



## Case report

# Persistent immune thrombocytopenia heralds the diagnosis of *Mycobacterium chimaera* prosthetic valve endocarditis

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## ABSTRACT

A 63 year old female was admitted for investigation of worsening renal insufficiency. During hospitalization she developed persistent immune thrombocytopenia refractory to supportive or immunosuppressive treatment. She was diagnosed with *Mycobacterium chimaera* prosthetic valve endocarditis and thrombocytopenia resolved with anti-mycobacterial therapy.

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## Introduction

*Mycobacterium chimaera* is a fastidious pathogen which has been reported to cause invasive infections after open-heart surgery [1]. Observational studies suggest that the organism is transmitted via aerosol generated through contaminated heater-cooler devices used in cardiac surgery [2–5]. We describe a case of prosthetic valve endocarditis presenting with persistent thrombocytopenia.

## Case description

A 63-year-old woman was admitted for evaluation of a 6 month history of generalized malaise, fatigue and 10 kg weight loss. Her past medical history was pertinent for St. Jude's mechanical aortic valve replacement (AVR) 6 years prior due to aortic insufficiency. Three years later she was diagnosed with renal insufficiency. On presentation to our institution her estimated glomerular filtration rate (eGFR) was 11 mL/min/1.73 m<sup>2</sup>. The patient denied history of fever and had no foreign travel over the past 5 years. She denied

taking antimicrobials over the past year, since they had last been prescribed for prophylaxis prior to a minor dental procedure.

A bone marrow biopsy performed at an outside facility for investigation of leukopenia showed a non-specific granuloma, Congo red stains together with stains for fungi and acid-fast bacilli were reported as negative. A transesophageal echocardiogram (TEE) prior to admission showed thickening of the aortic annulus with root cavitation. A linear echodensity was seen over the ventral aspect of the mechanical aortic prosthesis (Fig. 1). Cardiac magnetic resonance imaging (MRI) confirmed a 5 mm linear mobile density with abscess formation on the aortic root. However she was afebrile without specific clinical findings of endocarditis and no growth was detected on blood cultures after 14 days of incubation.

On arrival the patient was alert, afebrile (36.4 °C [range 36.4 °C–37.0 °C]) with a pulse 85 beats per minute, her blood pressure was 115/70 mmHg and oxygen saturation 96% on 2 L per minute via nasal cannula. Her examination was notable for a grade II/VI systolic ejection murmur at the upper right sternal base and a prominent 'metallic' second heart sound. There was no peripheral edema and jugular venous pressure was normal. Lungs were clear. No lymphadenopathy or organomegaly were appreciated. The patient developed a fever of 38.9 °C on her first night of admission. Blood cultures were drawn.

Pertinent laboratory findings on admission (reference ranges provided parenthetically) included a hemoglobin 8.5 g/dL (12.0–15.5 g/dL), mean corpuscular volume 80.0 fL (81.6–98.3 fL), leukocyte count  $2.4 \times 10^9/L$  ( $3.5\text{--}10.5 \times 10^9/L$ ), platelet count  $182 \times 10^9/L$  ( $150\text{--}450 \times 10^9/L$ ), serum sodium 132 mmol/L (135–145 mmol/L),

