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*Dorota Wyrostkiewicz[1], Monika Szturmowicz[1], Izabela Siemion-Szcześniak[1], Lilia Jakubowska[2], Anna Zabost[3], Jan Kuś[1]

Nontuberculous mycobacterial lung disease in the patient with chronic obstructive pulmonary disease and bronchiectasis – case report

Mikobakterioza płuc u chorej na przewlekłą obturacyjną chorobę płuc i rozstrzenie oskrzeli – opis przypadku

[1]I Department of Lung Diseases, National Tuberculosis and Lung Diseases Research Institute, Warszawa
Head of Department: prof. Jan Kuś, MD, PhD
[2]Department of Radiology, National Tuberculosis and Lung Diseases Research Institute, Warszawa
Head of Department: Iwona Bestry, MD
[3]Department of Microbiology, National Tuberculosis and Lung Diseases Research Institute, Warszawa
Head of Department: prof. Ewa Augustynowicz-Kopeć, MD, PhD

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Słowa kluczowe

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Summary

Mycobacterial lung disease is caused by nontuberculous mycobacteria (NTM), also known as atypical mycobacteria. NTM are widely distributed in the environment, particularly in soil and water. The NTM lung disease develops mostly due to inhalation of pathogens included in water aerosols.

The risk groups of NTM disease are patients with chronic lung diseases (such as cystic fibrosis, COPD, previous tuberculosis, bronchiectasis, silicosis, pulmonary alveolar proteinosis) or those with immunodeficiency. The most common species of NTM isolated in patients with chronic lung diseases are *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii* and *Mycobacterium abscessus*.

In some patients the disease caused by NTM develops, in others – NTM are cultured intermittently from respiratory specimens without a significant lung disease. The differentiation between these conditions is often problematic, thus it is important to follow the recognition guidelines of ATS/IDSA. In this paper, we present mycobacterial lung disease caused by *Mycobacterium avium* in a patient with COPD (chronic obstructive pulmonary disease) and bronchiectasis.

Streszczenie

Mikobakteriozy to choroby wywoływane przez prątki niegruźlicze (ang. *nontuberculous mycobacteria* – NTM), zwane również prątkami atypowymi. Prątki niegruźlicze występują dość powszechnie w środowisku, przede wszystkim w glebie i w wodzie. Do zakażenia układu oddechowego dochodzi przeważnie na skutek inhalacji aerozoli wodnych zawierających mikobakterie. Grupami ryzyka zachorowania na mikobakteriozy są chorzy na przewlekłe choroby płuc (takie jak: mukowiscydoza, przewlekła obturacyjna choroba płuc, przebyta gruźlica, rozstrzenie oskrzeli, pylica krzemowa, proteinoza pęcherzykowa) oraz pacjenci z obniżoną odpornością. Badania epidemiologiczne wskazują, że większość zakażeń prątkami niegruźliczymi u chorych na przewlekłe choroby płuc jest wywołanych przez szczepy: *Mycobacterium avium complex*, *Mycobacterium kansasii* i *Mycobacterium abscessus*. Obecność NTM w plwocinie pacjentów z przewlekłymi chorobami płuc może wskazywać na przejściowe zanieczyszczenie, kolonizację lub zakażenie. Różnicowanie tych stanów jest niekiedy bardzo trudne, dlatego istotne jest, aby rozpoznanie mikobakteriozy spełniało kryteria ATS/IDSA. W pracy opisujemy problemy diagnostyczne i terapeutyczne związane z rozwojem mikobakteriozy wywołanej przez *Mycobacterium avium* u chorej na przewlekłą obturacyjną chorobę płuc i rozstrzenie oskrzeli.

Address/adres:

*Dorota Wyrostkiewicz
I Department of Lung Diseases
National Tuberculosis
and Lung Diseases Research Institute
ul. Płocka 26, 01-138 Warszawa
tel. +48 (22) 431-21-43
fax +48 (22) 431-24-43
d.wyrostkiewicz@igichp.edu.pl

INTRODUCTION

Mycobacterial lung disease is caused by nontuberculous mycobacteria (NTM), known also as atypical mycobacteria or mycobacteria other than tuberculosis (MOTT). NTM are widely distributed in the environment, they are present in soil, and in water, both from natural and artificial water reservoirs.

NTM are human saprophytes, colonizing the respiratory, alimentary and urinary tracts (1-3). The risk groups for NTMLD are among others (4-6):

- patients with chronic lung diseases such as chronic obstructive pulmonary disease, cystic fibrosis, silicosis, pulmonary alveolar proteinosis, bronchiectasis and patients with postuberculotic lesions in the lungs,
- immunocompromized patients (e.g. in the course of HIV infection, neoplastic disease) and those receiving immunosuppresive treatment due to solid organ or bone marrow transplantation, or due to autoimmunological disorders.

