Septic Arthritis Caused by *Mycobacterium fortuitum* and *Mycobacterium abscessus* in a Prosthetic Knee Joint: Case Report and Review of Literature

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**Abstract**

Nontuberculous mycobacterium (NTM) is an infrequent cause of prosthetic knee joint infections. Simultaneous infection with different NTM species in a prosthetic knee joint has not been previously reported. A case of prosthetic knee joint infection caused by *Mycobacterium abscessus* and *M. fortuitum* is described in this report. The patient was successfully treated with adequate antibiotics and surgery. The clinical features of sixteen previously reported cases of prosthetic knee joint infection caused by NTM are reviewed.

**Key words:** septic arthritis, nontuberculous mycobacteria, *Mycobacterium fortuitum*, *Mycobacterium abscessus*

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**Introduction**

Over 150 nontuberculous mycobacteria (NTM) species have been described, one-third of which have demonstrated clinical significance. Compared with *Mycobacterium tuberculosis*, NTM has lower virulence and lacks human-to-human transmission. However, NTM exist in some important sources for nosocomial infections, including povidone iodine, saline, various injectable medications, hemodialysis systems, continuous ambulatory peritoneal dialysis systems, and cooling solutions for cardioplegia (1). Though epidemics and outbreaks are reported, the majority of cases occur sporadically.

The use of prosthetic joints has increased gradually for the purpose of improving the mobility of individuals with degenerative joints (2, 3). Infections may complicate 1%-5% of prosthetic joints and *Staphylococcus* is the most common agent of prosthetic joint infection (3, 4). NTM is an infrequent cause of prosthetic joint infections. *M. fortuitum* and *M. abscessus* belong to a group of organisms known as rapidly growing *Mycobacteria* (RGM), equivalent to Runyon group IV in the classification scheme of NTM. To our knowledge, simultaneous infection of two *Mycobacterium* species in a prosthetic knee joint has not been previously reported. This is the first reported case of a prosthetic knee joint infection caused by *M. abscessus* and *M. fortuitum*. The patient was treated successfully by resection of arthroplasty, prolonged usage of effective antibiotics, and reimplantation. This article reports this clinical experience and a review of the literature on NTM prosthetic knee joint infection.

**Case Report**

A 72-year-old woman was admitted due to painful swelling of her right knee for one month. She was a farmer and had right knee pain for several years, especially when walking. She was diagnosed with osteoarthritis in a local clinic and started to take 75 mg of oral diclofenac sodium for re-
On admission, the plain film showed soft tissue swelling of her right knee (a). During her hospitalization, right knee prosthesis was removed and a spacer was inserted (b). Histopathologic examination of the excisional synovium demonstrated granuloma formation with multinucleated giant cells (c, d).

Lievig had painful swelling of her right knee one year prior to this admission. However, her knee pain progressed and could not be relieved by oral analgesics 7 months previously. She received intra-articular dexamethasone injection and her knee pain subsided temporally. During a two-month period, she received three injections of intra-articular dexamethasone. However, the effect of this treatment diminished gradually. Five months prior to this admission, she received right total knee replacement at a regional hospital. After surgery, she could walk as usual without knee pain. Unfortunately, she had painful swelling of her right knee one month prior to this admission. The pain gradually became aggravated rendering her unable to walk. She took diclofenac and tramadol but her symptoms still progressed.

At the time we met the patient, she was febrile with painful swelling of her right knee. Laboratory tests upon admission disclosed mild normocytic anemia (hemoglobin, 11.5 g/dL), a normal leukocyte count (9,020/mL), and a platelet count of 114,000/μL. The serum C-reactive protein level was 13.38 mg/L and an erythrocyte sedimentation rate (ESR) was 96 mm/h. Results of other routine laboratory tests were within normal limits. A chest film was normal. The plain film showed soft tissue swelling of right knee without destruction of bone or loosening of prosthesis (Fig. 1). The physician performed arthrocentesis and obtained mucoid orange synovial fluid with polymorphonuclear leukocytes predominance. The results of Gram and acid-fast stains of synovial fluid were negative. Aerobic and anaerobic bacterial cultures were sterile. She received 2 g intravenous oxacillin every 6 hours and 80 mg gentamicin every 8 hours after admission. However, her symptoms persisted. Removal of prosthesis and synovectomy were done with insertion of a spacer on the 5th day after admission (Fig. 1). At the operation, turbid pus was noted and collected for culture. Histopathologic examination of synovium evidenced marked infiltration of lymphocytes, epithelioid cells, and multinucleated giant cells, compatible with granuloma formation (Fig. 1). Neither periodic acid-Schiff nor acid-fast staining micro-organisms were documented in the tissue sample.

