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Case report

Prosthetic valve endocarditis from *Mycobacterium chimaera* infection causing granulomatous interstitial nephritis

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ABSTRACT

Mycobacterium chimaera is a rare infection associated with cardiopulmonary bypass. We describe a case of granulomatous interstitial nephritis caused by *M. chimaera* in a patient with prosthetic aortic valve endocarditis. A 63-year-old female with a mechanical aortic valve replacement developed fatigue, 20 lbs. weight loss, anemia, and an elevated creatinine. Fat pad aspirate at an outside hospital was suspicious for amyloidosis which prompted hematology referral at our institution. Bone marrow biopsy revealed a single granuloma, negative for amyloid or acid fast bacillus (AFB). She was admitted to our hospital for worsening kidney function refractory to intravenous fluid challenge. Transesophageal echocardiogram showed aortic root abscess and valve vegetation with negative blood cultures at seven days. Renal biopsy showed granulomatous interstitial nephritis and negative AFB stain. Prednisone 40 mg was started and renal function partially improved. Blood cultures obtained before biopsy subsequently grew *M. chimaera*. Three-drug antimicrobial therapy was initiated and prednisone discontinued. One month later, creatinine improved and follow up echocardiogram showed no lesion. Our case highlights this rare infection inducing granulomatous interstitial nephritis despite lack of positive AFB or gram stains on renal biopsy.

Introduction

The incidence of infective endocarditis due to *Mycobacterium chimaera* after heart surgery has been increasing [1]. Clinically, these infections begin to manifest after a lag time of several months to years [2]. Surgical reports suggest causation with cardiopulmonary bypass heater-cooler units as a reservoir for the organism during surgery with both bioprosthetic and mechanical valves becoming infected [2–4]. *M. chimaera* has been associated with pulmonary infections but appears to be less virulent than *Mycobacterium avium* and *Mycobacterium intracellulare* [1]. Infections are characterized by a poor prognosis with a case fatality rate around 50 % despite treatment [3]. Typical symptoms include fever, shortness of breath, fatigue and weight loss with laboratory studies demonstrating anemia, elevated creatinine and C-reactive protein, lymphocytopenia and thrombocytopenia [2]. We present a case of disseminated *M. chimaera* in a patient with prosthetic valve replacement presenting with symptoms of fatigue, weight loss, hematologic derangements, and granulomatous interstitial nephritis on biopsy.

Case report

A 63-year-old female with history of mechanical aortic valve surgery six years prior presented at an outside facility for evaluation of anemia and elevated serum creatinine of 2.8 mg/dL (unknown baseline creatinine) without known history of renal disease. She was subsequently hospitalized for progressive fatigue, 20 lbs. weight loss, and transfusion dependent anemia. Bone marrow biopsy and fat pad aspirate were suspicious for possible amyloidosis. She was empirically treated with prednisone for 2 weeks and referred to our hematology department for a second opinion. Bone marrow biopsy showed a solitary granuloma with bone marrow acid-fast bacterium (AFB) and Gram stains negative. Free light chains were elevated but the ratio was normal, and Congo red staining of fat pad biopsy was negative. Transthoracic echocardiogram revealed a suspicious lesion on her aortic valve prompting admission to our hospital. Transesophageal echocardiogram (TEE) raised concern for possible aortic root abscess and vegetation attached to the

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ventricular aspect of the prosthetic valve; however, cardiac MRI indicated that these abnormalities could be related to complications during aortic prosthetic valve placement surgery. She was started on vancomycin and ceftriaxone, but blood cultures were negative at seven days. Patient remained afebrile without any peripheral stigmata of endocarditis or evidence of elevated inflammatory markers thereby prompting discontinuation of antibacterials. Creatinine initially increased to 4.0 mg/dL but improved to 3.3 mg/dL with intravenous (IV) fluids. Patient was discharged from hospital for outpatient management.

