CASE PRESENTATION

In an endemic country with tuberculosis, don't miss nontuberculous mycobacteria

Mohammad Yahya Abdulrazaq [a], Hiba Adnan Hameed [b], Nadia Abdulkareem Al Ani[c]

ABSTRACT

Nontuberculous mycobacteria (NTM) represent over 190 species and subspecies, some of which can produce disease in humans of all ages and can affect both pulmonary and extra-pulmonary sites.

The most common slowly growing NTM pathogens are Mycobacterium avium complex, Mycobacterium kansasii, and Mycobacterium xenopi. Mycobacterium abscessus is the most common among the rapidly growing NTM.

Here, we present three cases from Baghdad misdiagnosed as tuberculosis and proved to be NTM followed by a full course of NTM treatment with improvement in their condition and their health-related quality of life.

Key words: Tuberculosis, Nontuberculous mycobacteria, Mycobacterium kansasii, Mycobacterium abscessus.

INTRODUCTION

Nontuberculous mycobacteria (NTM), also known as environmental mycobacteria, atypical mycobacteria, and anonymous mycobacteria, refers to Mycobacteria other than Mycobacterium tuberculosis (Mtb) complexes like *M. africanum* and *M. bovis*, and organisms causing leprosy like *M. leprae*.[1] These organisms are ubiquitous in the environment and have been isolated from air, soil, dust, plants, natural and drinking water, milk and food products.[2]

NTM are characterised by a thin peptidoglycan layer surrounded by a thick outer lipid-rich coating that enables NTM attachment to rough surfaces and offers resistance to antibiotics and disinfectants, helping NTM survive in low oxygen and carbon concentrations and other adverse conditions.[3] Many of these organisms are resistant to high temperature and relatively low pH.[4] Mycobacterium organisms other than tuberculosis (TB) were identified soon after Koch identified TB in 1882 but were not recognised to cause human disease until the 1950s.[5]

The incidence and prevalence of NTM cases and the strain distribution are highly variable across different geographical locations. A global survey of NTM species isolated from human specimens found that about one-half of them belong to the *M. avium complex* (MAC). However, the relative frequency of MAC varies widely by geographical region; 31% of isolates are from South America, 52% are from North America, and 71% are from Australia.[6] It is also common in the West and Southeast areas of the United States.[7] It is reported that *Mycobacterium kansasii* infection is one of the most common causes of nontuberculous mycobacterial lung disease worldwide.[8]

Human infections due to NTM were earlier believed to be acquired mainly from contaminated environmental sources through aerosols; however, recent reports also indicate person-to-person transmission.[9] Recognising that many NTM may cause pulmonary disease in both immunocompetent and immunocompromised hosts is important. Thus, the pathogenic significance of a NTM specimen must be de-

a: CABM, FIBMS, FRCP; Consultant pulmonologist & Consultant Internist, National Tuberculosis Institute. Baghdad, Iraq. *b:* FIBMS; Family medicine specialist. National Tuberculosis Institute. Baghdad, Iraq. *c:* DM. Pulmonologist, the National Tuberculosis Institute. Baghdad, Iraq.

Corresponding Author: **Mohammad Yahya Abdulrazaq**, E mail: **ntp.mohammad@gmail.com.**

Table 1 | Clinical and microbiologic criteria for diagnosis of nontuberculous mycobacterial pulmonary disease

Clinical	Pulmonary or systemic symptoms	**Both are required**
Radiological	- Nodular or cavitary opacities on chest radiograph - Bronchiectasis with multiple Small nodules on high-resolution Computed tomography scan	
And	Appropriate exclusion of other diagnoses	
Microbiologic	1. Positive culture results from at least two separate expectorated sputum samples. If the results are non-diagnostic, 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 histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.	

termined in the context of a patient's clinical presentation.[10] Although diabetes mellitus (DM) confers susceptibility to TB, the association between NTM infections and DM remains unclear. Few studies have indicated DM as a co-morbid condition in soft tissue and pulmonary NTM infections.[11,12]

