Kocova et al., J Clin Case Rep 2016, 6:1
DOI: 10.4172/2165-7920.1000680

Journal of Clinical Case Reports

Case Report Open Access

# Nontuberculous Mycobacteriosis (Different Faces of Two Most Common Nontuberculous Mycobacteriosis)

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## Abstract

Nontuberculous mycobacteriosis are chronic granulomatous diseases caused by different types of mycobacteria. Plain chest X-ray and high resolution computed tomography are highly nonspecific but absolutely neccesary in detection and follow-up of patients with pulmonary mycobacterial infection. Treatment of infection caused by *Mycobacterium avium* complex is often successful. However treatement is successful only in 55% of patients with pulmonary infection caused by *Mycobacterium abscessus* complex. The results of therapy is dependent on sensitivity to macrolides whitch are cornerstones of medical therapy. In our case serie of four patients with cystic fibrosis show that results of therapy in patients with preexistent lung disease can be very different and is not dependent only on type of mycobaterial infection and sensitivity to antimicrobial treatment. In such cases, therapy of *Mycobacterium avium* complex infection can last even several years.

**Keywords:** Nontuberculous mycobacteriosis; *Mycobacterium avium* complex, *Mycobacterium abscessus* complex, Cystic fibrosis, Computed tomography

## Introduction

Nontuberculous Mycobacteriosis (NTM) is chronic granulomatous inflammatory disease caused by a different types of mycobacteria. They are potentially pathogenic for people. NTM were isolated from water, soil, dust, flowers and animal hair and secretions [1]. Person to person transmision is rare, mostly by respiratory tract, in some cases by skin contact (skin abrasion) or ingestion. NTM infection is rare in healthy persons. Due to a diferent time of growth on culture media NTM can be divided into two groups – rapidly growing and slow growing. Rapidly growing NTM are *Mycobacterium fortuitum*, abscessus, chelonei, smegmati, mucogenicum, gondii a immunogenum. Slowly growing are *Mycobacterium avium* complex (MAC), kansassi, marinum [2]. Rapidly growing NTM are typical for they rapid growth on culture media during a few days and their in vitro resistant to common antiturculotics. The most common NTM in the Czech Republic are *Mycobacterium avium* intracellulare and Mycobacterium kansassi [3]. NTM can be diagnosed either in imunocompetent or imunodeficient patient. The risk factors are previous lung disease as asthma bronchiale, chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, lung fibrosis, deformities of the chest (pectus excavatum) and imunosupresion (imonodeficiency, human immunodeficiency virus HIV, patients after transplantations). NTM affects predominantly lungs and lymphatic nodules but it can affect only skin, soft tissues, joints, bones or urogenital tract. In immunodeficient patient NTM can be presented as disseminated form of disease with multiorgan impairment [4,5]. Clinical manifestation is nonspecific – fatigue, fever, weight loss, night sweating. Manifestation of lunf infection is caught, which can be productive or hemoptysis. The typical example of imunocomponent patient preconditioned for NTM infection is older woman, smoker with some lung disease - called lady Windermere syndrom [6]. In imunodeficient patients with cystic fibrosis is in more than 50% NTM infection caused by *Mycobacterium abscessus* complex [7]. The diagnosis is based on all three conditions: 1 clinical symptoms, 2 radiological image, 3 culture media positivity (at least two times positive finding from sputum or one positive finding from bronchoalveolar lavage (BAL) or histological identification of granulomatous inflammation and one positive cultivation from BAL [8,9].

Radiological images are variable – thin wall cysts in apical and ventral segments of upper lung lobes, infiltrations of lung parenchyma, nodularities. More specific patterns are revealed by High Resolution Computed Tomography (HRCT). Peribronchial infiltrations, centrilobular nodules, bronchiectasis, consolidations and cavitations can be seen [10]. In differential diagnosis it is necessary to rule out *Mycobacterium tuberculosis* infection (in this case isolation of patient is neccessary), other oportunistic infections, noninfectious granulomatous disease and bronchogenic carcinoma. Treatment is based on long terms aplication of antibiotics and antituberculotics. They are administered further 12 month after all negative cultivations. The surgical treatment is indicated in the case of isolated lung form of NTM infection or relapsing hemoptysis [9].

