Clinical and epidemiological characteristics of *M. kansasii* pulmonary infections from Rio de Janeiro, Brazil, between 2006 and 2016

Telma Goldenberg[1] , Regina Gayoso[1] , Roberto Mogami[2] ,
Maria Cristina Lourenço[3] , Jesus Paes Ramos[1] , Luciana Distasio de Carvalho[4] ,
Margareth Pretti Dalcolmo[1] , Fernanda Carvalho de Queiroz Mello[5]

1. Centro de Referência Professor Hélio Fraga, Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz, Rio de Janeiro (RJ) Brasil.
2. Serviço de Radiologia, Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
3. Laboratório de Bacteriologia e Bioensaios, Instituto Nacional de Infectologia, Fundação Oswaldo Cruz, Rio de Janeiro (RJ) Brasil.
4. Laboratório de Micobactérias, Centro de Referência Professor Hélio Fraga, Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz, Rio de Janeiro (RJ) Brasil.
5. Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

ABSTRACT

Objective: To evaluate clinical, tomographic, and microbiological characteristics of pulmonary disease caused by *M. kansasii* (MKPD) in patients treated at an outpatient unit from 2006-2016. **Methods:** We studied thirty eight patients, and analyzed socio-demographic, clinical-radiological, laboratory, and therapeutic characteristics. **Results:** The mean age was 64 years (SD = 10.6; IIQ = 57-72; median = 65.0), and 22 (57.9%) male patients. Pulmonary comorbidity was present in 89.5% of the patients. The most frequent comorbidity was bronchiectasis (78.9%). Previous treatment for pulmonary tuberculosis (PTB) was found in 65.9%. The most used therapeutic regimen was rifampicin, isoniazid and ethambutol (44.7%). Chest tomography (CT) showed bronchiectasis (94.1%), architectural distortion (76.5%), septum thickening (67.6%), and cavities (64.7%). Disease was bilateral in 85.2%. We observed 10.7% resistance to rifampicin, 67.9% resistance to ethambutol, and sensitivity to clarithromycin. **Conclusion:** In patients with structural lung disease, it is important to search for NTM, the main differential diagnosis with PTB. Chest CT showed different patterns that overlapped with structural disease caused by PTB or other lung diseases. We observed resistance to ethambutol, a drug component of the recommended regimen.

Keywords: Nontuberculous mycobacteria; *Mycobacterium kansasii*; Epidemiology; Treatment.

INTRODUCTION

Historically, pulmonary mycobacteria infections in humans were caused almost exclusively by *Mycobacterium tuberculosis* (Mtb).[1] Initially, non-tuberculous mycobacteria (NTM) were regarded only as environment organisms with limited clinical relevance, obfuscated by *M. tuberculosis*.[2] The AIDS pandemic highlighted the widespread disease caused by *M. avium* and *M. intracellulare* as opportunistic germs, which has caught the attention of the medical community.[2] NTM can be found in soil, in treated or untreated waters, often forming biofilms, sewage, animal surfaces and aerosols generated in the environment.[3,4] The latter is the most frequent source of infection for man, especially disease involving the respiratory system, as described in 94% of NTM cases.[4] Although the most accepted paradigm for transmission continues to be the inhalation of environmentally generated aerosols, mostly from shower,[3-5] conflicting reports suggest that transmission may occur from person to person.[4,6]

Mycobacterium kansasii (MK) is one of the six most isolated NTM species worldwide. Central Europe is a common geographical location of MK.[7] Its presence may be related to distribution systems of treated water and highly urbanized areas.[7,8] Disease presents as apical fibro-cavitary pulmonary disease with great similarity to pulmonary tuberculosis. Other less frequent form is nodular with bronchiectasis.[7]

The four major categories of people susceptible to NTM infection described include:[9] 1) Patients with structural involvement of the pulmonary parenchyma, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, of pulmonary tuberculosis (PTB) sequelae, bronchiectasis; 2) Patients on immunobiological use, neoplasia, organ transplants; 3) People infected with HIV, who are more prone to disease disseminated by NTM, 4) Genetic diseases with mutation in pathways such as interferon gamma and interleukin 12. Another important group would be postmenopausal women,

non-smokers with characteristic phenotype including low weight, scoliosis, pectus excavatum and mitral valve prolapse.[9]

In the last two decades, developed countries saw an increase in prevalence of disease caused by NTM and a decrease in tuberculosis incidence. TB control, population aging, the HIV epidemic and the development of new laboratory techniques allowed the isolation and identification of new species of mycobacteria in material from the respiratory tree.[10,11]

