Case Report

Pulmonary *Mycobacterium abscessus* and Response to Treatment in an Outpatient Setting: Case Series

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Abstract

Pulmonary disease due to *Mycobacterium abscessus (*Mab*)* has become an increasing cause of health concern, particularly among individuals infected with nontuberculous mycobacteria. Since Mab is intrinsically resistant to many antibiotics, it is very challenging to treat patients with symptomatic disease. In this case series, we report four patients with symptomatic pulmonary Mab who had prior history of antituberculosis treatment intake and declared cured at the end of treatment. The current episode was confirmed to be due to Mab infection by molecular and clinical diagnosis and received species specific-antibiotics therapy. All were periodically monitored for the sputum smear and culture conversions throughout the treatment period. The clinical course was variable though all received similar antibiotic regimen and showed varied treatment outcomes. The time of diagnosis and the treatment outcome indicate that a better understanding of host-pathogen interactions is essential for the successful treatment of pulmonary Mab infection.

Keywords: Antibiotics, line probe assay, *Mycobacterium abscessus*, oral macrolide, pulmonary disease

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Introduction

Nontuberculous mycobacteria (NTMs) are ubiquitous free-living organisms that cause clinical syndromes indicating the skin and soft-tissue infection as well as pulmonary and disseminated infections with wide virulence phenotype. *Mycobacterium abscessus* (Mab) contributes to a large proportion of NTM-pulmonary cases primarily in persons with host risk factors like genetic disorders, lung diseases and co-infections. These infections are extremely difficult to treat and to eradicate, as Mab is naturally resistant to most antibiotics, including anti-tuberculous agents.[1] The recommended treatment for pulmonary Mab infections had been a combination of an oral macrolide, an intravenous (IV) aminoglycoside along with linezolid or clofazimine for at least 12–16 months.[2-4]

In a recently published study from our group, patients with recurrent chest symptoms unresponsive to TB treatment were screened for NTMs. Among them, *Mycobacterium kansasii* was the most frequent followed by *Mycobacterium intracellulare* and Mab. The treatment was given as per the original ATS guidelines and treatment continued for 12 months following culture negativity.[5] Here, we report the four cases of confirmed pulmonary Mab with varied response to treatment and their long-term follow-up.

Case Reports

Four cases of pulmonary Mab infections who were culture and smear positive and identified as Mab by Line probe assay (LPA) using GenoType Mycobacterium CM VER 2.0 (Hain Life Sciences) upon admission are presented in this case series. All

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four cases had a previous history of pulmonary tuberculosis treated for 6 months using first-line anti-tuberculosis (TB) drugs. The clinical and laboratory findings of all four cases are given in Table 1.

Case 1

A 60-year-old lady, homemaker had a previous history of two episodes of multidrug-resistant (MDR)-TB. Although the culture conversion was rapid, she had relapse of MDR and took treatment. By September 2014, she again developed respiratory symptoms – productive cough with breathlessness and loss of appetite for more than a months' duration. By this time, with repeated injectable aminoglycoside in her treatment regimen, she developed decreased hearing of the left ear secondary to bilateral moderately severe sensory-neural hearing loss with high frequency. Chest X-ray [Figure 1] was abnormal with cavitary disease and extensive opacities of the lung involving all 3 zones. She was initially treated with Clarithromycin 500 mg; Ciprofloxacin 500 mg; Doxycycline 100 mg BD, and IV Amikacin 500 mg. Injection Amikacin 500 mg was withheld for a week after 5 months of treatment due to reported side effects like giddiness and continued for another 2 months as per the consultation with otolaryngologist. Her symptoms improved but sputum remained culture and smear positive and hence was recommended surgery for her right lung. The patient showed unwillingness for surgery as well as amikacin injections in spite of counseling given to her. Due to cardiac arrythmia, the patient was on and off treatment for the next 2 years. Failing suitable treatment options and with deteriorating health condition she died in February 2017.

