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CASE REPORT

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Crystalglobulinemia causing cutaneous vasculopathy and acute nephropathy in a kidney transplant patient

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We present a rare case of crystalglobulinemia causing cutaneous vasculopathy and acute nephropathy in a 66-year-old female kidney transplant recipient. The patient presented with acute kidney injury (AKI), volume overload, anuria, retiform purpura, and blue-black necrosis of her toes. She received a living kidney transplant 7 months earlier with baseline creatinine of 0.6 mg/dl. Transplant kidney biopsy showed massive pseudo-thrombi filling glomerular capillary lumina. Electron microscopy of thrombi revealed an ultrastructural crystalline pattern of linear and curvilinear bundles with ladder-like periodicity typical of crystalglobulin-induced nephropathy. Similar crystalline pseudo-thrombi were detected ultrastructurally in a skin biopsy specimen, indicating systemic involvement. She required several sessions of hemodialysis. Plasmapheresis was initiated to decrease the number of circulating crystalglobulins. In order to treat the underlying paraproteinemia, the patient was started on bortezomib and dexamethasone. After treatment with five cycles of bortezomib, the patient's free kappa to lambda ratio improved to 2.35 from 5.52. Acute kidney injury (AKI) and the cutaneous vasculopathy gradually improved with treatment. This is an extremely rare occurrence of crystalglobulin in a living kidney transplant recipient.

KEYWORDS
clinical research/practice, kidney failure/injury, kidney transplantation/nephrology, plasmapheresis/plasma exchange

1 | INTRODUCTION

Crystalglobulinemia is a rare variant of cryoglobulinemia in which monoclonal immunoglobulins self-assemble into crystalline arrays and deposit within the lumina of small arteries and arterioles. These pseudo-thrombi or "cryo plugs" lead to vascular endothelial injury and activate the coagulation cascade, leading to occlusion of vessels. The condition was first described by Von Bonsdorff in 1938.[1] Patients often present with multiorgan involvement, including rapidly progressive kidney injury, polyneuropathy, polyarthropathy, and cutaneous manifestations including retiform purpura, ulcerations, and necrosis.[2] Crystalglobulinemia may be the initial presentation of multiple myeloma,[3] and it has been reported in patients with monoclonal gammopathy of renal significance (MGRS).[4]

2 | CASE PRESENTATION

The patient was a 66-year-old Caucasian woman with end-stage kidney disease secondary to IgA nephropathy who underwent a second

Abbreviations: AKI, acute kidney injury; DIF, direct immunofluorescence; HD, hemodialysis; MGRS, monoclonal gammopathy of renal significance; MGUS, monoclonal gammopathy of unknown significance; PD, peritoneal dialysis; SPEP, serum protein electrophoresis; TEM, transmission electron microscopy.

kidney transplantation 7 months earlier. Her maintenance immunosuppression included tacrolimus and mycophenolate mofetil. She presented to the emergency department for shortness of breath, decreased urine output, and anasarca; she was found to have AKI. For the week prior, the patient reported gross hematuria and progressive swelling. Initial blood chemistry showed: sodium 123 mmol/L, BUN 49 mg/dl, and creatinine 5.33 mg/dl (elevated from a baseline of 0.6). Hemoglobin concentration was low at 8.8 g/dl and platelet count was normal at 197 k/cumm.

Six weeks prior to admission, she experienced extreme pain, swelling, and redness of the left foot and progressive blue-black discoloration over the left second toe. The pain worsened with leg elevation and improved in the dependent position. She was admitted to an outside hospital before transfer and was treated with topical nitroglycerin paste and hyperbaric oxygen therapy, without significant improvement. Three weeks prior to presentation, she also developed right foot pain and purpura.

Transesophageal echocardiogram was negative for intracardiac thrombus. Bilateral lower extremity arterial Doppler study showed normal perfusion. Serum cryoglobulins and cryofibrinogens were negative. Extended hypercoagulable work-up was negative, including DRVVT, PT/INR, rheumatoid factor, ANA, Factor V Leiden, Cardiolipin IgG and IgM, Beta 2 glycoprotein IgG and IgM, Protein C/S activity, and clotting time. Serum protein electrophoresis (SPEP) revealed elevated monoclonal protein with an elevated M protein at 0.31 gm/dl, and low beta and gamma levels at 0.52 and 0.59 gm/dl, respectively. Immunofixation showed IgG kappa monoclonal protein. Free kappa to lambda ratio was elevated at 6.8. She had a known history of monoclonal gammopathy of unknown significance (MGUS), and bone marrow biopsy twice before transplantation showed 4%–5% kappa light chain-restricted plasma cells, with hyperploidy; free kappa to lambda ratio at that time was 9.8. Bone survey was negative for any lytic lesions suggesting multiple myeloma. Laboratory studies before and after transplantation are summarized in Table 1.

