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Clinical and radiological features of *Mycobacterium kansasii* and other NTM infections

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Summary

Background: Mycobacterium kansasii infection is one of the most common causes of nontuberculous mycobacterial lung disease in the world. However, it is not possible to differentiate completely between *M. kansasii* and other nontuberculous mycobacteria (NTM) because of a lack of direct comparative studies. This retrospective study sought to identify their clinical and radiological features systematically.

Methods: The sample included 98 consecutive patients with a culture-positive diagnosis of NTM infection, derived from the databases of the Laboratory of Microbiology of a tertiary medical center and two outpatient tuberculosis centers. Sixty-four patients had *M. kansasii* infection. All patients fulfilled disease criteria for treatment. Data on patient background and clinical features were collected, and chest radiographs were evaluated.

Results: In the *M. kansasii* group, $n = 27$ (42%) were native-born Israelis compared to 9.4% ($n = 3$) of all other NTM groups ($p = 0.0001$). Similar rates of co-morbid diseases, including diabetes mellitus, heart disease, lung diseases, and malignancy were noted in both groups. Old TB was less common in the *M. kansasii* group compared to the other NTM (3.1% vs. 23.5%, $p = 0.003$). Clinical symptoms were significantly more common in patients with *M. kansasii* infection. On radiological study, *M. kansasii* infection was associated with more cavitations and unilaterality. Patients with *M. kansasii infection* had a higher likelihood of right upper lobe disease ($p = 0.001$). Pleural effusions and lymphadenopathy were found only in a few patients in each group.

Conclusion: Major differences in the epidemiologic and clinical features of *M. kansasii* infection and other NTM have important diagnostic and clinical implications.
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Introduction

Nontuberculous mycobacteria (NTM) have been identified in clinical specimens as early as 1885. However, their pathogenic role in humans was long overshadowed by that of *Mycobacterium tuberculosis*. With recent improvements in techniques for isolating and identifying mycobacteria and controlling tuberculosis, the importance of NTM, especially in immunocompromised hosts, has been recognized.

Mycobacterium kansasii has traditionally been considered the most virulent of the NTM.[1,2] It is the second most common NTM after *Mycobacterium avium complex* and is one of the common causes of NTM lung disease in the UK and western Europe.[2-5] *M. kansasii* infection likely occurs via an aerosol route. Tap water is a major reservoir and the only environmental (water or soil) source of the bacterium identified to date.[6,7] However, isolation of *M. kansasii* from tap water can be intermittent, which might explain why some investigators failed to recover it from this source. Risk factors for *M. kansasii* infection include chronic lung disease, previous mycobacterial disease, malignancy, and alcoholism.[2,7-12] In immunocompetent patients, pulmonary disease is the most frequent clinical manifestation,[7] although approximately 40% have no associated illness.[2] When the infection is treated appropriately, outcome is good.[13-16]

The major clinical and therapeutic implications of infection with these pathogens and their diverse prevalence in different countries warrant ongoing surveillance of species distribution of mycobacterium isolates. Furthermore, to the best of our knowledge, there are no systematic studies comparing the clinical and radiological features of *M. kansasii* with other NTM infections, which was the goal of this study.

Patients and methods

Patients and setting

All patients from whom a sputum specimen had grown NTM between April 2007 and April 2010 were identified from the Tuberculosis Clinic database of the tuberculosis centers in the cities of Tel Aviv and Rehovot. These centers are part of the Pulmonary Institute of Meir Medical Center that is affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. Data on the clinical features of the patients (including systemic co-morbid disease and smoking status), radiological findings, and outcome were abstracted from the case notes and laboratory records by a single investigator.

Patients for whom there was a high clinical suspicion of tuberculosis, but negative sputum smears underwent bronchoscopy with bronchoalveolar lavage and trans-bronchial biopsy to confirm the diagnosis. All patients ful-filled disease criteria for treatment according to the American Thoracic Society (ATS) guidelines, as follows: appropriate symptomatology, compatible radiographic abnormalities, and culture-positive respiratory specimens.[17,18]

All patients were tested for human immunodeficiency virus (HIV). 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. The radiographs were assessed for 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. Patients with fibrotic changes in the left or right upper lobes or clinical history of TB were diagnosed as having old tuberculosis.

The study was approved by the Ethics Committee of Maccabi Medical Service, Tel Aviv, Israel.

