

A Case of Mild Pulmonary Disease Due to *Mycobacterium shimoidei* with a Favorable Outcome

Nadia Galizzi,^a Enrico Tortoli,^b Andrea Gori,^a Fulvia Morini,^c Giuseppe Lapadula^a

Clinic of Infectious Diseases, San Gerardo Hospital, Monza, Italy^a; Emerging Bacterial Pathogens Unit, San Raffaele Scientific Institute, Milan, Italy^b; Division of Microbiology, San Gerardo Hospital, Monza, Italy^c

We describe a case of mild *Mycobacterium shimoidei* disease with a favorable course after treatment. Characteristics of nine *M. shimoidei* isolates in Italy between 1989 and 2009 were also reviewed. The *M. shimoidei* genome was highly conserved. Based on antimicrobial susceptibility, the combination of ethambutol, clarithromycin, and rifabutin appears to be a reasonable treatment.

CASE REPORT

We report on a case of pulmonary infection by *Mycobacterium shimoidei* in a 53-year-old woman from Monza, Italy, who was HIV negative and otherwise healthy, with a history of tuberculosis without sequelae in her childhood (more than 40 years earlier).

Since 1996, the patient had reported chronic cough and after an episode of hemoptysis in 1999, pulmonary high-resolution computed tomography revealed bronchiectasis with right middle lobe and lingula involvement. Since then, she reported persistent cough and recurrent bronchitis, treated with standard antibiotic treatment.

At the end of 2008, the patient presented recurrent episodes of sore throat, dry cough, and dyspnea upon exertion. For these symptoms, different antibiotic therapies were administered without success. In February 2009, a new lung computed tomography showed bronchiectasis, cystic bronchiolectasis, and peribronchial consolidations, with a tree-in-bud aspect. One bronchoalveolar lavage specimen was positive using auramine-rodamine staining (2 to 18 bacilli per 50 fields). Liquid culture grew in 28 days using Bactec MGIT 960 mycobacterial detection system (Becton, Dickinson), while Lowenstein-Jensen cultures remained negative after 60 days of incubation. The mycobacterium was subsequently identified as *M. shimoidei* by the combination of the two molecular DNA-probe GenoType *Mycobacterium* systems, CM and AS (Hain Lifescience), since it hybridized with the specific *M. shimoidei* probe included in GenoType AS. The identification was later confirmed by genome sequencing of 4 different genomic regions.

The isolate was not considered clinically significant, and no treatment was administered. Two months later, a new lung computed tomography showed an increase in the sizes and numbers of micronodular lesions and accentuation of the tree-in-bud aspect. A new bronchoalveolar lavage specimen was strongly positive (4 to 36 bacilli per field), and *M. shimoidei* grew in both solid (18 days) and liquid (14 days) cultures. Pending the results of drug susceptibility testing (DST), treatment with ethambutol (1,200 mg once daily), amikacin (1,000 mg three times weekly), rifabutin (300 mg once daily), and clarithromycin (500 mg twice daily) was prescribed. One month later, DST showed resistance to rifampin and ciprofloxacin. DST results, along with MICs, are shown in Table 1. Rifabutin was subsequently discontinued due to intolerance, whereas amikacin was continued up to month 3 of treatment. After 3 months, regression of symptoms, radiological im-

provement, sputum negativization, and bronchoalveolar lavage culture conversion were obtained. The therapy with clarithromycin and ethambutol was prolonged up to 18 months of treatment. The patient was followed for 1 year after treatment completion. Smears and sputum cultures remained negative, and no symptom relapsed.

On the occasion of the present finding, eight additional strains of *M. shimoidei* previously isolated in Italy were retrieved. All had been grown from respiratory specimens: one in Cortona (1991) (1), one in Varese (1995), three in Florence (1996, 1998, and 2001), one in Perugia (2001), one in Milan (2006), and one in Modena (2008). Four genetic regions (16S rRNA, the *hsp65* and *rpoB* genes, and internal transcribed spacer 1 [ITS1]) were sequenced in the nine strains. The nine strains presented identical sequences in 16S rRNA and ITS1; they were 100% identical to the sequences of the type strain of *M. shimoidei* present in GenBank. In the *rpoB* gene, the sequence was identical in eight strains, while it differed by 2 nucleotides in the Modena strain (one transversion from cytosine to adenine and one transition from guanine to adenine—both silent mutations), resulting in a similarity of 99.7%. No complete sequence of such a region was present in GenBank for *M. shimoidei*, and it was deposited by us in GenBank. The sequence data confirmed that all of the strains mentioned above belong to the species *M. shimoidei*.

