapy with Bortezomib. Her renal function gradually improved and was eventually taken off from hemodialysis after 4 months. Repeat urine studies showed proteinuria of 5.3 g/d, serum creatinine of 3.2 mg/dl with estimated creatinine clearance of 17 ml/min. Repeat cryocrit was 1% and skin rash also resolved.

DISCUSSION

MGRS is a recently described term that refers to clonal proliferative disorders that produce nephrotoxic MIg but do not meet hematological criteria for specific treatment.[1,3] MGRS renal lesions associated with MIg deposition are divided into 3 large categories based on their ultrastructural appearance: lesions with granular deposits (e.g., monoclonal Ig deposition disease, proliferative glomerulonephritis with monoclonal Ig deposits); lesions with fibrillary or microtubular deposits (e.g., AL amyloidosis, cryoglobulinemic glomerulonephritis types I and II, immunotactoid glomerulopathy), and lesions with crystalline deposits or inclusions.[1] MGRS lesions with crystalline deposits can be separated into 2 categories based on whether the crystals are intracellular or extracellular/intravascular. Lesions with intracellular crystals include light chain proximal tubulopathy with crystals "light chain Fanconi syndrome" in which the crystals are located within proximal tubular cytoplasm, and crystal-storing histiocytosis characterized by crystalline light chain inclusions within interstitial histiocytes and occasionally in tubular cells, glomerular cells, and other organs, particularly the bone marrow.[4,5] Very rarely, few needle-shaped crystals are seen in the cytoplasm of intracapillary infiltrating macrophages or endothelial cells in otherwise typical pathologic features of cryoglobulinemic glomerulonephritis. Paraprotein-induced crystalline nephropathies with predominantly extracellular crystals are exemplified by crystalglobulin-induced nephropathy associated with crystalglobulinemia and crystalcryoglobulinemia that is characterized by large extracellular crystals within the lumen of arterioles, arteries, and/or glomerular capillaries with or without secondary vascular thrombosis.[6]

Podocyte crystals associated with plasma cell dyscrasia have only rarely been described in the literature, typically in association with crystals within proximal tubular cells and interstitial histiocytes in the setting of crystal-storing histiocytosis.[7–9] Patients who typically have IgG kappa monoclonal gammopathy (MGRS or symptomatic multiple myeloma), present with proteinuria with or without renal insufficiency, and light microscopy may show focal segmental glomerulosclerosis.[7–S1] However, 2 cases of IgG kappa MIg-associated isolated crystalline podocytopathy (i.e., without crystals in other renal cells or histiocytes) have been recently reported, one of which was associated with focal segmental glomerulosclerosis.[S2,S3] To our knowledge, our case is the first case of monoclonal gammopathy–associated crystalline podocytopathy associated with crescentic and necrotizing glomerulonephritis. In this patient, large crystals were seen in

podocytes and the urinary space, which on ultrastructural examination showed a lamellated substructure consistent with MIg crystals.[6,S2] The crystals focally were present in areas of crescents and fibrinoid necrosis, suggesting that extravasation of large amount of light chain crystals from podocyte into the urinary space may have caused endothelial injury triggering an in situ severe inflammatory reaction leading to crescentic and necrotizing glomerulonephritis. In the case reported by Yang *et al*. podocyte crystals protruded into the urinary space and formed cilia-like membrane spikes on the cell surface supporting that the light chain crystals in the urinary space were coming from podocytes.[S2] In our patient, it is possible that the circulating MIg kappa light chains have passed through the glomerular basement membrane, entered the podocyte cytoplasm through endocytosis (supported by staining of podocyte protein droplets for kappa light chain by immunofluorescence) and then crystallized inside their lysosomes. The absence of crystals within proximal tubular cells or tubular lumina argues against the possibility that podocyte crystals originated from the urinary space after backflowing from the tubules (Table 1). No crystals were seen within vessels or glomerular capillaries, arguing against crystal cryoglobulinemia-associated crystalglobulin-induced nephropathy, although focal arterial thrombosis was seen, which could be secondary to adjacent unsampled intravascular crystals. The patient had cryoglobulinemia with a skin rash, but the biopsy findings were not consistent with this diagnosis considering the absence of endocapillary hypercellularity, intracapillary infiltrating monocytes, membranoproliferative features, or mesangial, subendothelial, or intraluminal deposits.

Notably, the glomerular crystals did not stain for kappa or lambda light chains by immunofluorescence on frozen tissue, by immunofluorescence on pronase-digested paraffin tissue, or by the immunoperoxidase method, as has been described in a minority of cases of crystalline light chain proximal tubulopathy[5] and crystal-storing histiocytosis including cases with podocyte involvment.[4,8] This could be due their highly organized structure that potentially prevents the antibodies from reaching their target epitopes. It is also possible that the crystals contain only fragments of the variable domain of MIg, as reported in crystal-storing histiocytosis,[4] leading to false-negative results with the commercially available anti-Ig light chains that are directed against epitopes in the constant domains. Protein droplets within podocytes/urinary space in our patient stained positive for kappa with negative lambda by immunofluorescence, similar to the circuiting paraprotein light chain isotype, favoring that the crystals are likely composed of kappa light chain.