Gastroesophageal reflux disease (GERD) is a common comorbidity of nontuberculous mycobacteria pulmonary disease (NTM-PD), Patients with GERD presented with more symptoms and more severe NTM-PD.[13] The prevalence of NTM-PD increases with age[14] and in female sex.[15]

Nontuberculous mycobacterial pulmonary diseases (NTM-PD) have two main presentations. The first is a fibro-cavitary in patients with pre-existing pulmonary diseases, such as chronic obstructive pulmonary disease, bronchiectasis, previous tuberculosis or other structural lung disease. The second presentation is a nodular-bronchiectatic disease of primarily the lingula and middle lobe.[16] Radiologically, it appears as nodular or cavitary opacities on chest radiograph or multifocal bronchiectasis with multiple small nodules on HRCT.[17] The 2007 guideline included clinical, radiographic, and microbiologic criteria for diagnosing NTM pulmonary.[18] The current guideline also recommends using these criteria to classify patients with NTM pulmonary disease.[19] see **table 1**

NTM species are divided into two categories based on their speed of growth: slow-growing mycobacteria, which take up to 12 weeks to culture, and rapid-growing mycobacteria, which culture within seven days, see **Table 2**.[20]

Diagnosing NTMs has many challenges; first, both Mtb and NTMs show positivity to the conventional smear acid-fast bacillus (AFB) staining method, underestimating the incidence of NTMs in TB-endemic countries.[21] Second, not all positive NTM cultures represent infection; a recent analysis showed that approximately half of the culture-positive NTMs are infection.[22]

AFB staining would identify mycobacteria; it would not discriminate NTM from Mtb. Therefore, growing NTM from clinical specimens, such as sputum, bronchial wash, or lavage, is recommended on a solid and/or liquid media. Culturing of mycobacteria on growth media is preferred for identifying rapid and slow-growing species and is considered a "gold standard" diagnostic method.[23]

Identifying specific NTM species in the clinical specimen is crucial since the treatment

Table 2 | Examples of clinically relevant slow- and rapid-growing NTM Species.

Slow-Growing NTM Species	Rapid-Growing NTM Species
M avium complex, comprising:	*M abscessus complex*, comprising:
- *M avium*	- *M abscessus* subspecies *abscessus*
- *M intracellulare*	- *M abscessus* subspecies *massiliense*
- *M chimaera*	- *M abscessus* subspecies *bolletii*
M kansasii	*M chelonae*
M malmoense	*M fortuitum*
M xenopi	

regimens differ strikingly among different NTM strains. Various biochemical tests, including niacin accumulation, arylsulfatase, nitrate reduction, catalase estimation, and growth in MacConkey agar media, are commonly used for NTM species identification.[24] One of the vital biochemical tests used routinely in clinical laboratories to discriminate Mtb from NTM is the p-nitro benzoic acid test (PNB). In the PNB inhibition test, while the growth of Mtb is inhibited, NTMs grow on culture medium containing PNB, as they are resistant to PNB.[25]

Molecular methods also help in NTM species identification in clinical samples. Accuprobe analysis, which involves nucleic acid hybridisation assay that allows rapid identification of Mtb complex, MAC, M. intracellulare, M. gordonae, and M. kansasii is one of the most extensively used methods.[26]

The treatment goals for NTM-LD should include reducing symptom severity, improving health-related quality of life (HRQL), reducing acute exacerbation, and preventing respiratory failure.[27] The NTM species showed heterogeneous susceptibility to standard anti-TB drugs. Thus, treating NTM diseases usually involves using macrolides and injectable aminoglycosides. Although international guidelines are available, treatment of NTM disease is mostly empirical and not entirely successful. In general, the duration of treatment is much longer for NTM diseases, compared to TB, and surgical resection of the affected organ(s) is part of treatment for patients with NTM diseases that do not respond to antibiotic treatment.[28]