On the 11th day after admission, the mycobacterial culture of synovial fluid collected at admission yielded NTM. Empirical therapy was changed to 1,000 mg intravenous cefoxitin every 8 hours, 500 mg intravenous amikacin every day, and 500 mg oral clarithromycin every 12 hours. Her joint swelling subsided gradually. On the 14th day after admission, the mycobacterial culture of synovial fluid collected at the operation yielded NTM. However, the NTM isolates collected at different times were finally identified as different NTM species according to conventional methods, the former as *M. abscessus* and the later as *M. fortuitum*. Colonies of *M. abscessus* and *M. fortuitum* were inoculated respectively into the PCR amplification mixtures. 16s rRNA genes were amplified and sequenced. The sequence results were analyzed by BLASTn (Basic Local Alignment Search Tool) and respectively compatible with the 16sRNA gene of *M. chelonae/abscessus* complex and *M. fortuitum* complex. The susceptibility tests of *M. abscessus* isolate revealed a
minimum inhibitory concentration of 0.25 μg/mL for ciprofloxacin, 0.5 μg/mL for amikacin, >128 μg/mL for cefoxitin, >8 μg/mL for clarithromycin, and >16 μg/mL for doxycycline. The susceptibility test of M. fortuitum revealed a minimum inhibitory concentration of 1 μg/mL for amikacin, 0.5 μg/mL for clarithromycin, 0.5 μg/mL for doxycycline, >128 μg/mL for cefoxitin, >4 μg/mL for ciprofloxacin, and >16 μg/mL for imipenem.

Based on final susceptibility, her antibiotics were changed to 100 mg oral doxycycline every 12 hours, 400 mg oral ciprofloxacin every 12 hours and 500 mg oral clarithromycin every 12 hours. Four months after the initiation of treatment, the serum ESR returned to 6 mm/h from 96 mm/h. She received implantation of a prosthetic joint. In addition to doxycycline, ciprofloxacin, and clarithromycin, she received 500 mg intramuscular amikacin from one month prior to the surgery to one month post-surgery. After implantation of the prosthetic joint, we traced her serum ESR every month. She continued taking doxycycline, ciprofloxacin and clarithromycin till 5 months post-surgery due to two consecutive normal results of her serum ESR. She remained symptom-free at the 10-month follow-up examination.

Discussion

Arriving at the diagnosis of a prosthetic joint infection caused by NTM requires a high index of suspicion. Acid-fast stains are often negative. Most clinical laboratories discard routine culture media after 48-72 hours. Thus the organism is not typically detected in routine bacterial culture. Specific mycobacterial cultures are required for prosthetic knee joint infection when routine bacterial culture does not yield pathogens.

Co-infection with different NTM species had not been reported in prosthetic knee joint infection. However, co-infection with NTM and M. tuberculosis had been reported in pulmonary infection or osteomyelitis (5, 6). In the present case, two kinds of NTM species were isolated from the same infectious site. However, the co-infection may be questioned because they were not isolated from the same sample. Although environmental contamination in the lab had been suspected, the possibility was very small. First, no other synovial or sterile samples yielded NTM at the same time in the lab. Second, both of the isolated NTM species do not belong to the species commonly considered as a contamination, like M. gordonae, M. mucogenicum, or M. terrae complex. In clinical practice, different Mycobacterium species are suspected in one sample by different morphologies of Mycobacterium species. The morphology of M. fortuitum colony is very similar to M. abscessus colony in solid culture medium, which causes the technical staff to miss different NTM species existing in the culture medium. When coinfection is not identified in NTM joint infection, therapeutic failure may occur due to different drug susceptibility. So, multiple samples could be considered for NTM culture to avoid the possibility of mis-identification.

Epidemiological investigations have identified soil, tap water, water-containing solutions, and ice as environmental reservoirs of RGM (1). Low oxygen concentrations as a consequence of reduced or intermittent water flow in households and microbial-driven oxygen consumption may not limit NTM growth (7). M. fortuitum has been isolated from the saliva of healthy persons (8). However, the source of NTM prosthetic knee joint infection is unclear. The most likely pathogenesis of infection is now considered either through minor trauma or the skin unnoticed by the patient or intraoperatively (1, 9-11). In the present case, the pathogenesis of NTM prosthetic knee joint infection is also considered as direct seeding from outer environment because it is impossible for different NTM species to seed simultaneously into a prosthetic joint through hematogenous spreading in immunocompetent patients. In addition, NTM can attach to the surfaces of a foreign body and permit their persistence in habitats due to the presence of a lipid-rich outer membrane (12, 13). This may explain why NTM prosthetic joint infection does not occur as an immediate postoperative complication (11). As such, we are not able to ascertain if seeding of NTM occurred before or during total knee replacement in the present patient.