## Case 1

### Patient with cystic fibrosis and pulmonary infection *Mycobacterium abscessus* complex (MABSC) subspecies *bolleti*

Twenty year old patient with cystic fibrosis and bronchiectasis, with normal lung functional tests, with pancreatic insuficiency, gastroesophageal reflux and Body Mass Index (BMI) 18,6 had chronically colonization of airways with *Staphylococcus aureus*. The first detection of MABSC in sputum was when he was nineteen, in that time he was asymptomatic. On HRCT images were stationary changes due to cystic fibrosis (cylindric bronchiectasis mainly in midle lobe and in lingula), bronchial wall thickening, no consolidations, no mucous plugs (Figure 1). Control test on Bacillus Kochii(BK) in sputum was negative. Five month after the first positivity of MABSC in sputum was sputum again positive. In that time clinical symptoms appeared – fatigue, weakness, green sputum production without hemoptysis. On HRCT images (Figure 2) was seen progression of patterns – tree in bud patterns bilaterally (more in the left lung - in lingula and apical segment of left lower lobe), lymphadenopathy in mediastinum. All diagnostic

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**Received** November 08, 2015; **Accepted** January 06, 2016; **Published** January 13, 2016

**Citation:** Kocova E, Antusova Z, Elias P (2016) Nontuberculous Mycobacteriosis (Different Faces of Two Most Common Nontuberculous Mycobacteriosis). J Clin Case Rep 6: 680. doi:10.4172/2165-7920.1000680

critera were fulfilled so the medical therapy in accordance to American Thoracic Society (ATS) was started – combined per os and intravenous treatement for six weeks – amicacin, linezolid i.v. + claritromycin per os. After this treatement, clinical symptoms disapearred. Cultivation from sputum was repeatedly negative. For outpatient therapy, combination of Antituberculotics (AT) per os – claritromycin, tetracyclin, ciprofloxacin was recommended in accordance to European Society for Cystic Fibrosis (ECFC). However, during this therapy relaps of clinical symptomps came up – fatigue, weakness, green sputum production. Lung functional tests were normal. On HRCT images (Figure 3) there was progression of patterns – a lot of concolidations without cavitations, extensive ground glass opacities, progression of mediastinal and hilar lymphadenopathy. HRCT navigated bronchoscopy was performed (from lingula). Microbiological cultivation from BAL was highly positive for MABSC. In accordance to ECFS intravenous therapy started. In view of the fact of susceptibilty of MABSC and ECFS recommendations combinated therapy – amicacin, linezolid, tigecyclin i.v. and azitromycin per os was administred. After three month or therapy patient is oligosymptomatic (limited daily production of green sputum) but sputum cultivations on MABSC are still positive. There is only parcial regression of consolidations and ground glass opacities on HRCT images (Figure 4). For future combined therapy was recommended – inhalational amicacin, tetracyclin and moxifloxacin per os for one year. Regular controls of sputum cultivations and controls of unwanted effect of therapy is needed – due to toxic effect of aminoglycosides. If the clinical symptoms become worse, intravenous therapy will be administred again.

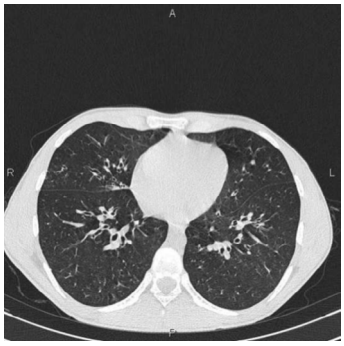

**Figure 1:** HRCT of the lung – typical changes accompanied with cystic fibrosis of the lung - cylindric bronchiectasis, bronchial wall thickening .

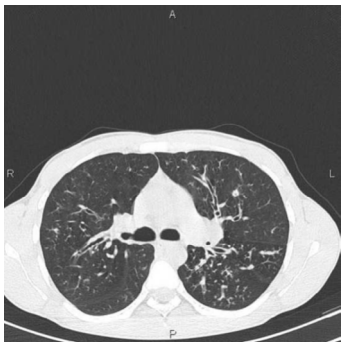

**Figure 2:** HRCT of the lung – signs of infection – bilaterally tree in bud patterns (mainlly in apical segment of left lower lobe), hilar lymphadenopathy.

**Figure 3:** HRCT of the lung - a lot of concolidations without cavitations, ground glass opacities, mediastinal lymphadenopathy.

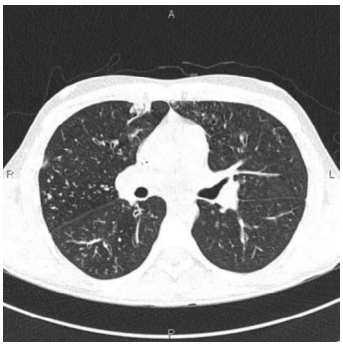

**Figure 4:** HRCT of the lung – residual small consolidations.

**Figure 5:** Chest Xray – patient with cystic fibrosis - bronchiectasis, bronchial wall thickenenig. In the right upper lung field bronchiectasis were with mucous plaques.