The treatment outcome of pulmonary NTM diseases is highly variable and determined by the host- and pathogen-derived factors and the nature of the treatment regimen. Despite using multiple antibiotics, sputum-conversion, from positive to negative, is often difficult to achieve in NTM cases, especially those infected with macrolide-resistant NTM species. Surgical resection may be considered to treat severe pulmonary NTM disease in patients with a focal disease or persistent symptoms[29] without having impaired gas exchange.[30] Generally, a regimen of 3-4 antibiotics is used to treat NTM-PD, administered either daily or thrice weekly depending on the severity of the disease, the patient's tolerance of the drugs and the occurrence of side effects. Therapy is continued for at least 12 months following sputum conversion.[31]

CASES PRESENTATION

Case 1

A 57-year-old male from Baghdad presented with a cough for two months duration, fever, weight loss, loss of appetite, and sweating mainly at night. His cough was dry in the early stage, then started to be associated with sputum, and lastly, it was associated with a tinge of blood. He consulted a doctor who ordered a chest X-ray and sputum for acid-fast bacilli. The patient already had an old history of tuberculosis nine years ago, for which he received anti-TB medication for six months. The result of sputum was positive for tuberculosis

The patient was referred to the district TB

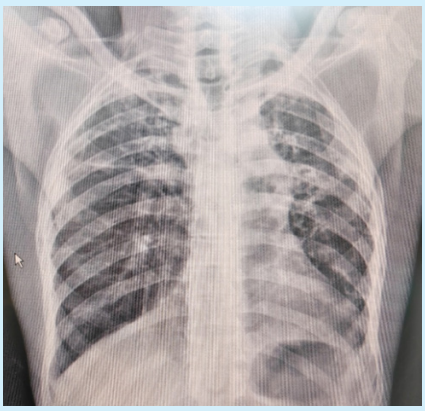

Figure 1 | CXR of the first patient shows fibrotic changes in the upper zone of the right lung field and in the upper and middle zones with few small cavities in the left lung.

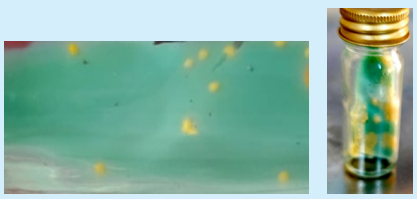

Figure 2 | Yellow pigmented growth suggesting NTM.

unit near his home and reported as a relapsed category 2 TB for which anti-TB medication was prescribed to him; he started with four tablets of fixed combined four anti-TB medicines for two months as the initial phase (Rifampicin 150 mg, INH 75 mg, pyrazinamide 400 mg, ethambutol 275 mg).

The patient showed some improvement in his condition, with no more sweating and no fever, but the cough was still present with sputum but not associated with blood. After completing two months of treatment with anti-TB medication and before changing to the continuation phase of treatment, the patient visited NTP for follow-up. On examination, he was dyspneic, febrile, and a BMI of 22. The chest was full of crepitation to auscultation.

Chest x-ray showed fibrotic changes in the upper zone in the right lung and upper and middle zones of the left lung, with few small cavities on the left lung. See figure 1

Two sputum samples for AFB direct smear were examined from the patient, and the result was positive (one of the samples was early morning). The HIV test was negative.

On the next day, other samples were examined: 3 were a direct smear for acid-fast bacilli (AFB) with culture and a sample for Genexpert test (Xpert(R) MTB/RIF) to exclude drug-resistant TB. The result of the sputum direct exam was also positive, but the Genexpert test for tuberculosis was negative. We decided to continue the initial phase of treatment pending the culture's result. After three weeks, the result of the culture was positive for NMT but not for mycobacterium TB complex.

The patient diagnosed as NTM-PD and the treatment was modified accordingly as follows: Clarithromycin 500 mg twice per day, Ethambutol 3 tablet (400 mg) per day, and Rifampicin 2 capsules (300 mg) per day.

Pulmonary rehabilitation advice was introduced to the patient, including airway clearance techniques, respiratory muscle training, postural drainage with the assistance of his family, walking, and a high-calorie intake/high protein diet rich with vitamins and minerals.

