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ARTICLE

Pulmonary *Mycobacterium simiae* infection: comparison with pulmonary tuberculosis

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Abstract To identify the clinical and radiological features distinguishing *Mycobacterium simiae* respiratory infection from pulmonary tuberculosis, the demographics, underlying conditions, and clinical and radiological findings of 121 consecutive patients with pulmonary tuberculosis and 102 with *M. simiae* respiratory infection were compared retrospectively. In the *M. simiae* group, the patients were older (mean age 69±16 years vs. 47±21 years, p=0.0001), with a female predominance (62% vs. 45%, p=0.008). Only 4% were of Ethiopian origin compared to 25% of the tuberculosis group (p=0.0001). *M. simiae* infection was associated with significantly higher rates of smoking history, underlying chronic obstructive pulmonary disease, zero human immunodeficiency virus (HIV) infection compared to 10% in the tuberculosis group (p=0.001), blunted symptoms, and noncavitary infiltrates in the lower/middle lobes on chest X-ray. HIV-negative patients with *M. simiae* respiratory infection are distinguishable from patients with pulmonary tuberculosis by several demographic, clinical, and radiological features. These findings have important diagnostic and therapeutic implications.

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Introduction

The rates of isolation and infection of mycobacteria other than tuberculous (MOTT) have increased in recent decades in many developed countries, mainly as a consequence of the human immunodeficiency virus (HIV) epidemic and growing numbers of immunocompromised patients [1]. However, there are few studies on the clinical and epidemiologic characteristics of MOTT infection compared to pulmonary tuberculosis, which has been much more extensively investigated [1].

Mycobacterium simiae is a slow-growing, nonpigmented mycobacterium. Being the only niacin-positive MOTT, it may be easily confused with *M. tuberculosis*. An estimated 9–21% of all *M. simiae* isolates recovered from humans are clinically relevant [2, 3], presenting as a pulmonary pathogen in patients with underlying pulmonary disease and causing disseminated disease in patients with acquired immune deficiency syndrome (AIDS) [2, 4, 5]. Most isolates are resistant to all first-line antimycobacterial drugs, and their response to chemotherapy is variable [3, 5]. For

patients with disseminated or progressive *M. simiae* pulmonary disease, initial therapy usually consists of the four-drug regimen recommended for *M. avium* complex (MAC) disease (clarithromycin, ethambutol, rifabutin, and streptomycin), modified as necessary according to the susceptibility test results of each patient's isolate.

The rates of isolation of *M. simiae* vary geographically, with studies reporting higher values in Cuba, the southwestern United States, Gaza, and Israel [2, 4].

In a recent study [1], we showed that MOTT accounted for the overwhelming majority of mycobacterial isolates recovered from the respiratory tract during the period 2000–2003 at our institution. Whereas MAC was the most frequently isolated MOTT (31%) in 1996–1999, followed by *M. kansasii* (29%) and *M. fortuitum* (12%), in 2000–2003, it was replaced by *M. simiae* (32%), followed by *M. fortuitum* (20%), MAC (17%), and *M. chelonae* (11%) [1].

Several authors have suggested that pulmonary infection with MOTT differs in presentation from infections caused by *M. tuberculosis* [6]. Distinguishing the two disorders on clinical or radiological grounds is important because, when indicated, a clinical suspicion of *M. simiae* infection might prompt physicians to include clarithromycin (or azithromycin) and streptomycin in the initial drug regimen, while awaiting culture results. On the other hand, it would also help clinicians to identify patients who would benefit from empiric anti-tuberculous drugs and adherence to infection control measures.

The purpose of the present study was to compare the clinical features and radiological appearance of pulmonary *M. simiae* and *M. tuberculosis* infection in Israel.

Patients and methods

Study group

At the Rabin Medical Center and its outpatient clinics, all clinical specimens from patients with suspected mycobacterial respiratory disease are routinely sent for analysis to the center's Laboratory of Clinical Microbiology. For the present study, we searched the *M. simiae* database of the laboratory for all consecutive culture-positive clinical specimens of respiratory origin (sputum, broncho-alveolar lavage, and lung biopsy) identified from 1996 to 2004. The corresponding patient files were then reviewed for demographics, country of birth, and underlying conditions, with special emphasis on lung diseases, previous tuberculosis, and immunosuppression, including HIV status. In addition, clinical signs and symptoms and radiological features on presentation were recorded. The clinical significance of *M. simiae* isolation was inferred according to the American Thoracic Society Guidelines for the diagnosis and treatment of disease caused by nontuberculous mycobacteria [7].

