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Factors predisposing to non-tuberculous mycobacterial lung disease in the patients with respiratory isolates of non-tuberculous mycobacteria

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Abstract

Introduction: An increasing incidence rate of respiratory isolates of non-tuberculous mycobacteria (NTM) has been noted recently in most European countries as well as in the US. Despite many publications, there is no consensus concerning the importance of different factors in promoting NTM lung disease (NTMLD).

The aim of the present retrospective study was to analyse patients with positive NTM respiratory isolates in search of factors predisposing to NTMLD.

Material and methods: 73 patients, 23 males, 50 females, median age 62.2 years, in whom NTM have been cultured from respiratory specimen (sputum and/or bronchial washings), in the period 2010–2015, entered the study.

Results: NTMLD (according to ATS/IDSA) has been recognised in 36 patients, airways colonisation by NTM — in 37 patients. NTMLD was diagnosed more often in the patients infected with *M. kansasii*, *M. abscessus* and *M. avium/M. intracellulare* comparing to those infected with *M. xenopi*, *M. goodii* and *M. fortuitum* ($p < 0.0001$). The proportion of females to males was significantly higher in the NTMLD group comparing to the colonisation group ($p < 0.007$). Previous tuberculosis or mycobacteriosis were noted significantly more frequently in the group of patients with NTMLD comparing to the colonisation group (28% vs 8%, $p = 0.038$). Univariate regression analysis revealed *M. kansasii*, female gender, and previous tuberculosis or mycobacteriosis as significant predictors of NTMLD.

Conclusions: The risk factors of NTMLD recognition in the presented group of patients were the following: female gender, *M. kansasii* isolation, as well as past tuberculosis or mycobacteriosis.

Key words: non-tuberculous mycobacteria, COPD, bronchiectasis, interstitial lung disease, corticosteroids

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Introduction

Non-tuberculous mycobacteria (NTM) are environmental organisms, present in natural and artificial water sources as well as in dust and in soil [1, 2]. They may colonise human bronchial, gastrointestinal and urinary tracts, causing no symptoms of the disease, never-

theless, in some individuals NTM may be pathogenic [3].

The increasing incidence rate of respiratory isolates of NTM as well as NTM caused lung disease (NTMLD) has been noted recently in most European countries as well as in the US [4–8]. This concerns especially the increase of *M. avium*, *M. fortuitum* and *M. abscessus* [4, 5, 8, 9]. The

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growing incidence of NTM caused lung disease is probably brought about by an increasing number of patients with risk factors, such as chronic lung diseases, immunosuppressive treatment as well as aging of the population [4, 8, 10–12].

NTM isolation from a respiratory specimen is not an unambiguous sign of NTMLD. The criteria of NTMLD are defined in the ATS/IDSA recommendations from 2007 [13] and the latest BTS recommendations [14]. The proportion of patients with positive respiratory isolates of NTM, in whom NTMLD is diagnosed depends on the pathogenic characteristics of NTM and clinical characteristics of the population [15]. Despite many publications, there is no consensus in the literature concerning the importance of different factors in promoting NTMLD development.

Thus, the aim of the present retrospective study was to analyse the clinical and microbiological data in search of factors predisposing to NTMLD in the population of patients with positive NTM respiratory isolates.

Material and methods

Population

73 patients, 23 males, 50 females, median age 62.2 years (20–85 years), in whom non-tuberculous mycobacteria (NTM) have been cultured from respiratory specimens (sputum and/or bronchial washings), in the period from 2010 to 2015, entered the study. The study approval was obtained from Ethics Committee (no 9/2015).

Diagnostic criteria

The criteria of the recognition of non-tuberculous mycobacterial lung disease (NTMLD) have been applied according to the ATS/IDSA recommendations (Table 1) [13]. The factors potentially influencing development of NTMLD, such as: age, gender, body mass index (BMI), smoking habits, comorbidities and their treatment, were analysed.

NTM cultures and identification

The respiratory specimens (sputum and/or bronchial washings) were decontaminated with the sodium hydroxide and N-acetyl-L-cysteine (NaOH/NALC) method. The strains were cultured on solid media: egg-based Lowenstein-Jensen medium, Stonebrink medium and in automated system MGIT (Becton Dickinson).