Case 2

A 49-year-old male, security man by occupation presented to the clinic in June 2016 with complaints of productive cough of 6 months duration, along with intermittent haemoptysis, loss of appetite, and loss of weight (of almost 9 kg in 6 months). Chest X-ray showed opacity of the left lung involving 3 zones. He was treated with intramuscular dose of amikacin 750 mg OD and oral dose of doxycycline 100 mg BD; Ciprofloxacin 500 mg BD; clarithromycin 500 mg BD for period of 10 months, injection amikacin was stopped in March 2017 due to repeated request from patient. However, the patient became sputum culture positive even after 10 months of treatment

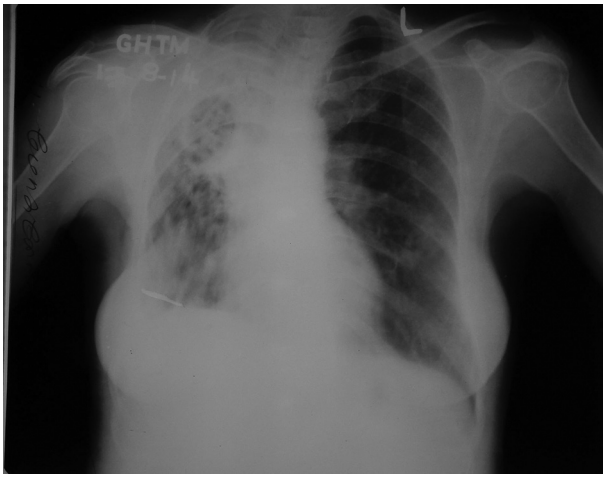

Figure 1: Chest X-ray at the time of delayed diagnosis of pulmonary nontuberculous mycobacteria

Table 1: Clinical findings and blood investigation report of the four patients with pulmonary *Mycobacterium abscessus* infection upon admission

Clinical findings				
Parameter	**Case 1**	**Case 2**	**Case 3**	**Case 4**
Weight (kg)	42.5	40	35.4	NA
Height (cm)	151	160	157	NA
Blood pressure (mm Hg)	110/70	135/85	80/60	91/85
Pulse (beats/min)	86	98	98	72
Oxygen saturation @Room air (%)	99	99	99	98

Blood investigations report					
	Normal range	**Case 1**	**Case 2**	**Case 3**	**Case 4**
Hemoglobin (g/dL)	13.0–18.0	12.6	10.0	10.6	14.9
RBC (million/µl)	4.50–6.50	4.63	3.61	3.71	4.65
Platelet (lakh/µl)	1.5–4.0	2.96	5.82	3.19	2.06
Total bilirubin (mg/dL)	0.3–1.2	0.3	0.3	0.4	0.3
SGOT (U/L)	5–35	33	27	19	36
SGPT (U/L)	5–45	36	13	13	41
Alkaline phosphatase (U/L)	30–120	69	122	74	134
Urea (mg/dL)	10–43	28	15	12	31
Creatinine (mg/dL)	0.3–1.3	0.7	0.3	0.5	0.8
Glucose (R) (mg/dL)	80–140	71	88	109	84
Uric acid (mg/dL)	1.5–7.5	4.5	3.2	3.2	6.0

Reference values are affected by many variables, including and the laboratory methods used. This would serve as a reference for the current study to compare the cases. SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, RBC: Red blood cell

and hence started on T. clofazimine 200 mg OD, T. linezolid 600 mg OD, T. moxifloxacin 400 mg OD, and T. rifabutin 150 mg BD. Patient culture converted to negative in August 2017 and remained negative till August 2018 with treatment stopped in September 2018.

