Prosthetic Joint Infection Caused by Mycobacterium alvei in an Elderly Patient

Chen-Hsiang Lee,1,2 Huey-Ling You,3 Jun-Wen Wang,4 Ya-Fen Tang,3 and Jien-Wei Liu1,2,*

Division of Infectious Diseases, Department of Internal Medicine,1 Nosocomial Infection Control Team,2 Department of Clinical Pathology,3 and Department of Orthopedic Surgery,4 Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

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We report the first case of prosthetic joint infection caused by Mycobacterium alvei, which was identified by PCR-restriction fragment length polymorphism and verified by analysis of nucleotide sequences of its amplified 16S ribosomal DNA. The pathogen was susceptible to linezolid, amikacin, ciprofloxacin, tigecycline, and trimethoprim-sulfamethoxazole. The clinical implications are discussed.

CASE REPORT

A 75-year-old woman received hemiarthroplasty and underwent bipolar endoprosthesis replacement for osteoarthritis involving her left knee. She had received numerous intra-articular injections of steroids for pain relief over her left knee before this procedure. Pain, redness, and swelling began insidiously developing over her left knee 2 months after the arthroplastic surgery. Laboratory tests disclosed an elevated erythrocyte sedimentation rate (ESR, 125 mm/h [normal is <20 mm/h]). Her chest radiograph was normal. During left-knee arthroscopic surgery, prosthetic implant loosening with extensive periprosthetic tissue necrosis was found. Analysis of synovial fluid revealed a leukocyte count of 10,424 cells/μl with 75% polymorphonuclear cells. Synovial fluid was negative for Gram staining and for aerobic and anaerobic bacterial cultures. The histopathology of the excised synovial tissue suggested acute and chronic inflammation. Resection arthroplasty was performed, and antibiotic-loaded cement beads (vancomycin, piperacillin, and amikacin in polymethylmethacrylate [PMMA]) were implanted. The patient then received intravenous teicoplanin injection for 4 weeks, followed by oral fusidic acid and rifampin for maintenance therapy, because methicillin-resistant Staphylococcus aureus was assumed to be the most likely culprit pathogen for her prosthetic joint infection (PJI).

Three months later, her PJI did not improve clinically, and her ESR was 151 mm/h, suggesting an intractable infection. A computed tomography scan revealed an edematous change in the muscular structure around the left knee and a loculated abscess located medial to the tibialis posterior. A pocket with yellowish necrotic tissue-like content in the soft tissue near the abscess located medial to the tibialis posterior. The histopathology of the excised synovial tissue disclosed granulomatous inflammation with the presence of multinucleated giant cells. Both acid-fast staining and Gram staining were negative. Culture of the excised synovium by spreading it on 5% sheep blood agar for 48 h of incubation turned out to be negative. Spreading of the excised synovium on egg-based Lowenstein-Jensen slants (bioMérieux, La Balme-les-Grottes, France) incubated at 37°C with 10% CO₂ developed scanty, buff-colored, rough colonies 2 weeks later. Microscopic examinations revealed short Gram-positive bacilli and acid-fast bacilli that formed clumps. Conventional biochemical reactions revealed a negative niacin test result and a positive nitrate reductase test result, suggesting that the acid-fast bacilli were nontuberculous mycobacteria. Identification of the isolated acid-fast bacilli started with PCR-restriction fragment length polymorphism (RFLP) using oligonucleotide primers MOTT-11 and MOTT-12 (5'-ACCAACGATGGTGTGTCCCAT-3' and 5'-CTTGGTCGAACCGCATACCCCT-3') for amplification of the 439-bp fragment of the hsp65 gene (12), followed by sequential digestions of PCR products each using restriction enzymes BstEII, HhaI, and HaeIII. The digested PCR products were then separately analyzed by agarose gel electrophoresis, which showed RFLP patterns similar to those of Mycobacterium alvei (3). To verify the identification, the partial 16S rRNA gene was amplified by PCR using universal forward primer 27F (5'-AGAGTTTGATCCTGGCTCAG-3') and universal reverse primer 907R (5'-CGTCAATTCCCTTGAGTTT-3') (16). Two PCR products, each with nucleotides 881 and 860, were sequenced with a 310 Genetic Analyzer (ABI Prism) and were compared to those searched from the GenBank database (http://blast.ncbi.nlm.nih.gov/BLAST.cgi). The two DNA samples were found to be a 100% match with the sequence of M. alvei. The growth of our isolate was in agreement with a previous publication reporting that, when cultured with Lowenstein-Jensen medium, M. alvei grew between 10 and 15 days at 37°C; M. alvei may grow within 5 days at 30°C (1). Antimicrobial susceptibilities were determined using the broth microdilution method, and the antibiotics included in the tests were as follows: amikacin, cefotixin, imipenem, ciprofloxacin, trimethoprim-sulfamethoxazole (all purchased from Sigma, St. Louis, MO), clarithromycin (Abbott, Abbott Park, IL.), linezolid, and tigecycline (Pfizer, New York, NY). Interceptions of susceptibility to the tested antibiotics, except for tigecycline and linezolid, were according to NCCLS/CLSI criteria.

