Kidney Medicine

Crystalglobulin-Associated Kidney Disease: A Case Report and Literature Review

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The kidney is commonly involved in multiple myeloma and other disorders producing monoclonal immunoglobulins. Crystalglobulinemia is a rare condition characterized by spontaneous crystallization and deposition of monoclonal immunoglobulins within the microvasculature of the kidney and other organs, leading to inflammation, ischemia, and end-organ damage. The present case and literature review highlight the clinical spectrum, diagnostic challenges, management, and outcomes of this underrecognized complication of monoclonal gammopathy. Crystalglobulin-associated kidney disease should be suspected in patients with rapidly progressive kidney disease associated with hematuria, proteinuria, extrarenal lesions (ie, skin and joints), and monoclonal gammopathy. Kidney biopsy is critical to the diagnosis, which relies on the identification by ultrastructural analysis of electron-dense crystalline structures composed of a monoclonal immunoglobulin within the kidney microvasculature. Conventional immunofluorescence on frozen tissue frequently fails to detect monoclonal protein deposits, and pronase-based antigen retrieval on paraffin-embedded material or immunoelectron microscopy is required to unmask antigenic epitopes located within crystalline inclusions. Early intervention combining treatment of clonal cell proliferation and plasma exchanges is warranted to reduce the burden of this rare but dramatic complication of monoclonal gammopathy.

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INTRODUCTION

Monoclonal gammopathy has emerged as an important cause of kidney injury.[1] Monoclonal immunoglobulins can cause kidney damage through various mechanisms that can be separated by the presence of a high or low tumor burden. Light-chain cast nephropathy represents the prototype of kidney injury from a high tumor burden and is characterized by intratubular obstruction from complexes of monoclonal light chains and uromodulin. Kidney disease due to monoclonal gammopathy with a low tumor burden can result either from organized (eg, amyloidosis, cryoglobulinemic glomerulonephritis, crystallopathies) or nonorganized (eg, monoclonal immunoglobulin deposition disease, proliferative glomerulonephritis with monoclonal IgG deposits) deposits of monoclonal immunoglobulins or from interference and dysregulation of the complement alternative pathway (eg, C3 glomerulopathy).[1] Early recognition of kidney disease caused by monoclonal gammopathy is crucial, as the suppression of monoclonal immunoglobulin production by clone-directed therapy is associated with better outcomes.[1]

Crystalglobulinemia is a rare complication of monoclonal gammopathy defined as the crystallization and deposition of monoclonal immunoglobulins in various tissues, including the kidneys, causing end-organ damage.[2] Prompt diagnosis of this clinical entity is challenging and requires a thorough multidisciplinary work-up by nephrologists, hematologists, and pathologists to ensure optimal clinical care. Here, we describe the presentation, treatment, and outcome of a patient with crystalglobulin-associated kidney disease and review reported cases of this underrecognized condition.

CASE REPORT

A previously healthy White woman in her 60s was referred for rapidly progressive kidney disease associated with purpura, skin necrosis, and joint pain. Physical examination showed high blood pressure, lower limb edema, purpuric rash, and necrotic skin ulcerations, which had developed over a 3-week period before admission (Fig 1A and B). Laboratory tests showed a recent-onset increase in the serum creatinine level (5.3 mg/dL vs 0.9 mg/dL 12 months earlier, corresponding to a baseline CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] estimated glomerular filtration rate of 66 mL/min per 1.73 m^2) and low serum C3 (27 mg/dL; normal, 90-180 mg/dL) and C4 (3 mg/dL; normal, 10-40 mg/dL) levels. The complete blood cell count, lactate dehydrogenase levels, and calcium levels were normal. The findings of autoimmune and viral serologic testing were negative. Urinalysis showed microscopic hematuria and nephrotic range proteinuria (5.3 g/d), mainly composed of albumin (95%) and a small, not quantified, amount of monoclonal κ light chain.

