

Nontuberculous Mycobacterium, Myobacterium and Mixed Pulmonary Infections: A Case Report



Saenghirunvattana S, MD

Sawang Saenghirunvattana, MD¹
 Maria Christina Gonzales, RN¹
 Kritsana Sutthisri, BSc¹
 Chitchamai Siangpro, BSc¹
 Pat Saenghirunvattana¹

Abstract

In the 1980's, nontuberculous mycobacteria (NTM) was recognized as the common cause of disseminated infection in patients who were severely immunocompromised. In Thailand, a study was reported where almost half of the disseminated NTM infections in HIV negative cases were related to farming. NTM contaminated soil and water lead to tissue invasion and cause disease. In recent years, Bangkok Hospital Medical Center has observed a constant rise of patients diagnosed with NTM with or without accompanying disease or infection. Diagnosing NTM has been made easier with the availability and aid of endobronchial ultrasound (EBUS) in collecting specimens for culture and to indicate sensitivity.

OBJECTIVES: To illustrate 10 different cases and management of NTM.

MATERIALS AND METHODS: From 2012-2014, data from NTM positive patients from culture and sensitivity results were collected.

RESULTS: 10 HIV negative cases of NTM were identified by bronchoscopy, endobronchial ultrasonogram guided sheath (EBUS-GS) and sputum culture. The age ranged from 41 to 89 years old with a mean of 64 years. There were eight females (80%), most were menopausal (87.5%) and two males (20%). Underlying conditions included diabetes mellitus (30%), coexisting Tuberculosis (50%) and 10% with lung cancer. All suffered from respiratory symptoms such as fever, dyspnea, sputum production and abnormal chest x-ray and chest CT scan results. All were identified by using EBUS (70%) or sputum culture (20%) or bronchoscopy (10%). Bacteria recorded were mycobacterium avium complex (MAC) (30%), mycobacterium intracellulare complex (MIC) (10%) and 60% were unidentified specific NTM bacteria. All responded well to Macrolide and Quinolone treatment. Specimens obtained from EBUS are highly reliable with the right laboratory setting to identify specific types of NTM.

Keywords: nontuberculous mycobacterium, NTM, myobacterium, endobronchial ultrasound

¹ Bangkok Hospital, Bangkok Hospital Group, Bangkok, Thailand.

* Address Correspondence to author:
 Sawang Saenghirunvattana, MD
 Bangkok Hospital Medical Center, Bangkok Hospital,
 2 Soi Soonvijai 7, New Petchaburi Rd.,
 Bangkok 10310, Thailand.
 e-mail: sawang.sa@bangkokhospital.com

Received: September 17, 2014.
 Revision received: September 18, 2014.
 Accepted after revision: September 25, 2014.
 Bangkok Med J 2015;9:31-35.
 E-journal: <http://www.bangkokmedjournal.com>

Nontuberculous mycobacteria (NTM) are environmental, free-living organisms with an effect of causing chronic disease in human beings. NTM is also known as “atypical” mycobacterial species or mycobacteria other than tuberculosis (MOTT). NTM only attracted attention after the AIDS epidemic and in non tuberculosis endemic countries. It was in the 1980's when NTM was recognized as the common cause of disseminated infections in patients who were severely immunocompromised.¹ There are more than 140 members of the genus mycobacterium. Mycobacterium avium complex (MAC) and mycobacterium kansasii (M. kansasii) specifically are the primary organisms causing pulmonary disease.² These microorganisms share common properties such as acid fastness and ability to cause pulmonary and extrapulmonary granulomatous disorders. As a class, they compromise different microbes with dissimilarities in their characteristics and pathogenicity to humans compared with mycobacterium tuberculosis (MTB).¹

In Thailand, a study was reported that almost half of the disseminated NTM infections in HIV negative cases were linked to farming. NTM contaminated soil and water leads to tissue invasion and causes disease.^{3,4}

In recent years, Bangkok Hospital Medical Center (BMC) has observed a constant rise of patients diagnosed with NTM with or without accompanying disease or infection. Diagnosing NTM has been made easier with the availability and aid of endobronchial ultrasound (EBUS) in collecting specimens for culture and sensitivity. This article will discuss 10 HIV negative cases of NTM and how our team managed each patient uniquely.