Media

Sputum smears stained with auramine were examined by fluorescent microscopy and the presence of acid-fast organisms was confirmed with Ziehl-Neelsen stain. All mycobacterial isolates were referred to the Public Health Laboratory Mycobacterial Reference Unit at Abo Cabir for identification and sensitivity testing.

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 labeled Middlebrook 7H12 broth using the Bactec 460 TB (Becton Dickinson, Franklin Lakes, NJ, 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 (Becton Dickinson, Franklin Lakes, NJ, USA). All media were inoculated in duplicate and incubated in parallel at 30 °C and 37 °C for 8 weeks.

Isolates of acid fast bacilli were identified as *M. tuberculosis*, *M. kansasii*, MAC, or other NTM by conventional biochemical reactions[1,2] and AccuProbe culture confirmation kits (Gen-Probe, San Diego, CA, USA). *Mycobacterium simiae* was identified by photochromogenicity, positive niacin, negative nitrate reduction, and TWEEN hydrolysis.

The resistance ratio method was used to test the susceptibility strains to all the drugs mentioned and not the MIC method.[19] This method is based on the growth of the tested strain relative to a standard sensitive (control) strain at five standard doubled drug concentrations. We calculated the resistance ratio of each test strain to each drug by dividing the minimum inhibitory concentration of the test by the model minimum inhibitory concentration. As doubling dilutions are used, the resistance ratio is 1 (or less), 2, 3, 4, or 8. Strains with a resistance ratio of 1 or 2 are reported as susceptible, those with a resistance ratio of 4 are resistant, and those with a resistance ratio of 8 are highly resistant.

Statistical analysis

Results are shown as mean $\pm$ standard deviation. To analyze between group differences in categorical variables, chi-square test or Fisher's exact test was used, as

appropriate. Pearson correlation coefficient (r) and its significance (p) were calculated between the variables. A p-value of 0.05 or less was considered statistically significant.

Results

Clinical characteristics

The study population included 64 patients with M. kansasii and 34 patients with other NTM. The most common NTM in the non-M. kansasii group was MAC (14 patients) followed by M. simiae (8 patients), Mycobacterium abscesus (5 patients), Mycobacterium gordonae (4 patients) and Mycobacterium chelonae (3 patients). The baseline characteristics of the patients are shown in Table 1. The mean age of the 64 patients with M. kansasii infection was 44 ± 19 (range 19−87) years; 23 (36%) were women. The mean age of the 34 patients with infected with other NTM infections was 63 ± 13 (range 51−85) years and 14 (41%) were women. The age differences were statistically significant (p = 0.0001).

Of the patients in the M. kansasii group, 42% were born in Israel; most of the remaining patients were immigrants from the former USSR (31%). In the other NTM group, most of the patients (91%) were immigrants from Ethiopia (31%), the Former Soviet Union (22%), and other countries (38%). This difference was also statistically significant (p = 0.0001). There were no significant differences between the groups in drug or alcohol use or smoking status.

The two groups showed significant differences in presenting symptoms. Chest pain, cough, and hemoptysis were more common in patients with M. kansasii infection than in patients with other NTM infections (Table 1). Past and concurrent comorbid conditions are also shown in Table 1. Significantly higher rates were noted in the Other NTM group for malignancy (p = 0.01), and old TB (p = 0.003).

Radiological features

Among patients with NTM other than M. kansasii, 5 (14.7%) had normal chest radiographs as did 2 patients (3.1%) with M. Kansasii infection, (p = 0.013). All remaining patients had findings of mycobacterial disease. Cavitary disease was noted in 34 patients (53%) with M. kansasii infection and only 2 patients (6%) with other NTM infections (p = 0.0001).

Table 1 Clinical characteristics and symptoms at presentation in patients infected with M. kansasii or other nontuberculous mycobacteria.