Serum protein electrophoresis detected a monoclonal immunoglobulin (29.9 g/L), identified as IgGκ on immunofixation. The ratio of serum free light chain (FLC) κ to λ was increased, at 11.93 (normal range for kidney disease, 0.37-3.10); the FLC κ level was 658 mg/L, and the difference between involved and noninvolved FLC values was 603. Serum testing showed a type I IgGκ cryoglobulin (cryocrit of 0.29 mg/mL). A bone marrow biopsy identified 11% of monotypic (κ-restricted) plasma cells. There was no evidence of lytic bone lesion on a skeletal survey, and kidney ultrasound was unremarkable.

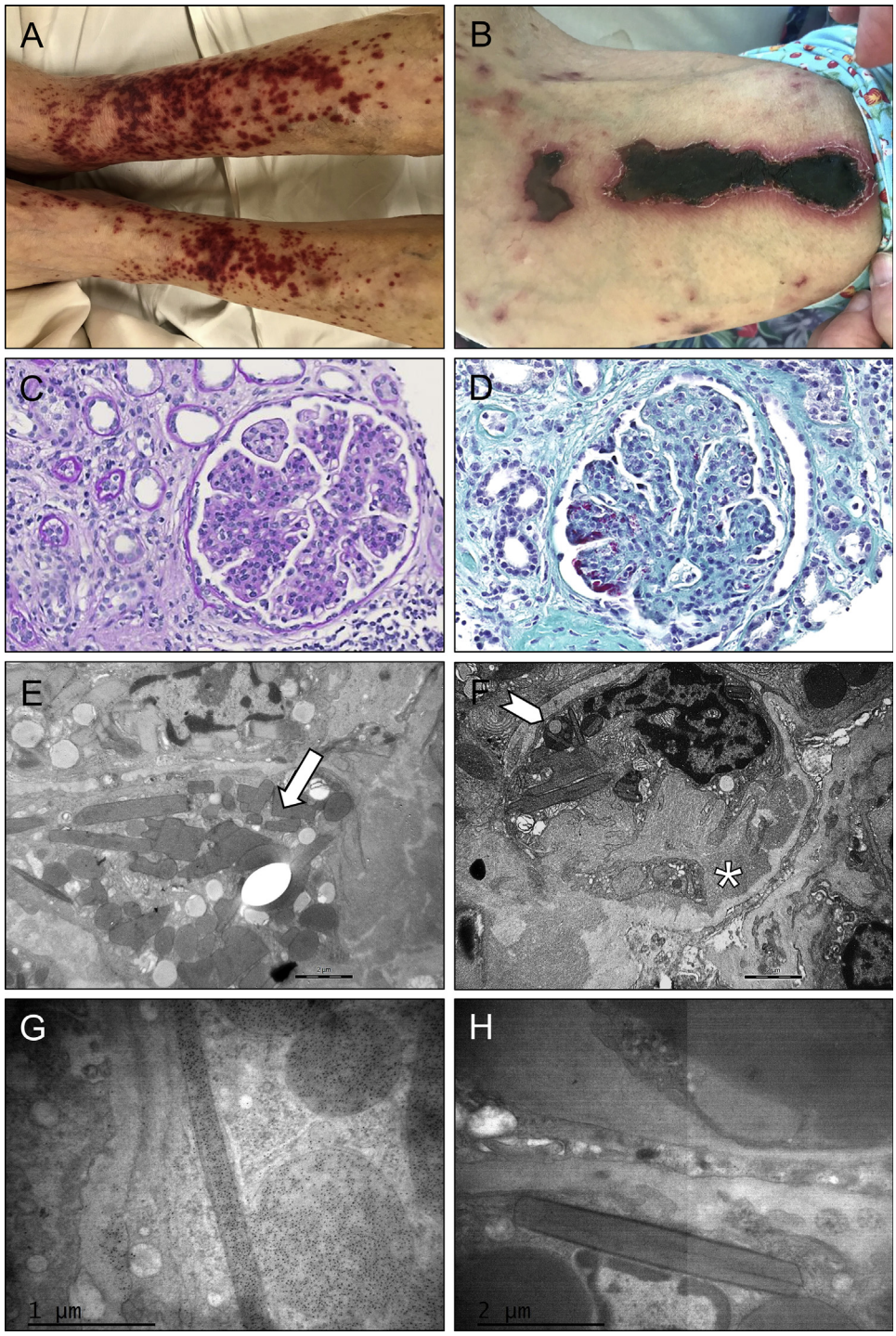

Figure 1. (A and B) Nonblanchable purpura of the lower extremities (A) with skin necrosis (B). (C and D) Representative images of light microscopy on the kidney biopsy showing lobular appearance of glomeruli, with global endocapillary hypercellularity, mesangial expansion and proliferation, and double contours of the glomerular basement membrane, compatible with a membranoproliferative pattern of injury (C), and focally eosinophilic precipitates in capillary walls (D) (periodic acid–Schiff stain: original magnification, ×240; or Masson trichrome stain: original magnification, ×340). (E and F) Representative images of transmission electron microscopy showing intracytoplasmic (arrow) and intralysosomal (arrowhead) crystalloid inclusions, as well as subendothelial cryoglobulin deposits along the lamina rara interna (asterisk; original magnification, ×3,000).(G and H) Representative images of immunogold electron microscopy using anti-κ (G) and anti-λ (H) antibodies showing κ staining of intracellular crystals, lysosomes, and subendothelial microtubular deposits. Scale bar 1 µm (G) and 2 µm (H).

