

AKI in a Patient with Fever, Rash, and Joint Pain

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Case Description

A 71-year-old man presented with new polyarthralgia and joint swelling. The next day, he developed fever, and a painful, palpable, purpuric rash on his legs (Figure 1). Initial laboratory evaluation was unrevealing, but within 48 hours his platelet and hemoglobin levels declined from normal values to 66 K and 11 g/dl, respectively. He developed anuric AKI with a peak serum creatinine of 5.2 mg/dl; hemolysis laboratories, infectious studies, and viral serologies, including hepatitis C, were negative.

Additional laboratory data demonstrated hypocomplementemia (C3: 34 mg/dl, C4: 2 mg/dl). Serum cryoglobulins, rheumatoid factor, ADAMTS13 activity, ANCA, anti-nuclear antibody, and antiphospholipid antibodies were negative. Serum-free light chains showed a kappa light chain of 4.3 mg/dl, lambda light

chain of 14.6 mg/dl, and kappa/lambda light chain ratio of 0.29 (normal range for AKI, 0.39–3.1). Flow cytometry revealed a monoclonal B cell consistent with a B cell lymphoproliferative disease.

Kidney biopsy revealed diffuse, acute tubular injury, necrotic glomeruli, and periodic acid–Schiff positive, Congo Red negative capillary plugs (Figure 2). Capillary plugs stained 2+ positive for IgG lambda without IgG kappa. On electron microscopy, capillary loops were occluded by in-parallel, 8.2–13.9 nm diameter tubular material, with global podocyte foot process effacement (Figure 3).

Given the patient's AKI, skin findings, depressed kappa/lambda light chain ratio, and lambda-restricted glomerular capillary loop plugs, a diagnosis of Type 1 cryoglobulinemia with vasculitis and GN was made. Treatment included pulse dose steroids, rituximab,



Figure 1. | Right lower-extremity rash. Patient presented with a painful, palpable, purpuric rash with fluid-filled blisters on both lower extremities.

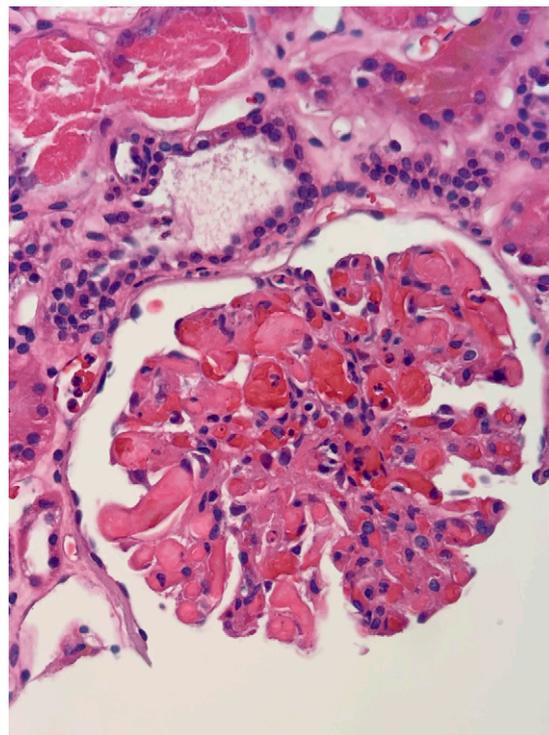


Figure 2. | Glomerulus on light microscopy. Single glomeruli demonstrating lobular accentuation, mesangial hypercellularity with intracapillary hyaline thrombi or “cryopugs” (hematoxylin and eosin $\times 40\times$).

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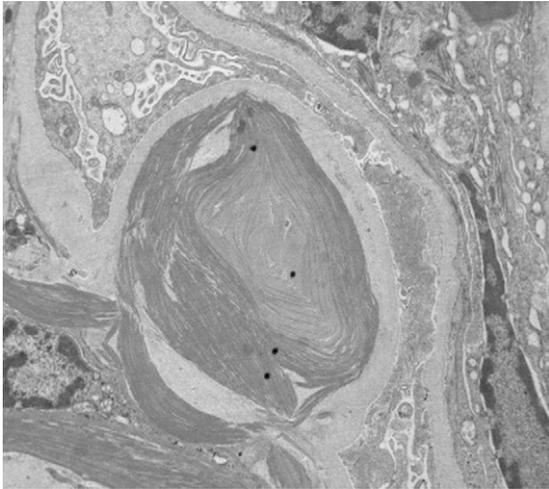


Figure 3. | Electron microscopy. Capillary loop occluded by in-parallel tubular material consistent “cryoplugs” seen on light microscopy. This appearance is atypical as typical deposits are curvilinear in appearance (transmission electron microscopy $\times 11,300$).

and plasma exchange. His vasculitic rash and AKI improved.

Discussion

Cryoglobulinemia is a very rare (1) disorder of circulating serum auto-Fc antibodies, which precipitate in temperatures $<37^{\circ}\text{C}$. The obstruction of small vessels and associated inflammation result in organ injury.

Cryoglobulinemia is subdivided into three types. Type 1 consists of monoclonal IgG and is associated with lymphoproliferative disorders. Types 2 and 3 result from either mixed IgM and IgG/IgA or polyclonal IgG, respectively. Cryoglobulinemia Types 2 and 3 are associated with infection or autoimmune disease, with hepatitis C resulting in 80%–90% of patients. In cases involving the kidney, Type 2 cryoglobulinemia is most common (65%), followed by Type 3 (28%), then Type 1 (7%) (2).

Cryoglobulinemia typically presents with fatigue, arthralgias, and vasculitis but can have multiorgan involvement. Kidney involvement including GN occurs in 30% of patients and has a 10-year mortality of 50%–90% (1,3). Hematuria and proteinuria are common and 5% of patients present with AKI (1). Biopsy shows membranoproliferative glomerular nephritis with hyaline thrombi in capillary loops known as “cryoplugs.” Typical electron microscopy demonstrates curvilinear tubular structures 20–30 nm in diameter.

Therapy focuses on treatment of the underlying disorder (*i.e.*, hematologic malignancy or chronic viral infection).

B cell depletion with rituximab to reduce cryoglobulin production and pulse-dose steroids with taper reduces inflammation. Plasma exchange is used with severe vasculitis or renal involvement.

This case demonstrates an uncommon presentation of rare type 1 cryoglobulinemia. Although the light microscopy findings are typical, the regular, parallel deposits on electron microscopy differ from the standard curvilinear deposits and are unusual.

Teaching Points

- Type 2 and 3 cryoglobulinemia are the most common and are highly associated with hepatitis C.
- Type 1 cryoglobulinemia is rare and associated with abnormal B cell proliferation.
- Cryoglobulinemia can cause mechanical obstruction and inflammatory injury of glomerular capillaries with hyaline “cryoplugs” seen on light microscopy, which appear as curvilinear material on electron microscopy.

Disclosures

All authors have nothing to disclose.

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Informed consent was obtained from the patient.

Author Contributions

A.W. Aron conceptualized the study and wrote the original draft; and U. Brewster provided supervision and reviewed and edited the manuscript.

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