Introduction

Mycobacteria other than *Mycobacterium tuberculosis* and *Mycobacterium leprae* are generally free-living organisms and are ubiquitous in the environment. These are grouped into the broad category of atypical or non-tuberculous mycobacteria (NTM). NTM organisms can inhabit body surfaces or secretions without causing disease. Thus, occasional isolates of NTM were largely considered contaminants or colonizers until the second half of the twentieth century. Despite their more recent recognition as potentially pathogenic organisms, the NTM usually do not cause severe disease in healthy individuals. The majority of NTM infections are recognized to be caused by *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii*. *Mycobacterium szulgai*, a slow-growing NTM, is a relatively rare pathogen, accounting for less than 0.2% of isolated strains in a study of over 36,000 NTM samples from 14 countries throughout Europe and the Middle East.\(^1\)\(^-\)\(^3\) Pulmonary infection is the most common manifestation of *M. szulgai* infection; however, it may be clinically and radiologically confused with active pulmonary tuberculosis. Extra-pulmonary infections due to this organism have been reported in the form of tenosynovitis of the hand, olecranon bursitis, osteomyelitis, keratitis, cervical lymphadenitis, and renal or cutaneous infection.\(^4\) *M. szulgai* was named after Dr T Szulga, a Polish microbiologist, who developed the lipid analysis method to identify this pathogen.\(^5\)\(^-\)\(^6\) It has been recovered from primarily environmental sources, including snails, aquarium water, swimming pools, tropical fish and hospital water supplies,\(^1\)\(^-\)\(^2\)\(^,\)\(^4\)\(^,\)\(^7\) and at present, no human-to-human transmission has been reported.\(^2\)\(^,\)\(^8\) However, some case reports illustrate that *M. szulgai* can cause disease by hematogenous spread.\(^9\) Given its low prevalence, there are no standardized treatment recommendations for treating infections caused by *M. szulgai*; however, it is susceptible in vitro to most anti-tuberculosis drugs and reports of successful treatment generally involve combination therapy with multiple active agents.\(^10\) This case reported herein describes a non-immunosuppressed patient found to have pulmonary disease caused by *M. szulgai* treated in Niagara Falls, NY, USA.

Case

A 42-year-old male with a history significant for chronic obstructive pulmonary disease (COPD), asthma, polyneuropathy, 1½-pack-per-day smoker for 30 years was admitted to hospital for non-resolving cough and left-sided chest pain in November 2016. One month prior to this admission, he was in the Emergency Department and was treated with a regimen of rifampin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampin, isoniazid and azithromycin for an additional 8 months. Symptomatic and radiographic resolutions were achieved.

Abstract

*Mycobacterium szulgai* is a non-tuberculous mycobacterium that is an uncommon cause of infection in humans. Risk factors for infection include immunosuppression and pre-existing lung pathology. Herein, we present a case of a 42-year-old male with chronic obstructive pulmonary disease with pulmonary infection caused by *M. szulgai* that was successfully treated with a regimen of rifampin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampin, isoniazid and azithromycin for an additional 8 months. Symptomatic and radiographic resolutions were achieved.

Keywords
Non-tuberculous mycobacteria, *M. szulgai*, respiratory tract infection

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5-day course of azithromycin for a presumed, left upper lobe pneumonia. Seeing no significant relief of his symptoms, he went to his primary care provider and was prescribed a 10-day course of levofloxacin. The patient reported good adherence to and completion of both courses of antibiotic. Despite these two courses of treatment, respiratory symptoms persisted, which led to hospitalization and further diagnostic work-up.

At the time of hospital admission, the patient was afebrile, had a blood pressure of 113/77 mm Hg, heart rate of 96 beats per minute, respiratory rate of 16 breaths per minute, and a body mass index of 17.5 kg/m². Physical exam revealed anterior cervical lymphadenopathy and coarse rhonchi in left upper zone anteriorly. Initial laboratory examination revealed the following: white blood cell count, 11.4 × 10³ cells/µL; neutrophils, 78.4%; red blood cell count, 4.08 × 10¹² cells/µL; hemoglobin, 12.2 g/dL; hematocrit, 37.0%; platelets, 570 × 10³ cells/µL; sodium, 140 mEq/L; potassium, 4.5 mEq/L; chloride, 104 mEq/L; CO₂, 28 mmol/L; anion gap, 8 mEq/L; blood urea nitrogen (BUN), 20 mg/dL; creatinine, 0.87 mg/dL; glomerular filtration rate (GFR) > 60 mL/min; magnesium, 2.2 mEq/L; aspartate aminotransferase (AST), 14 units/L; alanine aminotransferase (ALT), 25 units/L; albumin, 3.4 g/dL; and troponin < 0.01 ng/mL. Chest X-ray showed left upper lobe consolidation, and a computed tomography (CT) of chest showed dense consolidation and cavitation in the left upper lobe along with advanced COPD (Figure 1).

