Clinical and radiological features of *Mycobacterium kansasii* infection and *Mycobacterium simiae* infection

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**KEYWORDS**

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Diagnosis

**Summary**

This retrospective study sought to systematically identify clinical and radiological features of *Mycobacterium kansasii* and *Mycobacterium simiae* infections. The sample included consecutive patients with a culture-positive diagnosis of *M. simiae* infection (n = 102) or *M. kansasii* infection (n = 62) derived from the databases of the Laboratory of Microbiology of a tertiary medical centre and two outpatient tuberculosis centres. Data on patient background and clinical features were collected, and chest radiographs were analysed. Sixty percent of the *M. kansasii* group were native born compared to 18% of the *M. simiae* group (p < 0.0001). *M. simiae* infection was associated with a higher rate of co-morbid disease, including diabetes mellitus, heart disease, and malignancy. A similar rate of lung disease was found in both groups. Clinical symptoms were significantly more common in patients with *M. kansasii* infection. On radiological study, *M. kansasii* infection was associated with more cavitations, and *M. simiae* infection with more pulmonary infiltrates. Patients with *M. simiae* infection had a higher likelihood of middle and lower lobe disease whereas patients with *M. kansasii* infection had more upper lobe disease (p = 0.001). Pleural effusions and lymphadenopathy were found only in the presence of *M. simiae* infection. We concluded that there are major differences in the epidemiologic features of *M. kansasii* and *M. simiae* infection which have important diagnostic and therapeutic implications.

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**Abbreviations:** AIDS, acquired immune deficiency syndrome; CT, computed tomography; HIV, human immunodeficiency virus; NTM, nontuberculous mycobacteria; PANTA, polymyxin B, amphotericin B, nalidixic acid, trimethoprim and azlocillin.

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Introduction

Nontuberculous mycobacteria (NTM) were identified in clinical specimens as early as 1885. With recent improvements in techniques for the isolation and identification of mycobacteria and the control of tuberculosis, the importance of NTM, especially in immunocompromised hosts, has been recognized. Nevertheless, in contrast to the extensive epidemiologic study of tuberculosis, temporal changes in the epidemiology of NTM infections have hardly been explored.

*M. kansasii* has traditionally been considered the most virulent of the NTM.\(^1\)\(^2\) Infection by *M. kansasii* probably occurs via an aerosol route.\(^3\)\(^\text{-}^5\) Tap water is a major reservoir and the only environmental (water or soil) source of the bacterium identified to date.\(^6\) However, the isolation of *M. kansasii* from tap water can be intermittent, which may explain why some investigators failed to recover it from this source as well. Risk factors for *M. kansasii* infection include chronic lung disease, previous mycobacterial disease, malignancy, and alcoholism.\(^7\)\(^\text{-}^9\) In immunocompetent patients, pulmonary disease is the most frequent clinical manifestation,\(^9\) although approximately 40% have no associated illness.\(^7\) When the infection is treated appropriately, outcome is good.

Isolates of *M. simiae*, another common NTM causing lung disease.\(^15\) The frequency of isolation varies geographically, with high reported rates in Cuba, the southwestern United States, and Gaza, Israel.\(^15\)\(^,\)\(^16\) *M. simiae* isolates recovered from humans are clinically relevant in an estimated 9%–21% of specimens.\(^16\)\(^,\)\(^17\) They may present as a pulmonary pathogen in patients with underlying pulmonary disease and cause disseminated disease in patients with acquired immune deficiency syndrome (AIDS).\(^15\)\(^\text{-}^\text{19}\) *M. simiae* is endemic to Israel, accounting for 30% of all NTM pathogens isolated in the country in 1975–1981.\(^15\) Most cases were considered environmental, most probably transmitted via contaminated water.