* Corresponding author. Mailing address: Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, 123 Ta Pei Road, Niao Sung District, Kaohsiung 833, Taiwan. Phone: 886-7-7317123, ext. 8800. Fax: 886-7-7322402. E-mail: 88b0@adm.cgmh.org.tw.

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TABLE 1. Results of antibiotic susceptibility testing against the *Mycobacterium alvei* isolate

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptible (µg/ml)*</th>
<th>Intermediate</th>
<th>Resistant (µg/ml)</th>
<th>MIC (µg/ml) against <em>M. alvei</em> isolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≥16</td>
<td>32</td>
<td>≥64</td>
<td>1</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>≥16</td>
<td>32–64</td>
<td>≥128</td>
<td>32</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤4</td>
<td>8</td>
<td>≥16</td>
<td>8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
<td>8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
<td>0.5</td>
</tr>
<tr>
<td>Trimethoprim-</td>
<td>≤32</td>
<td></td>
<td>≥64</td>
<td>1</td>
</tr>
<tr>
<td>sulfoxamethoxazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>≥8</td>
<td></td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>≤4</td>
<td></td>
<td>&lt;0.03</td>
<td></td>
</tr>
</tbody>
</table>

* Susceptibility breakpoints are those recommended in NCCLS document M2-A (11) except for linezolid and tigecycline, for which the breakpoints are those proposed by Wallace et al. (14, 15).

(11). The breakpoints of linezolid and tigecycline for rapidly growing mycobacteria (RGM) have not yet been addressed by the CLSI. However, these two antimicrobial agents were recognized as active against some RGM isolates (6). The breakpoints used for linezolid and tigecycline susceptibility were those proposed by Wallace et al. (14, 15). The susceptibility testing disclosed that the *M. alvei* isolate was susceptible to amikacin, ciprofloxacin, trimethoprim-sulfamethoxazole, linezolid, and tigecycline but not to cefoxitin, imipenem, and clarithromycin (Table 1).

The patient received intravenous therapy with tigecycline and amikacin for 4 weeks, followed by oral ciprofloxacin and trimethoprim-sulfamethoxazole for the subsequent 6 months. Her ESR value was 24 mm/h on completion of the antibiotic therapy. Endoprostheses replacement for her left knee was performed, and it remained uneventful when the patient was last seen 6 months later.

*M. alvei*, an RGM, was first isolated from water, soil, and human sputum in 1992 (1). Being ubiquitously distributed in environmental sources, *M. alvei* may occasionally be found in respiratory secretions of humans as a colonizer. To our knowledge, only one patient with a lung infection (1) and a cat with pyogranulomatous panniculitis (2) caused by *M. alvei* but not *M. fortuitum* and *M. abscessus*, and *M. smegmatis* have been reported thus far. RGM isolates that have been reported in previous reports and ours suggest that tigecycline and linezolid but not to cefoxitin, imipenem, and clarithromycin (12).

Despite being able to grow on a blood agar, it usually takes 5 days for an RGM to develop visible colonies (5), and the culture agar plates are often discarded before that based on the standard procedures adopted by most clinical laboratories. Characteristically, the histopathology of the RGM-affected synovial tissue sampled at exploratory surgery reveals granulomatous inflammation with or without the presence of multinucleated giant cells (10), which is unfortunately not *Mycobacterium* species specific. Under these circumstances, clinicians usually empirically start antituberculosis therapy, as tuberculosis is more prevalent than infections caused by other *Mycobacterium* spp in some settings. The commonly used antituberculosis drugs, such as isoniazid, ethambutol, and rifampin, are unfortunately more often than not inactive against RGM. A high index of suspicion for RGM infections is therefore extremely important. Previous reports (9, 10) and ours suggest that patients with a history of localized trauma or intra-articular injection of steroids, regardless of their immunity status, are at high risk for septic arthritis due to RGM.

Once an RGM is isolated, laboratory staff may differentiate *M. alvei* from *M. fortuitum* and *M. chelonae* by the microbe’s failure to grow on MacConkey agar without crystal violet, as well as failure to degrade salicylate, and by its inability to grow in the presence of picric acid, ethambutol, kanamycin, capreomycin, and isoniazid (11). The identification of a mycobacterium to its species level and the availability of its antibiotic susceptibility profile are equally important, because antimicrobial therapy for PJI due to RGM should be guided by the microbe’s susceptibility profile as a result of the possible interspecies variability in antimicrobial susceptibility among mycobacteria (6, 7). Reported information about in vitro antimicrobial activities against *M. alvei* has been very limited thus far (6), and there is insufficient clinical and laboratory information in the published literature to make recommendations on how to treat infections caused by such a pathogen. However, the favorable MICs against RGM isolates (6, 14, 15) in previous reports and ours suggest that tigecycline and linezolid are potentially therapeutically useful for infections due to *M. alvei*. Further accumulation of reports on experiences with *M. alvei* infections is needed to help map out a recommended therapeutic strategy.

REFERENCES