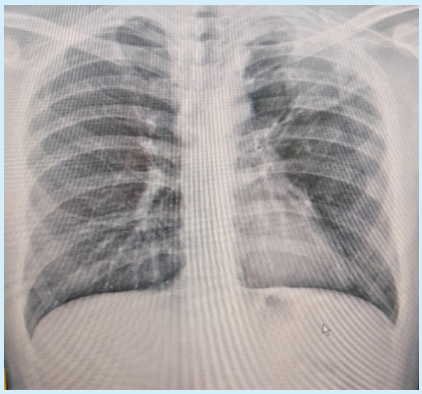

Figure 3 | CXR of the second patient shows a homogeneous opacity (consolidation) in the upper zone of the left lung.

After three months of treatment, the smear converted to a negative result with a reduction in the severity of symptoms and improved health-related quality of life for the patient. After smear conversion, the patient continued medication for 12 months with complete improvement in all of his symptoms, including BMI, without any exacerbations.

Case 2

A 46-year-old male from Baghdad presented with a cough for 3-weeks, loss of appetite, fever, and sweating mainly at night. He was diagnosed with pulmonary tuberculosis based on a positive AFB. Similarly, he received treatment at the district TB unit near his home. He was reported as having a new category 1 pulmonary TB, for which four tablets of fixed combined four anti-TB medication (Rifampicin 150 mg, INH 75 mg, pyrazinamide 400 mg, ethambutol 275 mg) continued for two months as the initial phase.

The patient showed clinical improvement after two months, and the sputum showed negative results, for which the patient changed to the continuation phase 4 tablets of fixed combined two anti-TB medications for four months (Rifampicin 150 mg, INH 75 mg). In the following three months, while the patient was using treatment, he reported some fever and cough in his follow-up visit to the NTP. On examination, the BMI was 27, and the chest was full of crackles on auscultation. Chest x-ray showed a

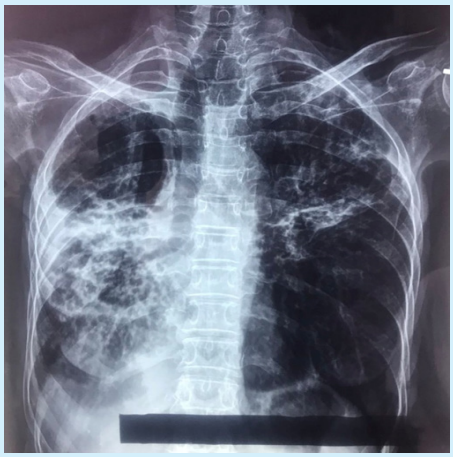

Figure 4 | CXR of the third patient shows extensive fibrosis with a large cavity seen at the right upper zone, causing volume loss and resulting in tracheal and mediastinal shift to the right side. Compensatory emphysematous changes were seen in the left lung. Broncheactasis is seen in the right middle and lower zones and the left upper zone.

homogeneous opacity on the upper zone of the left lung with a normal right lung field, Figure 3.

Two sputum samples, one early morning, for AFB smear were positive, and the patient was labelled as a failure of treatment. The next day, three sputum samples were sent for AFB examination with culture and another sample for the Genexpert test (Xpert (R) MTB/RIF). The direct smear tests were positive, but the Genexpert test was negative for TB. At the same time, the HIV test was negative.

We decided to reintroduce four tablets of fixed combined four anti-TB medications (Rifampicin 150 mg, INH 75 mg, pyrazinamide 400 mg, ethambutol 275 mg), waiting for the result of the culture, which was turned to be positive for NMT. He was labelled as NTM, and treatment was modified as follows:

Azithromycin 250 mg per day, ethambutol 400 mg three tablets daily, and rifampicin 300 mg two capsules daily. Pulmonary rehabilitation was introduced to the patient, including airway clearance techniques, respiratory muscle training, postural drainage, and walking. The patient was advised to consume a high-calorie intake/high protein content in his food and to use vitamins and minerals. Smear converted to negative results after two months with improving health-related quality of life. The patient continued medication for 12 months with complete improvement in all his symptoms without exacerbations.

