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Crystalglobulin-Induced Nephropathy: Unusual Presentation in a Patient With Seronegative Rheumatoid Arthritis and Leukocytoclastic Vasculitis

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INTRODUCTION

Monoclonal gammopathy of renal significance (MGRS) refers to clonal proliferative disorders that produce nephrotoxic monoclonal Ig, but do not meet hematological criteria for specific treatment.[1] Thus, MGRS includes hematologic conditions, such as monoclonal gammopathy of unknown significance, smoldering myeloma, smoldering Waldenström macroglobulinemia, stage 1 and 2 chronic lymphocytic leukemia, and low-grade lymphoma, if they cause kidney disease by the secreted monoclonal Ig but do not meet hematologic criteria for treatment based on their clonal characteristics alone.[2] Clonality and plasmacytosis in bone marrow is not prominent and is usually less than 10%. Pathological findings in such entities range from amyloidosis to much rarer forms, such as crystalglobulin-induced nephropathy. It is important to identify these conditions because they carry significant renal morbidity if not treated. Here in this report, a case of crystalglobulinemia and crystalglobulin-induced nephropathy is presented in association with seronegative rheumatoid arthritis and leukocytoclastic vasculitis.

CASE PRESENTATION

A middle-aged man with past medical history of seronegative rheumatoid arthritis presented to the emergency department with a painful rash in the extremities. Previously he was given sulfasalazine for 6 months to treat rheumatoid arthritis. He did not have any response to this therapy and methotrexate was discontinued after 2 months given liver dysfunction. A first dose of etanercept was given 10 days before admission. He developed a painful rash on his legs 7 days before admission that then progressed to involve his arms (Figure 1). He saw dermatology 2 days before admission. A biopsy of the rash was performed that showed leukocytoclastic small vessel vasculitis with intravascular thrombosis, and he was started on prednisone 20 mg per day.

On presentation, vital signs were as follows: blood pressure 158/86, pulse 70, temperature 96.7 °F (35.9 °C), respiration 16. On examination, there was extensive purpuric painful rash on the lower extremities up to the thighs and right buttock area. Bilateral upper extremities had ecchymotic nonblanching lesions that were tender to touch. Laboratory evaluation showed initial creatinine of 1.2 mg/dl with blood urea nitrogen of 31. White blood cell count was 2.7k and platelets were 137k.

Creatinine rapidly progressed to 8.1 mg/dl and blood urea nitrogen of 141 in 5 days. Platelets went down to a low of 71k before improving with treatment and later normalized by day 5 (Table 1). Other results showed unremarkable renal imaging except increased cortical echogenicity. No albuminuria, hematuria, or pyuria was noted on urinalysis. Urine protein-creatinine ratio was 0.8 g/g. Serum protein electrophoresis revealed monoclonal protein. Skin biopsy showed leukocytoclastic small vessel vasculitis.

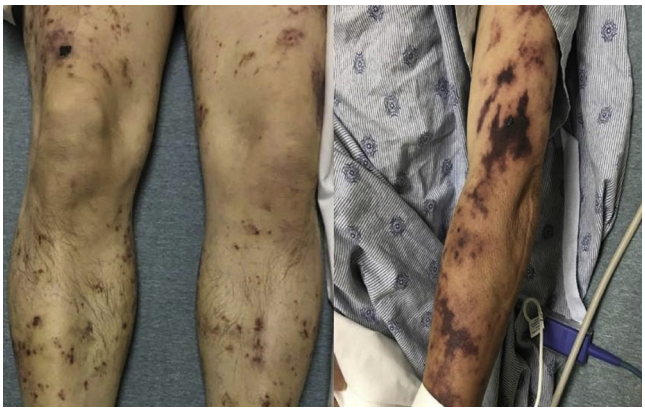

Figure 1. Leukocytoclastic small vessel vasculitis of skin.