Case 3

A 50-year-old female working in marketing field presented in February 2019 with complaints of cough and expectoration of 2 months duration followed by fever and breathlessness on exertion. She was emaciated with sunken cheeks and looked pale. Chest X-ray [Figure 2a] showed opacities in both lungs involving five zones. She was started on treatment with doxycycline 100 mg; clarithromycin 500 mg; ciprofloxacin 500 mg BD combined with Amikacin 350 mg IV dose, and showed clinical improvement [Figure 2b]. She culture converted to negative after 3 months of treatment and continued to remain so for a year.

Case 4

A 43-year-old business personnel-male was admitted following pulmonary symptoms of cough with expectoration, hemoptysis, and breathlessness in May 2015. His chest X-ray showed opacities of both lungs with involvement of four lobes. He was treated from June 2015 with amikacin 750 mg IM OD combined with doxycycline 100 mg; ciprofloxacin 500 mg, and clarithromycin 500 mg BD. Amikacin was withdrawn after 1 year and treatment continued with oral drugs till September 2017. Following successful treatment, he turned smear and culture negative and continued to be remain so for a year.

Discussion

In this report, we share our experience in the management of patients treated for pulmonary Mab infection and their varied treatment outcomes.

Mab pulmonary infection usually occurs when there is previous lung involvement as is the classical observation with all four cases in our study. Mab presents similar to tuberculosis with severe cough and breathlessness with the lungs showing bronchiectasis with the presence of cavity and nodules, a hallmark of Mab infection.[3] Mab infections are also reported higher among cystic fibrosis (CF) patients with person-to-person transmission, biofilm and drug resistance

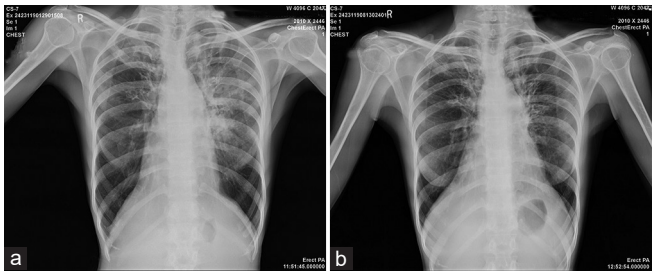

Figure 2: (a and b) Chest X-ray in patients where pulmonary non-tuberculous mycobacteria is diagnosed early; (a) At the time of diagnosis; (b) During 6th month of treatment of pulmonary nontuberculous mycobacteria

leading to progressive debilitation of the lung.[6] Interestingly, in a retrospective study among Mab infections across a 5-year period, it was shown that culture conversion was significantly likely in CF patients than non-CF patients. Spontaneous culture conversion was equally observed between CF and non-CF cases.[7] However, in our case series, no correlation to existing or previous CF history was observed. Mab infection is common in lung transplant recipients and has also occurred in patients on pacemaker with immunosuppression.[8,9] Although it is important to contain these nosocomial infections, Mab resisted most common hospital biocides as proven when assayed with different clinical isolates that indicated the need to identify an efficient hospital biocide to reduce Mab transmission among patients[10]

