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# Hypercalcaemia secondary to disseminated *Mycobacterium abscessus* and *Mycobacterium fortuitum*

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**Abstract**

**The incidence and prevalence of nontuberculous mycobacteria (NTM) infection is on the rise with many cases still going unreported. Given the vague and nonspecific clinical features of NTM infections, it is often missed or mistaken for *Mycobacterium tuberculosis*. The presumption that NTM infections are benign and do not contribute to morbidity no longer holds true. NTM infections need to be considered in patients with disseminated multisystem disease and in those not responding to standard *M. tuberculosis* treatment. As NTM infection is associated with granuloma formation, it can result in hypercalcaemia. Interestingly, there is evidence that there may be other mechanisms in play contributing to hypercalcaemia besides the increased calcitriol levels.**

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## Introduction

The environment is abundant in nontuberculous mycobacteria (NTM), but NTM rarely cause infection in immunocompetent humans. However, the incidence of NTM infections is increasing, and because of its diverse presentations diagnosis is often challenging.

## Case presentation

A 68-year-old Singaporean Indian female with a past medical history of hypertension, hyperlipidaemia and minor stroke presented to us with 3 days of fever and dysuria. Physical examination was unremarkable. Basic investigation showed leucocytosis, high C-reactive protein, acute kidney injury, mild hypercalcaemia and deranged liver enzymes (Table 1). Chest X-ray revealed bilateral consolidation, while urinalysis showed pyuria. Empirical intravenous co-amoxiclav was initiated as treatment for possible sepsis from community-acquired pneumonia and urinary tract infection.

Ultrasonography of the abdomen, performed to evaluate the deranged liver function tests, showed diffuse heterogeneous echogenicity involving both lobes of the liver. A contrast-enhanced CT of thorax, abdomen and pelvis was performed. The scan reported diffuse heterogeneous enhancement of the liver and spleen, with multiple ill-defined hypodense areas. Multiple patchy areas of ground-glass opacities and nodular densities were found scattered in bilateral lungs with enlarged left paracardiac-aortic nodes. The radiologist concluded that these findings were nonspecific and may be related to metastatic disease of unknown primary, disseminated infection or inflammation.

Both her parathyroid hormone and calcidiol levels were at the lower end of normal range. In the presence of hypercalcaemia with a relatively suppressed parathyroid hormone, disseminated malignancy was the top differential diagnosis at this stage. She was not taking medications or supplements that could lead to hypercalcaemia. Serum and urine protein electrophoresis showed no paraproteinaemia. An oesophago-gastro-duodenoscopy showed antral gastritis, while a colonoscopy revealed a few colonic polyps, the histology of which turned out to be tubular adenoma with low-grade dysplasia.

She subsequently underwent an ultrasound-guided liver biopsy. The histology showed necrotising granulomatous inflammation. The sample stained positive for acid-fast bacilli. Whilst awaiting the full culture results the patient was given a trial of tuberculosis (TB) treatment comprising isoniazid, rifampicin, pyrazinamide and ethambutol. Her hypercalcaemia was attributed to granulomatous disease and she was started on aggressive intravenous hydration. Despite this her calcium levels remained elevated at 2.7–2.9 mmol/l. She was given oral prednisolone 20 mg once daily for 2 weeks and her serum calcium level became normal at the end of steroid therapy. She was discharged with follow up with our

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**Table 1** Investigation results

| Investigation | Result | Reference |
|---|---|---|
| White cell count | 15.8 × $10^9$/l | 3.6–9.3 × $10^9$/l |
| Haemoglobin | 10.3 g/dl | 11–15 g/dl |
| Platelet | 362 × $10^9$/l | 170–420 × $10^9$/l |
| Creatinine | 179 µmol/l | 40–75 µmol/l |
| C-reactive protein | 211.7 mg/l | 0–5 mg/l |
| Albumin | 25 g/l | 35–48 g/l |
| Bilirubin | 10 µmol/l | 7–31 µmol/l |
| Alanine aminotransferase | 31 U/l | 14–54 U/l |
| Aspartate aminotransferase | 35 U/l | 15–41 U/l |
| Alkaline phosphatase | 268 U/l | 38–126 U/l |
| Gamma glutamyltransferease | 213 U/l | 7–50 U/l |
| Hepatitis B surface antigen | Negative | |
| Antihepatitis B core antibody | Negative | |
| Antihepatitis C antibody | Negative | |
| Prothrombin time | 14.8 s | 11.7–14 s |
| International normalised ratio | 1.2 | |
| Adjusted calcium | 2.77 mmol/l | 2.15–2.58 mmol/l |
| Phosphate | 1.0 mmol/l | 0.8–1.6 mmol/l |
| Parathyroid hormone (intact) | 1 pmol/l | 0.8–6.8 pmol/l |
| 25-hydroxy vitamin D (calcidiol) | 23 µg/l | 20–50 µg/l sufficient |
| Myeloma panel | No paraprotein | |
| Angiotensin-converting enzyme | 83 U/l | 8–53 U/l |
| HIV | Negative | |
| Thyroid function test | Normal | |
| Chest X-ray | Bilateral consolidation | |
| Induced sputum × 3 sets | Acid-fast bacilli stain: negative<br>Tuberculosis culture: negative | |
| Ultrasonography of abdomen | Diffuse heterogeneous echogenicity involving both lobes of the liver could be due to an infiltrative process such as diffuse metastases | |
| Blood culture × 4 sets | Negative | |
| Urine cultures | Negative | |

