

# Mycobacterium chimaera infection: a complex disease with many complications

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## Introduction and aims

- Mycobacterium chimaera (M. chimaera) is an environmental non-tuberculous mycobacterium and a member of the Mycobacterium avium complex.
- Cases of M. chimaera endocarditis and disseminated disease, associated with contaminated heater-cooler units used in cardiopulmonary bypass, have been seen following cardiothoracic surgery. The mechanism of transmission is thought to be aerosolisation of particles from infected water tanks. Since 2013 more than 100 cases have been reported in Europe and North America (1).
- The management of M. chimaera infection is extremely difficult. Balancing the duration of pharmacological therapy and number of drugs with associated side-effects and disease complications is complex with limited evidence base at present. Treatment regimens are currently based upon Mycobacterium avium-intracellulare studies and case studies in M. chimaera. The role and timing of surgery remains unclear, and outcomes from case studies are poor (2,3).
- Two cases have been managed in our tertiary clinical infection unit (CIU) in South-London
- Both were initially commenced on rifabutin, ethambutol and clarithromycin.
- This case review highlights four key complications of disease manifestation and treatment.

**Patient-X:**

- 71 year-old man; PMH type II diabetes mellitus, coronary artery disease and calcific aortic stenosis
- 2013: Elective tissue aortic valve replacement and coronary artery bypass
- May 2017: presented to local hospital; few months of fever, dry cough and night sweats
- At presentation: pancytopenia; bone marrow aspirate revealed granulomas
- Transferred to St George's for further investigation
- Repeat bone marrow aspirate : non-caseating granulomas, no acid-fast bacilli (AFB) seen and no growth on mycobacterial culture
- Transthoracic echocardiogram: small aortic valve vegetation consistent with infective endocarditis; no haemodynamic compromise and a well-seated valve
- Microbiological diagnosis of M. chimaera made with whole genome sequencing after culture from blood and sputum