In Brazil, the prevalence of pulmonary infections due to NTM (NTMPD) was unknown until the implementation of a surveillance system (SITETB).[12] In Brazilian series with cases of NTMPD, the frequency of *M. kansasii* disease ranged from 16.0 to 33.9%, according to the region studied.[13-15] Between 2014 to 2017 in our country, NTM infections due to *Avium* Complex were more prevalent. However, in Rio de Janeiro State, the disease was mainly due to MK.[12] With the predominance of MK infection in Rio de Janeiro State, this study aims to present an analysis of MK pulmonary diseases (MKPD) in patients attended at our outpatient clinic. Variables studied were demographic aspects, clinical and laboratory characteristics, therapeutic regimens, and treatment outcomes.

METHODS

This is a descriptive study, analyzing medical records from patients having diagnosis of pulmonary disease caused by *M. kansasii*, between January 2006 and December 2016. The study was carried out in an outpatient unit for the treatment of drug-resistant TB and NTM. Patients were referred from different regions of the Rio de Janeiro State (Professor Hélio Fraga Reference Centre (CRPHF/ENSP/FIOCRUZ). The study included patients with growth and identification of *M. kansasii* in two sputum samples, or a bronchoalveolar lavage sample.[16]

We analyzed demographic, clinical-radiological, laboratorial, and therapeutic characteristics including: gender, age, housing municipality, pulmonary and non-pulmonary comorbidities, respiratory symptoms (cough, sputum, hemoptysis, chest pain, dyspnea) and systemic symptoms (fever, sweating, weight loss), number of PTB treatments, previous treatment for MK, clinical specimen, culture conversion, sensitivity test (ST), outcome (favorable, unfavorable, abandonment, death), chest radiography (presence of cavity, unilateral or bilateral), high resolution computed tomography (HRCT) of the lung. HRCT exams had documentation of the sequential cuts of the parenchyma, mediastinum, and high-resolution windows without administration of venous contrast medium. Abnormalities were analyzed according to Fleischner Society[17] classification and the Brazilian guideline on descriptors terminology and patterns of chest CT.[18] The following variables were used: presence or absence of atelectasis, bubble, cavity, emphysema, opacity, septal thickening, bronchiectasis, air trapping, architectural distortion, centrilobular nodular pattern/budding tree, consolidation, pleural alteration, lymph nodes and others.

Data were analyzed with the statistical software "R". Descriptive analysis of continuous variables, the mean, median and interquartile range (IQR), and standard deviation (SD), were obtained as measures of central tendency and dispersion. Percentage values were calculated for categorical variables. Fisher test was done to evaluate the associations between the relevant categorical variables: a) presence of previous TB treatment with gender, age, symptoms, comorbidities, outcomes, type and location of the lesion on HRCT, and ST; b) gender with comorbidities, location and type of lesion on HRCT.

Study was approved by the Ethics and Research Committee of Clementino Fraga Filho Hospital of the Rio de Janeiro Federal University (HUCFF/UFRJ) under number 213/08.

RESULTS

Thirty-eight patients with a microbiological diagnosis of MKPD who fulfilled the criteria defined by the American Thoracic Society (ATS) were included.[16] There were 22 (57.9%) male patients. Mean age was 64 years (SD = 10.63, IQR = 57-72, median = 65). Minimum age was 39 years and 86.9% were 50 years or older (Table 1). Patients came from the metropolitan region of Rio de Janeiro. Of these, 26 (68.42%) were referred from Rio de Janeiro municipality and 12 patients (31.58%) came from Baixada Fluminense (districts adjacent to Rio de Janeiro City) (Table 1).

All patients had some type of comorbidity. These were subdivided into pulmonary and non-pulmonary comorbidities. Pulmonary comorbidity was present in 34 (89.5%), the most frequent condition being bronchiectasis (78.9%), chronic obstructive pulmonary disease (COPD) (55.3%), asthma (15.8%), and silicosis (5.3%) (Table 1). Smoking report was present in 60.5% patients. The most frequent non-pulmonary comorbidities were gastroesophageal reflux in 23.7% (Table 1). The most frequent symptoms were divided into three groups: respiratory, systemic and both. Most patients (94.7%) had respiratory symptoms, and 44.7% had respiratory and systemic symptoms. No patient had systemic symptoms only. Respiratory and systemic symptoms were cough (89.5%), sputum (86.8%), dyspnea (55.3%), chest pain (34.2%), hemoptysis (31.6%), weight loss (34.2%), fever (23.7%) and sweating (10.5%). (Table 1)

Most patients reported previous treatment for pulmonary tuberculosis (PTB) or were undergoing treatment. Of these, 25 (65.9%) patients reported previous treatment for pulmonary tuberculosis. The mean previous treatments was 1.7 (median = 2.0, SD = 0.79, IIQ = 1.0-2.0). Two patients previously treated MKPD. Twenty-seven (71.1%) patients were using a therapeutic regimen to treat suspected pulmonary PTB when diagnosed with MKPD. Regarding the therapeutic regimens used, 17 (44.7%) patients used rifampicin (R), isoniazid (H)

Table 1. Clinical and demographic characteristics, patients with MKPD, Rio de Janeiro, 2006-2016 (N = 38).