The higher prevalence of *Mycobacterium avium* complex (MAC) disease in non-smoking, postmenopausal, slim women was described as Lady Windermere's disease (3).

The infection with NTM is caused by the inhalation of aerosols with water droplets contaminated with mycobacteria or by the skin contact. The data concerning the transmition of NTMLD between humans are scarse and concern *M. abscessus* transmition between the patients with cystic fibrosis (7).

Chronic obstructive pulmonary disease (COPD) is the common, chronic lung disease, characterized by the progressive decrease of peripheral airflow, due to inflammatory process taking place in the lungs, caused by toxic smokes and/or dusts. In Poland most cases of COPD are caused by cigarettes smoking. COPD course is influenced in the individual patient by the episodes of disease exacerbation and by the coexisting pathology (8).

Chronic inflammation of the bronchial tract, leads to functional and structural changes in the lungs of COPD patients. One of such complications is the development of bronchiectasis. Both COPD and bronchiectasis are the risk factors of NTMLD (9, 10).

In the present report, we present NTMLD in the patient with COPD and bronchiectasis and discuss the problems concerning NTMLD diagnosing and treatment in such population.

CASE REPORT

63-years old female, diagnosed with COPD and bronchiectasis, was admitted in February 2011 to the Ist Department of Lung Diseases, National Tuberculosis and Lung Diseases Research Institute in Warsaw, due to productive cough, low grade fever and dyspnea on exertion. First symptoms appeared 5 months before hospitalization, and they gradually increased. One week before the admittion to the hospital the patient noticed hemoptysis. As an outpatient she received several antibiotics with clinical improvement, nevertheless the symptoms of disease reappeared after the therapy was stopped. The sputum culture revealed the presence of *Pseudomonas aeruginosa* and *Hemofilus influenzae*. In June 2010 *M. avium* was cultured from sputum for the first time.

Upon admittion, the patient was in good performance status, body temperature was within normal limits, resting haemoglobin oxygen saturation was 94%, systemic blood pressure – 130/80, heart rate – 97 bpm. On auscultation, bilateral wheezing and rrhonchi were found. ESR was 50 mm/2 hours, WBC – 7.16 x 10^3 (N: 4.23-9.07 x 10^3), polymorphonuclears – 73% (N: 40-68%), Hgb – 12.6 g/dl (N: 12-16 g/dl), T – 293 x 10^3 (N: 130-400 x 10^3). CRP was 31 mg/dl (N < 5 mg/dl), GGTP – 133 U/l (N: 8-78 U/l), GPT-86 U/l (N: 9-52 U/l), D-Dimer – 1057 mcg/l (N: < 494 mcg/l). PaO_2 was 62 mmHg, $PaCO_2$ – 37 mmHg, pH – 7.45.

Chest X-ray examination revealed bilateral peribronchial opacities in the lower parts of the lungs (fig. 1).

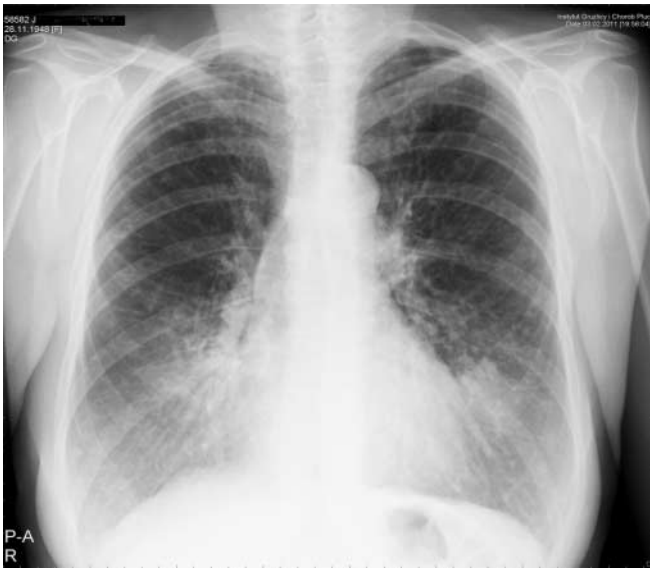

Fig. 1. Posteroanterior chest X-ray (03.02.2011). Tubular opacities in the lower zones represent dilated bronchi filled with impacted mucus, most evident on the left side

High resolution chest computed tomography of the lungs (HRCT) revealed the presence of multiple bronchiectasis, localized mostly in the middle lobe and lingula. The bronchial walls were thickened, with the signs of multiple mucous plugs. Ill defined centrilobular nodules were found in both lower lobes (fig. 2).