Utility of anti-TB drugs is limited in the management of Mab infections, since this bacterium possesses extremely high intrinsic and acquired antibiotic resistance, making its eradication more difficult.[1] The BTS and the updated ATS/IDSA guidelines indicated the importance of sub-speciation Mab into Mab, *Mycobacterium bolleti* and *Mycobacterium massiliense* since it is well established that Mab and *M. bolleti* carry an *erm41* gene that has inducible macrolide resistance and testing for *in vitro* susceptibility to macrolides is important. There are advances in genotyping methods and in fact, a newer LPA kit Genotype NTM DR ver 1.0 (Hain Lifesciences) is commercially available for rapid sub-speciation of Mab. A multilocus typing scheme was established using the whole genome sequencing data and MAB-MLST a Galaxy-based data analysis tool was implemented to better analyse whole genome data of Mab. The taxonomic classification and drug susceptibility was better established by genotyping using *hsp*65, *rpo*B, and *erm*41 genes which further reiterate the need for Mab subspeciation.[11] The guidelines discuss several case series of Mab and treatment recommendations based on the same are a minimum three drug regimen and four or more drugs when macrolide resistance is observed. An intensive phase of 3–12 weeks of IVs amikacin with or without IV tigecycline, imipenem, or cefoxitin along with oral macrolide like clarithromycin or azithromycin when tolerated and a continuation phase includes an oral macrolide, in addition to 2–3 oral antibiotics such as minocycline, clofazimine, moxifloxacin, linezolid, or co-trimoxazole. The updated ATS/IDSA further recommends addition of clofazimine and linezolid in both intensive and continuation phase and inhaled amikacin to the continuation phase.[2,4] The treatment duration is for 1 year following culture conversion (the time of conversion starts from the date of the first of three consecutive negative cultures) months.[2,4] The drug resistance pattern of Mab has been collected from international database for about a 20-year period and reviewed. The study indicated that only amikacin among the current choice of drugs such as amikacin, clarithromycin, imipenem, tigecycline retained the nonresistance property across years and recommended as the first choice of drug for Mab.[12] Besides, with regard to use of macrolide for CF, they are considered to encourage selection

and favour Mab sub sp. *abscessus* growth and more research is warranted to understand the same.[13]

There is an additional burden when parenteral drugs cannot be administered due to patient compliance issues or health concerns and it need to be replaced by oral alternatives to alleviate the condition. Currently, there are several Mab drugs that are newer or repurposed drugs like bedaquiline, delamanid, and pretomanid among others under evaluation in various phases of clinical trials for the treatment of Mab.[1,14,15] A clinical trial using several drug combinations (each 4–5) including oral drugs are ongoing to optimize treatment regimen for Mab.[16] *In vitro* susceptibility testing of Bedaquiline using Mab clinical isolates including the different subspecies have offered some promise to the addition of oral Bedaquiline to existing drug combinations.[17] Further reduction of minimum inhibitory concentration of drugs like clarithromycin and bedaquiline *in vitro* against Mab clinical isolates including its three subspecies was reported upon addition of efflux pump inhibitors (EPIs) like verapamil and reserpine. These data support the previous findings of effect of EPIs on anti-mycobacterial drugs but needs to be further explored for Mab.[18,19] Further refinement of Mab treatment using EPIs would help address Mab infections in future and help reduce treatment failures with conventional treatment regimens.

Long-term drug use results in adverse effects such as hepatotoxicity, gastrointestinal disturbances, hearing impairment, allergies, cardiac changes like prolonged QT, cytopenia, nephrotoxicity, and hypersensitivity as indicated. This requires constant clinical monitoring, blood profiling, ECG, audiometry among others during the start and along the course of antibiotic treatment.[2,4] In our study, we regularly monitored the four cases and treatment changes made accordingly. However, it is very clear that Mab pulmonary infection is clinically very challenging to treat with varied treatment outcomes as we observed and no standard regimen can hence be universally followed for Mab. In a previous case study, a Mab patient refractory to treatment with levofloxacin and tazobactam/piperacillin was diagnosed with secondary organizing pneumonia by bronchoscopy. Initiation of oral prednisone improved the condition indicating consideration of secondary pneumonia during treatment failure for Mab and pertinent therapeutic change.[20] With long treatment duration, patient compliance also plays a major role in treatment success. Besides, apart from the issue of treatment, there is possibility of emergence of drug resistance among NTM strains which make it more necessary to optimize the treatment regimen.[21] To optimize the treatment quality and duration, a personalized drug regimen for each case and wider choice of drugs as promised in the on-going studies for evaluation of newer and repurposed drugs would help the clinicians to tackle the disease.

Reference values are affected by many variables, including and the laboratory methods used. This would serve as a reference for the current study to compare the cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Ethical clearance

Institutional Ethics Committee of the National Institute for Research in Tuberculosis, Chennai.

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Conflicts of interest

There are no conflicts of interest.

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