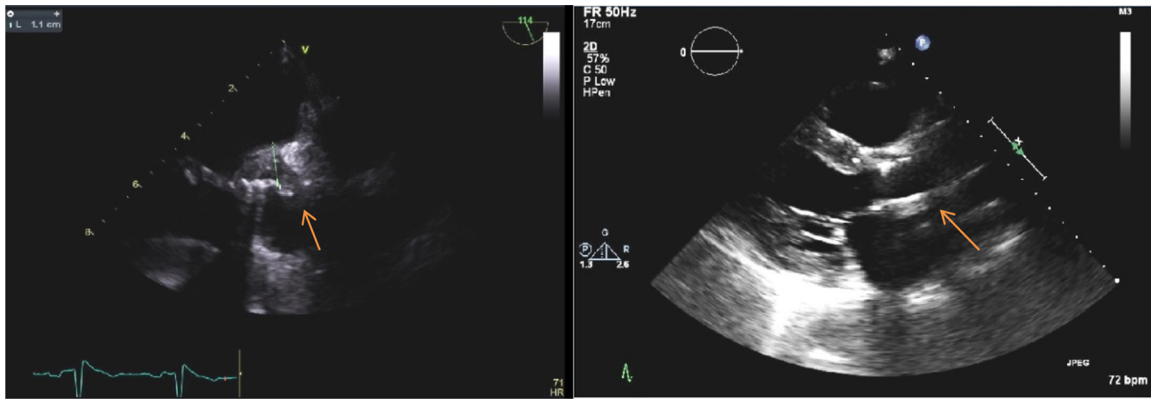
**Abbreviations:** ANA, anti-nuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; AVR, aortic valve repair; CT, computerized tomography; eGFR, estimated glomerular filtration rate; ENA, extractable nuclear antigen; HIV, human immunodeficiency virus; ITP, immune thrombocytopenia purpura; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; PVE, prosthetic valve endocarditis; TEE, transesophageal echocardiogram.

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**Fig. 1.** Transesophageal echocardiogram (TEE) images showing aortic root abscess (left) and abnormal thickening of aortic annulus and aortic root with cavitation (right).

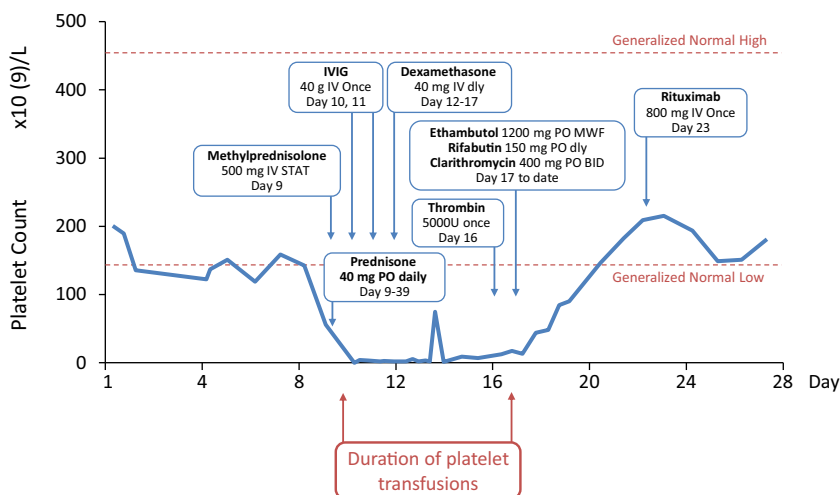
serum creatinine 4.2 mg/dL (0.6–1.1 mg/dL), blood urea nitrogen 39 mg/dL (6–21 mg/dL), aspartate aminotransferase 44 U/L (8–43 U/L), lactate dehydrogenase 314 U/L (122–222 U/L), prothrombin time 21.4 s (11.6–14.7 s), international normalized ratio 1.9 with patient being on warfarin for her mechanical aortic valve. Her erythrocyte sedimentation rate was 32 mm/1 h (0–29 mm/1 h) and serum haptoglobin <14 mg/dL (30–200 mg/dL). Complement C3 and C4 levels were within reference range. Serum assays for anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA) and extractable nuclear antigen (ENA) were below threshold to be clinically significant. Serologic studies for Legionella, Q fever and Bartonella were negative. Renal ultrasound showed mild increase in renal cortical echogenicity with no evidence of hydronephrosis. Renal biopsy showed granulomatous interstitial nephritis with computerized tomography (CT) of the abdomen showing diffuse small bowel granulomas.

Nine days into her hospitalization, the patient developed severe thrombocytopenia of  $3 \times 10^9/L$  ( $150\text{--}450 \times 10^9/L$ ) down from  $149 \times 10^9/L$  the day prior. This was associated with spontaneous epistaxis. Her thrombocytopenia was refractory to daily supportive pooled platelets administered over the subsequent 7 days. Intravenous immunoglobulin (IVIg) infusions together with 40 mg prednisone daily were administered. All interventions were unable to raise her platelet count above  $5 \times 10^9/L$  (Fig. 2). A repeat bone marrow biopsy showed a hypercellular marrow (55%) with erythroid and megakaryocytic hyperplasia consistent with a reactive process such as immune thrombocytopenia.