Identification of culture was performed using the molecular test GenoType CM (Hain Lifescience), version 1.0 and 2.0. The procedure for identifying strains consists of three steps: isolation of DNA, amplification using primers labeled with biotin and a reverse hybridisation. The GenoType CM test using the DNA-STRIP method allows the identification of *Mycobacterium tuberculosis* complex strains and 14 clinically relevant NTM within a single procedure.

Statistical methods

Data were analysed in R environment [16]. The differences between the groups concerning the distribution of categorical variables were assessed with chi-square test. Wilcoxon rank sum test with continuity correction was used for the comparison of continuous variables in two different groups. Univariate logistic regression concerning prediction of NTMLD was performed and odds ratios with its 95% confidence interval were calculated, p-value < 0.05 was considered as statistically significant.

Results

NTMLD has been recognised in 36 patients, airways colonisation by NTM — in 37 patients. Demographic data and smoking habits in the group of NTMLD versus the group with NTM colonisation are presented in Table 2.

The proportion of females to males was significantly higher in the NTMLD group comparing to the colonisation group. A tendency towards lower age and BMI was noted in the NTMLD group comparing to the colonisation group.

Table 1. Principles of recognition of NTMLD according to ATS/IDSA [13]

Clinical	1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules and 2. Appropriate exclusion of other diagnoses
Microbiologic	1. Positive culture results from at least two separate expectorated sputum samples or 2. Positive culture results from at least one bronchial wash or lavage or 3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or acid fast bacilli) and positive culture for NTM of: lung specimen, bronchial wash or sputum (at least one)

Table 2. Demographic data and smoking habits according to final diagnosis in 73 patients with positive respiratory isolates for non-tuberculous mycobacteria (NTM)

Diagnosis	No of pts	Age (years. median, range)	Males/females	Smokers No (%)	BMI (kg/m ²), mean, SD
NTMLD	36	58.5 (20–85)	6/30*	16 (44)	22.7 (± 4.74)
NTM colonisation	37	66.2 (20–78)	17/20*	17 (46)	24.4 (± 5.04)
Total	73	62.2 (20–85)	23/50	33 (45)	23.7 (± 4.9)

*p = 0.007; NTMLD: non-tuberculous mycobacterial lung disease; BMI: body mass index; SD: standard deviation

Table 3. Distribution of NTM species according to final diagnosis in 66 patients with positive respiratory isolates for single non-tuberculous mycobacteria (NTM)

Diagnosis	No of pts	NTM species						
		<i>M. kansasii</i>	<i>M. avium</i>	<i>M. intracel.</i>	<i>M. abscessus</i>	<i>M. gordonae</i>	<i>M. fortuitum</i>	<i>M. xenopi</i>
NTMLD	33	13	10	4	2	1	0	3
NTM colonisation	33	3	6	2	0	13	4	5
Total	66	16	16	6	2	14	4	8

NTMLD: non-tuberculous mycobacterial lung disease

The NTM species identification revealed: *M. kansasii* — in 16 patients (22%), *M. avium* — in 16 (22%), *M. gordonae* — in 14 (19%), *M. xenopi* — in 8 (11%), *M. intracellulare* — in 6 (8%), *M. fortuitum* — in 4 (6%), *M. abscessus* — in 2 (3%), more than one type of mycobacteria — in 7 patients (10%). The distribution of NTM species in the NTMLD group comparing to the colonisation group, was performed in 66 patients with a single respiratory NTM isolate (Table 3).

NTMLD has been diagnosed in both individuals infected with *M. abscessus*, in 81% of patients infected — with *M. kansasii*, 64% of subjects infected with *M. avium/M. intracellulare*, 38% of those with *M. xenopi*, 7% of infected with *M. gordonae* and none — with *M. fortuitum*. The proportion of NTMLD among patients with more pathogenic NTM types (*M. abscessus*, *M. kansasii* and *M. avium/M. intracellulare*) and those less pathogenic (*M. xenopi*, *M. gordonae*, *M. fortuitum*) — were 29/40 (73%) and 4/26 (15%), respectively, p < 0.0001.