Laboratory procedure

Throughout the 9-year study period, specimens from nonsterile body sites were processed with the standard N-acetyl-L-cysteine-NaOH digestion/decontamination method [8]. After neutralization and centrifugation (3,000g for 15 min), the pellet was resuspended in 2 ml of phosphate buffer (pH 6.8). Mechanically homogenized biopsies and sterile body fluids were treated in the same manner, but without the decontamination step. The concentrated sediments were used for Ziehl-Neelsen acid-fast staining smears [9] and for culture.

All specimens were inoculated into the solid L-J medium (Heipha Diagnostika Biotest, Germany). From 1996 to 2000, the laboratory used the liquid Bactec 460TB system (Becton Dickinson, USA), consisting of 12B bottles containing radio-labeled Middlebrook 7H12 broth. Prior to the procedure, the broth was supplemented with polymyxin B, amphotericin B, nalidixic acid, trimethoprim, and azlocillin (PANTA). The liquid medium used in 2001–2004 consisted of a modified Middlebrook 7H9 broth base supplemented with PANTA before use in the MGIT 960 Mycobacteria Growth Indicator Tube.

Isolates of acid-fast bacilli were identified as *M. tuberculosis*, *M. kansasii*, *M. fortuitum*, *M. chelonae*, or MAC by conventional biochemical reactions [1, 2]. In addition, AccuProbe culture confirmation kits (Gen-Probe, USA) were used for *M. tuberculosis*, *M. kansasii*, and MAC identification. *M. simiae* was identified by photochromogenicity, positive niacin, negative nitrate reduction, and Tween hydrolysis [8].

Comparison group

For the comparison group, we reviewed the databases of the tuberculosis centers of Tel Aviv and Rehovot for all consecutive patients with a diagnosis of *M. tuberculosis* infection who attended the centers from April 1999 to April 2005. The diagnosis of mycobacterial infection was based on the guidelines of the American Thoracic Society, namely, appropriate symptomatology, compatible radiographic abnormalities, and culture-positive respiratory specimens [10]. Patients in whom there was a high clinical suspicion of tuberculosis but negative sputum smears underwent bronchoscopy with bronchoalveolar lavage and transbronchial biopsy to confirm the diagnosis. Smears of respiratory specimens and mycobacterial cultures were performed as described previously [11].

All patients were tested for HIV. The readers of the chest X-rays were blinded to the mycobacterial culture results.

Statistical analysis

The results are shown as mean±standard deviation. Categorical variables were analyzed by the chi-square test or Fisher's exact test, as appropriate. Pearson's correlation coefficient (r) and its significance (p) were calculated between the variables. A p-value of 0.05 or less was considered to be statistically significant. The data were handled and analyzed with the Statistical Package for the Social Sciences version 11 (SPSS Corp., USA).

Results

During the study period, the Laboratory of Clinical Microbiology identified 112 patient-unique isolates of *M. simiae* in respiratory specimens. The medical records of 102 (91%) patients were found and reviewed. The findings were compared with those of 121 consecutive patients with *M. tuberculosis* infection treated at the two tuberculosis centers.

The baseline characteristics and signs and symptoms on presentation of the two groups are shown in Table 1. Compared to the *M. tuberculosis* group, the *M. simiae* group was characterized by significantly older mean age, female predominance, lower proportion of patients of Ethiopian origin, and a higher rate of smoking history. The two groups also had significant disparities in their presenting symptoms. Chest pain, fever, cough, hemoptysis, weight loss, and sweating were more common in the patients with pulmonary tuberculosis.

The underlying conditions in the two groups are presented in Table 2. Ten percent of the patients with tuberculosis were HIV-positive (n=12) compared to none of the patients in the *M. simiae* group. Diabetes mellitus, ischemic heart disease, malignancies, and chronic obstructive pulmonary disease (COPD) were more common in the *M. simiae* group, as was the intake of immunosuppressive drugs, such as corticosteroids and cytotoxic agents. There were no significant between-group differences in the rates of chronic liver disease, previous tuberculosis, and bronchiectasis.

Only signs of chronic lung disease on chest radiography were documented significantly more often in the *M. simiae* group (Table 3). Cavitating lesions were more common in the tuberculosis group, whereas pulmonary infiltrates were more common in the *M. simiae* group. Upper lobe involvement, bilateral disease, and lymphadenopathy were significantly more prevalent in the tuberculosis group; the middle and lower lobes were more frequently affected in the *M. simiae* group (Table 3).