Two weeks later, the patient was readmitted to hospital with fever of 102 °F and worsening renal function with serum creatinine of 6.1 mg/dL. At this time, nephrology was consulted. Pertinent findings on physical exam included a blood pressure 132/78 mmHg, no rashes, clear lung sounds, no edema or joint tenderness. Labs are depicted in Table 1. Urinalysis unrevealing for white blood cells, red blood cells or cellular casts on microscopic exam and random protein to creatinine ratio 0.99. Renal ultrasound did not show hydronephrosis. Blood and urine cultures for AFB and fungi were obtained. She was treated with supportive care and IV fluids with minimal response. Renal biopsy showed granulomatosis interstitial nephritis with eosinophils, moderate arteriolosclerosis, and mild interstitial fibrosis (Fig. 1). No cultures were performed on biopsy tissue, but AFB and Gram stains were negative. Based on the renal biopsy findings and lack of evidence of active infection, prednisone therapy was restarted.

Initially, her renal function recovered to a serum creatinine nadir of 2.6 mg/dL with the use of prednisone. However, she subsequently developed thrombocytopenia with platelets dropping to 3000 refractory to IV immunoglobulin infusions and platelet transfusion. AFB blood cultures obtained two days prior to renal biopsy turned positive for *M. chimaera* after 15 days of incubation triggering discontinuation of corticosteroids and treatment with clarithromycin, rifabutin, and ethambutol. The antimicrobial treatment resulted in improvement of thrombocytopenia, serialnegative follow up blood cultures at 1, 3, and 6 months after starting the treatment, and resolution of TEE findings. The serum creatinine improved to 2.3 mg/dL.

Table 1
Laboratory Data.

	Lab Result	Reference Range
Hemoglobin	10.7 g/dL	11.6–15.0 g/dL
White Blood Cells	4.4 × 10^9/L	3.4–9.6 × 10^9/L
-Neutrophils	67 %	50.0–75.0 %
-Lymphocytes	14 %	18.0–42.0 %
-Atypical Lymphocytes	8%	0%
-Eosinophils	0%	1.0–3.0 %
Platelets	112 × 10^9/L	157–371 × 10^9/L
Sodium	133 mmol/L	135–145 mmol/L
Potassium	3.9 mmol/L	3.6–5.2 mmol/L
Chloride	100 mmol/L	98–107 mmol/L
Bicarbonate	16 mmol/L	22–29 mmol/L
BUN	51 mg/dL	6–21 mg/dL
Creatinine	6.1 mg/dL	0.59–1.04 mg/dL
Phosphorus	3.6 mg/dL	2.5–4.5 mg/dL
Calcium	8.5 mg/dL	8.6–10.0 mg/dL
Albumin	3.2 g/dL	3.5–5.0 g/dL
C3	111 mg/dL	75–175 mg/dL
C4	67 mg/dL	14–40 mg/dL
CRP	12.8 mg/L	<8.0 mg/L
Sedimentation Rate	42 mm/hr	0–29 mm/hr
Angiotensin Converting Enzyme	84 U/L	16-85 U/L
p-ANCA / c-ANCA	Negative	Negative
Kappa / Lambda Ratio	1.22	0.26-1.65

Discussion

Granulomatous interstitial nephritis (GIN) is a rare histologic diagnosis that is present in less than 1% of all native and transplant renal biopsies [5]. Common etiologies of GIN include medications (allopurinol, anticonvulsants, antimicrobials, non-steroidal anti-inflammatory drugs), infections including fungi and mycobacteria, sarcoidosis, paraproteinemias, and granulomatosis with polyangiitis [6]. Macrophages infiltrate the renal interstitium differentiating into epithelioid and multinucleated giant cells which interact with T and B lymphocytes forming a granuloma [7]. This cellular deposition leads to a fibrotic response impacting organ function [8]. Treatment for GIN usually requires corticosteroids unless a primary infectious etiology is detected as seen in our case. Our patient's evaluation was complicated by granulomatous disease on renal biopsy without positive blood or bone marrow culture data suggesting the possibility of sarcoidosis thereby warranting reinstation of corticosteroids.