The patient was admitted to the medical service for non-resolving pneumonia. Given his symptoms, there was high suspicion of mycobacterial lung infection. He was placed in a negative pressure isolation room and work-up was started. Sputum for Gram stain and acid-fast bacilli (AFB) stain and culture were obtained, and purified protein derivative (PPD) test was placed. Three separate sputum samples were sent for AFB stain and culture based on our laboratory protocol, which includes a digestion-decontamination method using N-acetyl-L-cysteine-sodium hydroxide and cultivation with Lowenstein Jensen Medium and BACTEC MGIT 960 system (Becton Dickinson, MA, USA). Human immunodeficiency virus (HIV) screening was also ordered to assess for a possible source of immunosuppression which could pre-dispose the patient to NTM infection. The PPD, HIV test, and routine sputum cultures were negative; however, two out of three acid-fast smears came back positive with a semi-quantitative result of +1 AFB, reflective of 1–9 organisms per high powered field. Due to the long turnaround time for mycobacterial organism identification and susceptibility determination, the patient was started empirically on a four-drug treatment regimen of isoniazid, rifampin, ethambutol and pyrazinamide.

The patient’s condition slowly improved, though he remained symptomatic throughout his hospitalization. Initially, he experienced some nausea and vomiting associated with the antmycobacterial drugs; however, this improved with modification of the timing of his doses relative to meals. Once the patient was tolerating his medications, plans were made to discharge the patient. Coordination with the local health department helped facilitate the discharge to home, with instructions for staying at home and avoiding close contact with others for at least the first month of therapy. The discharge medication regimen included ethambutol 1200 mg oral daily, isoniazid 300 mg oral daily at bedtime, pyrazinamide 1500 mg oral daily at bedtime, pyridoxine 50 mg oral daily at bedtime and rifampin 600 mg oral daily at bedtime.

The AFB isolate was later identified as *M. szulgai*, using MALDI-TOF mass spectrometry analysis. Real-time polymerase chain reaction (PCR) was negative for *M. tuberculosis* complex DNA and MAC DNA. The species were discriminated using MALDI-TOF mass spectrometry analysis as *M. szulgai*. Specimens were later submitted to reference lab at National Jewish Health, Denver, CO, USA for drug susceptibility testing. Reference lab performed agar proportion antimicrobial susceptibility testing methodology using Middlebrook 7H11 agar. As there are no standard treatment regimens for this organism, he was continued on the four-drug regimen for 2 months of treatment, during which he showed progressive clinical improvement. Based on the susceptibility test results, the regimen was streamlined accordingly to rifampin, isoniazid and azithromycin after 2 months of standard anti-tubercular therapy. His sputum culture was negative for AFB within 2 months of therapy initiation and remained negative for throughout his treatment course. A repeat CT was done, which showed complete resolution of left lung consolidation with remnant scarring (Figure 2). Treatment was stopped after 10 total months of therapy. He was closely followed up and had surveillance sputum cultures which remained negative. Given the persistent scar, he had a positron emission tomography (PET) scan which showed increased uptake in left upper lobe, which could be reflective of either malignancy or mycobacterial infection. Given the patient’s history of cigarette smoking and concern for associated neoplasm, he was advised to undergo wedge resection, which was done 6 months after the
completion of therapy. Pathology revealed old granulomas, and AFB culture of the resected tissue was negative. No evidence of malignancy was identified. The patient’s clinical symptoms had resolved prior to the surgery and remained stable after the resection.