Table 1. Characteristics of Patients With Crystalglobulin-Associated Nephropathy

		Baseline Characteristics				Extrarenal Manifestations			Hematologic Disorder		Treatment			Outcome		
Pt	Ref	Sex	Age, y	sCreat, mg/dL	Dialysis	Any	Skin	Joints	MIg	Disease	Chemotherapy	Steroids Alone	Plasma Exchange	FU, mo	Death	Kidney Failure
1	3	M	52	14.7	+	-	-	-	IgGλ	MM	-	-	-	0.1	+	+
2	3	M	58	22.2	+	+	-	-	IgDλ	MM	Mel	-	+	1.7	+	+
3	4	M	82	4.3	+	+	+	+	FLCλ	MM	-	+	-	0.5	+	+
4	4	F	34	8.4	+	+	+	+	FLCλ	MM	Cy	-	+	0.6	+	+
5	5	M	51	4.1	+	+	+	+	IgGκ	MGRS	-	+	-	41	-	+
6	6	M	44	17.3	+	+	+	-	IgGκ	MGRS	BorD	-	+	12	-	+
7	2	F	61	5.2	+	+	+	-	IgGκ	MGRS	CyBorD	-	+	7	-	-
8	7	M	53	2.4	+	+	+	-	IgGκ	MGRS	Bor/Cy	-	+	19	+	+
9	8	M	44	6.3	+	+	+	-	IgGκ	MGRS	Unknown	-	+	15	+	+
10	9	M	56	5.4	-	+	-	+	IgGλ	MGRS	CyBorD	-	+	12	-	-
11	10	M	50	8.1	+	+	+	+	IgGκ	MGRS	Bor	-	+	NA	-	-
12	11	F	61	3.8	-	-	-	-	IgAλ	MGRS	CyBorD	-	+	NA	-	-
13	12	F	49	3.7	-	-	-	-	IgGκ	MGRS	CyBorD	-	+	9	-	-
14	13	F	74	4.2	+	+	+	+	IgGκ	MGRS	CyBorD	-	+	32	-	-
15	14	F	65	4.3	+	-	-	-	IgMκ	MGRS	-	+	-	2	-	+
16	15	F	40	4.4	+	+	+	-	IgGκ	MGRS	BorD/PD	-	+	180	-	+
17	16	M	63	4.1	+	+	-	+	IgAκ	MGRS	-	-	-	NA	-	+
18	17	F	66	5.9	+	+	+	-	IgGκ	MGRS	BorD	-	+	48	-	-
19	18	F	70	1.8	-	-	-	-	IgAκ	MM	CyBorD	-	+	6	-	-
20	Present	F	69	5.3	+	+	+	+	IgGκ	MGRS	CyBorD/LBorD	-	+	18	-	+