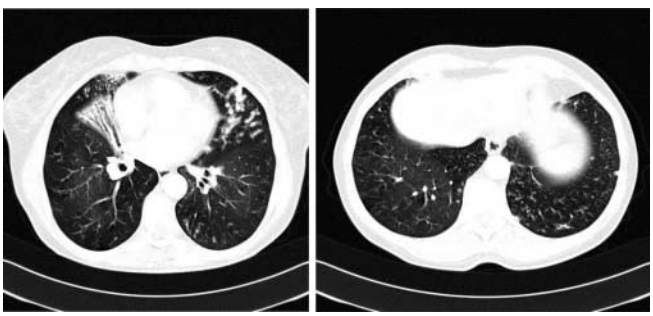

Fig. 2. High-resolution computed tomography of the lungs (05.02.2011). Partial loss of volume in middle lobe with bronchiectasis. Multiple mucous plugs in small lingular bronchi. Ill-defined centrilobular nodules are visible in both lower lobes

Fibreoptic bronchoscopy disclosed large amounts of purulent secretions. Antracotic incrustations and

posttuberculotic changes. The deformations of the small bronchi were also described. The culture of sputum and bronchial washings revealed no bacterial and no fungal pathogens. Bacterioscopy was negative for acid-fast bacilli, genetic probe for *M. tuberculosis* complex was negative. Tuberculin skin test (TST) and interferon gamma releasing assay (IGRA) (Quantiferon-TB Gold) were also negative. NTM were cultured from both sputum and bronchial washings on the fifth week of observation, MAC strain was identified by high pressure liquid chromatography (HPLC).

Based on clinical, radiological and microbiological criteria, NTMLD was recognized.

In April 2011 the treatment was started, according to ATS/IDSA guidelines (1, 2) with rifampicin 600 mg/day, ethambutol 1000 mg/day and clarithromycin 500 mg bid. The therapy was finished one year after the negative sputum cultures were obtained. Chest CT scan performed in March 2013 revealed less cenrilobular nodules and less mucous plugs in the bronchi. From 2013 to 2015 the patient has been admitted to the hospital twice, due to infective COPD exacerbations. *Acinetobacter baumanii*, *Citrobacter freundi* and *Pseudomonas aeruginosa* were cultured from the sputum. The results of culture for mycobacteria were negative and no signs of NTMLD relapse were found.

DISCUSSION

NTMLD has to be taken into account, especially in the patients with the exacerbation of chronic lung diseases and those with immunosuppression. The incidence rate of NTMLD is growing, in the United States of America it exceeds recently the incidence rate of tuberculosis (6). According to Andrejak et al., the risk of NTMLD is 16.5 times higher in the patients with chronic lung diseases comparing to healthy persons (9). The population studies performed in Denmark revealed the increased risk for NTMLD in COPD by 15.7 times, in astma – by 5.2-11.6 times, in bronchiectesis – by 187.5 times and in the patients with post tuberculous lesions – by 178 times (9). In all the mentioned above groups of patients, the risk of NTMLD was significantly increased by corticosteroids' use and it was dose-dependent (7, 9-11).

The interpretation of positive culture for NTM is often problematic due to wide environmental distribution of mycobacteria. NTM species are of low pathogenicity, the colonization of bronchial tract, without the signs of NTMLD, is frequent. Thus the recognition of NTMLD should be based in every case on ATS/IDSA criteria of the recognition of mycobacterial lung disease (1, 2). Microbiological criteria of NTMLD are as follows:

- at least two sputum or at least one bronchial washings cultures positive for NTM or
- histological features of mycobacterial lung disease (necrotizing granulomas with large cells contents and positive staining for acid-fast bacilli) combined with at least one positive culture for NTM (from sputum or bronchial washings).

The probability of NTMLD is the highest in case of culturing of *M. kansasii*, *M. malmoense* and *M. szulgai*, which are the most pathogenic types. Medium pathogenicity is attributed to: *M. avium-intracellulare*, *M. xenopi*, *M. abscessus* (12, 13). The remaining species are of low pathogenic characteristics.

NTMLD develops mostly in lungs, the involvement of lymph nodes and other organs – is rare. The disseminated NTMLD is diagnosed mostly in the patients receiving immunosuppressive or biological treatment (anti-TNF), and those with profound immunosuppression due to HIV infection or neoplastic disease (7).

The clinical picture of NTMLD in the patients with chronic lung diseases (COPD, cystic fibrosis) is non-characteristic. The vast majority of disease exacerbation episodes are of infective origin and they present with purulent sputum expectoration. Thus it's important to notice an additional symptoms suggestive of NTMLD, such as, generalized weakness, exercise intolerance, weight loss, night sweets, hemoptysis and chest pain (3).

In the presented patient, the low grade fever episodes, purulent sputum production and recurrent hemoptysis have been preceding NTMLD recognition. The therapy with antibiotics was only partly successful.

