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Mycobacterium simiae pulmonary infection: a case series and literature review

Hadi Lotfi[1,2], Mojtaba Sankian[3], Zahra Meshkat[1,2], Ahmad Khalifeh Soltani[4] & Ehsan Aryan[1,2]

[1]Antimicrobial Resistance Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Laboratory of Microbiology, Department of Medical Microbiology, Ghaem University Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.
[3]Immunobiochemistry Laboratory, Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
[4]Department of Infectious Diseases and Tropical Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

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Correspondence
Ehsan Aryan, Laboratory of Microbiology, Department of Medical Microbiology, Ghaem University Hospital, Mashhad University of Medical Sciences, Ahmad Abad Street, 91967-73117 Mashhad, Iran.
E-mail: aryane@mums.ac.ir

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Abstract

Incidence of *Mycobacterium simiae* pulmonary infection is increasing and diagnosis and treatment are challenging. We surveyed the clinical features, risk factors, diagnosis, and management in 20 patients from northeastern Iran diagnosed by line probe assay and confirmed by sequencing the *ITS* (*16S-23S*) *rRNA* region and carried out a literature review using the keywords "pulmonary infection" and "*Mycobacterium simiae*." The mean age of patients was 55.1 years, with 80% female and 90% diagnosed by sputum. Clinical symptoms included severe cough (90%), sputum production (70%), haemoptysis (50%), and chest pain (35%). Comorbidities included a history of tuberculosis (60%), smoking (40%), or chronic obstructive pulmonary disease (20%). Patients were treated with levofloxacin, clarithromycin, and co-trimoxazole. Except for two patients, the clinical symptoms improved. *Mycobacterium simiae* pulmonary infection is increasing in people with underlying diseases. Although choosing the most appropriate treatment remains a challenge, combining successful treatments could be useful in treating these patients.

Introduction

Non-tuberculous mycobacteria (NTM) are a large group of bacteria that include more than 200 species [1]. *Mycobacterium simiae* is one of the NTM that causes lung infections in many countries worldwide. *Mycobacterium simiae* are slow-growing and non-pigmented mycobacteria, and they are the only niacin-positive NTM that might be confused with *Mycobacterium tuberculosis* (tuberculosis (TB)) in terms of similar clinical manifestations [2]. This opportunistic agent is presented as a pulmonary pathogen in patients with underlying pulmonary disease and can cause disseminated disease in patients with AIDS [3]. It is one of the most common NTM causing pulmonary disease in patients with underlying disease. While some previous studies reported that the incidence of *M. simiae* is limited in several regions of the world, including Cuba, Gaza, and the southern United States [4], recent studies have widely reported this organism from other regions such as the Middle East [3]. There is limited information on the relationship between the in vitro sensitivity of this organism and the in vivo response to drugs. *Mycobacterium simiae* infections have usually shown a poor therapeutic response in vivo [4], and most clinical isolates are resistant to first-line TB drugs such as isoniazid and rifampicin [5]. The treatment regimen for *M. simiae* infections is quite different from the TB treatment regimen, and drugs such as moxifloxacin, clarithromycin, and cotrimoxazole are effective against this pathogen [4]. *Mycobacterium simiae* has been previously reported from Iran [5]. In the current study, we surveyed the clinical features, risk factors, diagnosis, and treatment of *M. simiae* pulmonary infection in Mashhad, Iran.

Case Series

We conducted a case series of all *M. simiae* infections among patients referred to Ghaem Hospital affiliated to Mashhad University of Medical Sciences, Iran, from 1 May 2018 to 1 May 2019. During the study period, all patients with symptoms such as night sweats, cough, and chest pain were treated with a standard six-month regimen including rifampin, isoniazid, ethambutol, and pyrazinamide. Respiratory specimens taken from patients included sputum and

Table 1. Sequenced *ITS* (16s-23s) *rRNA* gene results and finding mycobacterial tests.

