Early disseminated Mycobacterium Abscessus Complex Infection in an Infant with Coexisting Cystic Fibrosis and Progressive Familial Intrahepatic Cholestasis

A case report and literature review

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Abstract
Mycobacterium abscessus complex (MABSC) is a rapidly growing mycobacterium and may rarely cause disseminated infections in immunocompromised patients. In patients with Cystic Fibrosis (CF), it peaks between the ages of 11 and 15 years. We present a 5 months old infant with coexisting CF and Progressive Familial Intrahepatic Cholestasis (PFIC) who had pulmonary and cutaneous dissemination of MABSC infection. The management of this disseminated infection in an infant with two coexisting chronic diseases was challenging which resulted in a rapid deterioration of lung disease and the progression of PFIC to liver cirrhosis with a fatal outcome.

Keywords: Cystic Fibrosis; Atypical Mycobacterium; Mycobacterium abscessus complex; Progressive Familial Intrahepatic Cholestasis
Introduction

*Mycobacterium abscessus complex* (MABSC) belongs to a group of rapidly growing Mycobacteria (RGM), that can be clinically significant. Diseases caused by RGM have been increasingly reported during the past few decades due to various factors including improvement of molecular diagnostic methods and the increase in population at risk for non-tuberculous mycobacterial (NTM) diseases. MABSC is implicated in causing a wide range of clinical diseases, including localized skin and soft tissue infections and disseminated infections like osteomyelitis, lymphadenitis, cutaneous, lung, and bloodstream infections, particularly in the immunocompromised host. The presence of underlying chronic lung diseases predispose to pulmonary infections. It has been increasingly reported as a significant pathogen among Cystic Fibrosis (CF) patients and has been linked to poor prognosis among this group. Progressive Familial Intrahepatic Cholestasis (PFIC) is an autosomal recessive liver disease that can present with early-onset progressive liver failure.

We report a case of disseminated infection due to *M. abscessus* in an infant with coexisting CF and PFIC.

Case Report

A full-term male infant who has a 10-year-old sibling with CF, was referred to a tertiary care hospital at the age of 2 months with a chronic cough for one month and failure to thrive. He was diagnosed with CF based on elevated sweat chloride level (>60 mmol/l) and genetic testing that confirmed the presence of a homozygous 3120+1G>A CFTR mutation. He received intravenous antibiotics therapy and was started on pancreatic enzymes and fat-soluble vitamins. His throat swab culture was negative. He was discharged with an outpatient follow up.

At the age of 5 months, the infant was admitted through paediatric emergency department with a two-day history of fever, cough and difficulty in breathing. At the time of presentation, the baby was in respiratory failure with a respiratory rate of 70/min, low saturation of 76% in room air and bilateral crackles and wheeze. He required immediate tracheal intubation and mechanical ventilation. He looked icteric with a palpable liver 4-5 cm below the costal margin with no splenomegaly. Other systemic examination was unremarkable.
The initial laboratory tests revealed a haemoglobin level (Hb) of 12.1 g/dl with leukocytosis of 26.2 x 10⁹ cells/L, predominantly neutrophils. He had elevated liver enzymes including alanine transaminase (ALT) of 460 IU/L, aspartate aminotransferase (AST) of 768 IU/L and alkaline phosphatase (ALP) of 316 IU/L. The total bilirubin was 159 µmol/L (conjugated bilirubin 121 umol/L) and serum albumin level was normal. His coagulation profile was normal. Chest X-ray showed hyperinflated lungs, peri-bronchial wall thickening and bilateral lower lobe consolidations. The infant was started on intravenous piperacillin/tazobactam, gentamicin and oral oseltamivir for the management of severe pneumonia and cystic fibrosis pulmonary exacerbation. He did not have a previous positive respiratory culture to guide antibiotic choice but his sibling is known to have chronic *Pseudomonas aeruginosa* airway infection so that was taken into consideration.

During the first week of his Pediatric Intensive Care Unit (PICU) stay, there was a deterioration in his clinical condition, therefore piperacillin/tazobactam was changed to meropenem. Initial blood cultures and respiratory samples (obtained via an endotracheal tube) for bacterial and fungal cultures and respiratory viral panel polymerase chain reaction (PCR) were all negative. He continued to spike low-grade fever over the second week and had progressive worsening of his respiratory parameters which prompted performing a flexible bronchoscopy and obtaining bronchoalveolar lavage (BAL) fluid. The BAL sample was sent for bacterial, mycobacterium, and fungal cultures and extended viral PCRs. The BAL sample microscopy resulted positive for Acid Fast Bacilli (AFB) by Zeil-Neelson stain, while Tuberculosis PCR (GeneXpert) was negative which raised the suspicion of NTM. Chest computed tomography (figure-1) showed bilateral cystic bronchiectasis and nodules. Given the lack of improvement on broad-spectrum antibiotics, the isolation of NTM from BAL and the CT changes, the child met the American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) diagnostic criteria for non-tuberculous mycobacterial pulmonary disease. On day 20 of admission, anti-tuberculous drugs which included rifampicin, ethambutol, clarithromycin were commenced while meropenem was continued.