The radiological signs of NTMLD are described either as cavitating infiltrates, usually well visible on chest X-ray, looking similar to tuberculotic lesions, or the nodular and bronchiectatic pattern of disease, that is usually recognized on HRCT. Rarely, solitary pulmonary nodule or other types of focal lung lesions are found. Pleural involvement is less frequent in NTMLD than in tuberculosis (1, 2). The recognition of bronchiectatic form of NTMLD may be extremely difficult in the patients with cystic fibrosis, due to very similar lung radiological appearance of patients infected and non-infected with NTM. In the presented patient the chest CT-scan revealed the presence of centrilobular nodules, and bronchiectasis, the picture was suggestive of bronchiectatic form of NTMLD.

The microbiological methods of NTMLD diagnosing are based on culturing of various specimens: sputum, bronchial washings and lung tissue. In case of the positive result of bacterioscopy the use of genetic probe directed towards *M. tuberculosis* complex is recommended. The result of such probe is positive in case of the disease caused by *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*) and negative – in case of the disease caused by MOTT. The HPLC or different genetic probes are used to further identify the cultured NTM strains. The type of pathogen depends on the environmental exposure, nevertheless some NTM strains were found in association with certain

type of disease. Chu et al. noticed the predominance of disease caused by MAC in bronchiectatic form of NTMLD, *M. abscessus* and *M. kansasii* were cultured less frequently (14). In non-bronchiectatic form of NTMLD the most frequent NTM strains were: *M. kansasii* and *M. xenopi* (MAC was cultured in 10% of cases only) (14). In the presented patient the NTM was cultured after 5 weeks both in sputum and in bronchial washings. The type specification was performed with the use of HPLC.

TST and IGRA are the two supplemental diagnostic methods for the recognition of M. tuberculosis infection. TST may be positive in NTMLD, because NTM and *M. tuberculosis* express the common antigens for all mycobacterial species. The result of IGRA test is usually negative in NTMLD, nevertheless in the disease caused by *M. kansasii*, *M. marinum* and *M. szulgai* positive IGRA may be obtained, due to the presence of ESAT-6 and CFP-10 proteins that are recognized as belonging to *M. tuberculosis* complex.

In the presented patient with the disease caused by MAC, the results of both tests were negative.

Multidrug regimens are used to treat NTMLD infections according to ATS/IDSA recommendations (1, 2). NTMLD caused by MAC is treated with macrolids (clarithromycin 500-1000 mg/day or azithromycin 250 mg/day), ethambutol (15 mg/kg/day) and rifampicin (10 mg/kg/day, max 600 mg/day). In advanced form of MAC disease, parenteral treatment with aminoglycosides is added. Occasionally, the surgical treatment is implemented in combination with antituberculous therapy.

The effects of MAC treatment are not satisfactory in many cases, due to disease relapse. The other reason for poor response of MAC disease to therapy is the natural resistance to antituberculous drugs. Nevertheless the correlation between the chemoresistance obtained *in vitro* and clinical effectiveness of treatment is poor (1, 2). The results of treatment of MAC disease have been improved by the introduction of newer macrolides (clarithromycin and azithromycin) (15, 16).

The best results of treatment are obtained during the first course of antituberculous therapy. Therefore it is important to use the proper drugs in full recommended doses. Nevertheless in the older patients with slow disease progression, with coexising diseases, and with bad treatment tolerance, less aggressive type of therapy may be used (e.g. the drugs applied three times a week).

The optimal treatment of MAC disease resistant to macrolids is controversial. Some authors suggest to use rifampicin with higher doses of ethambutol – 25 mg/kg/day for the first two months and streptomycin for 3-6 months, and subsequently rifampicin with the standard dose of ethambutol – 15 mg/kg/day till the end of therapy. The others sugest using rifabutin instead of rifampicin and amikacin instead of streptomycin, quinolone may be also considered after the drug susceptibility testing. The promising results were also obtained in the pilot study with the amikacin used in inhalation (15 mg/kg) (17).

The control of treatment efficacy should be based on sputum cultures performed once a month. The clinical response is usually observed in the 3rd-6th month of treatment, negativisation of sputum cultures should be obtained by 12th month of therapy. According to data from the literature sputum conversion during MAC therapy is obtained in 60-100% of patients and the long term control of disease – in 50-82%. The treatment is more effective in brochiectatic form of MAC disease than in cavitary form (18).

The presented patient received standard treatment composed of rifampicin 600 mg/day, ethambutol 1000 mg/day and clarithromycin 1000 mg/day. The treatment has been continued for one year after the negative sputum cultures were obtained. During subsequent observation no signs of NTMLD relapse were found.

Despite many publications, the consensus concerning the optimal diagnosis and therapy of nontuberculous mycobacterial lung disease is often difficult. Awareness of the general practitioners concerning the possibility of NTMLD in a patient with recurring, infective exacerbations of chronic lung disease (despite antibacterial therapy), combined with general weakness, and weight loss, are crucial for the early recognition of the disease.

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