Sample	Accession number	Type of sample (sampling time)	Findings of mycobacterial tests
1	MN124509	Sputum (2 May 2018)	Direct smear*: ++++ Positive culture†: 13 May 2018
2	MN124510	Sputum (10 May 2018)	Direct smear: +++ Positive culture: 22 May 2018
3	MN174094	Sputum (26 May 2018)	Direct smear: + Positive culture: 10 June 2018
4	MN174098	Sputum (1 June 2018)	Direct smear: ++ Positive culture: 14 June 2018
5	MN174109	Sputum (5 June 2018)	Direct smear: ++ Positive culture: 17 June 2018
6	MN316668	BAL (15 June 2018)	Direct smear: + Positive culture: 29 June 2018
7	MN316669	Sputum (3 July 2018)	Direct smear: ++ Positive culture: 15 July 2018
8	MN316670	BAL (9 July 2018)	Direct smear: ++ Positive culture: 23 July 2018
9	MN316671	Sputum (15 July 2018)	Direct smear: +++ Positive culture: 27 July 2018
10	MN316672	Sputum (21 July 2018)	Direct smear: ++ Positive culture: 4 August 2018
11	MN640403	Sputum (22 August 2018)	Direct smear: (+++) Positive culture: 4 September 2018
12	MN640408	Sputum (13 September 2018)	Direct smear: ++ Positive culture: 26 September 2018
13	MT076064	Sputum 2 October 2018	Direct smear: +++ Positive culture: 14 October 2018
14	MT982145	Sputum (4 November 2018)	Direct smear: +++ Positive culture: 16 November 2018
15	MT982146	Sputum (15 December 2018)	Direct smear: ++ Positive culture: 28 December 2018
16	MT994360	Sputum (18 February 2019)	Direct smear: ++ Positive culture: 2 March 2019
17	MW040456	Sputum (21 March 2019)	Direct smear: +++ Positive culture: 3 April 2019
18	MW040458	Sputum (6 April 2019)	Direct smear: +++ Positive culture: 18 April 2019
19	MW040459	Sputum (20 April 2019)	Direct smear: +++ Positive culture: 2 May 2019
20	MW040460	Sputum (26 April 2019)	Direct smear: +++ Positive culture: 8 May 2019

***Direct smear microscopy for acid-fast bacilli using the Ziehl–Neelsen method. 1+, 1–9 AFB/100 fields; 2+, 1–9 AFB/10 fields; 3+, 1–9 AFB/field; 4+, >9 AFB/field.**

†Mycobacterial culture of the patient's samples on Lowenstein–Jensen medium.

BAL, bronchoalveolar lavage.

Table 2. Demographic and clinical manifestation of *Mycobacterium simiae* pulmonary infection.

	Sex, age (years)	Symptoms	Risk factors	Treatment	Follow-up
Patient 1	F, 65	CP, SC, S	History of TB	LVX, CLR, CTX	Sudden death
Patient 2	F, 42	CP, SC	History of TB	LVX, CLR, CTX	Good (12 months)
Patient 3	F, 52	CP, S	Smoking	LVX, CLR, CTX	Good (18 months)
Patient 4	F, 67	LW, S	History of TB	LVX, CLR, CTX	Good (18 months)
Patient 5	F, 55	LW, SC	History of TB	LVX, CLR, CTX	Good (18 months)
Patient 6	F, 32	CP, SC, HE	History of TB, malignancy	LVX, CLR, CTX	Good (12 months)
Patient 7	F, 67	SC, LW	History of TB, COPD, smoking	LVX, CLR, CTX	Good (18 months)
Patient 8	F, 23	SC, HE, S	Malignancy	LVX, CLR, CTX	Good (12 months)
Patient 9	F, 63	HE, SC, S	History of TB	LVX, CLR, CTX	Good (18 months)
Patient 10	M, 48	SC, S, HE	Smoking	LVX, CLR, CTX	Good (12 months)
Patient 11	M, 75	SC, S	History of TB, smoking	LVX, CLR, CTX	Good (18 months)
Patient 12	F, 85	SC, S	History of TB, COPD, smoking	LVX, CLR, CTX	Died myocardial infarction
Patient 13	M, 20	LW, HE, SC	COPD, smoking	LVX, CLR, CTX	Good (12 months)
Patient 14	F, 67	LW, S, SC	Smoking	LVX, CLR, CTX	Good (12 months)
Patient 15	F, 65	HE, S, SC	History of TB	LVX, CLR, CTX	Good (18 months)
Patient 16	F, 35	SC, S, HE	History of TB	LVX, CLR, CTX	Good (12 months)
Patient 17	F, 59	S, SC, CP	Bronchiectasis	LVX, CLR, CTX	Good (18 months)
Patient 18	F, 59	CP, HE, SC	Malignancy	LVX, CLR, CTX	Good (still on treatment)
Patient 19	F, 62	SC, S, HE	History of TB	LVX, CLR, CTX	Good (12 months)
Patient 20	M, 61	S, HE, SC,CP	COPD, smoking	LVX, CLR, CTX	Good (18 months)

CLR, clarithromycin; COPD, chronic obstructive pulmonary disease; CP, chest pain; CTX, co-trimoxazole; F; female; HE, haemoptysis; LVX, levofloxacin; LW, lose weight; M, male; S, sputum; SC, severe cough; TB, tuberculosis.

bronchoalveolar lavage (BAL). In addition, direct smear microscopy for acid-fast bacilli (AFB) and mycobacterial culture were performed on the patients' sputum samples. For the literature review, we searched Medline and Embase for articles in English published before January 2020, using the keywords "pulmonary infection" and "*Mycobacterium simiae*."