Discussion

*M. szulgai* is a relatively rare NTM that can cause pulmonary and extra-pulmonary infections in humans. *M. szulgai* is considered to be of low virulence compared to *M. tuberculosis* and therefore is most commonly diagnosed in patients with immune deficiency or structural lung damage. Thus, an important consideration in the work-up of a patient with a *M. szulgai* infection is the evaluation for HIV. The treatment considerations in HIV patients are affected by the presence of drug interactions with antiretroviral medications. Other immunosuppressive conditions that can increase risk of *M. szulgai* infection include rheumatoid arthritis, diabetes mellitus, solid organ transplant and stem cell transplant. Broadly immunosuppressive medications can also pre-dispose patients to susceptibility to *M. szulgai*, including corticosteroids, azathioprine, cyclophosphamide, mycophenolate and cyclosporine. Even targeted biologic therapies like tumor necrosis factor (TNF) inhibitors can increase risk of the disease.11

There are also several rare, monogenic disorders that confer susceptibility to disseminated NTM infection grouped together as Mendelian susceptibility to mycobacterial disease (MSMD) conditions.11 These conditions include (1) cytokine pathway defects such as mutations in IL-12 or interferon (INF)-γ; (2) phagocyte defects as seen in chronic granulomatous disease; (3) primary immunodeficiency syndromes like deficiency of the transcription factor GATA-2, severe combined immune deficiency, and CD4 T-cell deficiency; and (4) INF-γ auto-antibodies.

Structural lung disease can pre-dispose patients to pulmonary infection with a variety of organisms, including NTM like *M. szulgai*. These lung abnormalities include chronic obstructive pulmonary disease, cystic fibrosis, alpha-1 antitrypsin syndrome, non-cystic fibrosis bronchiectasis, pneumonia, pulmonary alveolar proteinosis and ciliary abnormalities. Other general risk factors for NTM include advanced age, low body mass index, thoracic skeletal deformities, severe Vitamin D deficiency, female gender, alcoholism and cigarette smoking.11

The clinical manifestations of NTM lung disease are often subtle and patients usually present with history of long-standing cough, fatigue, malaise, fever, weight loss, dyspnea, hemoptysis and chest discomfort. NTM pulmonary disease is clinically classified into three groups: (1) fibrocavitary disease, characterized by mostly upper lobe cavitory lesions resembling tuberculosis; (2) bronchietatic disease, characterized by centriflobular nodules and tree-in-bud appearance predominating in the middle lobe and lingula; and (3) hypersensitivity pneumonitis.2 Diagnosis usually requires a high degree of suspicion and often NTM lung disease is discovered when NTM are identified on sputum culture from a patient under evaluation for tuberculosis. Positive sputum cultures for NTM must be interpreted cautiously since these organisms have variable virulence and can be recovered from the respiratory tract without causing progressive infection (transient infection). In addition, NTM are common in the natural environment and may contaminate laboratory specimens. To overcome these diagnostic challenges the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) published diagnostic criteria for *M. szulgai* infection in 2007 that allows for more accurate diagnosis.12 These include considerations of respiratory symptoms, radiographic findings and culture results.

Although the ATS/IDSA NTM guidelines provide general guidance for diagnosis and treatment of NTM, specific standards for *M. szulgai* have not been established. Drug combinations similar to those used to treat *Mycobacterium avium-intracellulare* and *M. tuberculosis* are usually considered to be active against *M. szulgai*. Some evidence supports the use of isoniazid, rifampin and ethambutol, with or without streptomycin or pyrazinamide, for at least 18 months, or a 12-month regimen of rifampin, ethambutol and clarithromycin.9,13,14 In vitro susceptibility to macrolides, fluoroquinolones and dapsone have been demonstrated.2,5,14 Optimal duration of therapy is unknown, but can vary from 4 to 48 months.2 In certain cases, if there is no improvement with medical treatment and the disease is localized, resection of the diseased portion of the lung can be considered.

In our case, the patient had underlying chronic obstructive pulmonary disease and tobacco use as risk factors, although no specific immune deficiencies were identified. Initial treatment was with the four-drug regimen of rifampin, isoniazid, pyrazinamide and ethambutol for 2 months. Sputum cultures were negative at this time, and subsequently, he underwent 8 months of treatment with rifampin, isoniazid and azithromycin, for a total of 10 months of therapy. He experienced a resolution of clinical symptoms and improvement in

Figure 2. Chest CT after 4 months of treatment, showing significant improvement of the left upper lobe consolidation.
radiographic appearance, so it was decided to stop after the 10 months of treatment with close clinical follow-up to assess for relapse.

In conclusion, NTM including *M. szulgai* can be a potential cause of infection even in patients without severe immunosuppression. Suspected pneumonia that does not respond to traditional antibacterial treatment should prompt a more extensive work-up, including acid-fast sputum cultures to facilitate identification and subsequent treatment of organisms like *M. szulgai*.

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