

Case report

A wolf in another wolf's clothing

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ARTICLE INFO

Article history:

Received 8 December 2016

Received in revised form 13 February 2017

Accepted 13 February 2017

Keywords:

Infective endocarditis
 Mixed cryoglobulinemia
 Hepatitis C
 Clinical decision making
 Renal disease
 Clinical pathology

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.

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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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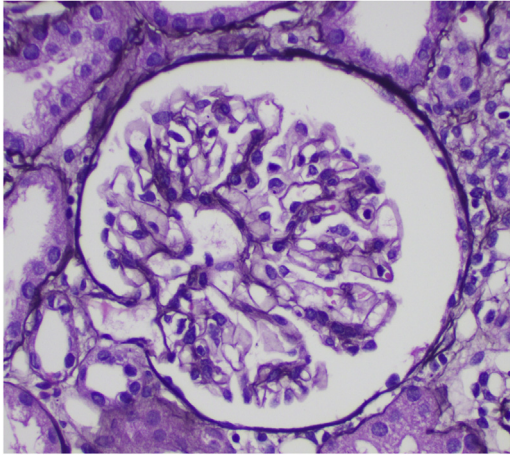


Fig. 1. Light Microscopy Jones' Silver Stain 40x. There is mild increase in mesangial matrix and cellularity. The glomerular basement membranes are unremarkable without spikes, holes, splitting, or corrugation.

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 transesophageal echocardiogram 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

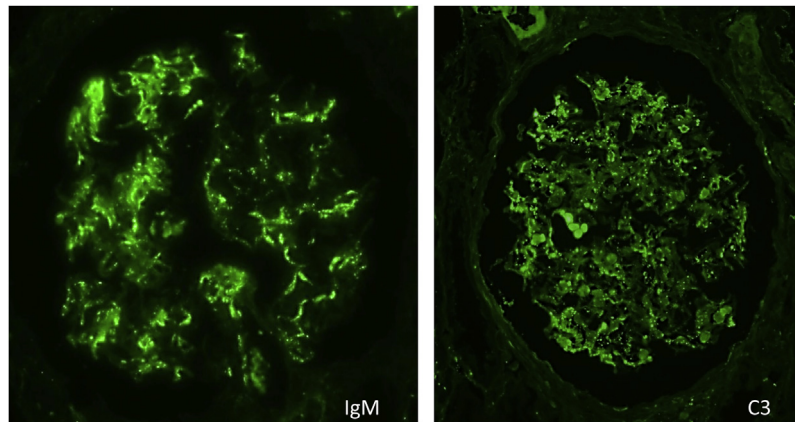


Fig. 2. Immunofluorescence. On a scale of 0–3+, there is 2+ diffuse global granular mesangial with very segmental capillary loop staining for IgM (left) and 1–2+ C3 staining (right) in a similar pattern.

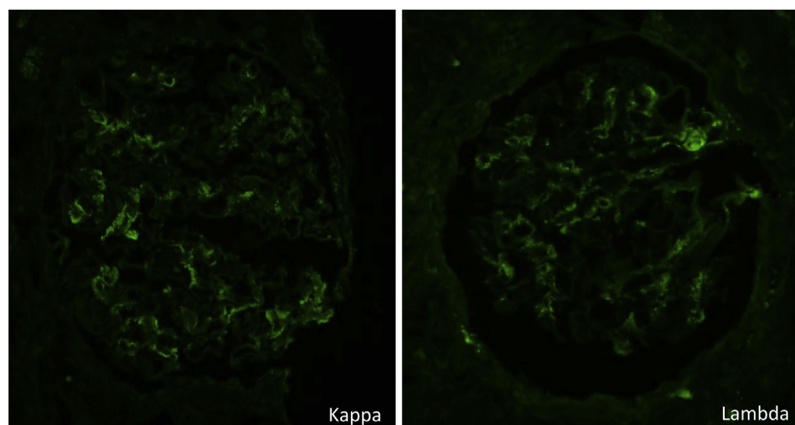


Fig. 3. Kappa and Lambda Immunofluorescence. On a scale of 0–3+, there is equal 1–2+ diffuse segmental to global granular mesangial staining for kappa and lambda.

