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Determination of Clinical Characteristics of *Mycobacterium kansasii*-Derived Species by Reanalysis of Isolates Formerly Reported as *M. kansasii*

Young-gon Kim, M.D.[1], Hong Yeul Lee, M.D.[2], Nakwon Kwak, M.D.[2], Jae Hyeon Park, M.D.[1], Taek Soo Kim, M.D.[1], Man Jin Kim, M.D.[1], Jee-Soo Lee, M.D.[1], Sung-Sup Park, M.D., Ph.D.[1], Jae-Joon Yim, M.D., Ph.D.[2,3], and Moon-Woo Seong, M.D., Ph.D.[1]

[1]Department of Laboratory Medicine, Seoul National University Hospital, Seoul, Korea; [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; [3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

Background: Seven genotypic subtypes of *Mycobacterium kansasii* were recently demonstrated to represent distinct species based on phylogenomic analysis. *Mycobacterium kansasii sensu stricto* (formerly known as subtype 1) is most frequently associated with human diseases; only a few studies have compared the diverse clinical characteristics of *M. kansasii* subtypes, including their drug susceptibilities. We determined the actual incidence of infections caused by each subtype of *M. kansasii* and identified their clinical characteristics.

Methods: We subtyped isolates identified as *M. kansasii* over the last 10 years at a tertiary care hospital. Percent identity score of stored sequencing data was calculated using curated reference sequences of all *M. kansasii* subtypes. Clinical characteristics were compared between those classified as subtype 1 and other subtypes. Student's *t*-test, Wilcoxon rank-sum test, and Fisher's exact test were used for comparisons.

Results: Overall, 21.7% of the isolates were identified as species distinct from *M. kansasii*. The proportion of patients with subtype 1 *M. kansasii* infection who received treatment was significantly higher than that of patients with other subtype infections (55.3% vs. 7.7%, $P=0.003$). Only patients with subtype 1 infection received surgical treatment. Non-subtype 1 *M. kansasii* isolates showed a higher frequency of resistance to ciprofloxacin and trimethoprim/sulfamethoxazole.

Conclusions: Non-subtype 1 *M. kansasii* isolates should be separately identified in routine clinical laboratory tests for appropriate treatment selection.

Key Words: *Mycobacterium kansasii*, subtypes, subtype 1 *M. kansasii*, Non-subtype 1 *M. kansasii*

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Corresponding author:
Moon-Woo Seong, M.D., Ph.D.
Department of Laboratory Medicine Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-4180
Fax: +82-2-747-0359
E-mail: mwseong@snu.ac.kr

INTRODUCTION

Mycobacterium kansasii is a common non-tuberculous mycobacterial (NTM) species with relatively high pathogenicity [1, 2]. It can cause severe lung diseases, similar to that caused by *Mycobacterium tuberculosis* [3, 4]. Seven subtypes of *M. kansasii* have been described, based on restriction fragment length polymorphism analysis of *hsp65* [5-7]. PCR-restriction enzyme analysis of *rpoB* and *tuf* has also been used to distinguish subtypes [8, 9]. Among these subtypes, *M. kansasii sensu stricto* is considered the most pathogenic and is isolated most frequently [4, 10-13]. Reports of human diseases caused by subtype 2 are

rare, demonstrating its higher association with immunosuppression than subtype 1 [7, 14]. There is a consensus that the other subtypes (subtypes 3–7) are not human pathogens, although this opinion is controversial owing to the limited evidence caused by the paucity of isolates of these subtypes [4]. "*Mycobacterium kansasii* complex" has been proposed as an inclusive term comprising all subtypes of *M. kansasii* and *M. gastri*, which is a closely related species but indistinguishable from *M. kansasii* by 16S rRNA sequencing [4, 15].

Although the difference in the pathogenicity of *M. kansasii* subtypes has been recognized, these subtypes have recently been differentiated into distinct species [15, 16]. Unlike subspecies, subtypes are not a part of the standard taxonomic classification system, and reporting of subtypes in mycobacterial identification by clinical laboratories is not mandatory [17, 18]. However, the recently published *M. kansasii*-derived species, which were formerly classified as *M. kansasii* subtypes, have not been included as target species of commercial kits for NTM identification [15]. Genotyping of at least one discriminatory target, such as *rpoB* and *hsp65*, is required for accurate species identification.