	M. kansasii N = 64 (%)	Other NTM N = 34 (%)	P value
Age (yr)[a]	44 ± 19	63 ± 13	**0.0001**
Sex			
Male	41 (64)	20 (59)	0.611
Female	23 (36)	14 (41)	
Origin			
Israel	27 (42)	3 (9)	**0.0001**
Former USSR	20 (31)	7 (22)	
Ethiopia	3 (5)	11 (31)	
Other	14 (22)	13 (38)	
Smoker	23 (36)	15 (43)	0.711
Alcohol intake (>14 units/week)	3 (5)	1 (4)	0.358
Drug abuse	0 (0)	3 (10)	0.254
Symptoms at presentation			
Chest pain	47 (74)	3 (9)	**0.003**
Cough	53 (86)	5 (15)	**0.0005**
Hemoptysis	27 (42)	4 (17)	**0.001**
Weight loss	20 (32)	11 (32)	0.890
Sweats/Fever	25 (39)	70 (58)	**0.028**
Diagnosis by bronchoscopy	8 (13)	14 (14)	0.493
Comorbid conditions			
Chronic liver disease	2 (3.1)	1 (2.9)	0.851
Diabetes	1 (1.6)	2 (5.9)	0.538
Cardiac disease	3 (4.7)	0 (0)	0.260
Malignancy	0 (0)	2 (5.9)	**0.032**
Chronic obstructive pulmonary disease	7 (10.9)	5 (14.7)	0.324
Bronchiectasis	8 (12.5)	4 (11.8)	0.957
Old Tuberculosis	2 (3.1)	8 (23.5)	**0.003**
Drug addiction	4 (6.2)	0 (0)	0.254
Use of immunosuppressive medication	1 (1.6)	1 (2.9)	0.462

Bold values signify P ≤ 0.05.
[a] Mean±SD. All other values are n (%).

Table 2 Radiological findings in patients infected with *M. kansasii* or other NTM.

	M. kansasii N = 64	*Other NTM*[a] N = 34	*P* value
Normal chest x-ray	2 (3.1)	5 (14.7)	**0.013**
Infiltrates	33 (51.6)	12 (35.3)	0.410
Cavitation	34 (53.1)	2 (5.9)	**0.0001**
Location on chest x-ray			
Right upper lobe	39 (60.1)	8 (23.5)	**0.0001**
Left upper lobe	20 (31.3)	12 (20)	**0.001**
Middle lobes	3 (4.7)	2 (5.9)	0.632
Lower lobes	1 (1.6)	4 (11.8)	**0.018**
Bilateral disease	3 (4.7)	7 (20.6)	**0.013**
Pleural effusion	2 (3.1)	1 (2.9)	0.887
Lymphadenopathy	1 (1.6)	1 (2.9)	0.532
Miliary pattern	0 (0)	0 (0)	0.128

[a] NTM = nontuberculous mycobacteria.
Bold values signify *P* ≤ 0.05.

The anatomic distribution of the radiological findings differed between the groups (Table 2). Upper-lobe disease was diagnosed in 39 patients (60%) with *M. kansasii* infection compared to 8 patients (23.5%) with other NTM infections (*p* = 0.0001). Bilateral disease was noted in association with other NTM infections (7 vs. 3 patients; *p* = 0.013).

Other radiological findings are presented in Table 2. Pleural effusions, lymphadenopathy and miliary pattern were seen in the minority of patients in both groups.

Treatment

The basic treatment regimen in both groups was rifampicin (600 mg), ethambutol (25 mg/kg for the first 2 months, then 15 mg/kg), and clarithromycin (1000 mg/d) administered daily for at least 12 months of negative sputum culture results. Patients with resistant strains were treated according to the susceptibility tests. All *M. kansasii* isolates were sensitive to rifampicin, all but one isolate (borderline) were sensitive to ethambutol and ofloxacin, and all but two isolates (borderline) were sensitive to clarithromycin. Sensitivity rates to ethionamide and cycloserine were 91% and 94%, respectively, with one isolate resistant to each. A high rate of resistance was noted for ciprofloxacin (33%) and capreomycin (26 isolates, 74%); 2 isolates (6%) were highly resistant to capreomycin. Among the NTM infections other than *M. kansasii*, 66% and 36% were resistant to ethambutol and ofloxacin, respectively and 77%, 84%, 64% were sensitive to clarithromycin, ethionamide and cycloserine, respectively. Of the patients with *M. kansasii,* 98% were treated with the basic regimen compared to 39% in the other NTM group.

Outcome

Follow-up ranged from 28 to 108 (mean 39) months. No relapses were detected during the follow-up period in the *M. kansasii* group. However, 6 (17.6%) patients had a treatment failure (2 with *M. avium*, 2 with *M. simiae*, 1 with *M. gordonae* and 1 with *M. abscesus*). There were no deaths in the *M. kansasii* group. Five patients in the Other NTM group died, but none of the deaths was directly related to mycobacterial disease (3 were due to cerebral stroke and 2 to cardiac disease).

