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Mycobacterium kansasii as the Primary Etiology of Pulmonary Infections due to Non-Tuberculous Mycobacterium (NTM) in Patients Without Human Immunodeficiency Virus (HIV): Experience from a Center in Buenos Aires, Argentina

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Abstract

Introduction: Pulmonary diseases due to non-tuberculous mycobacterium (NTM) lung infection in HIV-negative patients are rarely described in the literature. Currently, NTM consist of more than 150 species, and they are globally ubiquitous in both natural and man-made environments.The objective of this study was to define the most frequent species of NTM causing pulmonary disease in HIV-negative patients in the city of Buenos Aires, Argentina. The prevalence of pulmonary diseases caused by NTM is difficult to determine since the isolation of NTM does not necessarily indicate disease.

Methods: A retrospective review of all the respiratory cultures positive for NTM in the Bacteriology Laboratory of Posadas Hospital between January 2010 and December 2015 was performed. 31 patients without Human Immunodeficiency Virus (HIV) from whom NTM was isolated in respiratory samples, which fulfilled diagnostic criteria for NTM disease were included.

Results: The mean age was 50 years at the time of the diagnosis (SD ± 17.2); and 19 patients (61.3%) were males. *Mycobacterium kansasii* was the most commonly isolated NTM (68%) followed by *Mycobacterium avium Complex* (MAC) (19%). *M. kansasii* was the most common cause of pulmonary infection by NTM in these HIV-negative patients. Cultures should be performed to identify the species and to treat accordingly. 46% of the patients included in the study, there was no evidence of risk factors. Only 32% of the subjects had respiratory comorbidities, and the most common radiologic finding was cavitation (55%).

Discussion: Our study indicates that *M. kansasii* is the primary etiology of NTM pulmonary disease in HIV-negative patients in our service area in Buenos Aires. This finding supports the consideration that patients with symptoms compatible with pulmonary tuberculosis should also be evaluated for NTM with appropriate acid-fast bacilli cultures, as treatment regimens differ vastly according to the specific pathogen isolated, although clinical and radiographic presentations may have overlapping features. The possibility of *M. kansasii* pulmonary disease or other NTM should be considered in patients treated empirically for TB without appropriate clinical response.

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Introduction

The clinical interpretation of the presence of a non-tuberculous mycobacterium (NTM) lung infection in respiratory samples is challenging, unlike tuberculosis (TB) the isolation of an NTM in a respiratory culture does not automatically imply pathogenicity. Currently, NTM consist of more than 150 species, and they are globally ubiquitous in both natural and man-made environments [1]. In certain scenarios, the microorganism could be a transient colonizer or even a contaminant generated at the time of sample collection or processing in the laboratory. The diagnosis of disease is based on clinical, radiological and microbiological criteria [2].

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NTM are ubiquitous microorganisms with nearly 100 different species found in soil and water. The fatty-acid and wax-rich impermeable cell wall of the mycobacteria can form biofilm that allow for adherence to solid substrates such as pipes and leaves, allowing the organism to persist despite treatment with common disinfectants, most notably chlorine based disinfectants [1, 3]. According to Nishiuchi, Iwamoto and Maruyama, the formation of aerosols containing NTM arising from shower water, soil, and pool water implies that these niches can be infection sources. Furthermore, genotyping has shown that clinical isolates are identical to environmental ones from household tap water, bathrooms, potting soil, and garden soil [4]. There is no evidence of person to person or zoonotic transmission despite that mycobacteria can cause infection in both humans, livestock and wildlife. *Mycobacterium avium Complex* (MAC) is the most

common NTM cause of pulmonary disease worldwide [5].
It is difficult to compare the incidence and prevalence of NTM diseases across geographic areas. Because reporting NTM disease to public health authorities is not required in most countries, studies of the incidence and prevalence of NTM disease are performed differently in different countries. To compare reports regarding changes in the incidence and prevalence of NTM disease over time in a limited geographic area, one must compare reports that used the same methods. Many epidemiological reports and reviews have shown that NTM disease have been increasing since the 1950s [1,6].