The detection frequency of *M. kansasii* subtypes in clinically relevant populations have been reported; however, only a few studies have compared the clinical characteristics among infections caused by *M. kansasii* subtypes [4, 13]. Several studies on the clinical relevance of *M. kansasii* have not separately analyzed the subtypes, resulting in substantial variability (17%–88%) in the reported rate of pulmonary diseases caused by *M. kansasii* isolates and diversity in radiological findings [1, 2, 19–24].

To fill this knowledge gap, we reanalyzed the sequencing trace files of all isolates reported to involve *M. kansasii*, from an up-to-date database of reference sequences, and compared the clinical characteristics of infections caused by different *M. kansasii* subtypes.

MATERIALS AND METHODS

Participants and samples

This study was approved by the Institutional Review Board of Seoul National University Hospital (SNUH), Seoul, Korea. We reviewed the medical records of 60 consecutive patients with *M. kansasii* infection, diagnosed based on a routine NTM identification testing performed from June 15, 2011 to April 8, 2020 at SNUH. The routine NTM identification was performed by in-house method which was based on PCR amplification of the two target regions, the 5' end of the 16S rRNA gene (about 500 bp) and a part of *rpoB* gene, and subsequent Sanger sequencing. Informed consent from patients was not obtained, as this was a retrospective study performed using medical records and raw data files. The patient selection process is shown in Fig. 1. For patients with NTM identification testing being requested two or more times, we preferentially selected the tests with drug susceptibility testing results. For patients with no drug susceptibility testing results or two or more drug susceptibility testing results, earlier NTM identification testing results were chosen. All samples included in the analysis were cultured colonies from sputum (53, 88.3%), bronchial wash or bronchoalveolar lavage fluid (6, 10.0%), and joint fluid (1, 1.7%).

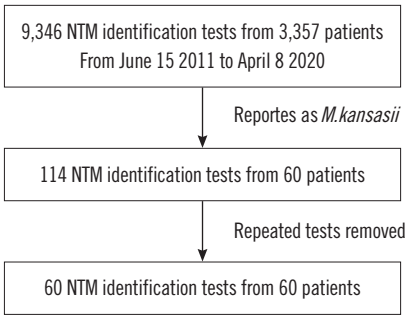

Fig. 1. Among 9,364 isolates in the non-tuberculous mycobacterial (NTM) identification tests, 114 isolates were identified as *M. kansasii* (1.2%). After removing repeated isolates for the same patients, 60 isolates reported as *M. kansasii* were included in this analysis.

Identification of *M. kansasii* subtypes

Sequencing data generated from routine identification testing were used. For the 60 patients, percent identity score was calculated based on curated reference sequences of each subtype of *M. kansasii*. The reference sequences of the 16S rRNA gene and *rpoB* were curated from the List of Prokaryotic Names with Standing in Nomenclature (http://www.bacterio.net) and NCBI Genbank (https://www.ncbi.nlm.nih.gov/genbank/), respectively. SnackNTM software (https://github.com/Young-gonKim/SnackNTM, last accessed August 27, 2020) was used for aligning sequencing data to the curated reference sequences.

Grouping of patients

The patients were divided into two groups for comparison. Group 1 comprised patients infected with *M. kansasii* subtype 1, the most pathogenic subtype [4, 10–13]. Group 2 comprised patients infected with other subtypes, *M. kansasii* subtypes 2, 3, and 6. Baseline characteristics of patients, clinical manifestations, outcome, and drug susceptibility of the isolates were compared between the groups.

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Review of medical records

Patient characteristics including age, sex, body mass index, and smoking history were retrieved from the medical records. Medical histories of tuberculosis, malignancy, diabetes mellitus, liver diseases, kidney diseases, and immunocompromising diseases were reviewed. Radiologic findings and pulmonary function test results including forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC were retrieved. Clinical course of NTM isolation, such as co-infection with other NTM organisms, presence of NTM pulmonary diseases, and treatment initiation were reviewed. The drug susceptibility test results were also reviewed.

