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Case report

A wolf in another wolf's clothing

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ABSTRACT

This case of infective endocarditis masquerading as mixed cryoglobulinemia in a man with a history of intravenous drug use (IVDU) and hepatitis C virus (HCV) highlights the importance of maintaining a broad differential and continually re-evaluating the working diagnosis as new information presents itself. The patient presented to an outside hospital and was treated for presumptive mixed cryoglobulinemia with corticosteroid therapy. When the patient did not improve, he was transferred to a tertiary care center for possible Rituximab and/or plasmapheresis. Further investigation revealed *Enterococcus* bacteremia with subsequent workup consistent with infective endocarditis (IE). This case highlights a diagnostic dilemma and demonstrates the importance of a thorough evaluation as it pertains to overlapping features of IE and mixed cryoglobulinemia.

Introduction

Cryoglobulinemia (CG) occurs when the serum contains cryoglobulins, either single or mixed immunoglobulins, which precipitate at low temperatures. This can result in an immune-complex mediated, small-to-medium vasculitis that most commonly affects the kidneys and the skin [1]. IE also has the ability to manifest clinically through immune-mediated phenomena and thus can cause overlapping symptoms, namely positive rheumatoid factor (RF) and glomerulonephritis (GN) [2].

Case

A 42-year-old man with known history of IVDU and HCV infection presented with complaints of bilateral lower extremity edema, rash, increasing abdominal girth, diffuse abdominal pain, and generalized fatigue. His lower extremity edema had been present for 6 months and he had been evaluated for it on 2 previous occasions with negative lower extremity ultrasound examinations and had taken a 30-day course of furosemide with some improvement; all other symptoms were new to this presentation. Initial laboratory values were significant for creatinine 1.7 mg/dL (reference range 0.8–1.4 mg/dL), elevated white blood cell count of 18, 000/mcL (4500–11,000/mcL) and HIV screening test that was non-reactive. The patient's kidney injury failed to improve with corticosteroid therapy. A percutaneous kidney biopsy was subsequently performed revealing IgM dominant mesangioproliferative GN with features suggestive of CG (Figs. 1–4), likely related to chronic infection including chronic hepatitis C or chronic bacterial infection. The patient was treated with corticosteroid therapy for presumed mixed CG, however on hospital day 3 his renal function continued to deteriorate and the patient was transferred to our tertiary care center for further evaluation for possible Rituximab and/or plasmapheresis therapy. Upon arrival, the patient's physical exam was notable for anasarca, a grade 2 diastolic murmur and several painless, small, erythematous macules on bilateral lower extremities, not extending to the soles of his feet. There was no appreciable organomegaly or lymphadenopathy. Initial laboratory results were significant for creatinine 3 mg/dL (0.8–1.4 mg/dL), total protein 8.4 g/dL (6.3–8.2 g/dL), albumin 2.4 g/dL (3.4–5.0 g/dL), hemoglobin 8 g/dL (13.5–17.5 g/dL), white blood cell count 35,000/mcL (4500–11,000/mcL) and urinalysis with 30 mg/dL of protein; platelet count and the remainder of the comprehensive metabolic panel were within normal limits. Other pertinent laboratory studies revealed low C3 and C4 complement levels (C3 level 88–252 mg/dL, C4 88–206 mg/dL), negative RF, and negative cryoglobulins. Blood and urine cultures obtained prior to transfer both grew *Enterococcus faecalis,* leading the care team to ascribe the bacteremia to a urinary source and the patient was started on daptomycin and ceftriaxone (due to a previous adverse reaction to ampicillin). Repeat blood cultures

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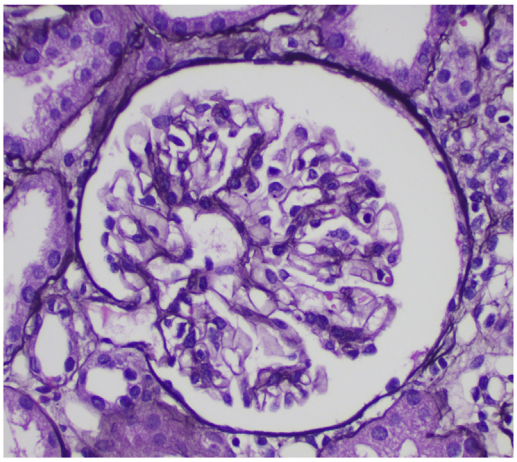