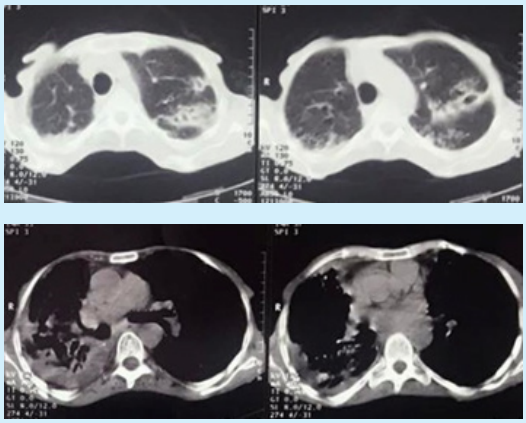

Figure 5 | A CT scan picture, mediastinal window (the uppers) and lung window (the lowers) shows volume loss in the right lung with fibrotic changes on both lungs. bronchiactasis and cavitation are also seen.

Case 3

A 70-year-old female from Baghdad presented with dyspnea and cough, and she was diagnosed with asthma and treated with a SABA inhaler with slight improvement.

In 2019, the patient complained of fever, night sweats, productive cough associated with hemoptysis, and loss of appetite. Then, she was diagnosed with pulmonary TB based on a positive smear AFB. She enrolled on the first line of anti-TB treatment, and she did well initially, with a relapse later on. The AFB continued

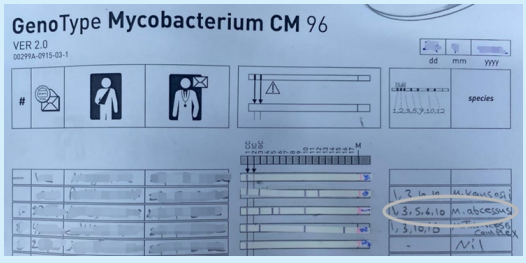

Figure 6 | The result of the line probe test of the third patient, it shows M. abcessuss.

to be positive, so she referred to the NTP as a presumptive drug-resistant TB. A Genxpert test was ordered for her, and the result was negative. Sputum samples were sent for culture, and the growth started within one week, suggesting a rapidly growing NTM. Line probe assay, which was available at the national referral laboratory, showed positive results for M. abcessuss.

On reviewing the images of the patient, chest X-ray showed extensive fibrotic and infiltrative changes with a large cavity seen at the right upper zone, causing volume loss and resulting in tracheal and mediastinal shift to the right side. Compensatory emphysematous changes were seen in the middle and lower zones of the left lung. Broncheactatic changes were seen involving the right middle and lower zones and the left upper zone. No pleural effusion was seen.

Chest CT scan showed evidence of cystic bronchiectasis and fibrosis involving both right middle lobe and left lingual, with less extent in both upper lobes, with surrounding consolidation, associated with calcification, tree in bud bronchial pattern. Associated pleural thickening was seen at right upper middle and left upper zones, normal heart, central mediastinum, no enlarge lymph nodes , no pleural effeusion, no bone lesion, normal diaphragm, normal hila and no mass

The patient received 1000 mg of Amikacin, 500 mg of Azithromycin, and 600 mg of Linezolid as the initial phase of treatment. On treatment, the patient's symptoms improved, and the temperature subsided, and after 3 months, the sputum turned negative. After the initial phase of treatment, the patient received daily Azithromycin 500 mg and Linezolid 600 mg for more than one year.

DISCUSSION

All cases were presented with chronic constitutional and respiratory symptoms and did not respond to first-line anti-TB. All showed a positive direct sputum exam for the AFB, with a negative genexpert result suggesting an NTM infection. The confirmation was made by culture for more than one sample for each case. Morphologically, the positive culture for mycobacterium tuberculosis is mostly smooth white non-pigmented, while it is pigmented yellow to orange for NTM.

The culture of the first two cases yielded a slowly growing Mycobacterium, over three weeks, suggesting *Mycobacterium avium complex*, *Mycobacterium kansasii*, or *Mycobacterium xenopi*. In contrast, the culture of the third case yielded a rapidly growing bacteria, less than one-week suggesting *Mycobacterium abscessus*.