Discussion

This study is the largest to date that directly and systematically compared the clinical and radiologic features of *M. kansasii* and other NTM infections. Our findings validate the commonly assumed differences between these two groups.

We found that most patients with *M. Kansasii* were younger, native-born Israelis, and had symptoms of chest pain, cough, and hemoptysis compared to patients with other NTM infections who tended to be older, immigrants, with a history of old tuberculosis, and presented with weight loss, fever, and sweating.

On radiological study, patients with *M. kansasii* infection had more cavitations, unilateral disease, and a higher likelihood of right upper lobe disease.

As noted, most patients in the *M. kansasii* group in our series were either native-born Israelis or immigrants from the former USSR (42% and 31%, respectively). In contrast, patients with other NTM infections were mainly immigrants (69%). This demographic difference could be due to the geographic heterogeneity of the NTM species, racial/ethnic differences between patient groups, an interaction with relative frequencies of TB in the *M. kansasii* versus non-*M. kansasii* groups, or some combination of these factors. This study however, was not designed to address this issue.

Hemoptysis occurred in 42% of the *M. kansasii* group patients, which is slightly higher than the rates of 20%–30% reported in earlier studies.[17,18] Hemoptysis in pulmonary infections may be related to the degree of endobronchial disease and the erosion of bronchial vessels by cavitation. Although there are no available data on the relative incidence of endobronchial disease, the reported incidence of cavitation in *M. kansasii* infection is 57%,[4,20–22] which is close to our hemoptysis rate. It is noteworthy that cavitations were much less common in patients with other NTM infections.

Compared to patients with *M. kansasii,* patients with other NTM were more likely to have a history of old

tuberculosis. This observation emphasizes the higher rate of pre-existing lung disease, particularly old tuberculosis, in NTM pulmonary infection compared to *M. kansasii* infection.[3,17] In our series, there was a higher incidence of history of tuberculosis only in those with other NTM infections and not in the *M. kansasii* group, although not statistically significant (Table 2). This could be explained partially by demographic changes. Moreover, NTM species groups are less pathogenic than *M. kansasii*. So, the less pathogenic organisms may require a greater reduction or breach in the normal local host defenses that can be provided in the presence of "old TB" with parenchymal destruction. *M. kansasii* on the other hand is considered a more pathogenic organism that can more readily establish a significant infection in relatively normal lung tissue.

The radiographic features of NTM pulmonary infections have been variably reported to be indistinguishable from tuberculosis,[23–25] highly suggestive of NTM infection,[25–27] or quite different from *M. tuberculosis* infection.[28,29] These discrepancies may be explained in part by the different diagnostic methods used. Our study is the first to compare the radiological features of *M. kansasii* and other NTM infections and our radiologists were blinded to the clinical data and the infecting organism. Our findings yielded several noteworthy differences. Importantly, all patients had several radiological characteristics including lack of lymphadenopathy, pleural effusion, and miliary pattern in non-HIV population. The lack of pleural effusion in other NTM infections is in accordance with the literature on NTM.[18–21] However, as noted above, *M. kansasii* infection was associated with cavitary infiltrates and a predilection for upper lobe disease, whereas other NTM infections were associated with noncavitary disease and lower and middle lobe predominance. It should be kept in mind, that others have recognized noncavitary lung disease as part of the spectrum of *M. kansasii* infection,[4,7] and that in our series, cavitary disease occurred in 53% of the *M. kansasii* group compared to 5.9% of the Other NTM group. Although the radiographic picture of *M. kansasii* infections was not pathognomonic, the disease usually occurred unilaterally without a pleural component or lymphadenopathy.

Our study found a high rate of upper lobe predominance in NTM infections other than *M. kansasii* (23.5% and 20% in the right and left upper lobes, respectively). These findings are higher than those recently reported in North American studies, where it is believed that a mid-zone, nodular, bronchiectatic form of pulmonary NTM is more common. This may be due to the high proportion of prior TB in this population in our cohort.

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

Summary

The clinical and radiological appearance of *M. kansasii* and other NTM infections differ significantly. Findings of lower and middle lobe disease, pleural effusions, or mediastinal lymphadenopathy make the diagnosis of *M. kansasii* infection very unlikely. NTM infections other than *M. kansasii* appear to occur more often in older people, and are associated with a lower rate of cough and hemoptysis at presentation. Continuous surveys of mycobacterial species and analyses of the clinical significance of these differences are warranted.

Conflict of interest statement

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