All three samples obtained from the patients were smear-positive for AFB using the Ziehl–Neelsen method. Also, a mycobacterial culture of the patients' samples on

Table 3. Case series of *Mycobacterium simiae* pulmonary infection.

Author, year	Age (mean), sex	Symptom	Risk factors	Treatment	Follow-up
Hamieh, 2018 [8]	62.7 28 (55%), M 23 (45%), F	LW: 7 (21%) S: 30 (91%) CP: 0 HE: 9 (27%) SC: 51 (100%)	Previous TB: 0 COPD: 24% Bronchiectasis: 34% HIV infection: 0 Malignancy: 12% Smoking: 23 (53%)	Clarithromycin, TMP/SMX, or moxifloxacin Clarithromycin with clofazimine were used in two patients	Six to 24 months Four patients noted improvement Two patients received a combination of clofazimine and clarithromycin improvement
Coolen-Allou, 2018 [9]	57 39.1%, M 60.9%, F	LW: 48.4% S: 68% SC: 68% HE: 3.1% CP: 0	Previous TB: 15.5% COPD: 24.7% Bronchiectasis: 49.5% HIV infection: 4.1% Malignancy: 14.4%	Macrolides, rifampin, ethambutol, moxifloxacin, clofazimine, and amikacin	Two patient treatment failure, other patient no relapse with *M. simiae*
Baghaei, 2012 [11]	58.23 13 (50%), M 13 (50%), F	LW: 20 (76.9%) S: 19 (73.1%) CP: 7 (26.9%) SC: 24 (92.3%) HE: 0	Previous TB: 21(80.8%) COPD: 0 Bronchiectasis: 1 (3.8%) HIV infection: 1 (3.8%) Smoking: 9 (34.6%) Malignancy: 0	Clarithromycin, ofloxacin, and co-trimoxazole	12 months 24 patients were cured and two patients failed the treatment
Shitrit, 2008 [3]	69 39 (38%), M 63 (62%), F	LW: 41 (34%) HE: 17 (17%) S: 0 CP: 8 (8%) SC: 14 (14%)	Previous TB: 18 (15%) COPD: 38 (37%) Bronchiectasis: 19 (19%) HIV infection: 0 Malignancy: 15 (15%) Smoking: 38 (37%)	Rifampicin, ethambutol, and clarithromycin	12 months, Five patients died, but none of the deaths were directly related to the mycobacterial disease (three were due to cerebral stroke and two to cardiac disease)

Table 3. Continued

Author, year	Age (mean), sex	Symptom	Risk factors	Treatment	Follow-up
Van Ingen, 2008 [10]	73 2 (46%), M 4 (54%), F	LW: 4 (66%) S: 6 (100%) CP: 5 (83%) HE: 3 (50%) SC: 6 (100%)	Previous TB: 34% COPD: 83% Bronchiectasis: 34% HIV infection: 0 Malignancy: 0 Smoking: 50%	Rifampicin, ethambutol, ciprofloxacin, and clarithromycin	One of them was cured, one relapsed, and one died
This study, 2020	55.1 4 (20%), M 16 (80%), F	LW: 5 (25%) S: 14 (70%) CP: 6 (30%) HE: 10 (50%) SC: 18 (90%)	Previous TB: 60% COPD: 20% Bronchiectasis: 5% HIV infection: 0 Malignancy: 15% Smoking: 40%	Levofloxacin, clarithromycin, and co-trimoxazole	18 months, except for two patients where one due to myocardial infarction and the other due to hepatic encephalopathy died, other patients had improved clinical signs

CH, xxxx; COPD, chronic obstructive pulmonary disease; CP, chest pain; F, female; HE, haemoptysis; LW, lose weight; M, male; S, sputum; SC, severe cough; TB, tuberculosis; TMP/SMX, trimethoprim/sulfamethoxazole.

Lowenstein–Jensen medium showed positive results for AFB (Table 1). Cases were identified using the native reverse line probe assay (LPA) [5]. The results were also confirmed by the sequencing of the *ITS* (*16S-23S*) *rRNA* spacer region with an accession number (Table 1). Therefore, treatment was done with regimen including levofloxacin 1000 mg/daily, clarithromycin 1000 mg/daily, and co-trimoxazole 800 mg/daily. Patients were treated with a regimen for 12–18 months, depending on the improvement of clinical symptoms and negative smear and sputum culture (Table 2). Except for two patients, the clinical symptoms of other patients improved with negative smear and sputum culture.