M. avium complex was suggested for the first case based on the presence of the cavity, so it was treated according to the official ATS/ERS/ESCMID/IDSA clinical practice guideline, and the patient showed clinical and bacteriological improvement. *M. avium complex* needs some susceptibility to infection like underlying lung disease or immunosuppression.[32] Our patient was immunocompetent, but he had a previous history of lung disease (tuberculosis).

A combination of azithromycin, rifampin, and ethambutol administered three times weekly is recommended for nodular bronchiectatic disease, whereas daily use of the same regimen is recommended for cavitary disease. [32] We administered clarithromycin, rifampin, and ethambutol daily according to ATS/ERS/ESCMID/IDSA guidelines.

The most common site of MAC infection in immunocompetent patients is the respiratory tract,[32] as in our case. MAC pulmonary infection has a wide spectrum of clinical manifestations, ranging from asymptomatic colonisation to indolent infection to progressive, symptomatic disease. For a cavitary type it usually affects males over 50 with underlying lung disease; [32] this goes with our patient, who was a 57-year-old male with underlying lung disease.

The second case was diagnosed *M. kansasii* because it showed response and smear conversion to anti-TB medication in the initial phase. Still, later on, the sputum sample became positive again. The patient showed clinical response to a full course of treatment according to an of-

ficial ATS/ERS/ESCMID/IDSA clinical practice guideline. In most cases, *M kansasii* causes lung disease that is clinically indistinguishable from tuberculosis. Symptoms may be less severe and more chronic than Mycobacterium tuberculosis infection.[33] Our case was clinically undistinguished from M. tuberculosis infection for five months.

The most common symptoms of pulmonary *M. kansasii* infection include cough (91%), sputum production (85%), weight loss (53%), breathlessness (51%), chest pain (34%), hemoptysis (32%), and fever or sweats (17%) [34] The common physical findings of *M. kansasii* infection include fever, pulmonary crackles and wheezing, and Lymphadenopathy.[35] Our patient had a cough, loss of appetite, fever, and sweating, and on examination, he was febrile and had diffuse crackles on chest auscultation.

The third case proved to be *Mycobacterium abscessus* by culture and line probe assay test that was unavailable for the first two cases. The patient received a full course of treatment according to an official ATS/ERS/ESCMID/IDSA clinical practice guideline with clinical improvement. Patients with lung disease due to *M. abscessus* are usually white, female, nonsmokers, older than 60, without particular predisposing factors.[36] Our patient was a 70-year-old non-smoker woman. Clinical presentation of M. abscessus pulmonary infection can range from asymptomatic to severe bronchiectasis and cavitary lung disease, with significant morbidity and mortality. High-resolution chest CT showed bronchiectasis and nodular opacities in 98% of patients and cavities in 44%.[37] Our patient presented with dyspnea and cough associated with hemoptysis and loss of appetite. The chest CT scan showed bronchiectasis and fibrosis involving the right middle lobe and left lingual, surrounded by consolidation. The changes were less prominent in both upper lobes.

CONCLUSION

In a country endemic with tuberculosis, we should not miss NTM. Clinical features suggestive of NTM in immune-competent or suppressant patients should draw attention, especially in poor response to the usual first-line anti-TB. Characteristically, a patient with NTM shows a positive direct sputum smear for AFB with a negative Genexpert test for TB. Culture is important to differentiate between slow-growing NTM and rapid-growing NTM. The line probe assay test is the test that can be used to distinguish between the different species of NMT.

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Abbreviations Acid-fast bacillus (**AFB**), American Thoracic Society (**ATS**), Body mass index (**BMI**), Diabetes mellitus (**DM**), European Respiratory Society (**ERS**), European Society of Clinical Microbiology and Infectious Diseases (**ESCMID**), Gastroesophageal reflux disease (**GERD**), Health-related quality of life (**HRQL**), High-resolution computed tomography (**HRCT**), Infectious Disease Society of America (**IDSA**), Isoniazid (**INH**), Mycobacterium avium complex (**MAC**), Mycobacterium tuberculosis (**Mtb**), Nontuberculous mycobacteria (**NTM**), Nontuberculous mycobacteria pulmonary disease (**NTM-PD**), p-nitro benzoic acid test (**PNB**), Tuberculosis (**TB**).

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