The major clinical and therapeutic implications of infection with these pathogens and their diverse magnitudes in different countries warrant ongoing surveillance studies of species distribution of *Mycobacterium* isolates. Furthermore, although some authors have referred to clinical differences between pulmonary *M. kansasii* and *M. tuberculosis* infections,\(^3\)\(^,\)\(^5\)\(^,\)\(^16\) to the best of our knowledge, there are no systematic studies comparing the clinical and radiological features of *M. kansasii* and *M. simiae* pulmonary infections. We chose to compare *M. kansasii* with *M. simiae* because these two species are the most common NTM isolates in Israel according to previous reports in Israel.\(^17\)

The aim of the present study was to compare the clinical features, radiological appearance and outcome of pulmonary *M. kansasii* and *M. simiae* infection.

Patients and methods

Patients and setting

The sample included consecutive patients with a culture-positive diagnosis of *M. simiae* infection (n = 102) or *M. kansasii* infection (n = 62) who presented at Rabin Medical Center or attended one of two outpatient tuberculosis centres in Israel from April 1999 to April 2005. Rabin Medical Center is a first-line and tertiary 900-bed facility serving an urban population of 1,000,000. It includes departments of medicine, neuro- and thoracic-surgery, oncology, and haematology, a paediatric bone-marrow transplantation unit, and a unit for solid organ transplantation. In all cases, the diagnosis of mycobacterial infection was made by the hospital’s Laboratory of Microbiology according to the guidelines of the American Thoracic Society (ATS), as follows: appropriate symptomatology, compatible radiographic abnormalities, and culture-positive respiratory specimens.\(^16\)\(^,\)\(^17\) Patients for 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. Computed tomography (CT) was performed in all cases of a suspected or confirmed abnormality on chest radiograph.

All patients were tested for human immunodeficiency virus (HIV).

The study was approved by the Ethics Committee of Rabin Medical Center.

Media

The solid L–J medium (Heipha Diagnostika Biotest, Germany) was applied to all specimens. The liquid medium used during the first period consisted of 12B bottles containing radio labelled Middlebrook 7H12 broth using the Bactec 460TB (Becton Dickinson, USA) system. Before use, the broth was supplemented with polymyxin B, amphotericin B, nalidixic acid, trimethoprim and azlocillin (PANTA). The liquid medium used during the second period contained modified Middlebrook 7H9 broth base, supplemented with PANTA before use in the MGIT 960 Mycobacteria Growth Indicator Tube. All media were inoculated in duplicate and incubated in parallel at 30 °C and 37 °C for 8 weeks.

Identification of microorganisms

Isolates of acid-fast bacilli were identified as *M. tuberculosis*, *M. kansasii*, or MAC by conventional biochemical reactions\(^1\)\(^,\)\(^2\) and AccuProbe culture confirmation kits (Gen-Probe, USA). *M. simiae* was identified by photochromogenicity, positive niacin, negative nitrate reduction, and Tween hydrolysis.

Data collection

Data on the clinical features of the patients (including systemic co-morbid disease and smoking status), radiological findings, and outcome were obtained from the case notes and laboratory records by a single investigator.

Radiological assessment

Two radiologists who were blinded to the infecting organism and the clinical findings independently read the chest radiographs taken within 2 weeks of diagnosis of mycobacterial disease.
We also compared the previous CXR with the current CXR in patients with radiological evidence of lung diseases from the past.

The radiographs were assessed for the following features: previous or co-existent lung disease, site of abnormality, loss of lung volume, air space shadowing, circumscribed opacities and cavitations, bronchopulmonary spread, local pleural disease, pleural effusions, lymphadenopathy, and evidence of a primary focus.

Statistical analysis

Results are shown as mean ± SD. To analyse between-group differences in categorical variables, chi-square test or Fisher’s exact test was used, as appropriate. Pearson correlation coefficient (r) and the significance for it (p) were calculated between the variables. A p value of 0.05 or less was considered statistically significant.

Results

Background characteristics

The baseline characteristics of the patients are shown in Table 1. The mean age of the 62 patients with M. kansasii infection was 44 ± 18 (range 19–87) years; 21 (34%) were women. The mean age of the 102 patients with infected M. simiae infection was 69 ± 16 (range 51–85) years and 63 (62%) were women. These differences were statistically significant (p = 0.001).