Skin examination revealed a blackened and necrotic left second toe consistent with dry gangrene, a 2 cm, retiform necrotic violaceous plaque on the left medial foot, and several red to violaceous, non-blanching macules and retiform patches in a watershed pattern on the bilateral lower legs and feet (Figure 1A–C). Eyes and oral mucosa were normal. Both lower extremities showed 2+ pitting edema above the knees. Dorsalis pedis pulses were bounding.

The initial differential diagnosis included cryoglobulinemia type I, cholesterol or other arterial emboli, acquired hypercoagulable state like antiphospholipid antibody syndrome or paraproteinemia, and a medium-vessel vasculitis. The absence of palpable purpura mitigated against a diagnosis of cutaneous small vessel vasculitis, including IgA vasculitis.

3 | PATHOLOGY OF BIOPSY SPECIMENS

After obtaining the patient's consent, percutaneous needle core biopsy was performed on the renal allograft and punch core biopsy was executed on the right foot. Portions of both specimens were aliquoted into 10% neutral buffered formalin and Michel's buffer before processing into paraffin and frozen tissue blocks for examination by brightfield and widefield epifluorescent microscopy, respectively. Renal cortex was fixed in 3% buffered glutaraldehyde and processed for examination by transmission electron microscopy (TEM), whereas skin was retrieved from the paraffin block and back-processed for ultrastructural examination. When examined by brightfield microscopy, paraffin kidney sections stained with Jones' methenamine silver showed prominent pseudo-thrombi or "plugs" occupying glomerular capillary lumina (Figure 2A). When surveyed by TEM, these thrombi corresponded to ultrastructural deposits with an organized crystalline pattern (Figure 2B). At higher magnification, the crystals were composed of tightly packaged linear and curvilinear bundles with ladder-like periodicity (Figure 2C,D), typical of crystalglobulin-induced nephropathy. Ultrastructurally, the crystalline bundles had a mean width of 74.4 nm (range 53.0–93.8 nm) and were composed of smaller fibers with a mean thickness of 9.9 nm (range 7.03–13.0 nm).

Using direct immunofluorescence (DIF), no reaction to crystalline deposits was seen in frozen kidney sections incubated with fluorescein-tagged antibodies targeting the following: heavy chain immunoglobulins (Ig) IgG, IgA, and IgM, light chain Ig kappa and Ig

TABLE 1 Laboratory studies before and after treatment

Labs	Before	At diagnosis	One year posttreatment	Reference range
Hemoglobulin, g/dl	12.5	7.4	12.5	13–17
WBC, k/μl	5.3	15.5	4.8	4–11
Serum creatinine, mg/dl	0.6	5.93	1.1	0.5–1.4
Kappa, mg/L	346.15	57.17	28	3.3–19.40
Lambda, mg/L	44.7	10.36	13	5.7–26.3
K: L ratio	7.74	5.52	2.16	0.26–1.65
M protein Gm/dl	1.24	0.48	Not detected	Not detected
Plasma cells, marrow	4%, 5%	not done	not done	1%–2%
Tacrolimus, ng/ml	6–8	5–6	3–4	4–12