Statistical analysis

Statistical analysis was performed using R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria). For quantitative variable comparison, Shapiro test was used to evaluate the normality of data. Student's *t*-test was used when the normality assumption was satisfied; otherwise, the non-parametric Wilcoxon rank-sum test was used. Fisher's exact test was used to compare categorical variables between groups. $P < 0.05$ were considered statistically significant.

RESULTS

Among the 60 isolates included in the analysis, 13 were reclassified as one of the newly reported *M. kansasii*-derived species (21.7%), including 10 (16.7%) isolates of *M. persicum* (former subtype 2), 2 (3.3%) isolates of *M. pseudokansasii* (former subtype 3), and 1 (1.7%) isolate of *M. attenuatum* (former subtype 6). The remaining 47 isolates were classified as subtype 1.

The baseline characteristics of the two patients' groups are shown in Table 1. FVC was significantly lower in Group 1 than in Group 2 (88.0% vs. 97.5% predicted, $P=0.025$), leading to a significantly higher FEV1/FVC ratio in Group 1 (74.0 vs. 70.5, $P=0.038$). Non-cavitary nodular bronchiectatic lesions were commonly observed in Group 2 (34.0% vs. 76.9%, $P=0.010$) and fibrocavitary lesions were observed only in Group 1 (38.3%

Table 1. Patients' characteristics including comorbidities, pulmonary function, and radiologic findings

Characteristics	Group 1: *M. kansasii* former subtype 1 (N=47)	Group 2: *M. kansasii* former subtypes 2, 3, and 6 (N=13)	*P*
Age (yr), median (IQR)	62.0 (49.3–71.2)	63.4 (50.4–75.6)	0.378
Male, N (%)	31 (66.0)	8 (61.5)	0.755
Body mass index (kg/m^2), median (IQR)	21.2 (19.6–22.8)	22.0 (20.7–22.8)	0.385
Smoking, N (%)	26 (57.8)	6 (46.2)	0.535
Underlying disease, N (%)	32 (68.1)	9 (69.2)	1
Previous history of tuberculosis, N (%)	17 (36.2)	8 (61.5)	0.122
Previous history of tuberculosis treatment, N (%)	11 (23.4)	7 (53.8)	0.046
Malignancy, N (%)	13 (27.7)	1 (7.7)	0.264
Diabetes Mellitus, N (%)	10 (21.3)	3 (23.1)	1
Chronic kidney disease, N (%)	1 (2.1)	0 (0)	1
Chronic liver disease, N (%)	3 (6.4)	0 (0)	1
Immunocompromised, N (%)	8 (17.0)	0 (0)	0.182
Sputum smear positivity, N (%)	6 (12.8)	1 (7.7)	1
FEV1 (% predicted), median (IQR)	93.0 (79.5–102.5)	99.0 (78.3–103.0)	0.688
FVC (% predicted), median (IQR)	88.0 (79.0–96.5)	97.5 (91.8–108.8)	0.025
FEV1/FVC, median (IQR)	74.0 (70.0–81.5)	70.5 (57.0–71.8)	0.038
Erythrocyte sediment rate (mm/h), median (IQR)	25.0 (12.5–42.5)	25.0 (7.0–34.8)	0.762
Radiographic characteristics, N (%)	39 (83.0)	11 (84.6)	1
Non-cavitary nodular bronchiectatic lesion	16 (34.0)	10 (76.9)	0.010
Cavitary nodular bronchiectatic lesion	5 (10.6)	1 (7.7)	1
Fibrocavitary lesion	18 (38.3)	0 (0)	0.006

Abbreviations: IQR, interquartile range; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

vs. 0%, $P=0.006$).

The clinical course of the two groups is summarized in Table 2. Co-infection with *M. avium* complex was more frequent in Group 2 (19.1% vs. 53.8%, $P=0.029$). The proportion of patients who satisfied the NTM pulmonary disease (NTM-PD) diagnostic criteria did not differ between the groups (85.1% vs. 76.9%, $P=0.675$). However, the proportion of treated patients was significantly higher in Group 1 than in Group 2 (55.3% vs. 7.7%, $P=0.003$).