## Case 2

### Patient with cystic fibrosis and lung infection *Mycobacterium abscessus* complex (MABSC) subspecies *abscessus*

Eighteen year old man with cystic fibrosis. On chest Xray he had bronchiectasis, bronchial wall thickeness. Some of the bronchiectasis in the right upper lung field were filled with mucous plaques (Figure 5). He had chronic colonization of airways by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, short bowel syndrom (after resection due to impairment with cystic fibrosis) what resulted in long lasting parenteral nutrition. BMI at the time of diagnosis of NTM was 19. Fever and patological breathing phenomenons appeared during scheduled hosptalization. On chest X ray there was new consolidation in the rigt lower lung field and lymphadenopathy in the right hilum (Figure 6). On HRCT images cylindric bronchiectasis in both lower lung lobes, some lung consolidations with affection of adjacet pleura mainly in apical segments of lower lobes (predilection to the right) and mediastinal lymphadenopathy could be seen (Figure 7). Specific antibiotic

treatement was without any effect so HRCT navigated bronchoscopy with BAL was performed. In BAL were found acidoresistent bacteries. Sputum was for several times positive for MABSC. In accordance to short bowel syndrom per os monotherapy with claritromycin was started. As a part of regular antipseudomonade treatement amicain intravenously for fourteen days every three month was aplicated. During this therapy, clinical symptoms and concolidation on chest X ray partially resolved very quickly (Figure 8). Sputum cultivation was negative in two months. On HRCT images in one year (Figure 9) was well-marked regression with only small residual reticulations and small consolidation in the right lower lobe. After the first negative sputum cultivation claritromycin monotherapy was stopped.

**Figure 6:** Chest Xray - consolidation in the rigt lower lung field and lymphadenopathy in the right hilum.

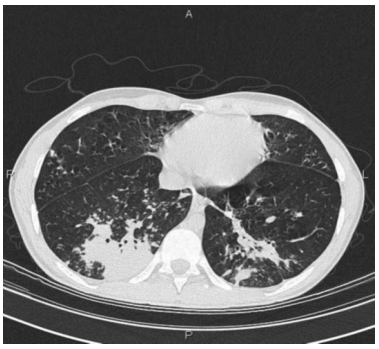

**Figure 7:** HRCT of the lung - cylindric bronchiectasis in both lower lung lobes, lung consolidations with affection of adjacet pleura mainly in apical segments ofright lower lobe.

**Figure 8:** Chest Xray – partiall regression of consolidation in the right lower lung field.

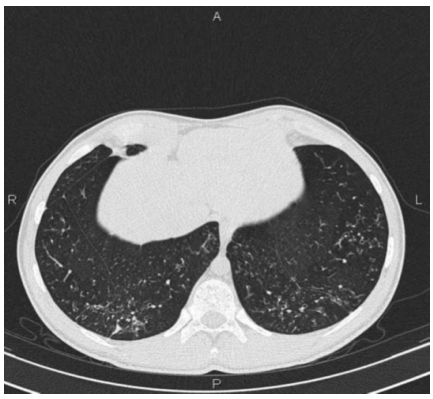

**Figure 9:** HRCT of the lung - small residual reticulations and small consolidation in the right lower lobe.

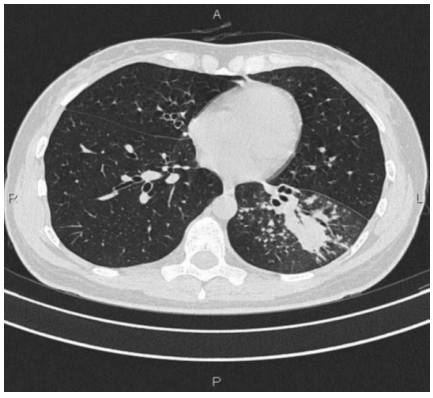

**Figure 10:** HRCT of the lung – bronchiectasis in the left lower lobe, consolidation with ground glass opacities and tree i bud patterns.