Discussion

This study yielded significant differences in several clinical and radiological variables between patients with *M. simiae* respiratory infection and patients with pulmonary tuberculosis. These findings have important diagnostic and therapeutic implications.

M. simiae is endemic to Israel. Recently, we observed an emergence of *M. simiae* as the most frequently isolated MOTT in respiratory specimens in our institution, followed

Table 1 Baseline characteristics and symptoms at presentation in patients infected with *Mycobacterium simiae* or *M. tuberculosis*

	M. simiae, n=102	*M. tuberculosis*, n=121	p-value
Age (years)[a]	69±16	47±21	0.0001
Sex			
Male	39 (38)	67 (55)	0.008
Female	63 (62)	54 (45)	
Origin			
Israel	18 (18)	18 (15)	0.0001
Former USSR	45 (44)	48 (40)	
Ethiopia	4 (4)	30 (25)	
Other	35 (35)	25 (20)	
Smoking	38 (37)	22 (18)	0.003
Alcohol intake 14 units/week	4 (4)	10 (8)	0.269
Drug abuse	2 (2)	8 (7)	0.116
Symptoms at presentation			
Chest pain	8 (8)	32 (26)	0.0001
Cough	14 (14)	120 (99)	0.0001
Hemoptysis	17 (17)	62 (51)	0.0001
Weight loss	17 (17)	41 (34)	0.006
Sweating/fever	9 (9)	70 (58)	0.0001

[a] Mean±SD. All other values are n (%)

Table 2 Underlying conditions in patients with *M. simiae* or *M. tuberculosis* infection (%)

	M. simiae, *n*=102	*M. tuberculosis*, *n*=121	*p*-value
HIV	0	12 (10)	0.001
Chronic liver disease	3 (3)	12 (10)	0.058
Diabetes mellitus	30 (29)	7 (6)	0.0001
Ischemic heart disease	28 (28)	3 (2.5)	0.0001
Malignancy	15 (15)	2 (1.6)	0.0001
Previous tuberculosis[a]	21 (21)	18 (15)	0.291
Chronic obstructive pulmonary disease	38 (37)	5 (4)	0.0001
Bronchiectasis	19 (19)	14 (12)	0.185
Use of immunosuppressive medication	31 (31)	19 (16)	0.009

[a] According to the patient's medical history

by *M. fortuitum*, MAC, and *M. chelonae* [1]. The present study showed that most patients affected by *M. simiae* respiratory infection are female and older (mean age 69 years) than patients with pulmonary tuberculosis.

In the United States, studies conducted from 1981 to 1983 reported that MAC, *M. kansasii*, and *M. abscessus* were the most frequently isolated pulmonary MOTT pathogens [12]. A male predominance was noted for pulmonary disease caused by all MOTT species, except for *M. chelonae*, *M. abscessus*, and *M. simiae*, which is in agreement with our findings. The mean age of the patients was 57 years.

By the mid-1990s, the Centers for Disease Control and Prevention (CDC) identified MAC, *M. kansasii*, and *M. fortuitum* as the most often isolated pulmonary pathogens in the United States [13]. In that study, disease caused by all species except *M. abscessus* was characterized by a male predominance. The majority of isolates were obtained from patients aged 50 years or more. More recently, Al-Abdely et al. [14] reported a surge in the number of *M. simiae* isolates recovered from clinical specimens at their center in San Antonio, Texas, in line with the earlier report from our center [1]. However, most of their patients had AIDS, cancer, or COPD. By contrast, the main underlying diseases in our study group were diabetes mellitus and ischemic heart disease, followed by solid and hematologic malignancies and COPD; there was also a relatively high rate of intake of immunosuppressive drugs. Nevertheless, in the majority of cases in both studies, the isolates were not associated with clinically relevant disease.

Accordingly, although early surveillance studies suggested that 21% of *M. simiae* isolates were indicative of clinical disease, more recent studies point to a much lower incidence [2, 5]. Most of the case reports involved immunocompromised groups, such as patients with AIDS or with underlying lung disease. *M. simiae* disease usually affects the lungs, although there are also reports of intraabdominal infections and of disseminated disease in immunocompromised patients. Recent pseudo-outbreaks involving contaminated water supplies have also been described [2].