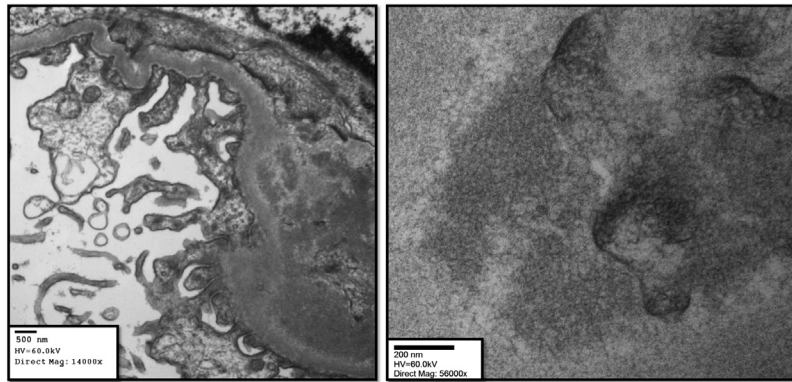


Fig. 4. Electron Microscopy. There are scattered mesangial immune complex deposits (leH) with vague annular substructure (right).

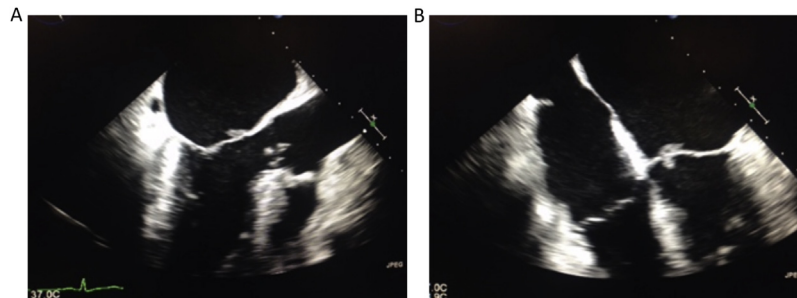


Fig. 5. Transthoracic Echocardiogram. Vegetations seen on the aortic valve (A) and mitral Valve (B).

disorders such as Henoch-Schonlein purpura, systemic lupus erythematosus, Sjogren syndrome, connective tissue disease, sarcoidosis and others, but also has been described as resulting from HCV infection [6].

Infective endocarditis has an incidence of 15 people per 100,000 [7]. Risk factors include: age greater than 60 years old, male gender, history of IVUD, poor dentition, structural heart disease, intracardiac or intravascular access devices, chronic hemodialysis, diabetes mellitus, and HIV infection [7]. The most commonly identified causative organisms are *Staphylococcus*, *Streptococcus* and *Enterococcus* [8]. Duke criteria comprise a collection of major and minor criteria to establish a diagnosis of IE (outlined in Table 1) [9]. Some clinical findings of IE overlap with CG including arthralgias, abdominal pain, petechiae, renal dysfunction, positive RF, elevated

ESR and CRP. While C4 levels are typically low in both processes, reflecting ongoing consumption by immune complexes, C3 is also low in IE but is generally unaffected or only mildly diminished in CG [10].

In CG, the renal disease is most commonly attributed to immune complex deposition, but may be a result of thrombotic disease [11]. Microscopy of kidney tissue samples most often yields results consistent with mesangioproliferative GN with hypercellularity from an influx of inflammatory cells, immune deposition, and thickening of glomerular elements. In IE, renal disease is thought to be sequela of vascular occlusion by microthrombi that lead to local immune-mediated vasculitis. [12]. As with CG, a membranoproliferative-pattern GN with IgG and C3 deposition is the traditional pattern of injury for IE. However, a recent study of clinical specimens demonstrated that IE presented most

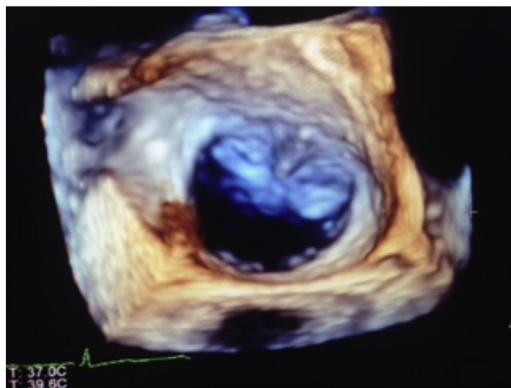


Fig. 6. Transthoracic Echocardiogram. Three dimensional reconstruction showing a vegetation on the aortic valve.