Abbreviations: Bor, bortezomib; Cy, cyclophosphamide; D, dexamethasone; F, female; FLC, free light chain; FU, follow-up; L, lenalidomide; M, male; Mel, melphalan; MGRS, monoclonal gammopathy of renal significance; MIg, monoclonal immunoglobulin; MM, multiple myeloma; NA, not available; P, pomalidomide; Pt, patient; Ref, reference; sCreat, serum creatinine.

A kidney biopsy was performed. Light microscopy showed 25 glomeruli, of which 5 were globally sclerotic, whereas the remaining glomeruli showed a membranoproliferative pattern of injury and the presence of inert, fuchsinophilic material occluding the lumen of capillaries (Fig 1C and D). There were no fibrin thrombi, and Congo red staining was negative. The interstitial fibrosis and tubular atrophy score was 3 (>50%). Immunofluorescence studies on frozen sections were negative for immunoglobulins, complement fractions, and FLC. Immunofluorescence on pronase-digested paraffin sections was attempted; however, no glomerulus was present in the available residual material. An ultrastructural analysis showed abundant rhomboid-shaped crystalline structures within the cytoplasm and phagolysosomes of glomerular endocapillary cells (Fig 1E and F) and organized microtubular subendothelial deposits and thrombi. On immunoelectron microscopy, intracytoplasmic crystals and organized microtubular structures were stained with the anti-κ but not anti-λ gold conjugate (Fig 1G and H). These pathognomonic features established the diagnosis of crystalglobulin-associated kidney disease.

The patient started receiving hemodialysis. She was treated with plasma exchange and clone-targeted chemotherapy combining cyclophosphamide, bortezomib, and dexamethasone. Second-line treatment with lenalidomide, bortezomib, and dexamethasone was required to achieve a partial hematologic response. Attempts to interrupt plasma exchanges were followed by the recurrence of skin lesions. Twenty-eight months after the diagnosis, the serum FLC ratio had decreased to 3.32, the serum FLC κ level had decreased to 182 mg/L, and the difference between FLC values had decreased to 20. However, the patient remained dependent on dialysis.

LITERATURE REVIEW

We screened PubMed for English-language reports and included all cases presenting with kidney disease and pathologic evidence of crystal deposition within the kidney vasculature reported between 1985 and 2021.

Table 1 summarizes the clinical presentation, treatment, and outcomes in 20 patients, including ours.[2-18] The mean age at diagnosis was 56 years (range, 34-82 years). Patients presented with a mean serum creatinine level of 6.7 mg/dL (590 μmol/L), and dialysis was required in 16 (80%) patients. Urinalysis (reported in 11 of the 14 nonanuric patients) typically showed microhematuria (8 of 11 cases; 73%) and proteinuria (11 of 11 cases; 100%), sometimes of nephrotic range (6 of 10 cases; 60%). Extrarenal involvement symptoms were common (15 of 20 cases; 75%), mainly involving the skin (12 of 20 cases; 60%) and/or joints (8 of 20 cases; 40%). Other extrarenal lesions were also reported, including those in peripheral nerves, brain, eyes, gastrointestinal tract, and cardiovascular system.

Symptomatic multiple myeloma and monoclonal gammopathy of renal significance were identified in 5 (25%) and 15 (75%) cases, respectively.[1] Among monoclonal gammopathy of renal significance cases, the nature of the clone could be identified in 13 cases, including plasma cell and a B-cell clone in 10 and 3 cases, respectively. The monoclonal immunoglobulin was IgGκ in most patients (11 of 20; 55%). Type 1 cryoglobulinemia was detected in the serum in 3 of 20 cases (15%).