Achermann et al. reported two cases of immunocompromised hosts with prosthetic valve endocarditis due to *M. chimaera* [4]. One patient was prescribed corticosteroids for a working diagnosis of systemic sarcoidosis whereas the other patient had a primary immune deficiency disorder. Both cases showed granulomatous inflammation in kidney biopsy specimen. However, the patient on steroid treatment did not stain positive for *M. chimaera* on kidney biopsy in contrast to the patient with an immune deficiency who had macrophages containing acid-fast staining bacterium on kidney biopsy. In our patient, the negative AFB staining on kidney tissue suggests GIN is more likely an immunogenic response to the endocarditis rather than a direct *M. chimaera* kidney infection. Similar to our case, the patient treated with steroid was initially diagnosed as systemic sarcoidosis based upon granulomatous inflammation in kidney, liver and reticular pattern noted on chest imaging. The use of corticosteroids in that case resulted in unmasking of underlying *M. chimaera* infection as the cause of granulomatous inflammation as well. A case series by Kohler et al. reviewing 10 patients with prior cardiac surgery using prosthetic material demonstrated mycobacterial infection in the absence of severe immunodeficiency [2]. Clinical presenation included fever, night sweats, weight loss and nonspecific laboratory findings that included anemia and elevated creatinine. 3 out of the 10 patients were noted to have nephritis with two renal biopsies demonstrating granulomatosis inflammation. Clinicians need to maintain a high index of suspicion for non-tuberculosis mycobacterial infection in patients with cardiac prosthetic material presenting with signs of disseminated disease without identification of a causative pathogen.

Our patient was diagnosed and treated before any signs of valvular heart failure. While on antimicrobial therapy, her thrombocytopenia resolved, creatinine improved to 2.3 mg/dL, follow up blood cultures were negative at 1, 3, 6 months after starting the treatment, and repeat TEE showed resolution of the vegetation. This case highlights the importance of thoroughly investigating for uncommon infections such as *M. chimaera* in patients with a prosthetic valve presenting with GIN. *Mycobacterium species* can require 14–21 days of incubation on culture media before detection; therefore, delaying empiric use of corticosteroids may prevent further morbidity and mortality should cultures become positive [9].

In conclusion, clinicians should be aware of this unique presentation of *M. chimaera* endocarditis in patients who have prosthetic valve replacement, renal injury, anemia, and granulomatous disease on renal biopsy. As noted in other case studies, failure to identify and treat will result in high mortality due to valvular failure.

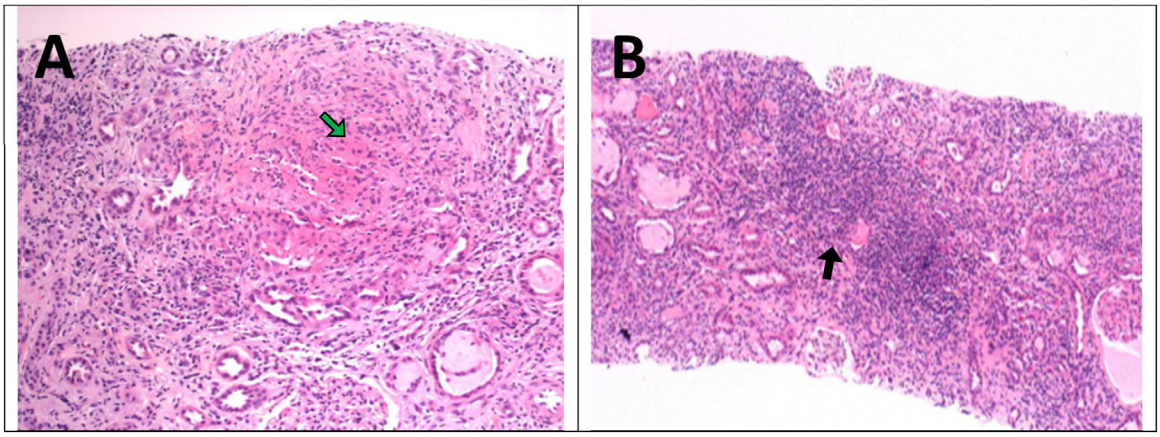

Fig. 1. Renal biopsy.
A) Low powered magnification with hematoxylin and eosin stain highlighting an interstitial granuloma (green arrow). (B) Low powered magnification of renal cortex with hematoxylin and eosin stain showing chronic interstitial inflammation (black arrow).

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Declaration of Competing Interest

None.

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