For all of the strains, the antimicrobial susceptibility to a large panel of drugs potentially active against slowly growing mycobacteria (2) was tested by MIC determination. Linezolid, rifabutin, ethambutol, and clarithromycin revealed *in vitro* activities against the large majority of the strains. Clarithromycin and ethambutol were successfully used in the present case (Table 1).

Mycobacterium shimoidei was described for the first time from a respiratory infection in a Japanese patient in 1975 by Tsukamura, Shimoide, and Schaefer (3, 4). This species has been isolated

Received 9 May 2013 Returned for modification 30 May 2013

Accepted 29 July 2013

Published ahead of print 7 August 2013

Address correspondence to Giuseppe Lapadula, g.lapadula@hsgerardo.org.

Copyright © 2013, American Society for Microbiology. All Rights Reserved.

doi:10.1128/JCM.01028-13

TABLE 1 Results of drug susceptibility testing of 9 strains of *M. shimoidei* isolated in Italy between 1989 and 2009

Antibiotic	MIC ($\mu\text{g/ml}$) for isolate from ^a :							
	Cortona, 1989	Varese, 1995	Florence		Perugia, 2001	Milan, 2006	Modena, 2008	Monza, 2009 ^b
			1998	2001				
Ciprofloxacin	0.25 (S)	<0.12 (S)	0.25 (S)	4 (R)	0.25 (S)	0.25 (S)	2 (S)	4 (R)
Gatifloxacin	0.25	0.12	0.25	ND	0.12	0.25	ND	4
Moxifloxacin	0.5 (S)	0.25 (S)	1 (S)	<0.12 (S)	1 (S)	1 (S)	<0.12 (S)	2 (S)
Linezolid	<0.5 (S)	<0.5 (S)	<0.5 (S)	32 (R)	1 (S)	1 (S)	2 (S)	4 (S)
Rifampin	4 (R)	1 (S)	2 (R)	4 (R)	8 (R)	0.25 (S)	4 (R)	8 (R)
Rifabutin	0.12 (S)	0.25 (S)	0.12 (S)	0.5 (S)	0.25 (S)	0.25 (S)	0.5 (S)	0.5 (S)
Sulfamethoxazole	2.5 (S)	2.5 (S)	2.5 (S)	9.5 (S)	2.5 (S)	2.5 (S)	5 (S)	9.5 (S)
Minocycline	1	<0.5	1	16	1	1	16	32
Ethambutol	4 (S)	1 (S)	4 (S)	2 (S)	4 (S)	4 (S)	2 (S)	1 (S)
Clarithromycin	4 (S)	4 (S)	4 (S)	0.25 (S)	4 (S)	4 (S)	<0.06 (S)	0.5 (S)
Amikacin	>64 (R)	32 (S)	>64 (R)	2 (S)	>64 (R)	>64 (R)	<1 (S)	2 (S)
Streptomycin	4	2	4	16	8	8	16	4

^a Drug susceptibility testing was performed by the broth microdilution method. Inocula were prepared from solid culture, colonies were resuspended in sterile distilled water, and turbidity was adjusted to a 0.5 McFarland standard. The interpretation of MICs is based on cutoffs suggested by CLSI for *Mycobacterium kansasii* and miscellaneous slowly growing nontubercular mycobacteria (2). In parentheses is shown resistance (R) or susceptibility (S). ND, not determined.

^b This study.

only from the human respiratory tract: no environmental source has been detected, and no human-to-human spread has been reported (3, 5). Like other nontuberculous mycobacteria, *M. shimoidei* is an opportunistic pathogen, and it has been previously isolated only among subjects with preexisting lung diseases (emphysema, previous tuberculosis, silicosis, or lung carcinoma) (1, 5–8) or who are severely immunocompromised (9). The large majority of cases were found in males on average 60 years old (1, 3, 5, 6). The clinical presentation of *M. shimoidei* disease is similar to tuberculosis; the symptoms include productive cough (6, 7, 10), hemoptysis (7), fever (8), weight loss (5–7), and night sweats (6), while the thorax X-ray usually presents cavitations (1, 3, 5–8). Although a number of cases of *M. shimoidei* infection have been reported worldwide (1, 3–10), the disease is rare.