Sixty percent of the patients in the M. kansasii group were born in Israel (60%) and most of the remainder were immigrants from the former USSR (28%), whereas in the M. simiae group, most of the patients were immigrants from the former USSR (44%) or other countries (39%). This difference, too, was statistically significant (p = 0.0001).

There were no significant differences between the groups in drug or alcohol use or in smoking status.

Past and concurrent morbidities are shown in Table 2. Significantly higher rates were noted in the M. simiae group for diabetes mellitus (p = 0.01), ischaemic heart disease (p = 0.002) and malignancy (p = 0.04). The M. kansasii group was characterised by a higher rate of chronic liver disease (p = 0.003). Only one patient (with M. kansasii infection) was HIV-positive.

There were no significant between-group differences in rates of associated lung disease, including bronchiectasis. Previous tuberculosis had also similar rate in the M. simiae group and in the M. kansasii group.

Presenting symptoms

The two groups showed significant differences in presenting symptoms. M. kansasii infections were mostly symptomatic. Chest pain, cough and haemoptysis were all more common in patients with M. kansasii infection than in patients with M. simiae infection. In contrast, sweat and fever were more common in patients with M. simiae (Table 1).

Radiological features

M. kansasii infection had normal chest radiographs in six patients (10%) and in 38 patients (37%) with M. simiae infection (p = 0.0001). However, most of these patients (34 patients) had hyperinflation, oligaemia and chronic lung changes in the base of the lungs. Most of them were asymptomatic. All remaining patients with abnormal CXR had symptoms of mycobacterial disease.

The anatomic distribution of the radiological findings differed between the groups (Table 3). Upper lobe disease was diagnosed in 50 patients (80%) with M. kansasii

| Table 1 Baseline characteristics, symptoms at presentation, and outcome in patients infected with M. kansasii or M. simiae |
|-----------|-----------------|-----------------|----------|
| M. kansasii, n = 62 | M. simiae, n = 102 | p Value |
| Age (yr)a | 44 ± 18 | 69 ± 16 | 0.001 |
| Sex | | | 0.001 |
| Male | 41 (66) | 39 (38) | | |
| Female | 21 (34) | 63 (62) | | |
| Origin | | | 0.0001 |
| Israel | 37 (60) | 18 (18) | | |
| Former USSR | 17 (28) | 45 (44) | | |
| Ethiopia | 4 (7) | 4 (4) | | |
| Other | 3 (5) | 35 (35) | | |
| Smoking | 26 (42) | 38 (37) | 0.634 |
| Alcohol intake | 4 (6.5) | 4 (4) | 0.358 |
| 14 units/week | | | |
| Drug abuse | 4 (6.5) | 2 (2) | 0.149 |
| Symptoms at presentation | | | |
| Chest pain | 46 (74) | 8 (8) | 0.0001 |
| Cough | 53 (86) | 14 (14) | 0.0001 |
| Haemoptysis | 26 (42) | 17 (17) | 0.001 |
| Weight loss | 20 (32) | 41 (34) | 0.480 |
| Sweat/fever | 25 (40) | 70 (58) | 0.018 |
| Hoarseness | 2 (4) | 0 (0) | 0.114 |
| Diagnosis by bronchoscopy | | | |
| Outcome, alive | | | 0.147 |

All other values are n (%).