Nontuberculous Mycobacterium (NTM) Infection

Case Report # 1

A 56-year-old female who was diagnosed of MAC infection three years ago. She was prescribed clarithromycin 500 mg (1 tablet once daily (OD)) for nine months then discontinued the medicine when her sputum culture and sensitivity results were negative. Four months later, she started exhibiting hemoptysis again. She then decided to seek further treatment. She has underlying dyslipidemia and hypertension (HT). Her medication history includes: atorvastatin 10 mg (1 tablet OD), allopurinol 300 mg (1 tablet OD) and phentermine 15 mg (1 capsule OD). Her chest x-ray revealed calcific granulations at the right upper lung. She was prescribed clarithromycin 500 mg tab (1 tablet OD) and ethambutol 400 mg (2 tablets OD). She was showing improvement following the treatment, until four months later when she complained of blurred vision. She was referred to an ophthalmologist and medications were revised. Moxifloxacin 400 mg (1 tablet OD) was given to replace ethambutol. Her liver function was being monitored during the course of treatment. Her latest chest x-ray revealed no active pulmonary infiltration or nodule. No pleural effusion or pneumothorax was seen.

Case Report # 2

A 41-year-old female who was diagnosed of MAC infection from another facility, and has been taking rifampicin 600 mg (1 tablet OD) and moxifloxacin 400 mg (1 tablet OD) for 22 months. She seems to be responding well to treatment. However, her chest x-ray revealed fibro-patchy opacity at the right upper lung. Treatment was continued for a further two months until she fully recovered. Annual chest x-ray and follow-up checkup was advised.

Case Report # 3

A 68-year-old woman who sought a medical consultation due to breathlessness and sinusitis. The CT scan of chest revealed a patchy-nodular opacity about 5x6mm in the subpleural region of the right middle lobe which is too small to characterize. EBUS-GS was performed to investigate further. NTM tested positive. She was prescribed clarithromycin 500 mg (1 tablet OD) and moxifloxacin 400 mg (1 tablet OD). Two months following treatment

she complained of a bitter taste with clarithromycin. The drug was discontinued and was replaced by zithromax (2 tablets OD before dinner). A week later, she came back complaining of nausea and vomiting, anorexia and abdominal discomfort. Zithromax was discontinued and amoxicillin and clavulanate 1 gram was prescribed instead. She seems to be responding well and did not report any untoward reactions to amoxicillin and clavulanate.

Case Report # 4

A 64-year-old foreign woman, who sought consultation due to a cough and mild decrease in body weight. She has underlying HT, diabetes mellitus (DM) and osteoporosis. Her medications includes: rosuvastatin 10 mg (1 tablet at night), insulin glargine 300 units/3 ml (32 units subcutaneous before dinner), metformin 500 mg (1 tablet OD), glyburide 5 mg (1 tablet OD) and baby aspirin (1 tablet OD). The CT scan of chest revealed a small polygonal shape nodule size about 0.45x0.3x0.3 cm at the posterior segment of the right upper lobe. No intralesional calcification or fat density was seen. A three dimensional ratio of about 0.75 (transverse diameter/vertical diameter = 0.3/0.4) was noted. EBUS-GS was advised for further assessment and evaluation. During bronchoscopy, findings revealed snoring and airway obstruction particularly at the right upper lobe. Secretions were suctioned and specimens were sent to the laboratory for cytology, culture and sensitivity, for Stain AFB and PCR-TB. For sleep apnea, continuous positive airway pressure (CPAP) was suggested as a treatment option. Results came back negative for malignancy but positive for NTM. Since she has already returned to her home country, antibiotics for two years and a visit to her local physician for prescription were highly recommended.

Case Report # 5

An 89-year-old woman who was referred to our clinic due to cough for three to four days and mild dyspnea for three weeks. She was previously prescribed with azithromycin and ciprofloxacin but did not respond well to treatment. Rhonchi were heard upon lung auscultation. She has underlying HT, DM and vertigo. Her medication history includes: clonazepam 0.5 mg (1 tablet at night), atenolol 40 mg (half tablet twice daily) and betahistine 16 mg (1 tablet twice daily). The chest x-ray revealed fibroinfiltration at the right upper lobe and endobronchial spread at the right lower lobe. White blood cell (WBC) was significant at $3.87 \times 10^3/\text{mm}^3$. Fiberoptic bronchoscopy was advised to investigate further. She tolerated the procedure well. Results were negative for malignancy and pulmonary tuberculosis but positive for NTM. She was prescribed moxifloxacin 400 mg (1 tablet OD), azithromycin 250 mg (2 capsules OD) and acetylcysteine 600 mg (1 tablet OD). A week following treatment, she no longer complained of cough and dyspnea.