In majority of patients — 70/73 (96%), coexisting diseases that could predispose to NTMLD were noted: in 25/73 (34%) — one, in 26/73 (36%) — two, and in 19/73 (26%) — more than two diseases. Analysis of coexisting disorders is presented in table 4. Most frequent comorbidities were:

bronchiectasis — in 24 patients — 33%, chronic obstructive pulmonary disease (COPD) — in 18 individuals (25%) and interstitial lung diseases (ILD) — in 18 subjects (25%): lung fibrosis due to collagen tissue disease (4 cases), cryptogenic organising pneumonia (3), sarcoidosis (3), hypersensitivity pneumonitis (2), Langerhans cell histiocytosis (1), NSIP (1), lung fibrosis not classified (4). Oral corticosteroids (CS) were used by 17 (23%) patients, in 10 — as the only therapy, in 7 — combined with immunosuppressive therapy. The median prednisone dose was 10 mg/day (range 5–40 mg). Immunosuppressive drugs were used by 9 (12%) patients: azathioprine 100–150 mg/day — by 4, methotrexate 10 mg/week — 1, rituximab — 1, hydroxychloroquine — 1, and systemic chemotherapy due to lung cancer — by 2 individuals.

The influence of various pre-existing diseases on NTMLD development has been investigated (Table 4). Previous tuberculosis or mycobacteriosis were noted significantly more frequently in the group of patients with NTMLD comparing to the colonisation group (28% and 8%, respectively, p = 0.038). COPD was diagnosed more often in the colonisation group comparing to NTMLD (30% and 19% respectively), nevertheless, the differences were not significant.

Table 4. Coexisting diseases and their treatment according to final diagnosis in 73 patients with positive respiratory isolates for non-tuberculous mycobacteria (NTM)

Coexisting disease	NTMLD 36 pts no (%)	Colonisation 37 pts no (%)	Total 73 pts no (%)	p
Bronchiectasis	12 (33)	12 (33)	24 (33)	0.94
COPD	7 (19)	11 (30)	18 (25)	0.25
Astma/ABPA	2 (6)	5 (14)	7 (10)	0.24
ILD	10 (28)	8 (22)	18 (25)	0.63
CTD	5 (14)	5 (14)	10 (14)	1.0
CF	3 (8)	1 (3)	4 (6)	0.63
NPL	9 (25)	7 (19)	16 (22)	0.62
Diabetes	4 (11)	9 (24)	13 (18)	0.19
Hypothyreosis	8 (22)	6 (16)	14 (19)	0.59
Previous tbc/myco	10 (28)	3 (8)	13 (18)	0.038
None	2 (6)	1 (3)	3 (4)	0.52
Systemic glucocorticoids	10 (28)	7 (19)	17 (23)	0.53
Immunosuppressive drugs	4 (11)	5 (14)	9 (12)	0.97

NTMLD: non-tuberculous mycobacterial lung disease; COPD: chronic obstructive pulmonary diseases; ABPA: allergic bronchopulmonary aspergillosis; ILD: interstitial lung diseases (details in the text); CTD: collagen tissue diseases-mixed collagen tissue disease (1), rheumatic polymyalgia (1), autoimmune cholangitis (2), primary biliary cirrhosis (1), rheumatoid arthritis (2), CTD- not classified (2), Sjogren’s syndrome (1); CF: cystic fibrosis; NPL: previous or actual neoplastic disease — lung cancer (6), lymphoma (2), colon cancer (2), breast cancer (1), gastric cancer (1), urinary bladder cancer (1), thyroid gland cancer (1), uterus cancer (1), basocellular skin cancer (1)

Table 5. Factors significantly influencing NTMLD recognition, univariate regression analysis

Univariate regression analysis			
Factor	OR	95%CI	p
<i>M. kansasii</i>	4.87	1.42–16.72	0.012
<i>M. gordonae</i>	0.044	0.005–0.36	0.003
Female gender	3.69	1.23–11.05	0.02
Age	0.96	0.927–0.999	0.041
BMI	0.894	0.805–0.992	0.035
Previous TBC, NTMLD	4.074	1.018–16.306	0.047

OR: odds ratio; CI: confidence interval; BMI: body mass index; TBC: tuberculosis; NTMLD: non-tuberculous mycobacterial lung disease

The proportions of ILD and collagen tissue disease (CTD) in the groups of NTMLD and colonisation were equal. In the patients with NTMLD comparing to colonisation, the percentages of individuals treated with corticosteroids alone or in combination with immunosuppressive therapy were: 28% and 19 % respectively, with the difference being nonsignificant.