	N (%)		N (%)
Gender		*Previous treatments*	
Male	22 (57.9)	MK previous treatment	2 (5.3)
Female	16 (42.1)	TB previous treatment	25 (65.8)
Age (years)		On TB treatment	27 (71.1)
30 to 49	4 (10.5)	*Comorbidities*	
50 to 60	9 (23.7)	*Pulmonary comorbidity*	
61 to 70	12 (3.6)	Bronchiectasis	30 (78.9)
71 to 80	12 (31.6)	Smoking	23 (60.5)
> 80	1 (2.6)	COPD	21 (55.3)
Place of residence		Asthma	6 (15.8)
Northern Zone	16 (42.1)	Silicosis	2 (5.3)
Baixada Fluminense	13 (34.2)	*Other comorbidity*	
West Zone	5 (13.2)	GER	9 (23.7)
South Zone	3 (7.9)	Diabetes	4 (10.5)
Centre	1 (2.6)	Alcoholism	5 (13.2)
Respiratory symptoms		Hepatitis	5 (13.2)
Cough	34 (89.5)	Immunosuppressive use	4 (10.5)
Expectoration	33 (86.8)	Drug addiction	1 (2.6)
Dyspnea	21 (55.3)	HIV infection	1 (2.6)
Hemoptysis	12 (31.6)	*Clinical specimen*	
Thoracic pain	13 (34.2)	Sputum	26 (68.4
Weight loss	13 (34.2)	BAL	12 (31.6
Systemic symptoms		*Thorax X-ray*	
Fever	9 (23.7)	Cavitary bilateral	18 (47.4)
Sweating	4 (10.5)	Cavitary unilateral	11 (28.9)
Respiratory symptoms		Non-cavitary bilateral	6 (15.8)
Yes	36 (94.6)	Non-cavitary unilateral	2 (5.3)
No	2 (5.3)	Normal	1 (2.6)
Systemic symptoms		*Cavities X-ray*	
Yes	17 (44.7)	Yes	29 (76.3)
No	21 (55.3)		
Both symptoms			
Yes	17 (44.7)		
No	21 (55.3)		

MKPD: *Mycobacterium kansasii* pulmonary Disease; N: Case number; TB; tuberculosis; COPD: Chronic Obstructive Pulmonary Disease; BAL: Bronchoalveolar lavage; HIV: Human Immunodeficiency Virus; GER: Gastroesophageal Reflux; MK: *M. kansasii*.

and ethambutol (E). Of these, seven (18.4%) patients used rifampicin, isoniazid (H) and clarithromycin (CLA) and seven (18.4%) patients used RHE and clarithromycin (Table 2).

Regarding the outcomes, after discharge from the treatment, we had two recurrences (5.3%); two deaths (5.3%) due to hemoptysis following discontinuation of the treatment regimen; and three (7.9%) patients discontinued treatment.

We collected two sputum samples from 26 patients (68.4%), and bronchoalveolar lavage in 12 patients (31.6%). The mean time for culture conversion was 75 days (median = 62). Twenty-eight sensitivity tests were performed (Table 2). Only three (10.7%) showed resistance to rifampicin, 19 (67.9%) tests detected resistance to ethambutol, and all tests were sensitive to clarithromycin, moxifloxacin and amikacin.

All patients underwent chest radiography. Eighteen (47.4%) patients showed bilateral cavitary lesion (BC), 11 (28.9%) unilateral cavitary lesion (UC), six (15.8%) bilateral non-cavitary lesion, and (5.3%) had unilateral non-cavitary lesion (UNC), and one (2.6%) with normal radiography. It is noteworthy that 29 (76.3%) patients presented with cavities.

Thirty-four CT scans were analyzed focusing on the frequency of the lesions observed and the location of the lesions in the lung. Lesions were preferentially located in the upper lobes (LSD: 94.1% and LSE: 85.3%). (Table 3) In the upper right lobe the segments most affected were posterior segment (88.2%), apical segment (82.4%) and anterior segment (67.6%). In the upper left lobe: apicoposterior segment (76.5%), lingula (76.5%), and anterior segment (58.8%). In order of frequency, the lesions found

Table 2. Sensitivity test result (N=38).