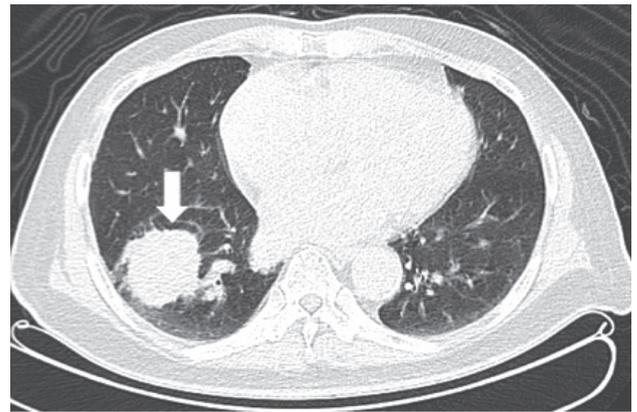
Nontuberculous Mycobacterium (NTM) and Mycobacterium Tuberculosis (MTB) infection

Case Report # 6

A 70-year-old woman who was referred to our service due to an incidental finding of right upper lobe nodular infiltrations and a para aortic node measuring 1.84 cm seen in the CT angiogram. She complained of intermittent cough with whitish sputum for a year. She was diagnosed with HT two months prior to consultation and has been treated for several episodes of upper respiratory tract infection over the past three years. Her medication history includes: valsartan 80 mg (1 tablet OD before breakfast), atorvastatin 10 mg (half tablet OD) and nebivolol 5 mg (1 tablet OD). EBUS-GS and endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) were advised for further investigations. Initial results came back positive for MTB. She was prescribed isoniazid 100 mg (3 tablets OD), rifampicin 600 mg (1 tablet OD) and ethambutol 400 mg (2 tablets OD). A week after the procedure, culture and sensitivity results returned positive for MAC. Clarithromycin 500 mg (1 tablet OD) and moxifloxacin 400 mg (1 tablet OD) were prescribed in addition to the Anti-TB drugs given. Her liver function was being monitored during the course of treatment. Her recent chest x-ray revealed that the lungs were clear and she did not manifest untoward signs and symptoms.

Case Report # 7

A 74-year-old Burmese man saw his primary physician in his home country due to chest pain and later found from a chest CT scan a lobulated mass of soft tissue attenuation, measuring about 4.9x4.5x5.3 cm in the right lower lobe (Figure 1). A biopsy was recommended by his physician for further investigation but he decided to seek a second opinion at Bangkok Hospital. He was a smoker but stopped once he was diagnosed with the lung mass. He has underlying hypertension and diabetes mellitus. His medication history includes: vastarel MR 35 mg tab (1 tablet twice daily), losartan 50 mg (1 tablet OD), digoxin 0.25 mg (1 tablet OD), glimepiride (amaryl) 1mg (1 tablet OD) and atorvastatin sandoz 10 mg (1 tablet at night). The carcinoembryonic antigen (CEA) was significant at 5.82 ng/ml. EBUS-GS and EBUS-TBNA were advised for further investigations. Bronchial brushing and needle aspiration were performed. Results returned negative for malignancy but positive for MTB and NTM. Aside from his anti-hypertensive and oral hypoglycemic medications, he was also prescribed the following treatment: isoniazid 100 mg (3 tablets OD), rifampicin 600 mg (1 tablet OD), ethambutol 400 mg (2 tablets OD), moxifloxacin 400 mg (1 tablet OD), acetylcysteine 600 mg (1 tablet OD) and roflumilast 500 mcg (1 tablet OD). A PET/CT scan was also suggested to rule out malignancy



Figures 1: A lobulated mass of soft tissue attenuation, at right lower lobe.

completely. The results revealed that the lung showed no significant change of the irregular mass involved at the anterior and lateral basal segments of right lower lobe, about 5.8x4.6 cm, which anteriorly abutted the major fissure.

