Contrasting Presentations of Mixed Cryoglobulinemia as Acute and Chronic Disease Processes

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Introduction
Cryoglobulinemia is a relatively rare vasculitis that is associated with 5% of hepatitis C cases. It typically presents with a chronic, indolent course but on occasion it can present acutely with life-threatening sequelae. The following case series highlights two starkly different presentations of this disease process.

Case 1
A 51 year old male with a history of active IV drug use and hepatitis C initially presented to the emergency room multiple times in a three year period with an intermittent, palpable, non-blanching rash and lower extremity swelling. He was prescribed multiple courses of prednisone and counseled to follow up with rheumatology as an outpatient, which he deferred. On the day of diagnosis, he presented with fever, night sweats, lower extremity edema, and recurrent vasculitic rash. Notably absent was renal or neurologic injury.

Physical Exam
HEENT: No oral lesions, no lymphadenopathy.
Cardiovascular: RRR. Systolic murmur. No JVD.
Pulmonary: Clear to auscultation bilaterally.
GI: Soft, diffuse tenderness with guarding. No rebound tenderness. No hepatosplenomegaly.
Musculoskeletal: No joint effusions or erythema.
Neurological: No focal deficits.
Skin: Non-blanching raised purpuric rash of the lower extremities with 2+ pitting edema. Exquisitely tender to touch.

Clinical Course
- Prednisone 40 mg for 4 weeks with PJP prophylaxis.
- Referred to virology clinic for outpatient hepatitis C treatment.
- Did not pick up outpatient medications upon discharge.
- Lost to follow up.

Case 2
A 59 year old male with a history of hepatitis C, atrial fibrillation, hypertension, and ischemic strokes initially presented with lower extremity edema and a petechial, non-blanching rash. He was found to have an acute kidney injury secondary to glomerulonephritis. His course was complicated by encephalopathy concerning for CNS vasculitis. He was treated with prednisone and started on glexcaprevir-pibrentasvir for hepatitis C.

One week later, he presented with fever, somnolence, lower extremity edema, and persistent vasculitic rash. He was found to have recurrent acute kidney injury with severe hyperkalemia and new finger paresthesias.

Physical Exam
Gen: Somnolent but arousable. No acute distress. Toxic-appearing.
HEENT: No oral lesions, no lymphadenopathy.
Cardiovascular: RRR. Systolic murmur. No JVD.
Pulmonary: Scant bibasilar rales.
GI: Soft, non-tender, non-distended. No hepatosplenomegaly.
Musculoskeletal: No joint effusions or erythema.
Neurological: Exam limited by somnolence, moving all extremities spontaneously.
Skin: Non-blanching flat petechial rash of the lower extremities with 2+ pitting edema. Non-tender.

Clinical Course
- Plasmapheresis for 5 sessions.
- Rituximab weekly for 2 weeks.
- Prednisone 60 mg for 5 days followed by a slow taper with PJP prophylaxis.
- Glexcaprevir-pibrentasvir for hepatitis C.
- Re-admitted 2 months later for community-acquired pneumonia.

Pathology Findings Case 1 + 2

Skin Biopsy: Leukocytoclastic Vascularity

Skin Findings Case 2

Laboratory Findings Case 1

| 8.6 | 135 |
| 4.4 | 100 |
| 27 | 17 |

- Cryoglobulin Immunoassay: Positive for type II cryoglobulinemia with monoclonal IgM and polyclonal IgG
- RF: 36
- HCV PCR: 1,180,000
- C3: 81
- C4: 2.1
- CRP: 23.8
- ESR: 30

Laboratory Findings Case 2

| 13.1 | 162 |
| 9 | 61 |
| 27.8 | 3.3 |

- Cryoglobulin Immunoassay: Positive for type II cryoglobulinemia with monoclonal IgM and polyclonal IgG
- RF: 408
- HCV PCR: 130,000
- C3: 91
- C4: 4.8
- CRP: 88.8
- ESR: 45

Discussion

Epidemiology
- The prevalence of clinically significant cryoglobulinemia is approximately 1 in 100,000.

Pathophysiology
- Expansion of B cells and subsequent increased immunoglobulin production.
- Immune complex deposition in skin, joints, kidneys, or peripheral nerves.
- Inflammation of small and medium sized blood vessels

Clinical Features
- Rash - Typically manifests initially as erythematous papules and non-blanching palpable purpura of the lower extremities. Rash can occur years prior to systemic involvement.
- Arthralgias – Generally without arthritis.
- Peripheral Neuropathy - Sensory
- Renal Disease – Typically isolated proteinuria or hematuria. Occasionally presenting with glomerulonephritis (MPGN most common).

Classification
- Type I – Monoclonal IgG or IgM
- Type II – Mixed monoclonal + polyclonal IgA, IgG, or IgM
- Type III – Polyclonal IgG + polyclonal IgM

Diagnosis
- Cryoglobulin precipitation with immunoassay or ELISA
- Complement (particularly C4)
- Rheumatoid Factor
- Hepatitis C screen
- Creatinine + urinalysis
- Skin biopsy with leukocytoclastic vasculitis

Treatment
- Immunosuppression
- Glucocorticoids
- Rituximab or cyclophosphamide
- Plasmapheresis in patients with life-threatening disease
- Treatment of the underlying disease

References