TB Control Unit and her calcium levels were monitored in the outpatient clinic.

At her clinic appointment 6 weeks later, the tuberculous culture results were found to be negative. The liver tissue was also sent for a tuberculous nucleic acid amplification test (NAAT), which was also negative. The sensitivity of NAAT is high especially when the acid-fast bacilli smear is positive. It ranges between 96 and 98%.[1] Three sets of induced sputum were negative for *Mycobacterium tuberculosis*. Despite the negative results, given the high prevalence of TB in South East Asia accounting for one-third of the TB cases in the world,[2] TB was still top on the list of differentials and the patient was continued on anti-TB medications.

During her TB treatment, her calcium levels rebounded to 2.8 mmol/l. She was started on another course of steroids but her hypercalcaemia remained persistent. She was subsequently given one dose of intravenous zolendronic acid that resulted in normalisation of her calcium levels temporarily.

The TB treatment was given for 9 months but clinical response was poor. She continued to lose weight, her calcium level remained elevated, liver function tests continued to worsen (Table 2) and repeat CT scan showed increased pulmonary infiltrates and marginally bigger splenic and liver hypodensities.

As the patient was not showing any clinical improvement on anti-TB medications sputum cultures were repeated. The repeat sputum culture was positive for *Mycobacterium abscessus* and *Mycobacterium fortuitum*. A diagnosis of disseminated NTM infection was considered. She was

**Table 2** Investigation results

| Investigation | Result | Reference |
|---|---|---|
| White cell count | 21.1 × $10^9$/l | 3.6–9.3 × $10^9$/l |
| Haemoglobin | 9.3 g/dl | 11–15 g/dl |
| Platelet | 457 × $10^9$/l | 170–420 × $10^9$/l |
| Creatinine | 197 µmol/l | 40–75 µmol/l |
| C-reactive protein | 273 mg/l | 0–5 mg/l |
| Albumin | 23 g/l | 35–48 g/l |
| Bilirubin | 15 µmol/l | 7–31 µmol/l |
| Alanine aminotransferase | 87 U/l | 14–54 U/l |
| Aspartate aminotransferase | 95 U/l | 15–41 U/l |
| Alkaline phosphatase | 408 U/l | 38–126 U/l |
| Gamma glutamyltransferase | 342 U/l | 7–50 U/l |
| Adjusted calcium | 2.91 mmol/l | 2.15–2.58 mmol/l |
| Phosphate | 1.2 mmol/l | 0.8–1.6 mmol/l |

started on intravenous cefoxitin, amikacin along with oral clarithromycin, ciprofloxacin and doxycycline based on sensitivities. Her calcium levels normalised, and she showed clinical improvement with treatment of the disseminated NTM. As cases of disseminated NTM are not commonly seen in Singapore, it was not considered initially.

Further investigations were performed to detect any evidence of immunodeficiency. HIV screen was negative. Antibodies against interferon-γ and antigranulocyte macrophage-colony stimulating factor were positive proving presence of adult-onset immunodeficiency.

## Discussion

NTM are ubiquitous organisms that can be found in surface water, tap water, soil, domestic and wild animals, milk and food products.[3] However, these organisms inhabit body surfaces and secretions without causing disease except in patients with chronic illnesses and immunodeficiency.

The most common NTM is *Mycobacterium avium* complex followed by *M. abscessus* complex and *Mycobacterium kansasii*.[4] *M. abscessus* and *M. fortuitum* are classified as rapidly growing mycobacteria.