After a mean follow-up of 23.7 months, 12 (60%) patients had progressed to kidney failure and 4 (20%) could be weaned from dialysis. The use of clone-directed therapy was associated with a reduced incidence of kidney failure (7 of 15 [47%] vs 5 of 5 [100%] cases in patients treated with or without clone-directed therapy, respectively; $P = 0.05$). Six patients (30%) died during follow-up; kidney failure (n=4), cardiovascular complications (n=3), and/or sepsis (n=1) were identified as the causes of death.

DISCUSSION

Our case description and literature review highlight the clinical spectrum, diagnostic challenges, management, and outcomes of crystalglobulin-associated kidney disease, a rare and underrecognized complication of monoclonal gammopathy. The disease typically presents as a severe and rapidly progressive kidney disease with hematuria and proteinuria. Extrarenal manifestations are common and primarily involve the skin and joints. The differential diagnoses include systemic vasculitis, connective tissue disorders, antiphospholipid syndrome, and conditions such as infective endocarditis or cholesterol crystal emboli. The identification of a circulating monoclonal protein, mostly IgG, should raise the suspicion of crystalglobulin-associated kidney disease.

A kidney biopsy is critical for the diagnosis, and pathologic features include glomerular proliferation and the presence of inert, hematoxylin-eosin and trichrome–positive, periodic acid–Schiff–negative (or weakly positive) material. Conventional immunofluorescence on frozen tissue fails to detect monoclonal protein deposits in approximately 40% of cases. The use of pronase-based antigen retrieval on paraffin-embedded material and immunoelectron microscopy is helpful to unmask antigenic epitopes located within crystalline inclusions.[19,20] The final diagnosis relies on the identification by ultrastructural analysis of electron-dense crystalline structures composed of a monoclonal immunoglobulin within the kidney microvasculature.

Crystalglobulinemia results from symptomatic multiple myeloma or monoclonal gammopathy of renal significance, identified in 25% and 75% of cases, respectively. Monoclonal gammopathy of renal significance is associated with a low tumor burden and plasma levels of monoclonal immunoglobulins and does not meet the criteria for neoplastic disease per se.[1] However, because of their peculiar properties, secreted monoclonal proteins directly cause kidney damage. In crystalglobulin-induced kidney

disease, crystallization of monoclonal protein likely occurs due to Fc-Fc interactions of monoclonal immunoglobulin, possibly owing to abnormal glycosylation of the light-chain portion or through interactions with albumin.[2] The term cryocrystaglobulinemia refers to the minority of cases associated with a monoclonal protein that also has detectable cryoglobulin activity in plasma and kidney biopsy, as in our patient. However, considering the lack of sensitivity of the techniques used for serum cryoglobulin testing, it may be difficult to distinguish between these 2 conditions.

Treatment should be guided by the nature of the clone that produces the nephrotoxic monoclonal immunoglobulin. In this retrospective historical series, 60% of the patients required maintenance dialysis, and the use of chemotherapy was associated with a reduced incidence of kidney failure. As in other types of monoclonal immunoglobulin–associated kidney lesions, achieving the best hematologic response is the goal of therapy, to preserve long-term kidney and patient outcomes.[21] Although the role of plasma exchange is not established, it can be helpful to treat or prevent end-organ ischemic damage while awaiting hematologic remission.

In conclusion, crystalglobulin-associated kidney disease should be suspected in patients with rapidly progressive kidney disease, monoclonal gammopathy, and skin lesions. A thorough evaluation of kidney biopsy is crucial for an accurate diagnosis. Early intervention combining treatment of clonal cell proliferation and plasma exchanges is warranted to reduce the burden of this rare but dramatic complication of monoclonal gammopathy.

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