The child developed a confluent macular papular skin rash involving the face, trunk, limbs, palms and soles but sparing the mucus membranes. There was neither evidence
of desquamation, erythroderma or angioedema clinically nor any blood eosinophilia. Disseminated cutaneous infection due to atypical mycobacteria was highly suspected after excluding other causes including drug-related hypersensitivity reaction. Around the same time, the peripheral blood culture flagged positive for Gram-positive bacilli which were AFB positive (figure 2). These were subsequently identified as *M. abscessus* by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). Central line blood culture remained negative for bacterial growth. The BAL culture was identified as *M. abscessus* by Inno Lipa Line Probe Assay (LPA) method. Azithromycin-based combination therapy with parenteral amikacin and meropenem (imipenem was not available) was started as an intensive phase regimen based on the US Cystic Fibrosis Foundation (CFF) and European Cystic Fibrosis Society (ECFS) recommendations for 8 weeks. The isolate was not tested for standard drug sensitivity testing due to technical limitations. Subsequently, the treatment was switched to the continuation phase that included oral azithromycin, levofloxacin and nebulized amikacin. Furthermore, he had progressive cholestasis with elevated conjugated bilirubin and transaminitis. Based on a family history of PFIC in his first degree cousins, he underwent a liver biopsy which showed cholestatic hepatitis with fibrosis. A whole-exome sequence sample was sent to Centogene labs (Germany), which found a homozygous mutation in the ATP Binding Cassette Subfamily B Member 11 (ABCB11) gene, which confirmed the diagnosis of autosomal recessive PFIC type 2 in addition to CF. Given the early onset of NTM lung disease and the disseminated infection, the patient was extensively investigated for primary immunodeficiency disorders (PID) including Mendelian susceptibility to mycobacterial disease but no PID was found.

During his 5 months stay in the hospital, he remained on respiratory support mostly on non-invasive ventilation with recurrent ICU admissions requiring intubation and mechanical ventilation. Multiple respiratory cultures obtained through the endotracheal tube and BAL remained negative for *M. abscessus* over the initial 3 months of treatment. However, a repeat BAL sample resulted positive again for *M. abscessus* on the fourth month of treatment. Two samples were positive for *Aspergillus* species with no other laboratory findings suggestive of allergic bronchopulmonary aspergillosis. He received 4 weeks of voriconazole that was switched to amphotericine B due to
Despite being on ursodeoxycholic acid, his liver cirrhosis progressed and he developed portal hypertension.

Despite anti-bacterial, anti-tuberculous therapy and the supportive PICU care, the child developed an acute on chronic deterioration of his respiratory status. This led to a rapid respiratory failure and death after 5 months of inpatient hospital stay.

**Discussion**

Disseminated infections due to *M abscessus* are rare and occurs mostly in immunocompromised patients.\(^1\)\(^2\) Our patient was investigated thoroughly for PID but none was found. To our knowledge, the coexisting of CF and PFIC was never reported before. Although CF is a known risk factor for NTM lung disease, it is not usually associated with disseminated NTM infection. In addition, the onset of NTM lung disease in our infant was much earlier than what has been reported in the CF literature.\(^1\)\(^2\)\(^3\) PFIC type 2 results from a failure in the bile salt exporter pump (BSEP) protein which is responsible for exporting bile acids from hepatocyte to canaliculi. This results in early-onset and progressive liver failure.\(^8\) Reviewing the literature, PFIC or liver cirrhosis -in general- has not been shown to increase the susceptibility to NTM infection. It is possible that the coexisting of these two conditions resulted in a secondary immunodeficiency status which led to this disseminated infection. However, this conclusion cannot be made based on this single case.