Fig. 1. Light Microscopy Jones' Silver Stain 40x.
There is mild increase in mesangial matrix and cellularity. The glomerular basement membranes are unremarkable without spikes, holes, splitting, or corrugation.

were again positive for *E. faecalis*. Due to the persistent bacteremia and the patient's high-risk behavior, cardiac imaging was obtained to rule out IE. A transthoracic echocardiogram (TTE) demonstrated severe aortic insufficiency, severe left atrial enlargement, and thickening of the mitral valve leaflets with trace regurgitation. Subsequent transesophagealechocardiogram confirmed these results and revealed mitral and aortic valve vegetations (Figs. 5–7). The antibiotic regimen was changed to vancomycin and gentamicin, with subsequent improvement in abdominal pain, lower extremity edema, and renal function (creatinine 1.8 mg/dL (0.8–1.4 mg/dL)). The cardiothoracic surgery team evaluated the patient and recommended valve replacement following completion of the antibiotic course and scheduled the patient for a clinic visit in six weeks. The delay was due to concern for continued IVDU after the procedure and subsequent reinfection. The patient was discharged to a skilled nursing facility to receive a total six-week course of antibiotics for infective endocarditis. He recovered and returned home without issues, but failed to follow up with his clinic appointment for primary care or for surgical evaluation.

Discussion

The Brouet classification has subdivided CG into three types [3]. Type I is defined by the presence of a monoclonal immunoglobulin (Ig), predominantly resulting from hematologic diagnoses such as Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia, and multiple myeloma [4]. Type II is a mixture of polyclonal Ig and monoclonal Ig, predominantly resulting from infection such as HCV or human immunodeficiency virus (HIV) [5]. Type III consists solely of polyclonal Ig, often associated with autoimmune

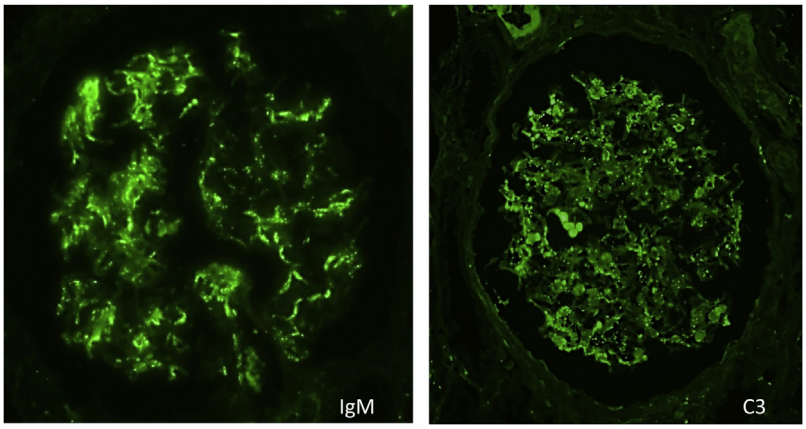

Fig. 2. Immunofluorescence.
On a scale of 0–3+, there is 2+ diffuse global granular mesangial with very segmental capillary loop staining for IgM (leH) and 1–2+ C3 staining (right) in a similar pattern.

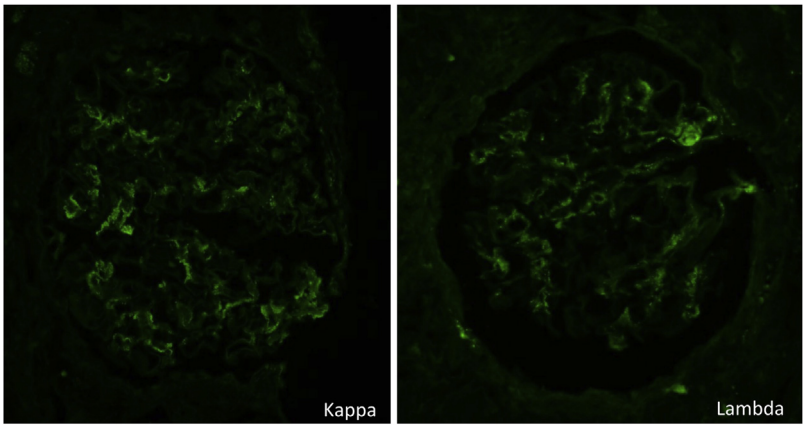

Fig. 3. Kappa and Lambda Immunofluorescence.
On a scale of 0–3+, there is equal 1–2+ diffuse segmental to global granular mesangial staining for kappa and lambda.