**Patient-Y:**

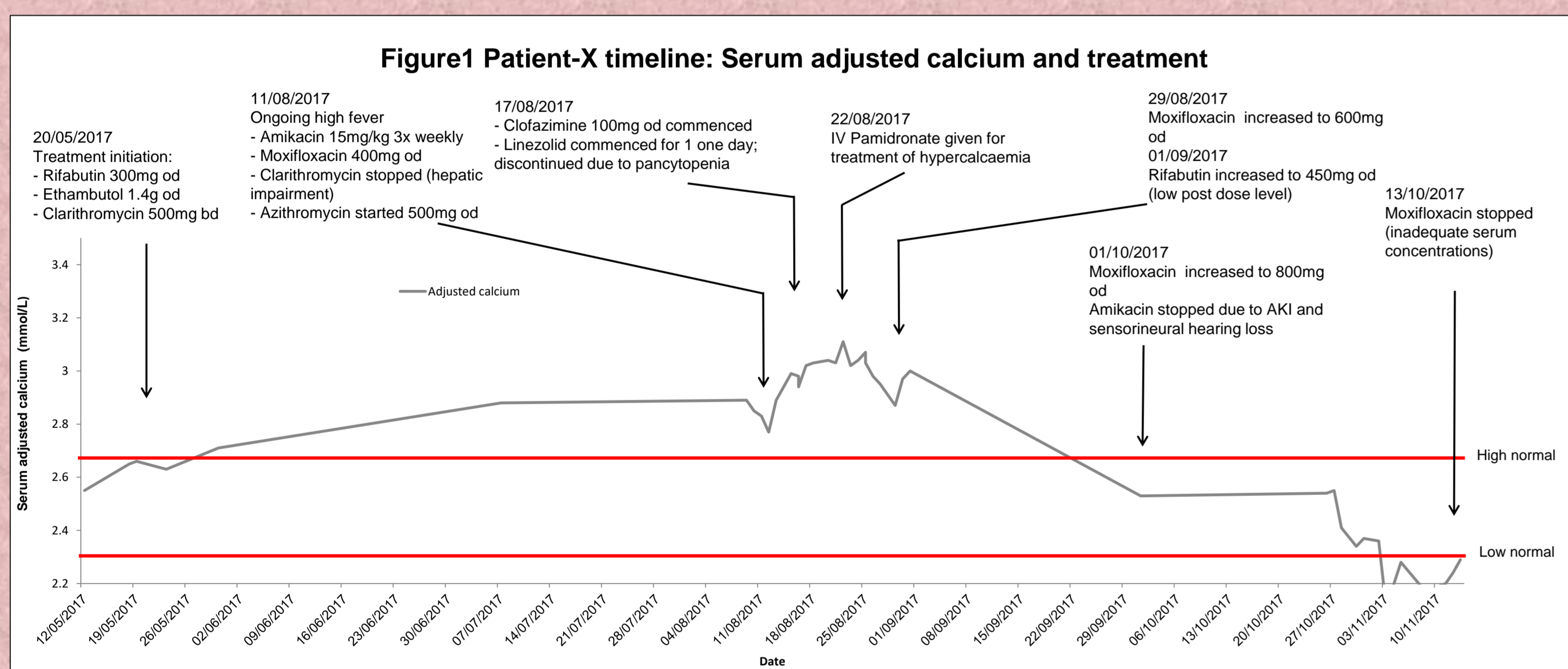
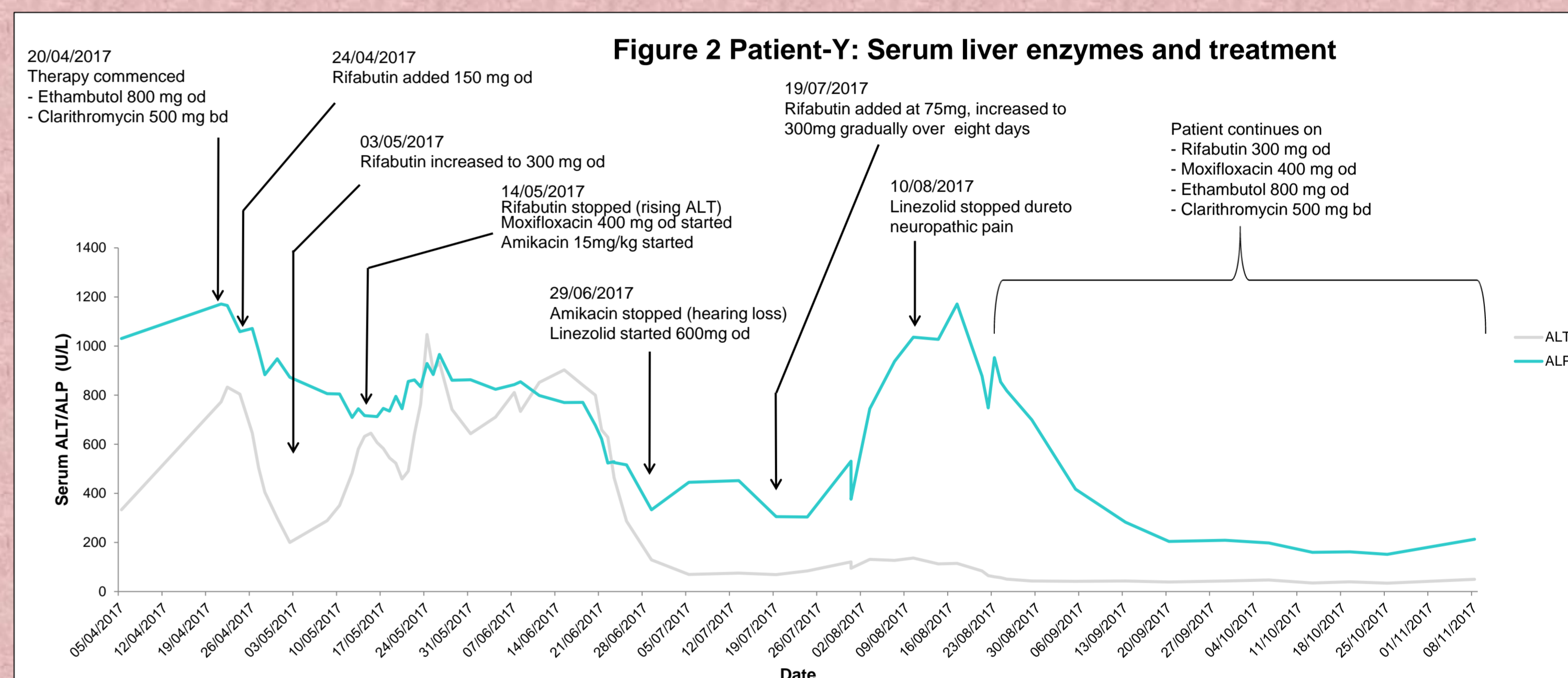
- 36 year-old female; PMH surgical repair of scoliosis, breast implants, restrictive lung disease secondary to scoliosis, oesophagitis and eating disorder
- 2014: Presented with acute heart failure secondary to mitral valve prolapse and cord rupture; urgent mitral valve repair with annuloplasty
- June 2015: presented to local hospital; three-month history of fever and lethargy, abdominal distension
- Deranged liver enzymes, hypercalcaemia and CT showed hepatosplenomegaly
- Liver biopsy: granulomatous hepatitis
- Commenced on steroids for sarcoidosis (raised serum ACE)
- Commenced on azathioprine for presumed sarcoid/autoimmune liver disease
- Bone marrow aspirate: granulomatous disease
- Repeat liver biopsy : granulomatous disease
- Splenectomy due to massive splenomegaly; histology showed granulomatous changes and AFB within the granulomas
- Commenced on quadruple therapy for presumed M. tuberculosis. Stopped after acute admission with liver enzyme derangement, vomiting
- April 2017: M. chimaera eventually cultured from liver and blood
- Transoesophageal echocardiogram: well seated mitral valve ring, large vegetation on mitral valve, mild mitral regurgitation. Normal biventricular size and function