Drug	Tested		Not tested (%)
	Resistant (%)	Sensitive (%)	
Clarithromycin	0	26 (100)	12 (31.6)
Rifampicin	3 (10.7)	25 (89.3)	10 (26.3)
Amikacin	0	26 (100)	12 (31.6)
Ciprofloxacin	17 (65.4)	9 (34.6)	12 (31.6)
Ethambutol	19 (67.9)	9 (32.1)	10 (26.3)
Moxifloxacin	0	26 (100)	12 (31.6)
Trimethoprim-sulfamethoxazole	25 (96.2)	1 (3.8)	12 (31.6)
Linezolid	1 (4.5)	21 (95.5)	16 (42.1)

Table 3. Location of lesions on HRCT (N = 34).

	N (%)
Right lung	33 (97.1)
Upper right lobe	32 (94.1%)
Anterior	23 (67.6)
Apical	28 (82.4)
Posterior	30 (88.2)
Middle lobe	19 (55.9%)
Medial	18 (52.9)
Lateral	18 (52.9)
Right lower lobe	23 (67.6%)
Superior	18 (52.9)
Anterior	17 (50.0)
Medial	14 (41.2)
Lateral	17 (50.0)
Posterior	17 (50.0)
Left lung	30 (88.2)
left upper lobe	29 (85.3%)
Anterior	20 (58.8)
Apicoposterior	26 (76.5)
Lingula	26 (76.5)
left lower lobe	21 (61.8%)
Superior	17 (50.0)
Anteromedial	17 (50.0)
Lateral	17 (50.0)
Posterior	18 (52.9)
Bilateral disease	29 (85.2)
Right lung disease (exclusive)	4 (11.8)
Left lung disease (exclusive)	1(3.0)

Table 4. Frequency of lesions at the HRCT scan (N = 34).

Lesion type	N (%)
Bronchiectasis	32 (94.1)
Architectural distortion	26 (76.5)
Septal thickening	23 (67.6)
Cavity	22 (64.7)
Opacity	21 (61.8)
Centrallobular nodules / budding tree	20 (58.8)
Atelectasis	16 (52.9)
Emphysema	13 (38.2)
Air trapping	10 (29.4)
Bubble	7 (20.6)
Pleural changes	6 (17.6)
Lymph node enlargement	3 (8.8)

HRCT: Higth Resolution Computed Tomography.

were bronchiectasis (94.1%), architectural distortion (76.5%), septal thickening (67.6%), cavities (64.7%), opacity (61.8%) and centrilobular nodules / budding tree (58.8%) (Table 4).

We observed no significant association among most categorical variables studied (Table 5). The data suggest association between previous treatment of PTB and pleural changes in tomography (p-value = 0.06, borderline). There is a statistically significant association between patient gender and presence middle lobe lesion on HRCT (p=0.017). No association was found between prior schedules for Tb and ethambutol resistance.

DISCUSSION

We observed a predominance of males (57.9%) with a mean age of 64 years, as found by others.[19-23] We assume that the predominance of males found in various publications may be related to habits such as smoking, prevalence of pulmonary comorbidities such as COPD and previous PTB treatments, more common in males. Lung infection caused by MK occurred mainly in the elderly, as found by Bakula et al. (2018), contrasting with studies from previous years in which patients were 10 to 20 years younger.[19-21] The most advanced mean age may be related to the greater longevity of the general population and associated comorbidities. In our population, there may be a delay in diagnosis due to the TB burden, and clinical and radiological similarity between them.

Most patients had pulmonary comorbidities. Bronchiectasis was the most frequent finding, with a higher occurrence than that reported by others.[8,19-23] Since the diagnosis of infection is late, pulmonary lesions are more severe on radiology. Prevalence of COPD is high and may be related to the tobacco load found (60.5%). Other authors also report distinct prevalence of COPD and smoking.[8,19-23] There are publications that associate MK infection with the sequelae of PTB in regions endemic for this disease.[8] At the time of diagnosis of MK, 65.8% patients were previously PTB treated, and 71% of them were on medication for TB. Recent Polish publication also mentions that half of the patients had a history of

Table 5. Fisher's test, variables with p-value <0.10.