Despite the high volume of arthroplasty procedures performed, very few cases of prosthetic knee joint NTM infections have occurred. A MEDLINE (National Library of Medicine) search of the literature for contemporary case reports of nontuberculous Mycobacterium prosthetic knee joint infection identified only 16 cases (including present case) (Table 1). There were 8 women and 8 men. The mean age was 65 years (range: 30-82 years). Except for the present case, the prosthetic knee joint infections in the other cases were caused by single Mycobacterium species (14-21). With the exception of one case infected with M. kansasi (18), the other cases were infected with rapid growing mycobacteria, including one M. smegmatis (20), one M. abscessus (20), four M. chelonae (19, 20), and eight M. fortuitum (14-17, 20, 21). Almost all cases were immunocompetent and had degenerative joint disease. The time from prosthesis implantation to the onset of symptoms varied. Of 14 cases of reported cure, 12 cases received resection of arthroplasty (14-17, 19, 20) and 2 cases retained the prosthesis (20).

NTM septic arthritis of knee joints still could occur in native joints of immunocompetent patients (22-25). However, most isolates in reported cases belonged to slowly growing Mycobacterium, not like the cases with prosthetic knee joint NTM infection. Early onset of prosthetic knee joint NTM infection is considered as a result of intraoperative contamination with Mycobacteria from tap water or tap water-derived fluids used during prosthesis implantation or in cleaning surgical instruments (20). Recently, a reported cluster of M. fortuitum prosthetic joint infections supported the theory of intraoperative contamination (21). Indeed, this epidemiologic association is well recognized in other RGM
# Table 1. Clinical Characteristics and Outcomes of Patients with Prosthetic Knee Joint Infection due to Nontuberculous Mycobacteria