The clinical significance of NTM isolation is not always clear and it is difficult to assess the incidence or prevalence of NTM disease due to several factors, notably its difficulty in differentiation from colonization. Although the detection of NTM colonies has been increasing since the 1950s [6] it is unclear why NTM disease have been increasing in humans. There are several potential contributing factors, such as, (i) an increase of mycobacterial infection sources in the environment, (ii) an increase in susceptible individuals, such as those Human Immunodeficiency Virus (HIV) positive, (iii) improvements in detection methods and laboratory equipment sensitivities (iv) an increasing life expectancy of those with chronic structural pulmonary disease (v) an increased awareness of NTM diseases [1,7].

In many countries, especially those in high-burden areas for TB, the diagnosis of TB is mainly based on the detection of acid-fast bacilli in a sputum smear, as well as on their symptoms and the results of a chest X-ray [1]. Pulmonary diseases caused by NTM could be presumptively treated as pulmonary tuberculosis (TB) as the microbiologic smear of the sputum does not distinguish NTM from TB, and the clinical manifestations are similar. In Latin America the prevalence of NTM is estimated to be much lower than that of TB. The incidence of tuberculosis in Argentina is of 23,91/ 100,000 inhabitants with wide regional variations. In the province of Buenos Aires, it is 30,27/100,000 inhabitants. There are differences in the relative abundances of mycobacterial species that cause NTM diseases across geographic areas, the NTM distribution is most notably associated with variants in environmental factors such as, soil and water distribution systems [1,7]. Pulmonary diseases due to NTM in HIV-negative patients are rarely described in the literature [8]. The objective of this study was to define the most frequent species of NTM causing pulmonary disease in HIV-negative patients in the city of Buenos Aires, Argentina.

Materials and Methods

A retrospective review of all the respiratory cultures positive for NTM in the Bacteriology Laboratory of Posadas Hospital between January 2010 and December 2015 was performed. Posadas Hospital is a high complexity hospital with 500 admission beds and a service area covering a population of approximately 4,400,000. IRB approval was obtained for this study.

Patients older than 15 years old that fulfilled the ATS/IDSA diagnostic criteria for pulmonary disease due to NTM were included in the study [2]. All patients in the study were screened for HIV and we excluded those who presented with positive HIV serology.

The method utilized to perform the cultures was the BACTEC MGIT (fluorescence) in addition to solid culture media (Lowenstein Jensen). Lateral flow immunoassay (LFA) were performed on positive cultures to differentiate NTM from TB.
The following variables were analyzed: age, sex, NTM species, and clinical and radiological characteristics. For the categorical variables, we used percentages as frequency measurements. The continuous variables were expressed as mean or median depending on the sample distribution. Statistical analysis was performed using the computing environment R version 3.4.3 software [9].

Results

From a total of 1205 positive cultures for mycobacteria, 113 (9.3%) correspond to NTM. 31 patients that fulfilled the inclusion criteria were included in the analysis. *M. kansasii* was isolated in 21 patients (67.7%), *M. Avium Complex* (MAC) was isolated in 6 patients (19.3%), *M. fortuitum* was isolated in 2 patients (6.4%), *M. abscessus* was isolated in one patient (3.2%) and *M. chelonae* was isolated in one patient as well (3.2%).

Culture samples were obtained from bronchoalveolar lavage (BAL) and/or bronchial lavage in 21 patients (67.7%) and from sputum in 10 patients (32.3 %). The mean age was 50 years at the time of the diagnosis (SD ± 17.2); and 19 patients (61.3%) were males.

In our series, 17 patients (55%) had some predisposing factor for NTM disease. Ten patients (32.2%) had a previous pulmonary disease: (a) radiologic sequela of TB was noted in 3 patients, (b) Chronic Obstructive Pulmonary Disease (COPD) was present in 2 patients, (c) pulmonary carcinoma was present in another 2 patients, (d) asbestosis in 1 patient, (e) diffuse interstitial pulmonary disease associated with Rheumatoid arthritis in 1 patient and (f) cystic fibrosis were noted in 1 patient. Eleven patients (35%) had a history of smoking. We found non-pulmonary comorbidities in four patients (12.9%): (a) rheumatoid arthritis, (b) multiple sclerosis (MS), (c) Acute myeloid leukemia (AML), (d) diabetes mellitus combined with hemolytic anemia. Three of these patients were receiving immunosuppressant. Four patients were older than 65 years without evidence of any comorbidities. (**Table 1**)