Haptoglobin was normal. Serum free light chain assay showed mildly elevated kappa chains with normal kappa-lambda ratio (1.3). Serum immunofixation showed IgG kappa monoclonal paraprotein (M protein 0.7 g/dl). Computed tomography of chest/abdomen/pelvis showed no mass or lymphadenopathy. Skeletal survey was negative. Peripheral smear showed hypochromic red blood cells. Platelets were decreased in number. Granulocytes were increased and showed no significant dysplastic features. Lymphocytes were predominantly small and mature-appearing with occasional activated forms. No suspicious lymphoid or blast population was identified. No significant schistocytosis was noted. Bone marrow biopsy showed normocellular marrow with trilineage hematopoiesis. No evidence of lymphoma or myeloma or plasma cell disorder. No amyloidosis was found. Flow studies showed no definitive immunophenotypic evidence of myeloid neoplasia, lymphoproliferative disorder, or plasma cell dyscrasia. Fluorescence *in situ* hybridization studies were normal. No clonal chromosome abnormality was noted on cytogenetics. Skin biopsy revealed leukocytoclastic small vessel vasculitis with intravascular thrombosis.

Kidney Biopsy

Most glomeruli on light microscopy showed numerous large intraluminal thrombi that stained hypereosinophilic on hematoxylin-eosin, and were negative for periodic acid–Schiff and silver (Figure 2a). When the hematoxylin-eosin slides were viewed with the condenser down, some of these thrombi showed packed needle-shaped crystals (Figure 2a). Some of the deposits were admixed with fibrin. Glomerular basement membranes were normal in thickness or contour. No crescents or necrotizing lesions. Tubules focally exhibited acute injury, and there was mild tubular atrophy and interstitial fibrosis involving approximately 10% of the cortex sampled, accompanied by mild interstitial inflammation. Many arterioles, including glomerular hilar arterioles, showed luminal occlusion by similar deposits/crystals (Figure 2b).

Table 1. Key laboratory studies

Assay	Values	Reference range
Hemoglobin, g/dl	12.4	13.1–17.2
White blood cell count, k/μl	2.7	4–11
Platelet count, k/μl	137	140–440
Blood urea nitrogen, mg/dl	31 (day of admission) 141 (5 days postadmission)	6–22
Serum creatinine, mg/dl	1.2 (day of admission) 8.1 (5 days postadmission)	0.5–1.2
SPEP, IFE	Monoclonal IgG kappa near gamma region. M protein measures 0.7 g/dl	NA
UPEP, IFE	Faint monoclonal IgG kappa in late gamma region	NA
HIV, HBV PCR, HCV RNA PCR	Negative	NA
C3, mg/dl	51	83–177 mg/dl
C4, mg/dl	9	10–40 mg/dl
ANA, units	Negative	NA
PR3-ANCA, units	<3.5	0–3.5 U/ml
MPO-ANCA, units	<9	0–9 U/ml
Anti-GBM, units	3	0–20 units
Cardiolipin IgA/IgM/IgG	<9	0–9 U/ml
Beta 2 Glycoprotein IgA/IgM/IgG		
CANCA and PANCA		
<9	0–9 U/ml	
<1:20	<1:20 titers	
Cryoglobulins	Negative	NA
Cryofibrinogen	Negative	NA

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CANCA, cytoplasmic antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; HBV, hepatitis B virus; HCV, hepatitis C; HIV, human immunodeficiency virus; IFE, immunofixation electrophoresis; MPO, myeloperoxidase; NA, not applicable; PANCA, perinuclear antineutrophil cytoplasmic antibody; PCR, polymerase chain reaction; PR3, proteinase 3; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis. Note: Conversion factors for units: serum creatinine in mg/dl to μmol/l, ×88.4; serum urea nitrogen in mg/dl to mmol/l, ×0.35

On immunofluorescence, the glomerular thrombi/crystals and some arteriolar thrombi stained 3+ for IgG, kappa (Figure 2f), and IgG1 (Figure 2e) with negative staining for lambda, IgG2, IgG3, IgG4, IgM, IgA, and C3. Some of the vascular thrombi/crystals also stained 3+ for fibrinogen.

On electron microscopy, glomerular capillaries were extended by highly electron-dense thrombi composed of packed crystals that ranged from needle to rod shapes and from short to very long (Figure 2c). On high magnification, some of the crystals were composed of linear microtubular substructures (Figure 2d).

Similar crystals/deposits were focally seen in the subendothelial zone and mesangium. Glomerular basement membranes were normal in thickness and contour. Podocytes showed mild foot process effacement.