Univariate analysis of factors possibly influencing NTMLD development is presented in table 5. The elements significantly increasing

probability of NTMLD were: *M. kansasii* isolate, female gender, and previous tuberculosis or mycobacteriosis. The risk of NTMLD was lower in those diagnosed with *M. gordonae*, older ones and those with higher BMI.

Discussion

The analysis of factors predisposing to NTMLD development in our material revealed that women were more susceptible than men. Female gender was confirmed as a risk factor of NTMLD in univariate analysis.

The published data concerning this subject are discrepant. Adzic *et al.* [6] documented that 66% of NTMLD cases registered between 2009 and 2016 in the University Hospital for Pulmonology in Belgrade involved men. US epidemiological studies concerning NTM respiratory isolates registered by Integrated Health Care Delivery Systems (2004–2006) found females’ predominance [11, 17, 18]. It seems that males predominate in the group of patients with NTMLD and underlying COPD [6, 19], whereas females — in the category of bronchiectatic form of NTMLD [15, 17]. Especially, the nodular bronchiectatic type of disease observed in non-smoking, thin and tall,

postmenopausal women, with pectus excavatum, and mitral valve prolapse (MVP), called *Lady Windermere syndrome*, may be responsible for female predominance in some published series [3, 20]. In our study, 3 non-smoking, postmenopausal women, with BMI 19.7–23.6 were identified, nevertheless, without MVP or pectus excavatum.

The microbiological analysis of our group of patients revealed that the most pathogenic among NTM species was *M. kansasii* (NTMLD developed in 81% of infected patients), and it was found to be an independent risk factor of NTMLD diagnosis. Another study coming from Poland confirmed high virulence of *M. kansasii* reporting clinically relevant lung disease in 82% of infected patients [21].

M. abscessus was identified by us in two patients only, nevertheless, both presented with NTMLD. Recent US report demonstrated the increase of NTM species belonging to *M. abscessus* group between 1994 and 2014 by 322% [4]. The current proportion of NTMLD caused by *M. abscessus* is 20% in Europe and 15% in Japan [22].

NTM belonging to *M. avium/M. intracellulare* complex (MAC) were less pathogenic in our material, nevertheless, in 64% of the patients infected with these strains NTMLD has been recognised. Although MAC is less pathogenic than *M. kansasii*, it is the cause of most cases of lung disease in the US, Europe and Japan, due to a high rate of identification, especially in the aging population [17, 22, 23].

The present study revealed high frequency of coexisting diseases that could predispose to NTM colonisation. 96% of patients had at least one illness diagnosed.

Among chronic lung diseases, the most frequent were COPD and bronchiectasis diagnosed in 25% and 33% of patients, respectively.

The relation between COPD and NTMLD has been the subject of many studies published recently. Hoefsloot *et al.* [24] found a 22% prevalence of NTM isolation in 73 consecutive patients with COPD exacerbation, the subjects with positive culture were significantly older than the others. Char *et al.* [25] confirmed the presence of necrotising granulomas in 10% of COPD patients, in whom lung volume reduction surgery has been performed.

The increased risk of NTMLD in COPD subjects may be partly associated with inhaled steroids use and dosage [26, 27]. Diel *et al.* [28] found an increased mortality rate among COPD individuals infected with NTM, comparing to those not infected.

Up to 30% of COPD patients are diagnosed with COPD-bronchiectasis overlap syndrome [29]. Gatheral *et al.* [30] found radiographic presence of bronchiectasis in 69% of COPD patients admitted with first exacerbation. The presence of bronchiectasis in COPD independently determined sputum isolation of *P. aeruginosa* and NTM [30] and correlated with increased frequency of exacerbations and mortality [31].