## Case 3

### Patient with cystic fibrosis and *Mycobacterium avium* complex lung infection

Next example of unsuccessful treatement is case of fourty-four year old woman. The diagnosis of cystic fibrosis was made when she was thirty-eight years old due to recurrent pneumonias in the left lower lobe (LLL). HRCT of the lung was indicated. On HRCT images were extensive bronchiectasis in the right upper lobe, left lower lobe, less in in the left upper lobe, lymphadenopathy in the left hilum (Figure 10). In the left lower lobe were several consolidations. Volume of left lower lobe was reduced. Her lung functions were normal, her airways were without chronic colonisations, pancreastic functions were sufficient, her BMI index was 20,3. In the year 2009 the diagnosis of lung infection *Mycobacterium Avium* Complex (MAC) was made due to clinical symptoms and repeatedly positive sputum and BAL cultivation for MAC and HRCT images – peribronchial infiltrations and tree in bud patterns in both lower lobes, small consolidations in all lung lobes. There was significant progression of extent of bronchiectasis to cystic form in the left lower lobe (Figures 11 and 12). Up to date patient is permanently treated in according to ATS – three months intravenous amicacim, rifampicin, etambutol and claritromycin per os initially. After this the treatment continued without amicacin. Regarding to permanent positive cultivation for MAC repeatedly therapy in accordance to actual susceptibility for antituberculotics was indicated. However sputum was positive. On HRCT images (Figures 13 and 14) are still signs of activity of illness – peribronchial infiltrations,

tree in bud paterns, consolidations of lung are in progression. Patient is oligosymptomatic, lung functions are in limits. Due to changes in the left lower lobe – carnification of the lobe, surgical resection of the left lower lobe was indicated because it at be origin of hemoptysis and infection complications. Patient this surgical treatment refused.

## Case 4

### Patient with cystic fibrosis and *Mycobacterium avium* complex lung infection

Twenty-six year old woman with cystic fibrosis and chronic colonization of airway with Burcholderia cepacia. In the time of MAC diagnosis her lung functions were limited, pancreatic functions were insufficient. She had another risk factor – inherited deformation of thorax – pectus excavatum. She was cachectic with BMI 13.3. Diagnosis of MAC was based on positive cultivation (two times from sputum, one positivity from BAL), radiological images and clinical symptoms (reduce of weight 10 kilograms in two months). On chest X-ray were changes typical for cystic fibrosis and consolidations with air bronchogram in the left lung and a lot of small consolidations in the right lung (Figure 15). On HRCT images were peribronchial infiltrations and tree in bud patterns mainly in both lower lobes (Figure 16). Medical therapy in accordance to ATS as in case No. 3 was started. During this therapy rapid partially regression of consolidations mainly in the left lung was achieved (Figure 17). Sputum cultivations were quickly negative and they are negative up today. Chest X-ray is without new pathology. The therapy will be finished after the first negativity of sputum cultivation.

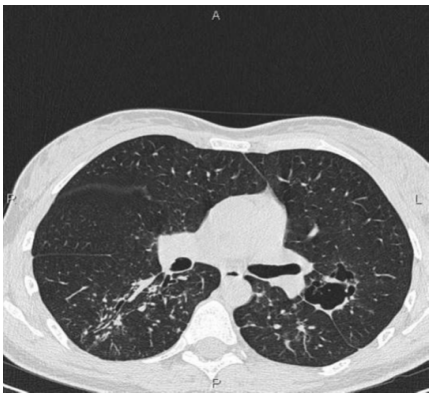

**Figure 11:** HRCT of the lung - extent of bronchiectasis to cystic form.

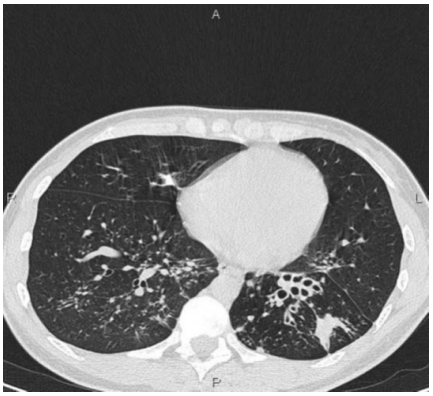

**Figure 12:** HRCT of the lung – progression of bronchial wall thickening.

**Figure 13:** HRCT of the lung - peri bronchial infiltrations, tree in bud patterns, consolidations.

**Figure 14:** HRCT of the lung – consolidation in the left lower lobe, volume regression and carnification of the left lower lobe.

**Figure 15:** Chest Xray – bronchiectasis and consolidations with air bronchogram in the left lung and a lot of small consolidations in the right lung.