Table 1 Patient characteristics in Posadas Hospital Buenos Aires, Argentina (n=31)

	n=31 n (%)
Age	
(mean age±SD)	50±17.5
Sex	
Male	19(61.3)
Female	12(38.7)
Samples	
Bronchoalveolar lavage	21(67.7)
Sputum	10(32.3)
Non-Pulmonary comorbidities	
Refractory Anemia (RA)	1(3.2)
Hemolytic anemia and Diabetes	1(3.2)
Multiple Sclerosis (MS)	1(3.2)
Acute myeloid leukemia (AML)	1(3.2)
Pulmonary comorbidities	
Chronic obstructive pulmonary disease (COPD)	2(6.4)
Drug-induced pulmonary disease (DIPD)	1(3.2)
TB Sequels	3(9.6)
Asbestosis	1(3.2)
Lung Cancer	2(6.4)
Bronchiectasis	2(6.4)
Cavitary infiltrate	17 (55)
Smoking	11 (35.5)
Threatening hemoptysis	2 (6.4)

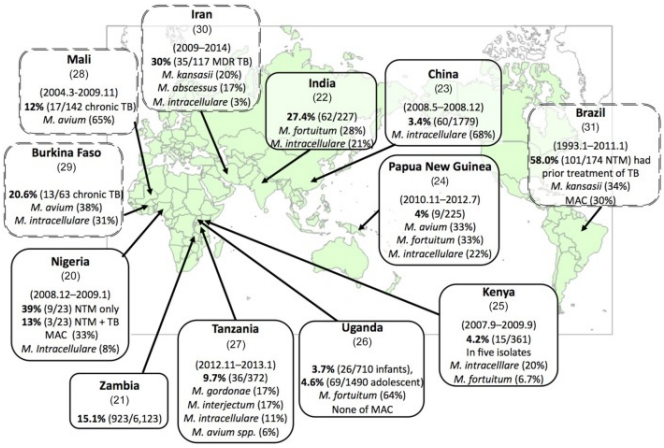

Figure 1 Substantial numbers of non-tuberculous mycobacteria (NTM) disease patients have been found among suspected tuberculosis (TB) and chronic TB patients worldwide [1].

The most frequent radiographic finding was pulmonary cavitation, observed in 17 patients (55%). This finding was most commonly associated with *M. kansasii*. Bronchiectasis was noted in 2 patients, one of which had underlying cystic fibrosis. (**Table 1**)

Three deaths were noted in the study population. Two deaths were related to NTM disease and one was due to acute myeloid leukemia. Two patients presented with fulminant hemoptysis which resulting in death in one of the patients. All the patients received treatment according to the American Thoracic Society (ATS) guidelines [1].

Discussion

The majority of pulmonary disease due to NTM is caused by slow-growing mycobacteria. The most commonly isolated species is MAC followed by *M. kansasii*. Amongst the rapid-growing mycobacteria, *M. abscessus* was the most commonly isolated [2]. In our series, the most frequent isolated species was *M. kansasii*, contrary to what has been previously described in the literature. However, in Argentina and South America in general, data on NTM prevalence is variable. Barnes et al. described 75% of NTM isolates in pulmonary and extra pulmonary samples as MAC and only 3% as *M. kansasii* in a study including immunocompetent and immunocompromised patients, in Buenos Aires [9]. Imperiale et al. described MAC as the most frequently isolated NTM (32.2% of isolates) in pulmonary and extra-pulmonary infections, with *M. kansasii* in fourth place (8% of isolates) in a study which also included HIV patients [11]. Mello et al. conducted a study in Brazil to identify clinical and therapeutic features of pulmonary nontuberculous mycobacterial disease which included patients with AIDS. They found that *M. kansasii* was the most frequently isolated organism (33.9%) and MAC the second one in frequency (30.4%) [12].

The significant geographic variability in the distribution of *M. kansasii* has also been observed in other areas of the world with a high prevalence of pulmonary disease caused by this NTM in western Europe, Switzerland, and the United Kingdom [8]. In many countries, the most frequently reported mycobacterial species is MAC. In Japan and Oregon, USA, MAC has been reported to account for 88.8% of all cases of NTM diseases. In Eastern Asia, MAC accounts for 68% of all cases of NTM diseases. MAC was isolated more frequently in Northern Europe (44% of all mycobacteria) than in Southern Europe (31%). MAC was the most common species complex (64–85% of cases) in North America, followed in most studies by *M. abscessus/ chelonae* (3–13%), *M. xenopi* (1–23%), *M. fortuitum* (<1–8%), and *M. kansasii* (<1–6%). In Central and South America, MAC was generally most common, and *M. kansasii* was also reported frequently [1,8].