Table 1. Teaching points

- There are several mechanisms by which monoclonal Igs cause renal injury, the pattern of which depends on the location of deposits in the kidney.
- Crystalline podocytopathy associated with plasma cell disorders is characterized by crystal deposition within the podocytes.
- Crystalline deposits can exhibit FSGS or a necrotizing crescentic pattern.
- The crystalline variant of pauci-immune crescentic GN is thought to be due to an inflammatory response triggered by the crystalline paraproteins extruding from podocytes.
- The monoclonal crystals may lack IF staining due to the highly organized structure of monoclonal crystals.

FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IF, immunofluorescence.

The principle of management of MGRS relies on identifying the underlying clonal cell and targeting therapy against the clone responsible for renal injury.[1] The treatment involves chemotherapeutic agents targeting plasma cell clone including Bortezomib in addition to steroid and cyclophosphamide (CyBorD), whereas rituximab is the preferred treatment against B-cell clones.[S4] Because their rarity, there has not been a standard treatment for paraprotein-related crystalline nephropathies, but clone-targeted therapy similar to other MGRS lesions is a logical approach. In our patient with a nephritogenic monoclonal plasma cell clone who presented with rapidly progressive glomerulonephritis, Bortezomib-based therapy led to improvement of kidney function with discontinuation of dialysis, but 3 months through therapy she continued to have proteinuria, which could be secondary to irreversible glomerular scars/fibrous crescents following the active crescentic glomerulonephritis and/or resulted from the concurrent diabetic nephropathy. The role of plasmapheresis is unclear in this condition, but might be more important in patients with high tumor burden to decrease the level of circulating MIg light chains. Our patient received plasmapheresis because of the crescentic phenotype, the rapid decline in renal function, and the circulating cryoglobulin.

CONCLUSIONS

This case describes an unusual presentation of paraprotein-related renal injury, with podocyte crystalline deposits and associated pauci-immune crescentic glomerulonephritis. Thus, MGRS-associated crystalline podocytopathy should be included in the differential diagnosis of antineutrophil cytoplasmic antibody–negative pauci-immune crescentic and necrotizing glomerulonephritis. The diagnosis of this lesion requires careful clinicopathologic correlation and ultrastructural examination of kidney biopsy, and treatment should be directed at the underling hematologic condition. Further research is needed to investigate the pathomechanisms of this rare lesion.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. A glomerulus with cellular crescent formation, fibrinoid necrosis (irregular dark red material), and karyorrhexis. Within the crescent, large bright red crystals (arrows) are seen (original magnification ×600).

Figure S2. Protein resorption droplets within podocytes and Bowman's space stain positive for kappa light chain with negative staining for lambda light chain (same glomerulus in both panels, immunofluorescence images, original magnification ×400).

Supplementary References.

REFERENCES

1. Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol*. 2019;15:45–59.
2. Leung N, Drosou ME, Nasr SH. Dysproteinemias and glomerular disease. *Clin J Am Soc Nephrol*. 2018;13:128–139.
3. Leung N, Bridoux F, Hutchison CA, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. *Blood*. 2012;120:4292–4295.
4. Kanagal-Shamanna R, Xu-Monette ZY, Miranda RN, et al. Crystal-storing histiocytosis: a clinicopathological study of 13 cases. *Histopathology*. 2016;68:482–491.
5. Stokes MB, Valeri AM, Herlitz L, et al. Light chain proximal tubulopathy: clinical and pathologic characteristics in the modern treatment era. *J Am Soc Nephrol*. 2016;27:1555–1565.
6. Gupta V, El Ters M, Kashani K, et al. Crystalglobulin-induced nephropathy. *J Am Soc Nephrol*. 2015;26:525–529.
7. Boudhabhay I, Titah C, Talbot A, et al. Multiple myeloma with crystal-storing histiocytosis, crystalline podocytopathy, and light chain proximal tubulopathy, revealed by retinal abnormalities: a case report. *Medicine (Baltimore)*. 2018;97:e13638.
8. Ito K, Hara S, Yamada K, et al. A case report of crystalline light chain inclusion-associated kidney disease affecting podocytes but without Fanconi syndrome: a clonal analysis of pathological monoclonal light chain. *Medicine (Baltimore)*. 2019;98:e13915.
9. Nasr SH, Preddie DC, Markowitz GS, et al. Multiple myeloma, nephrotic syndrome and crystalloid inclusions in podocytes. *Kidney Int*. 2006;69:616–620.