The *in vitro* drug susceptibility testing results of the available isolates are presented in Table 3. Among the 60 patients, 32 (25 from Group 1 and 7 from Group 2) had drug susceptibility testing results. Among the eight drugs, whose breakpoints are published in the CLSI guidelines [25], resistance to four drugs(ciprofloxacin, ethambutol, rifampin, and trimethoprim/sulfamethoxazole) was detected. Susceptibility frequencies for all the four drugs were higher in Group 1 than in Group 2. The frequency of ciprofloxacin susceptibility was significantly higher in Group 1 than in Group 2 (80.0% vs. 28.6%, $P=0.019$). However, there was no significant difference in the MICs of the antimicrobial drugs whose breakpoints are not available in the CLSI guidelines (cefoxitin, doxycycline, imipenem, and tobramycin) between the groups.

Table 2. Comparison of co-infection rate and clinical courses between Groups 1 and 2

	Group 1: *M. kansasii* former subtype 1 (N=47)	Group 2: *M. kansasii* former subtypes 2, 3, and 6 (N=13)	*P*
Co-infection with other organisms, N (%)	16 (34.0)	7 (53.8)	0.215
With *M. avium* complex	9 (19.1)	7 (53.8)	0.029
With *M. abscessus* complex	3 (6.4)	0 (0)	1
With other NTM	9 (19.1)	2 (15.4)	1
Met diagnostic criteria of NTM-PD, N (%)	40 (85.1)	10 (76.9)	0.675
Observed without treatment, N (%)	21 (44.7)	12 (92.3)	0.003
Spontaneous conversion, N (%)	6/14 (42.9)	3/7 (42.9)	1
Treatment initiation within three yrs, N (%)	26 (55.3)	1 (7.7)	0.003
Microbiologic cure* n/N (%)	18/20 (90.0)	1/1 (100)	1
Surgical treatment, N (%)	5 (10.6)	0.0	0.575

*Three or more consecutive negative results from cultures that were performed with intervals longer than one month.
Abbreviation: NTM-PD, non-tuberculous mycobacterial pulmonary disease.

Table 3. Comparison of *in vitro* drug susceptibilities between Groups 1 and 2

Antimicrobial	Group 1 *M. kansasii* former subtype 1 (N=25)		Group 2 *M. kansasii* former subtypes 2, 3, and 6 (N=7)		*P*
	MIC range (μg/mL)	Susceptibility (N, %)	MIC range (μg/mL)	Susceptibility (N, %)	
Amikacin	≤1–16	25 (100.0)	≤1–16	7 (100.0)	1
Cefoxitin	64 to >256		8 to >256		
Ciprofloxacin	0.5–8	20 (80.0)	0.25–8	2 (28.6)	0.019
Clarithromycin	≤0.5–1	25 (100.0)	≤0.5–1	7 (100.0)	1
Doxycycline	1 to >32		1 to >32		
Imipenem	8 to >64		16 to >64		
Ethambutol	0.5–16	21 (84.0)	1 to >32	5 (71.4)	0.590
Linezolid	≤2–8	25 (100.0)	≤2–4	7 (100.0)	1
Moxifloxacin	≤0.125–1	25 (100.0)	≤0.125–2	7 (100.0)	1
Rifampin	≤0.125–2	24 (96.0)	0.25–2	5 (71.4)	0.113
Tobramycin	1 to >32		4 to >32		
TMP/SMX	≤0.25/4.75 to 32/608	18 (72.0)	≤0.25/4.75 to 32/608	2 (28.6)	0.074

Abbreviations: TMP/SMX, trimethoprim/sulfamethoxazole; MIC, minimum inhibitory concentration.