Recently published population survey from Israel revealed the presence of positive respiratory isolates for NTM in 105/6274 (1.7%) patients with bronchiectasis [32]. The authors indicated female gender, age below 65 years, and antibiotic or prednisolone therapy as risk factors for NTM colonisation [32]. A multicentre, epidemiological study, conducted in the US, concerned the possible risk factors of NTMLD in two national samples of bronchiectasis patients [33]. Inhaled corticosteroids use have been reported by 30–40% of patients, in 60% of them for the time longer than 1 year [33]. These data indicate that further research is needed to clarify the safety of inhaled corticosteroids in the patients with bronchiectasis.

ILD have been noted in 25% of our group with positive NTM isolates. Various types of ILD have been recognised. NTM have been cultured in those with prolonged course of disease, lung fibrosis was present in most cases. This was true also for both patients with hypersensitivity pneumonitis, thus the positive NTM isolates were regarded as colonisation in the course of previously diagnosed lung disease and not the allergy to NTM antigens.

The data concerning the risk of NTM infection in ILD are scarce. Axson *et al.* [34] found ILD in 6% of patients with positive NTM culture in UK primary care centres. Ito *et al.* [35] documented ILD in 6.6% of subjects with pulmonary MAC-related disease. Park *et al.* [36] found NTMLD in 2% of patients with idiopathic pulmonary fibrosis, majority of them have not been treated with immunosuppressive drugs.

In our material, the percentage of individuals receiving oral corticosteroids due to ILD or CTD was larger in NTMLD comparing to the observation group (28% and 19%, respectively), nevertheless, the difference was not significant. The influence of immunosuppressive therapy on NTMLD development was difficult to assess, as in most patients it was combined with corticosteroids.

Brode *et al.* [37] noted an increased risk of NTM-related disease in the patients with rheumatoid arthritis receiving anti-TNF therapy, but also in those treated with corticosteroids in the dose

exceeding 20 mg/day or hydroxychloroquine. Our patients who developed NTMLD received prednisone in the median dose of 10 mg per day.

NTMLD, in our study, was significantly more probable in patients with previous history of tuberculosis or mycobacteriosis than in the remaining ones. This is an important observation, as substantial proportion of NTMLD in Poland, as well as in Serbia, develop in the individuals with past tuberculosis [6, 21, 38]. It is not known, whether those patients represent the genetic predisposition to mycobacterial lung diseases or whether post-tuberculous parenchymal abnormalities predispose to colonisation by NTM and further NTMLD.

Our group of patients with positive NTM respiratory specimens also included 4 individuals with cystic fibrosis (CF). In 3 of them NTMLD developed, in 1 — colonisation was recognised.

Growing evidence exists in the literature that CF is a risk factor for NTMLD [39–41]. The study concerning 16 153 CF patients above 12 years of age, conducted by Adjemian *et al.* [40] revealed at least one NTM isolation in between 2010 and 2014 in 20% of them. The growing prevalence of NTM isolates was noted: from 11% in 2010 to 13.4% in 2014 [40]. Another study concerning 5333 CF children and young adults below 16 years of age, indicated the increasing prevalence of positive cultures for NTM from 1.3% in 2010 to 3.8% in 2015 [41]. The types of NTM predominating both in children and in adults diagnosed with CF, were *M. avium*/*M. intracellulare* and *M. abscessus* [40, 41]. In our group of CF patients, the NTM identification revealed: *M. abscessus* — in 1, *M. intracellulare* — in 2, and *M. avium* — in 1 person.

In conclusion, the presented analysis of patients with positive NTM respiratory isolates showed that factors significantly increasing probability of NTMLD recognition were the following: female gender, *M. kansasii* respiratory isolate, or past tuberculosis or mycobacteriosis. *M. gordonae* isolate, as well as higher age and BMI were combined with a significantly lower risk of NTMLD development.

Conflict of interest

The authors declare no conflict of interest.

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