| Table 2 Past and present medical problems in patients infected with M. kansasii or M. simiae |
|-----------|-----------------|----------|
| M. kansasii, n = 62 | M. simiae, n = 102 | p Value |
| HIV | 1 (1.6) | 0 | 0.378 |
| Chronic liver disease | 10 (16) | 3 (3) | 0.003 |
| Diabetes | 8 (13) | 30 (29) | 0.01 |
| Cardiac disease | 5 (8) | 28 (28) | 0.002 |
| Malignancy | 3 (5) | 15 (15) | 0.04 |
| Previous tuberculosis | 7 (11) | 18 (15) | 0.335 |
| Chronic obstructive pulmonary disease | 22 (36) | 38 (37) | 0.477 |
| Bronchiectasis | 8 (13) | 19 (19) | 0.231 |
| Use of immunosuppressive medication | 8 (13) | 31 (31) | 0.394 |
infection compared to 27 patients (45%) with M. simiae infection \((p = 0.001)\). By contrast, most of the patients (55%) with M. kansasii infection had pulmonary infiltrates in the lower- and middle-zones. A right-side predominance was noted in association with M. simiae infection \((p = 0.001)\). In four patients (4%), the effusion was the only abnormality present. Lymphadenopathy was noted in three patients (3%), all from the M. kansasii group. Cavitary disease was noted in 35 patients (57%) in infection \((p = 0.001)\). In four patients (4%), the effusion was the only abnormality present. Lymphadenopathy was noted in three patients (3%), all from the M. kansasii group. Cavitary disease was noted in 35 patients (57%) in infection and only three patients (3%) with M. simiae infection \((p = 0.001)\).

### Treatment

All our patients treated with the regimen of rifampicin (600 mg), ethambutol (25 mg/kg for the first 2 months, then 15 mg/kg) and clarithromycin (1000 mg/day) given daily for at least 12 months of negative sputum cultures according to the ATS criteria.

### Outcome

The duration of follow-up ranged from 28 to 108 months (mean 39 months) for the M. kansasii group and from 44 to 105 months (mean 24 months) for the M. simiae group. No relapses were detected during the follow-up period in either group. There were no deaths in the M. kansasii group. Five patients in the M. simiae group died, but none of the deaths was directly related to the mycobacterial disease (three were due to cerebral stroke and two to cardiac disease).

### Discussion

The present study is the largest so far to directly and systematically compare the clinical and radiologic features of M. kansasii and M. simiae infections. Our findings revealed important differences, making it possible to reliably differentiate between these two diseases on clinical grounds.\(^{4,15}\)

<table>
<thead>
<tr>
<th>Location in chest X-ray</th>
<th>M. kansasii, (n=62)</th>
<th>M. simiae, (n=102)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal chest X-ray</td>
<td>6 (10)</td>
<td>38 (37)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Infiltrates</td>
<td>21 (34)</td>
<td>58 (57)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cavitation</td>
<td>35 (57)</td>
<td>3 (3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Location in chest X-ray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right upper lobe</td>
<td>30 (48)</td>
<td>15 (25)</td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>20 (32)</td>
<td>12 (20)</td>
<td></td>
</tr>
<tr>
<td>Lower/middle lobes</td>
<td>4 (6.5)</td>
<td>33 (55)</td>
<td></td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>7 (11)</td>
<td>4 (4)</td>
<td>0.075</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>16 (16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>0</td>
<td>3 (3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Miliary pattern</td>
<td>0</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Diabetes, cardiac disease, and malignancy were rare in the M. kansasii group, whereas associated lung disease, especially chronic obstructive pulmonary disease, and chronic liver disease were more common in the M. kansasii group than in the M. simiae group.

Regarding symptoms, chest pain, cough and haemoptysis were all more common in the M. kansasii group, and sweat and fever were more common in the M. simiae group. This finding is consistent with the statement of the American Thoracic Society that symptoms are more common in lung disease caused by NTM than in other NTM infections.\(^{20}\)

Most of the patients in both groups in our series were Caucasian (88% and 62%, respectively), either native Israelis or immigrants from the former USSR. These findings suggest that NTM infection may be less common in the non-white population. However, by group, native Israelis accounted for a significantly smaller proportion of the patients with M. simiae infection than M. kansasii infection (18% versus 60%, \(p = 0.0001\)).