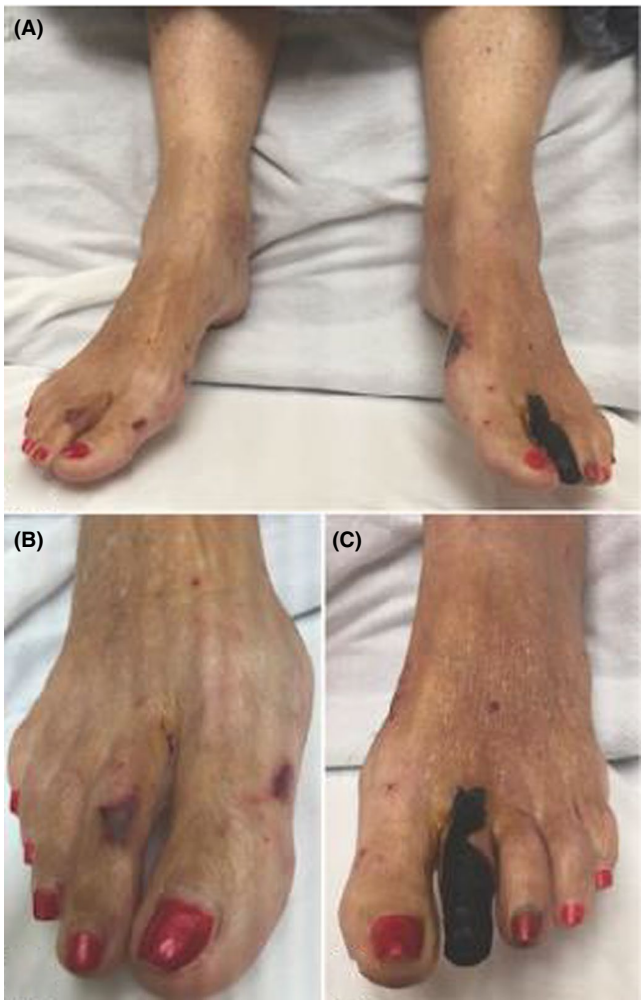

FIGURE 1 Watershed pattern of purpuric macules and plaques on the bilateral lower extremities (A), retiform purpuric plaques on the right foot (B), and dry gangrene of the left second toe and medial foot (C)

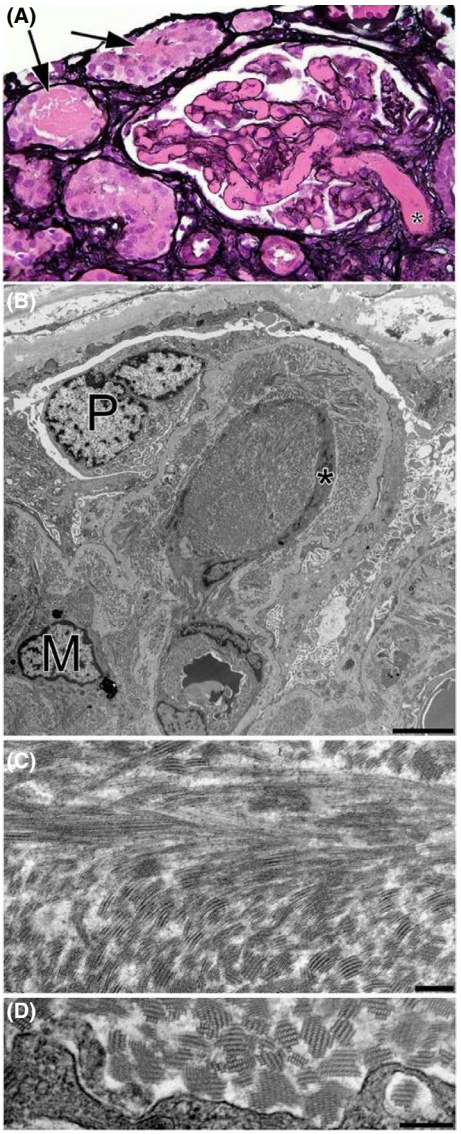

FIGURE 2 (A) Paraffin section of kidney stained with Jones' silver highlights eosinophilic "pseudo-thrombi" (pink material also called cryo plugs) within glomerular capillary lumina, which communicate with the lumen of an arteriole (asterisk at right). Cast material of similar staining quality was found in tubule lumina (arrows). (B) Transmission electron microscopy (TEM) shows extracellular, organized deposits in glomerular mesangia, along the subendothelia of duplicated capillary loop basement membranes, and as a pseudo-thrombus surrounded by endothelial cells (asterisk). M, mesangial cell; P, podocyte. (C,D) TEM at higher magnification shows deposits aligned in linear and curvilinear bundles and wafers with distinct, uniform ladder-like periodicity. Crystalline deposits were not seen in the lumina of tubules when examined by EM (not shown). Original magnifications of (A), (B), (C), and (D) are 400×, 5370×, 56 600×, and 90 800×, respectively. A scale bar equals 4 μm for (B) and 200 nm for images (C) and (D)

lambda, or complements C3, C1q, and C4d (not shown). Undetected epitopes in frozen kidney sections may have been masked by the tight crystalline alignment revealed by TEM.