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DISCUSSION

In this study, 21.7% of isolates previously identified as *M. kansasii* were reclassified as new species with reportedly lower pathogenicity than *M. kansasii sensu stricto*. As conventional line probe-based commercial kits cannot discriminate the species, a considerable proportion of isolates identified as *M. kansasii* may actually belong to different species with significantly different clinical implications [15]. Even sequencing-based methods cannot detect new species unless at least one discriminatory target, such as *hsp65* and *rpoB*, is incorporated in the test.

Most reports on *M. kansasii* subtype 1, *sensu stricto*, being the most pathogenic subtype are based on its detection frequency in clinically relevant populations [4, 10, 12, 13]. However, a recent report indicated that a specific genetic element, the *espACD* operon, is the main source of pathogenicity of this subtype [13]. We did not find a difference in the detection frequency of isolates that met the criteria for NTM-PD between Groups 1 and 2. However, other results suggested that subtype 1 isolates are more pathogenic than other subtypes. The significantly lower values of pulmonary function test parameters and FVC in Group 1 further support the higher pathogenicity of subtype 1, considering that lung destruction can decrease the FVC. Distinct radiographic findings were obtained for the two groups: Group 1 showed a higher frequency of fibrocavitary lesions, and Group 2 showed a higher frequency of non-cavitary nodular bronchiectatic lesions. These results support the assumption that the disease caused by subtype 1 is more aggressive.

Only a few studies have examined the drug susceptibility of *M. kansasii* subtypes [11, 12, 14]. The CLSI recommends susceptibility testing of clarithromycin and rifampin as first-line treatment, and isoniazid, ethambutol, streptomycin, amikacin, cotrimoxazole, moxifloxacin, linezolid, ciprofloxacin, and others as second-line treatment, because *M. kansasii* isolates are generally susceptible to these drugs [12]. Indeed, all isolates included in this study were susceptible to amikacin, clarithromycin, linezolid, and moxifloxacin. In contrast to the present study, a previous study found that the drug resistance frequency was consistently higher for subtype 1 isolates and attributed this result to the selection pressure due to higher exposure to drugs owing to a high frequency of treatment [14].

Our study had some limitations. First, the utilization of only two target regions, the 16S rRNA gene and *rpoB*, would not have provided enough information for distinguishing all *M. kansasii* subtypes. No single target could accurately distinguish all *M. kansasii* subtypes, requiring whole genome sequence-based approach for reliable subtyping [4]. It is possible that we have missed rarer subtypes of *M. kansasii* due to the limitation of the target regions used. Second, the number of isolates was limited, especially for non-subtype 1 *M. kansasii* isolates. We included only 2 subtype 3 *M. kansasii* isolates and 1 subtype 6 *M. kansasii* isolate. The adoption of laboratory methods capable of distinguishing these subtypes can provide more data.

In conclusion, approximately one-fifth of the isolates identified as *M. kansasii* were newly designated species derived from *M. kansasii* but with lower pathogenicity. Non-subtype 1 *M. kansasii* species should be identified by routine testing in clinical laboratories to select appropriate treatment strategies.

AUTHOR CONTRIBUTIONS

Kim YG identified patients with *M. kansasii* isolation, performed subtyping and drafted the manuscript. Lee HY and Kwak N reviewed medical records of included patients. Park JH and Kim TS interpreted the data and performed the statistical analysis. Kim MJ and Lee JS contributed to the revision of the manuscript. Park SS, Yim JJ, and Seong MW supervised the study and performed the final revision of the manuscript.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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None declared.

ORCID

Young-gon Kim	https://orcid.org/0000-0001-6840-6830
Hong Yeul Lee	https://orcid.org/0000-0002-3638-8890
Nakwon Kwak	https://orcid.org/0000-0002-1897-946X
Jae Hyeon Park	https://orcid.org/0000-0003-0261-2185
Taek Soo Kim	https://orcid.org/0000-0002-2093-1721
Man Jin Kim	https://orcid.org/0000-0002-9345-6976
Jee-Soo Lee	https://orcid.org/0000-0002-7005-5686
Sung-Sup Park	https://orcid.org/0000-0003-3754-4848
Jae-Joon Yim	https://orcid.org/0000-0002-9605-0074
Moon-Woo Seong	https://orcid.org/0000-0003-2954-3677

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