Haemoptysis occurred in 42% of the M. kansasii group, which is slightly higher than the 20–30% rates reported in earlier studies.\(^{20–22}\) Haemoptysis in pulmonary infections may be related to the degree of endobronchial disease and the erosion of bronchial vessels by cavitiation. Although there are no available data on the relative incidence of endobronchial disease, the reported incidence of cavitiation in M. kansasii infection is 57%,\(^{4,23–25}\) which is close to our haemoptysis rate. It is noteworthy that cavitations were much less common in M. simiae infections.

Although many previous studies emphasised the higher rate of pre-existing lung disease, particularly tuberculosis, in pulmonary NTM infection compared to M. tuberculosis infection,\(^3,20\) none of them used a controlled comparison design. In our series, there was a higher incidence of history of tuberculosis in the M. simiae group than the M. kansasii group (Table 2).

In Israel, most cases of HIV are identified in immigrants, and not in the native-born population. We found only one case of HIV infection in the M. kansasii group, and no cases in the M. simiae group. The relatively low incidence of HIV infection and AIDS in Israel may account for these low rates.

The radiographic features of NTM pulmonary infections have been variably reported to be indistinguishable from tuberculosis,\(^{26–28}\) highly suggestive of NTM infection,\(^{28–30}\) or quite different from M. tuberculosis infection.\(^{31,32}\) These discrepancies may be explained in part by the different diagnostic methods used. Our study is the first matched comparison of the radiological features of M. kansasii and M. simiae infection, and our radiologists were blinded to the clinical data and the infecting organism. Our findings yielded several noteworthy differences. As noted above, M. kansasii infection was associated with cavitary infiltrates and a predilection for upper lobe disease whereas M. simiae infection was associated with noncavitary disease and a lower-middle-lobe predominance. It should be borne in mind that others have recognised noncavitary lung disease as part of the spectrum of M. kansasii infection,\(^4,9\) and that in our series, cavitary disease occurred in only 57% of the M. kansasii group compared to 3% of the M. simiae group.

Although the radiographic picture of M. kansasii infections was not pathognomonic, the disease usually occurred...
unilaterally without a pleural component or lymphadenopathy. In accordance with the literature on NTM,21,24 pleural effusions were not noted in any patient in our M. kansasii group compared to 16% of the M. simiae group.

In CHF and cardiac disease the pleural effusion in most of the cases are bilateral with transudate characteristics. In all cases of pleural effusion due to M. simiae there were unilateral pleural effusions. In addition, none of the patients with malignancy had pleural effusion.

We also compared all CXRs with the previous CXRs in patients with co-morbid disease.

The similar high survival in the M. kansasii and M. simiae groups (100% and 95%, respectively) may be attributable to the low rate of extensive disease and the early mycobacterial treatment. None of the deaths that occurred were directly due to the NTM disease. These data support the application of early treatment regimens in NTM infection. All cases treated with combination of rifampicin, ethambutol and clarithromycin. We treated only patients according to the ATS criteria. Most of the data from US about the treatment of kansasii and simiae are from patients with HIV and mycobacterial disease. Most of these patients had severe lung disease and reduced outcome. As best we know, there is no study about the genotype of the M. simiae isolates. In addition, there is no data concerning M. simiae disease in Eastern Europe and Ethiopia.

Our study has several limitations: retrospective design; use of medical records for data collection; and radiological assessment based mainly on chest radiographs and not CT scans. Further, larger prospective studies are needed to corroborate our findings.

Summary

There are some significant differences in the clinical and radiological appearance of M. kansasii and M. simiae infections. Findings of lower- and middle-lobe disease, pleural effusions, or mediastinal lymphadenopathy make the diagnosis of M. kansasii infection very unlikely. M. simiae infection appears to occur more often in immigrants and is associated with a lower rate of fever and night sweats at presentation than M. kansasii infection. The outcome of both mycobacterial infections is excellent. These differences are important for diagnosis and in decisions regarding early empirical antimycobacterial therapy. Continuous surveys of mycobacterial species and analyses of the clinical significance of these differences are warranted.

Conflict of interest

None of the authors of this manuscript have conflict of interest.

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