Fig. 7. Transthoracic Echocardiogram. Color flow doppler image showing severe aortic insufficiency.

Table 1
Endocarditis Diagnostic Criteria – Modified Duke Criteria.

Major Criteria
Positive blood cultures Typical pathogens from at least two separate cultures (<i>Staphylococcus aureus</i> , <i>Streptococcus bovis</i> or <i>viridans</i> , HACEK [*] organisms, <i>Enterococcus</i>) Evidence of endocardial involvement by echocardiography Endocardial vegetation, perivalvular abscess, new partial dehiscence of prosthetics valve, new valvular regurgitation <i>Coxiella burnetii</i> blood culture Single positive culture or anti-phase 1 IgG antibody titer >1:800
Minor Criteria
Predisposition Heart condition, intravenous drug use, indwelling catheters, poor dentition, diabetes mellitus, hemodialysis Fever Greater than or equal to thirty-eight degrees Celsius Microbiologic evidence Positive blood culture not meeting major criteria Vascular phenomena Septic arterial or pulmonary emboli, mycotic aneurysms, intracranial or conjunctival hemorrhages, Janeway lesions Immune phenomena Rheumatoid factor, glomerulonephritis, Osler's nodes, Roth's spots

Highly probable: 2 major or 1 major and 3 minor or 5 minor criteria.

Possible: 1 major and 1 minor or 3 minor.

^{*} Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella.

commonly with crescentic GN, followed by diffuse proliferation, and finally mesangial proliferation without endocapillary proliferation or crescent formation, the latter of which was seen in this case [13]. Confounding this case is the presence of dominant IgM staining in addition to C3. IgM was found in only 37% of IE cases in the recent study. Thus, no definitive etiology could be identified by renal biopsy alone in this case.

Early recognition of IE is important as it is reported that in-hospital mortality is 18–23% and 6-month mortality is 22–27% [14]. However, in one case series, IE was unrecognized in almost 1/5 of cases at the time of nephrology consult [15]. If a patient is clinically stable, treatment can wait until blood culture results are available and targeted therapy can be delivered [16]. When patients are acutely ill, empiric treatment should be given after two or three sets of blood cultures are drawn and Vancomycin is an appropriate choice for most patients [17]. A cardiac surgery consultation is recommended for cases where complications arise or are suspected such as infection of prosthetic valves, heart block, systemic emboli, or new moderate to severe heart failure. Assessment of response is based on clinical observation; fever should resolve between 3–7 days, and repeat cultures should demonstrate clearance of bacteremia. Duration of therapy can vary based on organism, but is typically six weeks starting with the first day of negative blood cultures.

Conclusion

This case highlights the similarity in risk factors, clinical findings, and renal complications of IE and mixed CG. It also provides an opportunity for reflection on the use of heuristics and how bias can affect diagnosis and treatment. Healthcare providers must maintain a broad differential and continue to re-evaluate the patient as additional information arises. Due to HCV infection and acute kidney injury, it was reasonable to suspect CG in this patient. Kidney biopsy results added support for this diagnosis, but mesangioproliferative GN is not specific for CG and chronic infection can yield similar results. In addition, it is very common to see a urinary tract infection (UTI) in hospitalized patients. When blood cultures returned positive, they were believed to be from a urinary source, however IVDU should significantly elevate the suspicion for endocarditis. Anchoring to the original admit diagnoses, UTI and CG, led to the belief that two distinct processes

were occurring. However in this particular case, Occam's razor appears to prevail and all findings could be attributed to IE.

Conflicts of interest

None of the authors have any conflicts of interest to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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