Our case differs from the others reported in the literature because *M. shimoidei* was isolated from a paucisymptomatic woman without pulmonary cavitations and with no preexisting severe systemic disease or immunodepression.

Moreover, the favorable course of our case suggests that *M. shimoidei* infection is not necessarily associated with a severe prognosis. The high mortality previously reported is likely to have been driven by underlying disease, such as neoplasms, severe chronic lung disease, or other infective complications due to immunodepression (5). Moreover, an impact of late recognition of *M. shimoidei* disease or its improper treatment could also have negatively influenced the outcome of the previously reported cases.

In our case, diagnosis was obtained relatively early and empirical treatment was initiated and later adjusted, based on DST results. Susceptibility testing is generally not recommended for slowly growing mycobacteria, and usually the treatment is driven by guidelines. However, due to the rarity of isolation, no guidelines are available for *M. shimoidei*. Based on the antimicrobial susceptibility of the Italian strains, it seems that the treatment that is more likely to be effective against *M. shimoidei* is the combination of ethambutol, clarithromycin, and rifabutin. Nonetheless, DST could be useful in some cases, to adjust empirical treatment.

Nucleotide sequence accession number. The complete sequence of the *rpoB* gene for the *M. shimoidei* isolate in this study has been deposited by us in GenBank under accession no. [HM807416](https://www.ncbi.nlm.nih.gov/nucl/15807416).

ACKNOWLEDGMENT

This work has partially been funded by TB PAN-NET (www.tbpannet.org), which is sponsored by the European Commission's Seventh Framework Programme for Research (FP7-HEALTH-2007-B), project reference no. 223681.

REFERENCES

- Tortoli E, Simonetti MT. 1991. Isolation of *Mycobacterium shimoidei* from a patient with cavitary pulmonary disease. *J. Clin. Microbiol.* 29:1754–1756.
- CLSI. 2011. Susceptibility testing of mycobacteria, nocardiae and other aerobic actinomycetes: approved standard, 2nd ed. M24-A2. CLSI, Wayne, PA.
- Tsukamura M, Shimoide H, Schaefer WB. 1975. A possible pathogen of group III mycobacteria. *J. Gen. Microbiol.* 88:377–380.
- Tsukamura M. 1982. *Mycobacterium shimoidei* sp. nov., nom. rev., a lung pathogen. *Int. J. Syst. Bacteriol.* 32:67–69.
- Mayall B, Gurtler V, Irving L, Marzec A, Leslie D. 1999. Identification of *Mycobacterium shimoidei* by molecular techniques: case report and summary of the literature. *Int. J. Tuberc. Lung Dis.* 3:169–173.
- Goudge RJ, Mayall BC, Leslie DE, Holmes PW, Robinson SL. 1998. An Australian isolate of *Mycobacterium shimoidei*. *Pathology* 30:399–401.
- Auregan G, Ramarosan F, Génin C, Lévy-Frèbault V. 1997. A case of *Mycobacterium shimoidei* lung infection in Madagascar. *Bull. Soc. Pathol. Exot.* 90:75–77.
- Heller R, Jaulhac B, Charles P, De Briel D, Vincent V, Bohner C, Piémont Y, Monteil H. 1996. Identification of *Mycobacterium shimoidei* in a tuberculosis-like cavity by 16S ribosomal DNA direct sequencing. *Eur. J. Clin. Microbiol. Infect. Dis.* 15:172–175.
- Furrer H, Bodmer T, von Overbeck J. 1994. Disseminated nontuberculous mycobacteriosis in AIDS patients. *Schweiz. Med. Wochenschr.* 124:89–96. (In German.)
- Koukila-Kähkölä P, Paulin L, Brander E, Jantzen E, Eho-Remes M, Katila ML. 2000. Characterisation of a new isolate of *Mycobacterium shimoidei* from Finland. *J. Med. Microbiol.* 49:937–940.