## 1. Hypercalcaemia

At diagnosis Patient-X had a normal adjusted calcium (aCa) which rose on first-line triple therapy over three months. He continued to have high fevers (>40 degrees). Peak aCa was 3.11 mmol/L which was treated with IV pamidronate. Concurrently the treatment regimen was escalated to six agents and doses optimised. Over a period of four to six weeks the aCa fell to within normal limits. This normalisation of serum aCa mirrored a period of defervescence, which may reflect reducing disease activity (Figure 1).

Patient-Y was hypercalcaemic at presentation, contributing to her initial diagnosis of sarcoidosis. The hypercalcaemia was responsive to steroid treatment, but there has been recurrent relapse with hypercalcaemia and acute pancreatitis after attempts to wean her steroids (aCa peak 3.87 mmol/L). One such admission resulted in acute respiratory distress syndrome, type 1 respiratory failure and an ICU admission. She remains steroid dependant likely requiring long term maintenance therapy (Figure 3).

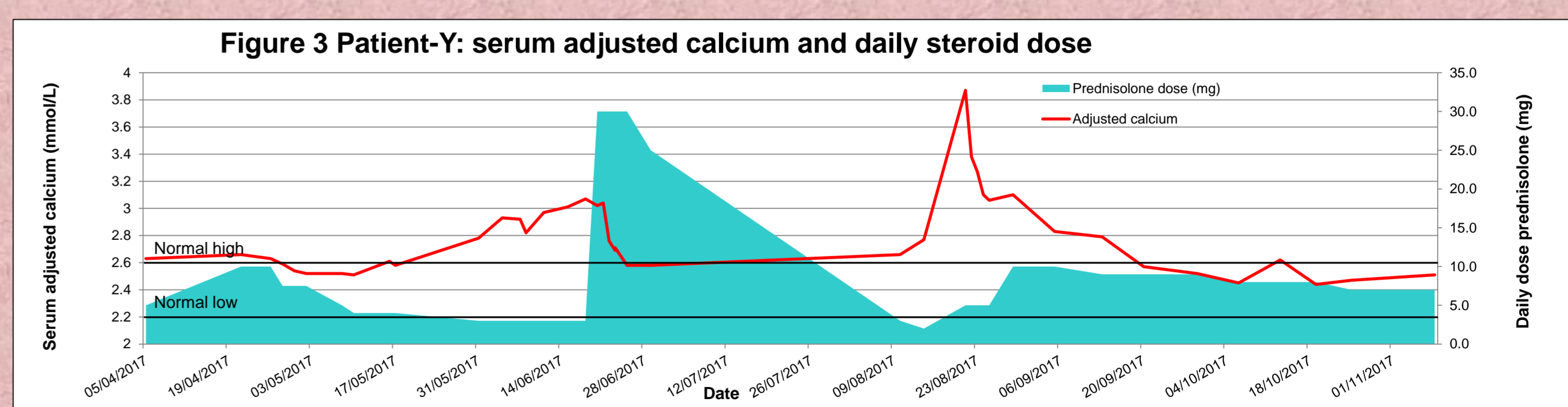
The mechanism for hypercalcaemia in granulomatous disease is thought to be increased intestinal calcium absorption (plus possibly increased bone resorption). This is a result of overproduction of activated vitamin D (calcitriol) by macrophages in granulomas (4).