A total of 20 patients were included in this study. All patients were Iranians, with a female predominance (80%). The mean age was 55.1 ± 15.8 years and a large proportion of patients had a history of previous TB (60%). *Mycobacterium simiae* was isolated from a total of 20 specimens and the distribution was as follows: sputum (18/20; 90%) and BAL (2/20; 10%). The most frequent comorbidities were structural lung diseases, including chronic obstructive pulmonary disease (COPD) (20%) and bronchiectasis (5%). Moreover, non-pulmonary comorbidities included malignancies (15%), and there was a history of smoking in patients (40%). Demographic data are provided in Table 2. Data on clinical symptoms were available for all patients (100% symptomatic). The most frequently reported symptoms were severe cough (90%), sputum production (70%), haemoptysis (50%), and chest pain (30%) (Table 2).

Using the PubMed database, we searched for articles with the keywords "*Mycobacterium simiae*" and "pulmonary infection." We limited the search to articles published in English language and involving humans after 1 January 2000. *Mycobacterium simiae* can cause infections in various parts of the body, including lungs. Symptoms of this infection include cough, sputum production, haemoptysis, fever, night sweats, and weight loss. Several previous studies reported production of sputum, severe cough, and weight loss as the most common clinical symptoms of *M. simiae* pulmonary infection [5]. Moreover, the infection is more common in the elderly people (age range: 57–73 years), especially elderly women (Table 3). *Mycobacterium simiae* infection often occurs in immunocompromised patients with underlying diseases. In addition, factors such as a previous history of TB, being infected with HIV, having malignancies, older ages, cardiovascular disease, diabetes mellitus (DM), smoking, and structural abnormalities of the respiratory system increase the risk of infection [5]. COPD, bronchiectasis, and a history of TB were the most common risk factors for *M. simiae* pulmonary infection [6]. Other factors such as malignancies, smoking, and HIV were also involved (Table 3). The Infectious Diseases Society of America (IDSA) guidelines in 2007 on NTM suggest a treatment regimen for *M. simiae* infections similar to *Mycobacterium avium* complex infections. According to IDSA, a macrolide-based treatment regimen with moxifloxacin, clofazimine, and streptomycin is recommended. Other macrolide therapies, such as a combination of clarithromycin with quinolones and trimethoprim/sulfamethoxazole (TMP/SMX), may be recommended for the treatment of *M. simiae* [7]. In previous studies, macrolides, such as clarithromycin, in combination with quinolones, such as moxifloxacin and TMP/SMX, had the greatest effect in eliminating the clinical signs of *M. simiae* pulmonary infection and improving patients (Table 3).

Discussion

Previous studies have shown that most patients with *M. simiae* pulmonary infection are middle-aged or elderly and have a history of TB or lung abnormalities [6]. A study by Maoz et al. [13] revealed that underlying conditions or diseases such as smoking, DM, solid and haematological malignancies, and COPD were all associated with *M. simiae* infection. In our study, all cases (100%) had underlying diseases or risk factors that predispose the person to infection. No infection was observed in immunocompetent cases or those without any underlying diseases. HIV test for all patients was negative. Previous studies focused on the underlying lung disease, especially TB, as an important risk factor for pulmonary NTM infection [8]. In our study, *M. simiae* were mostly isolated from patients who had been previously diagnosed with TB cases.

Van Ingen et al. revealed that *M. simiae* is poorly susceptible to first-line anti-TB drugs [10]. We considered their results along with the IDSA guidelines (2007) on NTM, and used a combination regimen of clarithromycin, cotrimoxazole, and levofloxacin to treat patients. Except for two patients who died (one due to myocardial infarction and the other due to hepatic encephalopathy), clinical signs of all other patients improved. Baghaei et al. also used a therapeutic regimen consisting of clarithromycin, ofloxacin, and cotrimoxazole to treat patients with *M. simiae* pulmonary infection [11], which was consistent with the results of our study. The treatment period continued until the patients' sputum culture was negative. The most commonly reported clinical symptoms of the infection include sweating, weight loss, coughing, haemoptysis, and sputum production [12]. In our study, sputum production, haemoptysis, chest pain, and weight loss were the most common symptoms. In addition, almost 90% of patients suffered from severe coughing. This is inconsistent with the results of Maoz et al. [13], who reported coughing in only 17% of patients. As most patients with *M. simiae* infection had a previous history of TB, it is possible that in areas where TB is common, TB is the most important underlying cause of *M. simiae* pulmonary infection.

There are two main limitations in this study: the lack of a second group to compare results and the limited number of patients. The presence of a control group to compare treatment protocols could help to achieve stronger results about the appropriate treatment protocol for *M. simiae* pulmonary infection.

In conclusion, *M. simiae*, as a cause of respiratory infection, is increasing among people with underlying diseases in Iran. Although choosing the most appropriate treatment protocol is still a challenge, combining successful treatment options could be useful in treating these patients.

Disclosure Statement

Ethical approval to report these cases were obtained from Mashhad University of Medical Sciences Regional Ethics Committee, Mashhad University of Medical Sciences, Mashhad, Iran (approval number: IR.MUMS.fm.REC.1396.638).

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