Disseminated NTM infections have been reported in the medical literature. Still NTM are often deemed as 'benign' infections and they are often not given the similar attention *M. tuberculosis* garners. NTM disease has an incidence rate of about 1.0–1.8 cases per 100,000 persons.[5] As NTM is not a reportable disease in most countries, the true incidence of NTM infections is not known. Studies have shown increased and higher than anticipated incidence of NTM infections.[6] The increased incidence may be attributed to greater exposure to large volume aerosols, the change in plumbing material and lower hot water temperatures.[7] Often NTM infections are misdiagnosed as *M. tuberculosis* infections as NTM still remains a diagnosis of exclusion. Although NTM disease commonly affects the lungs, it can also cause lymphatic, skin and disseminated disease.

The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) have proposed a diagnostic criterion for NTM in a statement released in 2007 (Box 1).[8]

There are various reasons why the initial cultures may have been negative. The agent used for sample decontamination can alter culture outcomes.[9] Also, the choice of culture media is vital. Liquid media are in general more sensitive than solid media, such as used in our case.[10] The culture media is incubated at a temperature of 35˚C, which is optimum for *M. tuberculosis* but not for NTM, which has optimum growth at the temperature of 30˚C.[11] Some NTM organisms require enrichment of the culture medium to enhance growth.[12]

Deciding when to treat NTM is challenging. The concept of colonisation without infection is often used but remains unproven. If the physician opts not to treat the positive NTM result, the patient needs to be followed up to monitor for clinical features that may suggest active infection. Repeated positive culture results are a strong indication for treatment.

A literature search for cases of hypercalcaemia associated with *M. abscessus* and *M. fortuitum* did not yield any results. There are cases reported of *M. avium* complex-associated hypercalcaemia in immunocompetent and immunodeficient patients.

Mechanism of hypercalcaemia in NTM infections, as in other granulomatous diseases, is thought to be mediated by elevated calcitriol due to increased 1α hydroxylase activity from activated macrophages trapped in the pulmonary alveoli and granulomatous inflammation.[13]

Our patient's calcidiol was at the lower end of normal range. Low calcidiol with elevated calcitriol has been described in patients with granulomatous disease.[14] However, there are case reports on hypercalcaemic patients with *M. avium* complex and sarcoidosis with normal calcitriol levels suggesting that a relative excess of calcitriol is sufficient to cause hypercalcaemia.[15] Calcitriol level was not checked for the patient in our case as it is costly and logistically challenging in the local setting. Also, it would not have aided in the diagnosis

**Box 1** American Thoracic Society and Infectious Diseases Society of America proposed diagnostic criteria for nontuberculous mycobacteria

**Clinical**

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules.

and

2. Appropriate exclusion of other diagnoses.

**Microbiologic**

1. Positive culture results from at least two separate expectorated sputum samples. (If the results from the initial sputum samples are nondiagnostic, consider repeat sputum AFB smears and cultures.)

or

2. Positive culture results from at least one bronchial wash or lavage.

or

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination.
5. Patients who are suspected of having NTM lung disease but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded.
6. Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.

AFB: acid-fast bacilli; NTM: nontuberculous mycobacteria

owing to the variability of calcitriol levels in granulomatous disease and the reliability of the assay and method used.[16]

Corticosteroids have been used in the treatment of hypercalcaemia secondary to granulomatous disease. Corticosteroids inhibit the conversion of calcidiol to calcitriol by 1-alpha-hydroxylase and also have anti-inflammatory effects on granulomas that produce vitamin D.[17]

However, there may be other mechanisms by which granulomatous diseases cause hypercalcaemia. A study has shown that expression of parathyroid-related peptide (PTHrP) is a feature of infectious granulomas regardless of aetiology or the tissue involved, suggesting that PTHrP expression is part of the normal granulomatous immune response.[18] This may explain why the calcium levels in our patient showed poor response to the second course of steroids.

Adult-onset immunodeficiency has been reported to be associated with opportunistic infection, including NTM.[19] Upregulation of interferon-γ after mycobacteria is phagocytosed by macrophages triggers neutrophils and macrophages to kill intracellular pathogens, including mycobacteria. This mechanism is important for the control of mycobacteria.[20] Studies have shown cell-mediated immunodeficiency in HIV-negative subjects being caused by antibodies to interferon-γ. A cross-sectional study in Thailand of 20 cases of opportunistic infections in non-HIV subjects showed that all had antibodies to interferon-γ.[21] A larger study of 203 patients in Thailand and Taiwan with opportunistic infections found that 88% of patients had neutralising anti-interferon γ antibodies.[22]

## Conclusion

NTM infections need to be considered in patients with disseminated disease when investigations for TB are negative. There also are mechanisms in addition to increased calcitriol levels that contribute to hypercalcaemia in granulomatous disease.

### Informed consent

Written informed consent for the paper to be published (including images, case history and data) was obtained from the patient/guardian for publication of this paper, including accompanying images.

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