An autoimmune etiology for her diffuse granulomas was suspected (bone marrow, bowel and kidney) given the negative bone marrow stains for possible infectious etiologies (mycobacteria and fungi). The patient had normal calcium and vitamin D levels with preserved CD4:CD8 ratio therefore a diagnosis of sarcoidosis was unlikely. Common variable immunodeficiency presenting with autoimmune thrombocytopenia was suspected (given the presence of non-specific granulomas). However, serial immunoglobulin levels were within reference range.

A repeat set of blood cultures was positive for mycobacteria yielding *Mycobacterium chimaera* after 16 days of incubation. The mycobacterium was sensitive to clarithromycin and resistant to moxifloxacin and linezolid. Her presentation was consistent with *M. chimaera* bacteremia secondary to subacute prosthetic valve endocarditis.

The patient was started on clarithromycin, ethambutol and rifabutin to treat *M. chimaera* bacteremia secondary to prosthetic valve endocarditis. After 2 days of antimicrobial treatment her thrombocytopenia resolved with resolution of spontaneous bleeding. The patient was subsequently slowly titrated off prednisone. The patient reported resolution of her constitutional symptoms after 2 weeks of initiating antimicrobials. Repeat TEE 4 weeks later showed no interval changes. She was seen by cardiothoracic surgery and is scheduled for AVR replacement following cessation of antimicrobial therapy.



**Fig. 2.** Medications administered during course of thrombocytopenia with resolution occurring after start of anti-mycobacterial therapy. Day 14 platelet count is an artefact as lab was drawn during platelet transfusion.

## Discussion

Infective endocarditis due to nontuberculous mycobacteria is a rare event. *M. chimaera* belongs to the group of *Mycobacterium avium* complex organisms which are the commonest cause for non-tuberculous mycobacterial infection in humans [6]. Kohler et al. described the clinical characteristics of 10 patients with disseminated *M. chimaera* infections following open heart surgery. All patients had prosthetic material-associated infections. Thrombocytopenia was present in all patients ranging between 28,000–177,000 platelets however no bleeding diathesis was reported. The duration from cardiac surgery to diagnosis of infection ranged from 5 to 40 months [1]. Our patient presented around 72 months after surgery with significant symptomatic thrombocytopenia.

The association between immune thrombocytopenia and mycobacterial infection has been previously described. In one case, the patient developed thrombocytopenia in the setting of disseminated tuberculosis with bone marrow involvement. Thrombocytopenia resolved following administration of oral prednisone with anti-tuberculous drugs [7]. Boots et al. reports a case of immune thrombocytopenia complicating pulmonary tuberculosis [8]. The patient's thrombocytopenia resolved with IVIG in conjunction with anti-tuberculous chemotherapy. A direct platelet suspension immunofluorescence was positive for platelet surface immunoglobulin G thus confirming immune thrombocytopenia purpura (ITP).

*Mycobacterium avium-intracellulare* has been reported as a cause for ITP in an HIV patient with resolution of thrombocytopenia noted after 2 weeks of initiating antituberculous treatment [9]. To our knowledge this is the first case of *M. chimaera* infection presenting with persistent thrombocytopenia that had a likely immune etiology. Although no assays for antiplatelet antibodies were performed this etiology was supported by persistent low platelet counts (less than  $5 \times 10^9/L$ ) despite platelet transfusion and bone marrow findings showing erythroid and megakaryocytic hyperplasia.

This case demonstrates that non-tuberculous mycobacterial endocarditis may present subacutely and a mycobacterial etiology should be considered in a differential diagnosis for persistent thrombocytopenia with evidence of granulomatous disease highlighting utility for prolonged blood culture incubation.

## Funding sources

None.

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