## 4. Liver disease

**Patient-X:** imaging suggested cirrhosis with portal hypertension. This was confirmed on trans-jugular liver biopsy showing granulomatous hepatitis with early cirrhosis. There were no AFB seen and unfortunately the sample wasn't cultured. Routine viral, autoimmune, metabolic and tumour marker screens for liver disease were negative. The degree of cirrhosis was consistent with prior undiagnosed cirrhosis due to non-alcoholic fatty liver disease with superadded granulomatous infiltration following M. chimaera infection. There was decompensation with ascites and jaundice, and management included recurrent paracentesis after limited benefit with diuretics. No AFB were seen on ascitic fluid with no mycobacterial growth. He developed hepatorenal syndrome type II (HRS2) and required IV terlipressin and human albumin solution infusions. In view of Child-Pugh stage C cirrhosis and HRS2, the prognosis is most likely limited by the liver disease. Further valve surgery for endocarditis was deemed too risky in view of cirrhotic liver disease.

**Patient Y:** hepatosplenomegaly at presentation, with deranged liver enzymes. Diagnosis was made through granulomatous hepatic histology and microbiological culture. Liver enzymes deteriorated on multiple occasions, felt to be a combination of M. chimaera liver involvement, drug toxicities and possibly an autoimmune response to infection (Figure 2). There are no features of decompensated liver disease at present. However, liver dysfunction has resulted in a delay to further valve surgery for endocarditis.



## 2. Treatment-related complications

**Amikacin:** Both patients have developed sensorineural deafness on amikacin treatment. Patient-X has moderate-to-severe bilateral hearing loss and required hearing aids. Patient-Y has two aetiologies of hearing loss; deterioration of right sided hearing over a period of months or years, which continued to worsen with amikacin. The possibility of M chimaera itself as a cause was raised. High frequency hearing loss was seen on the left side consistent with Brock grade 1 amikacin-related ototoxicity (Figure 3). Amikacin was discontinued in both patients.

**Linezolid** could not be used in Patient-X due to significant pancytopenia and was discontinued in Patient-Y due to painful peripheral neuropathy.

**Azithromycin** was initiated in place of clarithromycin for Patient-X due to cirrhosis. **Rifabutin** was introduced with caution in Patient-Y, but discontinued due to likely drug-induced liver injury. It was re-introduced gradually with no significant adverse effects (Figure 2).

## 3. Myelosuppression

**Patient-X** was pancytopenic at diagnosis and has remained so despite antimicrobial treatment. He has had symptomatic anaemia requiring frequent red cell transfusions. Worsening thrombocytopenia has required platelet transfusion prior to procedures (platelet nadir  $42 \times 10^9/L$ ). This is likely a reflection on marrow involvement and splenic sequestration from portal hypertension. Repeat bone marrow aspirations have yielded granulomatous histology, but normal tri-linear haematopoiesis.

**Patient-Y** was anaemic at presentation and has since required red cell transfusion. This was compounded during a period of treatment with azathioprine for the presumed sarcoidosis.

## Clinical learning points

- Hypercalcaemia can be severe and symptomatic and may mislead clinicians to suspect sarcoidosis; steroid treatment may be required
- Mycobacterial disease should remain in the differential for diagnosis for hypercalcaemia
- A spectrum of liver disease exists, dramatically exacerbated if there is pre-existing liver disease
- Disseminated disease will effect decisions on valve surgery
- Pancytopenia reflects bone marrow involvement and may be severe
- Drug toxicities are common and complicate treatment
  - Amikacin-related hearing loss
  - Peripheral neuropathy with linezolid
  - Liver dysfunction; rifabutin and clarithromycin
- Further studies are needed to guide treatment regimens and the timing/role of surgery

References  
(1) van Ingen J. et al. Global outbreak of severe Mycobacterium chimaera disease after cardiac surgery: a molecular epidemiological study. Lancet Infect Dis. 2017 Oct;17(10):1033-1041.  
(2) Tan N. et al. Disseminated Mycobacterium chimaera Infection After Cardiothoracic Surgery. Open Forum Infect Dis. 2016 Sep; 3(3): ofw131  
(3) Kohler P. et al. Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated Mycobacterium chimaera infections subsequent to open heart surgery. Eur Heart J. 2015 Oct 21;36(40):2745-53  
(4) Peter J. et al. Hypercalcaemia and Elevated 1,25-Dihydroxyvitamin D Levels in a Patient with End-Stage Renal Disease and Active Tuberculosis. N Engl J Med. 1984; 311:1683-1685