Hematoxylin and eosin-stained sections of the skin biopsy specimen revealed thrombosed superficial dermal blood vessels containing amorphous eosinophilic material with adjacent dermal red blood cell extravasation (Figure 3A). No calciphylaxis was identified. Immunohistochemical analysis of the intravascular material was strongly reactive for kappa light chain with no reaction for lambda light chain. DIF showed immunoreaction for intravascular fibrinogen, but no signal with antibodies directed to IgG, IgA, IgM, and C3. Electron microscopy performed on a paraffin-embedded skin biopsy specimen showed that the intravascular thrombi were composed of crystalline material with the same periodicity seen in the glomerular capillary loop lumina (Figure 2B). These histologic features confirmed a diagnosis of crystalglobulinemia secondary to the patient's underlying monoclonal gammopathy.

The patient was started on empiric high-dose prednisone due to concern for vasculitis. She required four sessions of hemodialysis for volume overload and AKI. Plasmapheresis was initiated to decrease the number of circulating crystalglobulins. Subsequently, her kidney function improved and she required no further hemodialysis. In order to treat the underlying paraproteinemia, the patient was started on bortezomib and dexamethasone. She was closely

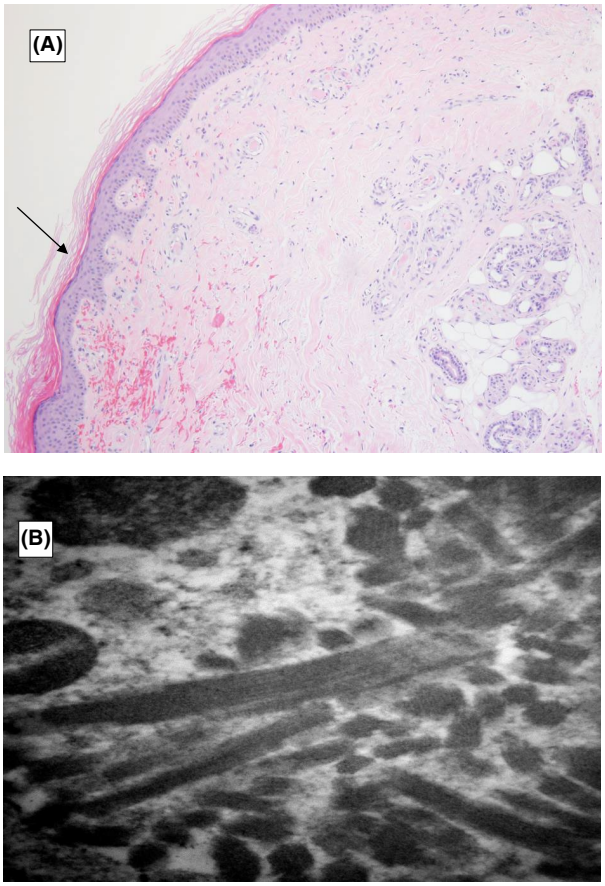

FIGURE 3 Thrombosed superficial dermal blood vessels with amorphous eosinophilic material and red blood cell extravasation (arrow) (A). Electron micrograph showing the same periodicity as seen in the glomerular capillary loops (B)

monitored for neuropathy, the most common side effect of bortezomib, as she had mild baseline peripheral neuropathy. After treatment with five cycles of bortezomib, the patient's free kappa to lambda ratio improved—2.35 from 5.52. Cutaneous vasculopathy gradually improved with treatment. The necrotic left second toe was eventually deemed non-viable, requiring a partial amputation. The acute crystalglobulin-induced nephropathy resolved. Mycophenolate was discontinued and she has been maintained on combination of tacrolimus and low dose prednisone. She has been in remission for over 4 years and on last check serum creatinine was 1.1 mg/dl.

4 | DISCUSSION

We report a case of a 66-year-old woman with crystalglobulin-associated acute transplant kidney nephropathy with known history of MGUS.

Crystalglobulinemia is a rare vasculopathy more commonly associated with multiple myeloma, though it rarely has been reported with MGRS and MGUS.[4] The classic clinical manifestations of this systemic vasculopathy include AKI, skin purpura or gangrene, polyarthralgias, and peripheral neuropathy. Vanga et al recently reported crystalglobulin-induced nephropathy in a patient with seronegative rheumatoid arthritis and leukocytoclastic vasculitis.[5]

To our knowledge, there is no report of crystalglobulinemia in a kidney transplant recipient. Our patient underwent repeat evaluation for plasma cell disorder before transplantation including bone marrow biopsy, but did not meet diagnostic criteria for diagnosis of multiple myeloma.