The final diagnosis was crystalglobulin-induced nephropathy.

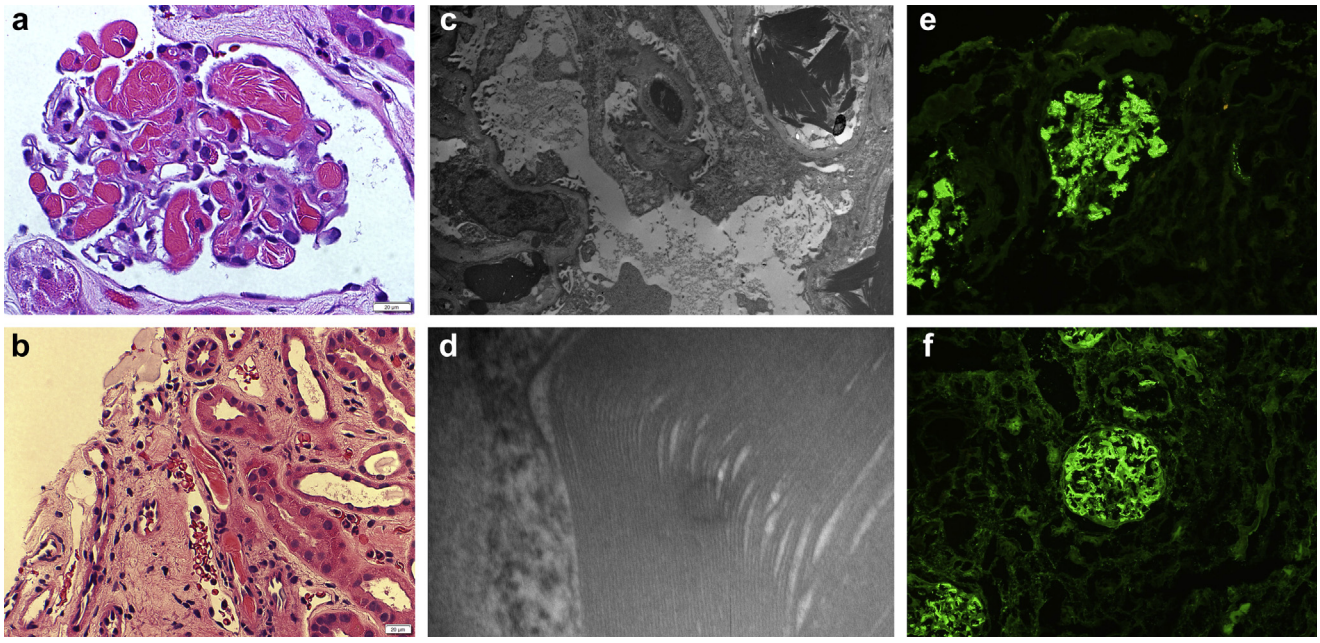

Figure 2. (a) Glomerular capillaries are extended by large hyper eosinophilic pseudo thrombi, some of which are composed of closely packed long needle-shaped crystals (hematoxylin and eosin; bar = 20 μm). (b) Similar thrombi/crystals are focally seen in arteriolar lumens (hematoxylin and eosin; bar = 20 μm). (c) Low-magnification electron microscopic images showing occlusion of glomerular peripheral capillaries by large highly electron-dense crystals (original magnification ×2000). (d) On high magnification, some of the pseudo thrombi show microtubular structure (original magnification ×40,000). (e) Bright glomerular staining for IgG1 is seen on immunofluorescence. (f) Bright glomerular staining for kappa is seen on immunofluorescence.

CLINICAL FOLLOW-UP

Following the biopsy results, the patient received 5 sessions of plasmapheresis with improvement in his M spike to 0.1 g/dl. He was also started on pulse steroids followed by steroid taper over the course of a month. His kidney function improved and he was off dialysis with serum creatinine decreasing to 1 mg/dl. He then received bortezomib (4 weeks on and 1 week off therapy for a total of 14 weeks), which was then stopped after his serum M spike became undetectable. The patient was then seen every 3 months and continues to do well with negative immunofixation and a serum creatinine of approximately 1.1 mg/dl.

