Mycobacterium simiae pulmonary infection: a case series and literature review

Hadi Lotfi1,2, Mojtaba Sankian3, Zahra Meshkat1,2, Ahmad Khalifeh Soltani4 & Ehsan Aryan1,2

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

Keywords
Mycobacterium simiae, pulmonary infection, review.

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.

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 BAL, bronchoalveolar lavage.

| 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.
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 2. Demographic and clinical manifestation of Mycobacterium simiae pulmonary infection.

| Patient | 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.
| 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%) S: 0 CP: 8 (8%) SC: 14 (14%) HE: 17 (17%) | 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) |
| Author, year         | Age (mean), sex | Symptom | Risk factors                  | Treatment                          | Follow-up                                      |
|----------------------|-----------------|---------|--------------------------------|------------------------------------|-----------------------------------------------|
| Van Ingen, 2008 [10] | 73              | LW: 4 (66%) S: 6 (100%) CP: 5 (83%) HE: 3 (50%) SC: 6 (100%) | Previous TB: 34% COPD: 83% Bronchiecasis: 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            | LW: 5 (25%) S: 14 (70%) CP: 6 (30%) HE: 10 (50%) SC: 18 (90%) | Previous TB: 60% COPD: 20% Bronchiecasis: 5% HIV infection: 0 Malignancy: 15% Smoking: 40% | Levofoxacin, 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).

**Acknowledgment**

The authors received financial support from Mashhad University of Medical Sciences (grant number 961176).

**References**

1. Shahraki AH, Heidarieh P, Bostanabad SZ, et al. 2015. “Multidrug-resistant tuberculosis” may be nontuberculous mycobacteria. Eur. J. Intern. Med. 26(4):279–284.
2. El Sahly HM, Septimus E, Soini H, et al. 2002. *Mycobacterium simiae* pseudo-outbreak resulting from a contaminated hospital water supply in Houston, Texas. Clin. Infect. Dis. 35(7):802–807.
3. Shitrit D, Peled N, Bishara J, et al. 2008. Clinical and radiological features of *Mycobacterium kansasii* infection and *Mycobacterium simiae* infection. Respir. Med. 102 (11):1598–1603.
4. Cowman S, Burns K, Benson S, et al. 2016. The antimicrobial susceptibility of non-tuberculous mycobacteria. J. Infect. 72(3):324–331.
5. Kamali Kakhki R, Aryan E, Meshkat Z, et al. 2020. Development of a cost-effective line probe assay for rapid detection and differentiation of *Mycobacterium* species: a pilot study. Rep. Biochem. Mol. Biol. 8(4):383–393.
6. Barrera L, Paul R, López B, et al. 2010. Enfermedad por *Mycobacterium simiae* y “Mycobacterium sherrissii” en la Argentina. Medicina 70:343–346.
7. Karami-Zarandi M, Bahador A, Kardan-Yamchi J, et al. 2019. Identification of non-tuberculosis mycobacteria by line probe assay and determination of drug resistance patterns of isolates in Iranian patients. Arch. Razi Inst. 74(4):375–384.
8. Hamieh A, Tayyar R, Tabaja H, et al. 2018. Emergence of *Mycobacterium simiae*: a retrospective study from a tertiary care center in Lebanon. PLoS One. 13(4):e0195390.
9. Coolen-Allou N, Touron T, Belmonte O, et al. 2018. Clinical, radiological, and microbiological characteristics of *Mycobacterium simiae* infection in 97 patients. Antimicrob. Agents Chemother. 62(7):e00395–e00318.
10. Van Ingen J, Boeree M, Dekhuijzen P, et al. 2008. Clinical relevance of *Mycobacterium simiae* in pulmonary samples. Eur. Respir. J. 31(1):106–109.
11. Baghaei P, Tabarsi P, Farnia P, et al. 2012. Pulmonary disease caused by *Mycobacterium simiae* in Iran’s national referral center for tuberculosis. J. Infect. Dev. Cntries. 6(1):23–28.
12. Hashemi-Shahraki A, Darban-Sarokhalil D, Heidarieh P, et al. 2013. *Mycobacterium simiae*: a possible emerging pathogen in Iran. Jpn. J. Infect. Dis. 66(6):475–479.
13. Maoz C, Shitrit D, Samra Z, et al. 2008. Pulmonary *Mycobacterium simiae* infection: comparison with pulmonary tuberculosis. Eur. J. Clin. Microbiol. Infect. Dis. 27 (10):945–950.