Prior to transplantation, the patient was on peritoneal dialysis (PD) for failure of her first kidney transplant. Before starting PD, biopsy of failing kidney allograft was consistent with chronic transplant glomerulopathy. It did not show any monoclonal deposition. Our patient did not develop crystalglobulin- associated symptoms while on PD. Although PD is not as effective in removing light chains as compared to hemodialysis (HD) or plasmapheresis, the possibility exists that some of the light chains were removed via PD.[6] That could be one of the reasons that she did not develop crystal-induced nephropathy in the failing transplant kidney. We cannot fully explain why her second kidney transplant developed crystalglobulin deposition without any significant change in serum-free light chain concentration. One explanation may be that her second transplant kidney was more sensitive to crystalglobulin-induced nephropathy due to immunosuppressive agents, especially tacrolimus-induced intrarenal vasoconstriction.[7]

The clinical differential diagnosis included cryoglobulinemia type I, cholesterol or other arterial emboli, acquired hypercoagulable state like antiphospholipid antibody syndrome or paraproteinemia, and medium-vessel vasculitis. The cryoglobulin and rheumatoid factors were both negative. Repeat hepatitis C and B serologies were also negative. The vascular testing showed good distal blood flow and the CT scan before transplant did not show any significant atherosclerosis in the leg blood vessels. Both Myeloperoxidase and Proteinase 3 antibodies were undetectable. Extensive testing did not reveal any evidence of hypercoagulable state. The skin biopsy did not show cholesterol emboli or evidence of vasculitis.

The differential diagnosis based on the biopsy included amyloid, fibrillary GN, and immunotactoid GN. The kidney biopsy did not show any evidence of amyloid as Congo red staining was negative. Crystalline bundles had a mean width of 74.4 nm. Each bundle was comprised of several smaller fibers with a mean thickness of 9.9 nm. The characteristic ultrastructural finding in fibrillary glomerulonephritis consists of randomly arranged, non-branching fibrils that typically measure 18 to 20 nm. On electron microscopy, immunotactoid glomerulopathy is characterized by the formation of microtubules, which are much larger than the fibrils observed in our case (30–50 vs. 9.9 nm in diameter). Immunofluorescence on pronase-treated paraffin kidney was not performed due to lack of tissue. It may not have any significant impact as the diagnosis was aided by serum tests, skin, and kidney biopsies.

Kidney disease with MGRS differs from that without MGRS. In a study of 29 patients with recurrent membranoproliferative glomerulonephritis after kidney transplantation, six were found to have circulating monoclonal protein and one had monoclonal deposits in the kidney. The recurrence rate was 71% in these seven patients versus 29% in patients without a detectable monoclonal gammopathy.[8] Although our recipient did have circulating monoclonal proteins,

there was no evidence of involvement of first kidney transplant based on the biopsy. Progression from true MGUS to multiple myeloma is rare after kidney transplantation if the monoclonal gammopathy was not the primary cause for kidney disease.[9]

Our patient had biopsy-proven cutaneous involvement. Crystalline deposits in the cutaneous vasculature may lead to retiform purpura with ulcerations on the distal extremities.[10] Cutaneous findings previously reported in crystalglobulinemia include: purpuric (often non-palpable) patches with ulceration and necrosis of the extremities,[2,3,11-13] cyanosis and livedo of the lower legs,[14,15] and hemorrhagic vesicles of the hands, and ulceration of the nasal septum.[2]

In crystalglobulinemia, intraluminal monoclonal protein crystals induce endothelial cell injury, thrombosis, and ischemic injury due to activation of the coagulation cascade activation. Treatment strategies are directed at lowering the level of paraproteinemia, thus impeding the ability of the monoclonal immunoglobulins to crystallize and occlude the microvasculature.

Nephrologists ought to consider crystalglobulinemia in the differential diagnosis of cutaneous and systemic vasculopathy in patients with a history of paraproteinemia and kidney injury. Diagnostic evaluation may include SPEP with immunofixation electrophoresis, determination of serum-free light chain ratio and kidney biopsy. Plasmapheresis is often required to remove light chains and to prevent new crystalglobulin formation. Appropriate therapy should be initiated against plasma cell clones.

Our case demonstrates that crystalglobulin is a very rare disease in the transplant kidney and early diagnosis and appropriate treatment may lead to reversal of AKI and skin manifestations.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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