Case Report # 8

A 55-year-old woman who sought medical consultation due to an incidental finding of a lung lesion. She was known to have a family history of lung cancer (maternal side). She was asymptomatic, complains of snoring but denies coughing, fever, dyspnea and weight loss. The CT scan of chest revealed mild bronchiectasis at both lungs, reticulonodular opacity up to 16 mm at the posterior subpleural lung zone of the right upper lung, reticulonodular opacity at the intermediate zone and at the medial-anterior peripheral zone of the right middle lung, multi-foci of reticulonodular and lobular opacities at the intermediate to peripheral zone of the right lower lung, peribronchial thickening and small infiltration at the anterior subpleural lung zone. Tuberculosis was a possible diagnosis. EBUS-GS and EBUS-TBNA were advised for further assessment and evaluation. The results returned negative for malignancy but positive for MIC and MTB. She was prescribed Isoniazid 100 mg (3 tablets OD), ethambutol 400 mg (2 tablets once OD), rifampicin 600 mg (1 tablet OD) and zithromax (2 tablets OD). A Watch-PAT ambulatory sleep study was also conducted to investigate sleep apnea. The results revealed the apnea/hypopnea index (AHI) to be 7.4, the respiratory disturbance index (RDI) was 8.1, the oxygen desaturation index (ODI) was 4.0, and the rapid eye movement (REM) was 7%. Based on these results, it was highly recommended that she use an Auto-CPAP to treat her episodes of apnea. Four weeks after the initial treatment, she complained of blurring of vision, so Ethambutol 400 mg (2 tablets OD) was discontinued and replaced by moxifloxacin 400 mg (1 tablet OD). Her liver function test was monitored and her recent chest x-ray result revealed a negative chest study.

Case Report # 9

A 55-year-old woman who sought consultation due to a sudden body weight loss of 3 kilograms and abnormal CT scan of chest results. The CT scan revealed a pulmonary nodule about 12x15 mm in the anterior segment of the right upper lobe. The carcinoembryonic antigen was elevated at 4.26 ng/ml. EBUS-GS was performed to investigate further. Results came back negative for malignancy but positive for NTM and Quantiferon TB. She was prescribed isoniazid 100 mg (3 tablets OD), rifampicin 600 mg (1 tablet OD), clarithromycin (klacid) 500 mg (1 tablet OD) and moxifloxacin 400 mg (1 tablet OD). Two weeks later, her body weight increased but she complained of a bitter taste with clarithromycin, which was replaced by zithromax (2 tablets OD before dinner). Three months following treatment, her chest x-ray revealed no pulmonary infiltration and normal pulmonary vascularity.

Case Report # 10

A 72-year-old patient came in for a consultation due to dyspnea on exertion (occurring for more than 10 years) and has been seeking treatment for asthma. He has the following underlying conditions: coronary artery disease, HT, DM, and kidney disease. He was also a previous smoker for 20 years. His medications include: furetic, aspirin, clopidogrel, zimox, concor, folic, isosorbide, crestor, metformin SR, colchicine, madiplot and seretide. The CT scan of chest revealed diffuse centrilobular emphysema in both lungs. Diffuse ill-defined centrilobular nodules were noted and patchy ground glass opacities in the left lower lobe and the posterobasal segment of the right lower lobe. This is possibly caused by infection. The diagnosis differed from chronic interstitial lung disease, respiratory bronchiolitis, granulomatous disease or tuberculosis. A small traction bronchiectasis and small cicatrizing atelectasis was seen in the right middle lobe, right upper lobe hilar region and lingular segment. A diffuse peribronchial thickening in both lungs was present; more so at the lower lobes. A few nodes were seen of up to a size of 9-10 mm, at the right paratracheal, pretracheal, precarinal, AP window and peri-aortic regions and a calcified right hilar node was also observed. The spirometry revealed FVC: 49%, FEF 25-75%: 27%. A six minute walk revealed desaturation of 93% and he exhibited wheezing. Laboratory markers were significant with hematocrit: 38.9%, platelet count: $142 \times 10^3/m^3$, hemoglobin: 13.4 g/dL. Potassium was 3.03 mmol/L and, carcinoembryonic antigen (CEA): 4.14 ng/mL. EBUS-GS and EBUS-TBNA were advised for further assessment and evaluation. He was advised to stop aspirin and clopidogrel for a week before undergoing the procedure. Post EBUS he did not manifest untoward complications. The results returned negative for malignancy but positive for quantiferon tuberculosis and NTM infection. He was prescribed the

following medications for treatment: isoniazid 100 mg (3 tablets OD), rifampicin 600 mg (1 tablet OD), ethambutol 400 mg (2 tablets OD), moxifloxacin 400 mg (1 tablet OD), zithromax (2 tablets OD), montelukast sodium 10 mg (1 tablet OD) and indacaterol 150 mcg (1 puff OD). He seems to be responding well to the medications.