Gender	N(%)	N(%)	p-value
	Male	Female	
HRCT - middle lobe damage			0.017
Yes	7 (36.8)	12 (63.2)	
No	12 (80.0)	3 (20.0)	
Previous TB treatment			0.098
Yes	17 (68.0)	8 (32.0)	
No	5 (38.5)	8 (61.5)	
Previous TB treatment			
Systemic symptoms			0.086
Yes	14 (82.3)	3 (17.7)	
No	11 (52.4)	10 (47.6)	
Both symptoms			0.086
Yes	14 (82.3)	3 (17.7)	
No	11 (52.4)	10 (47.6)	
HRCT- nodules / budding tree			0.080
Yes	15 (75.0)	5 (25.0)	
No	6 (42.9)	8 (57.1)	
HRCT-Pleural changes			0.062
Yes	6 (100.0)	0	
No	15 (53.6)	13 (46.4)	
Rifampicin resistance (N=28)			0.037
Resistant	0	3 (100.0)	
Sensitive	18 (72.0)	7 (28.0)	

p-value: significance probability; TB: Tuberculosis; HRCT: High Resolution Computed Tomography.

previous PTB treatment.[8] Past PTB and MK infection is observed less markedly in other studies, in which PTB prevalence was lower.[19-22]

The high frequency of previous treatments for PTB in cases of MKPD might be related to the high prevalence of PTB in Rio de Janeiro, clinical and radiological similarity between the two diseases, and finally, and the lack of diagnostic resources and trained personnel to diagnose NTMPD. Probably, several cases of NTMPD are treated with schedules employed in TB treatment.

The most frequent non-pulmonary comorbidity was gastroesophageal reflux, an illness that may be related to the pathophysiology of bronchiectasis. We found only one study that cites gastroesophageal reflux as a comorbidity.[8] In a cohort studying the etiology of bronchiectasis, GER was found in only 2.0%. The most common associated diseases with bronchiectasis were the post-infectious cause (PTB and pneumonia).[24] Predominant respiratory symptom was cough with expectoration. In several publications, the most frequent symptom was cough.[19-21,23] Hemoptysis is mentioned in all series studied with varying frequencies, probably caused by erosion of the bronchial vessel present in the cavities.[8,19-22] Systemic symptoms are present in almost half of the patients in sample.

Literature describes two main tomographic patterns of NTM-related lesions: fibrocavities

(tuberculosis-like) mainly located in the upper lobes, and nodular/ bronchiectasis.[16] We observed predominance of bilateral lung involvement, with predilection for lesions by the upper lobes, especially the right upper lobe similar to that found by Takahashi.[25] Late diagnosis that occurs in MKPD is possibly due to radiological similarity with PTB, and may explain the strong bilateral involvement found in our study. The high frequency of bronchiectasis with predilection for upper lobes and architectural distortion found may also be related to pulmonary sequelae caused by previous PTB treatments. NTM and MTb are classified as mandatory aerobic, and the high concentration of oxygen in the apices favors MK to be preferentially in this location. Our patients with MKPD showed predominance of cavities and the pattern of involvement of small and large airways, characterized by bronchiectasis and changes due to filling of bronchioles.

Even with high exposure to previous PTB treatments, we found no significant resistance to rifampicin. More than half of the patients were resistant to ethambutol. The higher resistance to ethambutol observed in MKPD may have genetic determinants similar to that occurring in TB. Other studies are needed to point out specific mutations or mechanisms that confer resistance to drugs in MK infection.[8] More than half of the patients used therapeutic regimens containing ethambutol. The combination of drugs in regimens containing rifampicin ensures

successful treatment of MK infection.[26] Despite the higher resistance attributed to ethambutol, patient's outcome was successful.

Presumably, due to the small sample studied, few associations were found. It is worth mentioning the presence of an association between gender and middle lobe lesion on HRCT. Studies that are more robust are needed to better elucidate this finding.

As the investigation was carried out with data from medical records, information bias may have occurred. The study was retrospective; therefore, some information may not have been recorded, like comorbidities and tests results. Even though it is a descriptive study, we must be attentive to the external validity since patients studied come from a population with a high TB burden. The small sample size probably influenced the few associations found between the variables.

We found MKPD in older patients with pulmonary comorbidities. We should be aware of NTM disease in patients with more advanced age with respiratory symptoms. Almost all patients had symptoms, mainly cough. Lesions present in radiology are like those found in tuberculosis, making radiological findings often indistinguishable. Most patients presented sensitivity to rifampicin, which makes possible the use of this drug in the treatment schemes and guarantee the therapeutic success.

Due to the high incidence of PTB in our state, the clinical and radiological similarity that we find between TB and pulmonary infection by MK, the late diagnosis of the disease is common, and consequently functional and structural pulmonary compromises are frequent.

ACKNOWLEDGMENTS

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