## Discussion

Incidence of nontuberculous mycobacteriosis is worldwide growing [9] mainly in patients with chronic lung diseases. Human transmission was confirmed by genotyping only in patient with cystic fibrosis – transmission of *Mycobacterium abscessus* subpecies massiliense [10]. Transmission of different types on mycobacteria or human transmission in patients without cystic fibrosis was never confirmed [9]. *Mycobacterium abscessus* complex is rapidly growing mycobacteria with subspecies *Mycobacterium abscessus massiliense*, *bolleti*, *abscessus*. Identification of subspecies is absolutely necessary for medical therapy. Cell wall of MABSC express erm(41)gene which

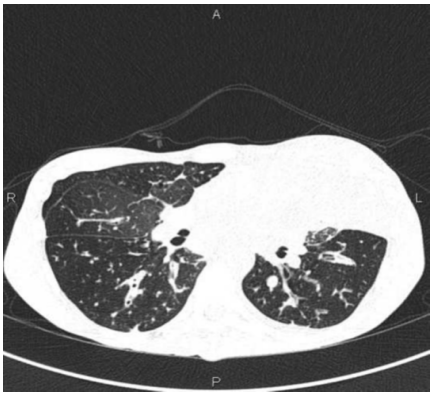


**Figure 16:** HRCT of the lung - peribronchial infiltrations and tree in bud patterns in both lower lobes.


**Figure 17:** Chest Xray – partiall regression of consolidations in the left lung.

is responsible for macrolides resistance. In *Mycobacterium abscessus* subspecies *masiliense* is this gene non-functional. This means that therapy is more successful than in subspecies *bolletii* and *abscessus*. Next essential drug in MABSC therapy is amicacin – this therapy is often limited with unwanted effect and toxicity. Its effect in inhalation therapy is in the study [11]. Due to deficiency of effective antibiotics and relatively often resistency to macrolides the therapy failed in 55% patients. Patients with cystic fibrosis and MABSC infection had worse prognosis and are contraindicated for lung transplantation. Risk factors for MABSC infection are: long term imunomodulating therapy by azitromycin, gastroesofageal reflux, deficiency of vitamin D, kachexia, malnutrition [7]. Radiological images of NTM are nonspecific. Chest X-ray has only low ratio value. HRCT of the lung is in diagnostics of NTM crucial. On HRCT images are seen consolidations with affection of adjacent pleura, ground glass opacities, many small nodularities mostly to 10 mm size, reticulations, thin walled cavitations, bronchiectases mainly in middle lobe and in lingula, bronchiolitis, air traping, fibrotic changes, lost of volume, lymphadenopathy. Ability to differentiate between nontuberculous *mycobacteria* and *tuberculous mycobacteria* on HRCT is limited. Tuberculosis has dominantly bronchial type of spread with tree in bud patterns unlike nontuberculous mycobacteria are spreading continually with cavitations and thin walled cysts [10]. But this has only orientation value and HRCT images are necessary mainly for BAL navigation. In the first case were typical bronchiectases located mainly in middle lobe and lingula. In the time of diagnosis of NTM on HRCT images appeared new nonregular consolidations in lingula and in apical segment of left lower lobe, many nodularities in both lung. There were no cavitations. In the second case there were on HRCT images consolidations with affection of adjaced pleura mainly on the right site without cavitations. Bronchiectases were mainly in apical segments of upper lobes but in literature they are described dominantly in middle lobe and in lingula. So these HRCT images were nonspecific. In both cases was seeen mediastinal lymphadenopathy. In both patients with MABSC was proved in vivo resistency to macrolides. In the first case therapy was not curative even after eight month in the second case therapy was curative quite quickly even the therapy was much vigorous. The reason is probably due to intravenous application of amicacin due to chronic pseudomonas infection. In the third case was indicated surgical resection of carnificated lower lobe after six years intensive therapy because it can be potentional cause of hemodynamic hemoptysis or infection complication (but it is probable that this could not be the only cause of MAC infection due to bronchiectases and bronchiolitis in the right lung). In the last case the treatment was curative after three month and her cultivations are still negative [12,13].

## Conclusion

Diagnosis and treatment of NTM infection is very complicated. Therapy must be also often modified due to unwanted effect of medications. These cases show how important is to keep in mind this diagnosis mainly in long time nonspecific clinical symptoms in patients with predispose lung disease. In differential diagnosis is necessary to exclude *Mycobacterium tuberculosis* or other pathogens. To the right diagnosis is absolutely necessary cooperation of pneumologist, radiologist and microbiologist. Radiologist is often the first who turns attention to suspicion of NTM infection. Also the role in navigation for BAL is irreplaceable.

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