Discussion

Chronic pulmonary disease is the most frequent manifestation of NTM caused by MAC followed by *M. Kansaii*. The two main pulmonary manifestations are cavitary or fibronodular and nodular bronchiectatic disease.⁵ At BMC, we have observed that that the most common species causing NTM infections is MAC (30%) followed by MIC (10%). Unfortunately, the remaining 60% of cases are caused by unidentified NTM bacterium.

Diagnosing pulmonary NTM is not easy for some clinicians. Clinical symptoms, radiological and pathological evidence of the disease all need to be gathered and specific microbes from the culture should be identified in order to prescribe the appropriate antibiotic treatment. NTM symptoms include chronic or recurring cough, sputum production and dyspnea. Other symptoms include fever, malaise, fatigue, and weight loss.⁵ The risk of infection rises in immunocompromised patients and those with underlying diseases. This makes it more difficult to diagnose.

In 2010, Gopinath K and Singh S⁴ cited five possible factors for the under-reporting of NTM from TB-Endemic countries. These are: 1). NTM infections are not reported; 2). There is not enough awareness among treating physicians and microbiologists; 3). There is a lack of adequate laboratory infrastructure for culture and identification of NTM; 4). Focus of healthcare team and government on high burden of TB and HIV and 5). Standardized criteria to define NTM respiratory disease is lacking. While we agree with these reasons, we believe that with the latest turn of events especially with the introduction of the EBUS, collection of specimens has become easier for some pulmonologists. With sufficient ability and availability of resources, EBUS can play an important role in a less complicated method of diagnosing NTM.

In NTM pulmonary infections, bronchial cultures should be obtained. Bronchoscope washing or lavage may be considered as diagnostic. Specimens obtained from a biopsy like the EBUS-TBNA, are viable and highly reliable to identify specific types of NTM with the right laboratory setting. Once microbes with susceptibility are identified, medical therapy can be started.

NTM is seen across the world most of the industrialized nations report 1-2 cases per 100,000 persons. In 2003,

the incidence of NTM in the United States was 14.1 per 100,000. Also, some specialists have reported that in the US, NTM is at least ten times more common than TB with at least 150,000 cases per year.⁶ According to Chan et al.⁷ in his study in 2010, there were several series of published case reports in the past 20 years that state that NTM lung disease has been observed in increased numbers in menopausal women. In Japan, Okumura et al.⁸ reported that in 273 newly diagnosed MAC lung infections, more than two thirds of the patients were women. At BMC, we have noticed that 70% of the NTM occurrences were in post-menopausal women and 10% of incidents were from pre-menopausal women. The remaining 20% came from male patients.

References

1. Ioachimescu O, Tomford JW. Nontuberculous mycobacterial disorders. (Accessed April 29, 2014 at <http://www.clevelandclinicmeded.com/medicalpubs/disease/>).
2. Griffith DE. Overview of nontuberculous mycobacterial infections in HIV-negative patients. (Accessed April 29, 2014 at <http://www.uptodate.com/contents/overview-of-nontuberculous-mycobacterial-infections-in-HIV-negative-patients/>).
3. Chetchotisakd P, Kiertiburanakul S, Mootsikapun P, et al. Disseminated nontuberculous mycobacterial infections in patients who are not infected with HIV in Thailand. *Clin Infect Dis* 2007;45:421-7.
4. Gopinath K, Singh S. Non-tuberculous mycobacteria in TB-endemic countries: are we neglecting the danger?. *PLoS Negl Trop Dis* 2010;4:e615.
5. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of non tuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;175:367-416.
6. Falkinham JO 3rd. Nontuberculous mycobacteria in the environment. *Clin Chest Med* 2002;23:529-51.
7. Chan ED, Iseman MD. Slender, older women appear to be more susceptible to nontuberculous mycobacterial lung disease. *Gen Med* 2010;7:5-18.
8. Okumura M, Iwai K, Ogata H, et al. Clinical factors on cavitary and nodular bronchiectatic types in pulmonary Mycobacterium avium complex disease. *Intern Med* 2008;47:1465-72.

While NTM prevalence has not been reported in Thailand, the latest technology to collect specimens and the identification of microorganisms for rapid diagnosis has been made available in TB endemic countries. This has resulted in significant improvements in the management of NTM.

Conclusion

Diagnosing NTM infection may be a challenge due to several factors, including misleading symptoms, the lack of resources of EBUS specimen collection and PCR-TB, in the processing of specimens to make a rapid diagnosis. The availability of these tests, may provide vital information for appropriate long term treatments, making a huge improvement in NTM disease management.