The presence of at least one of the following characteristics would define the disseminated disease: cutaneous manifestations, involvement of more than one organ with or without cutaneous involvement, affecting more than two groups of lymph nodes or positive blood culture.\(^1\)\(^2\) Cutaneous presentations can manifest as skin infections with discrete nodules, ulceration, multiple abscesses, diffuse maculopapular eruptions, or in contrast, as reactive skin lesions such as erythema nodosum, pustular psoriasis, generalized pustulosis and acute febrile neutrophilic dermatosis (Sweet syndrome).\(^1\)\(^4\) Our patient had maculopapular skin eruptions; however, the lesions were not biopsied but showed dramatic improvement after starting anti-NTM agents. Lymphadenitis is the most common presentation of NTM in immunocompetent children.\(^1\)\(^2\) NTM infects patients with underlying chronic lung diseases such as bronchiectasis, emphysema and healed tuberculosis. It has emerged as a frequently isolated pathogen among CF patients.
over the past few decades with prevalence rates up to 16% in USA and 13% in Europe.\(^4\)\(^5\) According to the US CFF registry data (2017), \(M\) \textit{abscessus} was found to be the second most common isolate after \(M.\) \textit{avium complex} accounting for 18% and 76% of positive cultures respectively.\(^4\) Isolation of \(M\) \textit{abscesses} from sputum culture does not necessarily indicate infection. Accurate differentiation of lung infection from lung colonization is challenging but important since the infection contributes to more fulminant disease outcome in CF patients.\(^1\)\(^5\) Furthermore, the recovery of \(M.\) \textit{abscesses} from routine bacterial cultures is often masked and easily missed due to overgrowth of other common respiratory tract pathogens and colonizing bacteria. In order to diagnose NTM lung disease, the following criteria should be fulfilled: clinical (persistent respiratory symptoms), radiological (nodular and/or cavitary opacities on radiograph or bronchiectasis with nodules on CT scan) and microbiological evidence.\(^6\) Microbiological diagnostic criteria for NTM lung disease requires persistent growth of NTM in respiratory specimens: at least positive AFB and culture in two separate expectorated sputum samples or in at least one bronchial wash or lavage.\(^6\) The presence of a central venous catheter is a common predisposing factor for \(M\) \textit{abscessus} bloodstream infections.\(^1\)\(^6\) Identification of the NTM from blood culture may be difficult and often misdiagnosed with \textit{Corynebacterium} \textit{spp.} which are usually considered as skin contaminants.\(^1\)\(^6\) This case highlights the importance of careful interpretation of Gram-positive bacilli which helps in the timely management of NTM disseminated infections.

Accurate and urgent identification of NTM up to species level is important in deciding the correct antibiotic choice. Different laboratory methods are used for the identification of NTM including biochemical tests, high-performance liquid chromatography (HPLC) and molecular tests.\(^6\)\(^9\) A reverse hybridization assay like “\textit{INNO-LiPA Mycobacteria v2}” is designed to amplify the mycobacterial 16S-23S rRNA internal transcribed spacer region (ITS) but it can’t differentiate \(M\) \textit{abscesses} into sub-species level.\(^9\)\(^1\)\(^7\) A recent study shows that MALDI-TOF MS can be used with promising results to identify NTM species including \(M\) \textit{abscessus}. (Concordance results with Reverse hybridization-based assay; 96.9% agreement).\(^1\)\(^8\)

Management of pulmonary and extra-pulmonary MABSC infection is faced with multiple challenges including intrinsic resistance to the common standard anti-
tuberculous agents, discordant in vitro susceptibility and clinical response, limited proven effective drugs, serious side effects, and the long duration required for clinical and microbiological cure. To overcome these difficulties, a multi-disciplinary team which includes chest physician, infectious disease expertise, clinical microbiologist, clinical pharmacist, physiotherapist, community nurse, patient and his family is needed. The ATS/IDSA 2007 guideline recommends a multi-drug macrolide-based regimen along with surgical resection, if possible, for both pulmonary and extra-pulmonary infections. As per the US CFF and ECFS consensus recommendations, the treatment is divided into an initial intensive phase (which can range from 3 to 12 weeks) followed by a continuation phase. The intensive phase includes an oral macrolide, intravenous amikacin and one or more of the following: intravenous tigecycline, imipenem, or cefoxitin. The decision to switch to the continuation phase should depend on the response to treatment, the severity of infection and if the regimen is tolerated by the patient. The continuation phase includes an oral macrolide, inhaled amikacin and two to three out of the following antibiotics: minocycline, clofazimine, moxifloxacin and linezolid. Antibiotic choices should be guided but not dictated by drug susceptibility testing. Inducible resistance to clarithromycin is another challenge and it is due to the presence of erythromycin ribosome methyltransferase (erm) gene in two of M. abscessus sub species: M abscesses subsp. abscessus and M abscessus subsp. bolletii. In comparison, M abscesses subsp. massiliense does not have inducible resistance to clarithromycin due to the non-functioning erm gene, making therapeutic response to macrolide-based therapy more effective and efficient. Unavailability of recently validated techniques such as multilocus sequence typing of hsp65, rpoB, and secA genes for differentiation into subspecies levels, was an additional limitation in optimizing antibiotic treatment in our case.

**Conclusion**

We have reported a fatal case of disseminated M. abscesses infection in an infant who had two chronic comorbid conditions of CF and PFIC discussing the diagnostic and therapeutic challenges. This case highlights the importance of having a high index of suspicion for NTM infection in children with CF presenting with an early deterioration of lung disease. More research in regards to the optimal management of NTM infection in this young population is required.
References


Figure 1: CT scan of the chest performed before (A) and 3 months after the initiation of NTM treatment showing progressive bilateral cystic bronchiectasis (B)

Figure 2: Gram stain showing thin beaded Gram-positive bacilli (A) and acid fast bacilli on AFB Zeal-Neilson stain (B)