DISCUSSION

We report a case of a middle-aged man with crystalglobulin-associated nephropathy in the setting of rheumatoid arthritis and leukocytoclastic vasculitis. As far as we know, there is no description of this condition in the literature with these associations. Crystallization of monoclonal proteins in vasculature is mostly described in multiple myeloma.[3–5] The term *crystalglobulinemia* refers to deposition of monoclonal protein crystals in microvasculature.[6] This eventually causes vascular thrombosis and related changes. Crystalglobulinemia is rarely described in patients with MGRS.[7] This case reinforces the broad differential of MGRS and the importance of renal biopsy in such scenarios to further clarify. Renal biopsy should be considered in these patients. Initiation of appropriate therapy against this indolent clone is essential in the management of these patients.[6] Plasmapheresis is often needed to prevent new monoclonal crystal formation, and the patient might need multiple sessions of these.[8] Bortezomib has shown improvement of renal function in such scenarios.[5] Renal replacement therapy is often required at presentation. Unlike light chain tubulopathy and crystal storing histiocytosis, deposition of crystals in crystalglobulin-induced nephropathy is extracellular and is within the microvasculature.[9]

From an outcome perspective, our patient was initially treated similarly to thrombotic microangiopathy, with pulse dose steroids and plasmapheresis with good initial response. Thrombotic microangiopathy was considered on the top of differential based on initial light microscopy findings on pathology while immunofluorescence and electron microscopy were still pending. Indeed, in crystalglobulinemia, the intraluminal monoclonal protein crystals cause endothelial cell injury and activation of the coagulation cascade leading to thrombosis and ischemic injury to organs.[6] As secondary thrombosis by this mechanism frequently occurs in crystalglobulin-induced nephropathy, it is not uncommon to misdiagnose crystalglobulin-induced nephropathy as

Table 2. Teaching points

1	Patients with skin vasculitis and acute kidney injury in association with monoclonal gammopathy should be considered for crystalglobulin-induced nephropathy.
2	Crystal deposits can be confused with thrombi if associated immunofluorescence and electron microscopy findings are not available. Hence, it is not unusual to make a diagnosis of thrombotic microangiopathy if immunofluorescence and electron microscopy are pending.
3	Cryocrystalglobulinemia, which is deposition of cryoglobulins in the form of crystals in microvasculature, is hard to distinguish, as serum cryoglobulin testing has a high rate of false negativity.
4	Early treatment with a regimen similar to multiple myeloma treatment is important in preventing permanent damage to kidneys.
5	Although the crystals demonstrated microtubular structures on ultrastructural analysis, this can be distinguished from other etiologies that have microtubular structures on ultrastructural analysis (like immunotactoid glomerulopathy) because the vast majority of deposits are intraluminal (also involve the arterioles, which does not occur in immunotactoid glomerulopathy).
6	Renal biopsy needs to be considered in every patient with monoclonal gammopathy of renal significance, as this can dictate treatment and thereby overall renal prognosis.

thrombotic microangiopathy. Most of the glomerular and vascular thrombi in this patient showed a crystallin substructure and stained brightly for IgG1 and kappa, favoring crystalglobulin-induced nephropathy with secondary thrombosis as the etiology for this patient's acute kidney injury; however, serum cryoglobulin level was negative. It is very hard to distinguish this from cryocrystalglobulin-induced nephropathy, as there is a very high false-negativity rate of the serum cryoglobulin test.[6] It is possible that the skin rash in our patient was a complication of crystalglobulinemia due to cutaneous crystal deposition with secondary endothelial cell injury, thrombosis, and vasculitis changes; however, we could not confirm this possibility because we were not able to perform immunofluorescence on the skin biopsy. This case in fact raises very valid teaching points regarding the diagnosis and management of MGRS, such as crystalglobulin-induced nephropathy (Table 2).

In conclusion, our case highlights that crystalglobulin-associated nephropathy is a rare and underrecognized etiology of MGRS. It can happen in unusual settings, such as rheumatoid arthritis and vasculitis. It can be confused with thrombotic microangiopathy if diagnosis is based on light microscopy in the absence of immunofluorescence and electron microscopy evaluation. Early treatment to decrease the burden of monoclonal crystals and eliminate the indolent clone with therapies such as plasmapheresis and bortezomib are often needed.

DISCLOSURES

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