The transmission of MAC and other non-tuberculous mycobacteria organisms are likely to be linked with human activities. Global human mobility and trade may promote the global transmission of MAC via fomites [1]. Climatic and ecological factors (water, biofilm, residential soil and dust), as well as the prevalence of comorbidities such as HIV infection, likely have an impact on the prevalence of different NTM species in each region. Bonnet et al. described water sources, particularly well water, as an important reservoir for NTM infection, in Cambodia [7].

The best-defined risk factors NTM infection are advanced age, immunosuppression (including HIV infection), and pulmonary disease (COPD, bronchiectasis, sequelae of previous TB, cystic fibrosis, etc.) [7,13,14] Anti-TNF-α agents (infliximab, etanercept, adalimumab), methotrexate and corticosteroids use also constitute risk factors for NTM disease. Low body mass index (BMI), skeletal abnormalities and gastroesophageal reflux have also been described as predisposing factors to NTM pathogenicity [15]. Children and teenagers rarely develop NTM disease. in the absence of underlying cystic fibrosis. In our study, the average age was 50 years old, less than the one described in the studies conducted in Europe or the USA [8].

Okoi et al. performed a systematic review of NTM isolated in respiratory samples in sub-Saharan Africa. In this review, the average age was 35 years old, likely related to the high prevalence rate of TB and a high rate of HIV coinfection in the region [16]. The clinical interpretation of the presence of NTM in respiratory cultures is problematic, as, unlike TB, the isolation of NTM in a respiratory sample does not imply pathogenicity. In certain situations, the microorganisms can be a transient colonizer

or contaminant. The diagnosis of the disease is based on clinical, radiological and microbiological criteria [2]. In several countries, such as Argentina, NTM disease is non-reportable and therefore its incidence and prevalence are unknown. The current available epidemiologic data on NTM infections in Argentina is from a single institution, described in a study by Barnes et al. and may not be representative of the entire country or region [9]. Many developing countries, where TB is presumed to be more prevalent than NTM (3.4–39%) (**Figure 1**) [1]. These TB prevalent countries follow their own established guidelines for the management of positive acid-fast bacilli cultures in a sputum smear, as well as on their symptoms and if available the results of a chest X-ray. Their treatment guidelines typically favor empiric therapy for TB and reserve more specific organism determination for certain clinical situations, such as suspected drug-resistant TB, TB treatment failures, children, immunocompromised patients, mycobacteriosis retreatment, health workers, prisoners, extra pulmonary disease, diabetes, immigrants from areas of high multidrug resistant tuberculosis rate and positive bronchoalveolar lavage and bronchial lavage samples. However, NTM disease patients are not cured by the 6-month anti-TB treatment and they are then potentially considered to have chronic or multidrug resistant TB. This then results in NTM patients who do not receive appropriate treatment for their NTM disease, annual TB reports that contain errors; and unnecessary expenses for TB treatments. Thus, a reliable, low-cost mycobacterial diagnostic method that results in species-level identification is urgently required [1].

The small sample size our study is a limitations, as well as the lack of surveillance for pulmonary NTM hinders the ability to test these hypotheses and ultimately prevent infection. In addition, our study samples were all collected at the same institution and may not be representative of other national or regional data. Furthermore, cultures were not obtained from all the samples, and environmental and occupational variables was not collected. One of the strengths of our study was that only patients who meet disease criteria were included and also HIV-positive patients were excluded allowing for an estimation of the prevalence of NTM disease in an immunocompetent population. There has been a global improvement in the ability to recognize NTM as human pathogens. Technological advances in laboratory methods have, in addition, allowed faster and more accurate identification of different NTM species and their antimicrobial susceptibilities. These factors have contributed to a more tailored approach to management, in alignment with established international guidelines for treatment of specific NTM infection.

In conclusion, our study indicates that *M. kansasii* is the primary etiology of NTM pulmonary disease in HIV-negative patients in our service area in Buenos Aires, Argentina. This finding supports the consideration that patients with symptoms compatible with pulmonary tuberculosis should also be evaluated for NTM with appropriate acid- fast bacilli cultures, as treatment regimens differ vastly according to the specific pathogen isolated, although clinical and radiographic presentations may have overlapping features. The possibility of *M. kansasii* pulmonary disease or other NTM should be considered in patients treated empirically for TB without appropriate clinical response.

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