In a study conducted in Israel from 1975 to 1981, 399 isolates of *M. simiae* were recovered from 287 individuals. Most of the cases were considered to be environmental, most probably caused by contaminated water. The patients with repeated culture-positive findings were middle-aged or older, with a history of tuberculosis. On the basis of these results, the authors suggested that *M. simiae* is capable of prolonged or temporary colonization in previously damaged lungs [4].

Although MOTT pulmonary disease is associated with variable and nonspecific symptoms, virtually all patients have chronic or recurring cough; some have sputum production, fatigue, malaise, dyspnea, fever, hemoptysis, chest pain, and weight loss. The significantly higher prevalence of these findings in our *M. tuberculosis* group,

Table 3 Radiological findings in patients with *M. simiae* or *M. tuberculosis* infection (%)

	M. simiae, *n*=102	*M. tuberculosis*, *n*=121	*p*-value
Signs of chronic lung disease	38 (37)	1 (0.8)	0.0001
Infiltrates	58 (57)	22 (18)	0.0001
Cavitation	3 (3)	83 (69)	0.0001
Chest X-ray findings			
Right upper lobe	15 (25)	50 (41)	0.002
Left upper lobe	12 (20)	40 (33)	
Lower/middle lobes	33 (55)	14 (12)	
Bilateral disease	4 (4)	35 (29)	0.0001
Pleural effusion	16 (16)	12 (10)	0.222
Lymphadenopathy	3 (3)	16 (13)	0.001
Miliary pattern	0	2 (1.6)	0.215

in addition to the near-total absence of such classical radiological findings as cavitating lesions, upper lobe involvement, and lymphadenopathy in the *M. simiae* group compared to the tuberculosis group, point to the colonization of *M. simiae* rather than disease. Indeed, hardly any of our patients were given specific therapy against *M. simiae* infection.

It is noteworthy that, unlike *M. kansasii* pulmonary infection, which presents with a similar clinical picture to tuberculosis [11], the rare association of common respiratory signs and symptoms in *M. simiae* infection eases its distinction from these other mycobacterial diseases. Other differences in clinical parameters found here from patients with tuberculosis were a higher rate of smoking history in the *M. simiae* group and a lower rate of Ethiopian origin. At the same time, for patients with predominantly noncavitary disease, the abnormalities on chest radiograph are primarily found in the mid- and lower lung field. Other MOTT species, including *M. abscessus*, *M. chelonae*, and *M. kansasii* (and probably others), can also present with this radiographic appearance [15, 16].

The optimal treatment of *M. simiae* infection has not as yet been standardized, but clarithromycin, quinolones, ethambutol, cycloserine, and ethionamide have been reported to be effective [2, 17, 18]. The newer 8-methoxy fluoroquinolone, moxifloxacin seems to be active against *M. simiae*, even for isolates resistant to ciprofloxacin. Some isolates are also susceptible in vitro to sulfamethoxazole and linezolid. Recent reports suggest a regimen including clarithromycin, moxifloxacin, and trimethoprim/sulfamethoxazole [19].

To the best of our knowledge, ours is the largest series of HIV-negative patients with *M. simiae* respiratory infection reported in the literature, and the first study comparing the clinical and radiological features of patients with respiratory *M. simiae* infection to patients with pulmonary tuberculosis.

Our findings need to be addressed given the growing prevalence of MOTT infection worldwide, and the emergence of *M. simiae* as the most common respiratory MOTT isolate in our center. There is no infection-control impact on hospitalized patients for *M. simiae*, and its isolation from respiratory specimens probably indicates colonization rather than disease in most cases. Therefore, the distinction of *M. simiae* respiratory infection from pulmonary tuberculosis on the basis of simple clinical and radiological features has significant practical importance. Furthermore, when the infection is considered to be clinically significant, our findings should be taken into account by physicians in the selection of early empiric antimycobacterial treatment while awaiting the laboratory and susceptibility test results.

Our study has several limitations. First, we derived our sample from two different databases, such that the patients in the two groups were treated and evaluated by different physicians, and their specimens were assessed in different laboratories. Therefore, a bias in selecting patients for tuberculous and other mycobacterial infections cannot be ruled out. Second, all of our patients who were culture-positive for *M. simiae* infection were HIV-negative. The clinical and radiological features of *M. simiae* pulmonary infection may differ in patients with AIDS, and our findings cannot be extrapolated to this population. Third, an analysis of the significance and outcome of *M. simiae* isolation was beyond the scope of this study. Further investigations of HIV-positive and immunocompromised patients are needed, including an evaluation of the clinical significance of *M. simiae* isolation, therapeutic intervention, and outcome.

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