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Pathogens</th>
<th>Predisposing factors</th>
<th>Time to onset of symptoms</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (PR)</td>
<td>72/F</td>
<td></td>
<td>M. fortuitum</td>
<td>1. Intra-articular steroid injection, 2. DJD</td>
<td>16 weeks</td>
<td>1. Resection of arthroplasty 2. DOX, CIP, and CLR × 3 months, then DOX, CIP, CLR × 1 month, then DOX, CIP, CLR × 5 months</td>
<td>No relapse under 10 months of follow-up</td>
</tr>
<tr>
<td>2. (14)</td>
<td>68/M</td>
<td></td>
<td>M. fortuitum</td>
<td>(No mention)</td>
<td>9 weeks</td>
<td>1. Resection of arthroplasty 2. AMK, DOX, CIP and CLR × 1 month, then DOX, CIP, CLR × 5 months</td>
<td>Reportedly cured</td>
</tr>
<tr>
<td>3. (15)</td>
<td>44/F</td>
<td></td>
<td>M. fortuitum</td>
<td>1. Renal insufficiency, 2. Peripheral vascular disease</td>
<td>4 weeks</td>
<td>1. Resection of arthroplasty 2. IPM, DOX, and AZT × 2 months, then DOX and AZM × 4 months 3. Revision total knee arthroplasty 4. Streptococcus agalactiae deep tissue infection 2 week later 5. Ceftazidime × 6 weeks, then Amoxicillin × 18 months</td>
<td>Reported cured</td>
</tr>
<tr>
<td>4. (16)</td>
<td>30/F</td>
<td></td>
<td>M. fortuitum</td>
<td>1. Juvenile rheumatoid arthritis, 2. Intra-articular steroid injection</td>
<td>2 weeks</td>
<td>1. AMK and CFX × 4 weeks, then resection of arthroplasty 2. AMK and CFX × 2 weeks, then DOX × 5 weeks 3. Revision total knee arthroplasty, then DOX and CFX × 2 weeks 4. Relapse of M. fortuitum septic arthritis, then DOX long-term suppression 5. S. aureus superinfection 1.5 years later, then resection of arthroplasty and joint fused with a Hoffman apparatus 6. CFX and AMK × 2 weeks, then CFX and DOX × 3 weeks</td>
<td>No relapse under 6 weeks of follow-up</td>
</tr>
<tr>
<td>5. (17)</td>
<td>62/F</td>
<td></td>
<td>M. fortuitum</td>
<td>DJD</td>
<td>2 weeks</td>
<td>1. Resection of arthroplasty and fusion of the knee 2. AMK, TCL, and INH × 4 weeks, then INH and TCL for several months</td>
<td>Reported cured</td>
</tr>
<tr>
<td>6. (18)</td>
<td>82/M</td>
<td></td>
<td>M. kansasi</td>
<td>(No mention)</td>
<td>288 weeks</td>
<td>1. EMB, RIF, CLR and OFL (ofloxacin) × 6 weeks, then resection of arthroplasty and arthrodesis 2. EMB, RIF, CLR and OFL (ofloxacin) × 1 year, then arthrodesis again due to nonunion of knee joint 3. EMB, RIF, CLR and OFL (ofloxacin) × 6 months</td>
<td>Unknown outcome</td>
</tr>
<tr>
<td>7. (19)</td>
<td>66/F</td>
<td></td>
<td>M. chelonae</td>
<td>(No mention)</td>
<td>6 weeks</td>
<td>1. Resection of arthroplasty, then CFX and AMK × 6 weeks, then TMP-SMX × 4 weeks 2. Revision total knee arthroplasty 18 weeks after resection, then CIP for long-term suppression</td>
<td>No relapse under 2 years of follow-up</td>
</tr>
<tr>
<td>8. (20)</td>
<td>74/F</td>
<td></td>
<td>M. chelonae</td>
<td>DJD</td>
<td>312 weeks</td>
<td>1. Resection of arthroplasty, then CLR × 16 weeks 2. Arthrodesis 4.5 months after REA</td>
<td>No relapse under 30 months of follow-up</td>
</tr>
<tr>
<td>9. (20)</td>
<td>78/M</td>
<td></td>
<td>M. chelonae</td>
<td>DJD</td>
<td>364 weeks</td>
<td>1. Resection of arthroplasty 2. CLR × 17 weeks, then CFX and CLR × 6 weeks 3. Arthrodesis, then CLR × 7 months</td>
<td>No relapse under 58 weeks of follow-up</td>
</tr>
<tr>
<td>10. (20)</td>
<td>60/M</td>
<td></td>
<td>M. rugosum</td>
<td>DJD</td>
<td>1 week</td>
<td>1. Resection of arthroplasty and two times of surgical debridement 2. DOX and AMK × 2 weeks, then CIP and TMP-SMX for 16 weeks, followed by MMP and CIP for 4 weeks 3. Revision of total knee arthroplasty 30 weeks after surgical intervention 4. CIP × 6 weeks</td>
<td>No relapse under 107 weeks of follow-up</td>
</tr>
<tr>
<td>11. (20)</td>
<td>76/M</td>
<td></td>
<td>M. fortuitum</td>
<td>DJD</td>
<td>368 weeks</td>
<td>1. Debridement and retained prosthesis 2. Mox, TMP-SMX, and AZM for long-term suppression</td>
<td>No relapse under 24 weeks of follow-up</td>
</tr>
<tr>
<td>12. (20)</td>
<td>66/F</td>
<td></td>
<td>M. fortuitum</td>
<td>DJD</td>
<td>13 weeks</td>
<td>1. Debridement and retained prosthesis 2. LEV and TMP-SMX for long-term suppression</td>
<td>No relapse under 189 weeks of follow-up</td>
</tr>
<tr>
<td>13. (20)</td>
<td>69/M</td>
<td></td>
<td>M. chelonae</td>
<td>DJD</td>
<td>125 weeks</td>
<td>1. CLR and DOX × 23.3 weeks, then TMP-SMX × 3 weeks 2. Resection of arthroplasty, then CLR and DOX for 14.7 weeks 3. Revision of total knee arthroplasty, then CLR and Mox for long-term suppression</td>
<td>No relapse under 23 weeks of follow-up</td>
</tr>
<tr>
<td>14. (20)</td>
<td>71/F</td>
<td></td>
<td>M. abscessus</td>
<td>Rheumatoid arthritis</td>
<td>652 weeks</td>
<td>1. Resection of arthroplasty 2. CFX and CLR × 2 weeks and palliative care</td>
<td>Unknown outcome</td>
</tr>
<tr>
<td>15. (21)</td>
<td>70/M</td>
<td></td>
<td>M. fortuitum</td>
<td>DJD</td>
<td>2 weeks</td>
<td>1. Debridement, then Clarithromycin, ciprofloxacin, and doxycycline × 10 weeks 2. Resection of arthroplasty, then Clarithromycin, ciprofloxacin, and doxycycline × 90 days 3. Revision of total knee arthroplasty</td>
<td>No relapse under 7 months of follow-up</td>
</tr>
<tr>
<td>16. (21)</td>
<td>60/M</td>
<td></td>
<td>M. fortuitum</td>
<td>DJD</td>
<td>5 weeks</td>
<td>1. Debridement and resection of arthroplasty, then Cefoxitin and doxycycline 2. Repeated debridement, then Clarithromycin, doxycycline, and ciprofloxacin × 4 months 3. Revision of total knee arthroplasty</td>
<td>No relapse under 2 months of follow-up</td>
</tr>
</tbody>
</table>

Abbreviation: AMK, amikacin; AZM, azithromycin; CFX, cefoxitin; CIP, ciprofloxacin; CLR, clarithromycin; DJD, degenerative joint disease; DOX, doxycycline; EMB, ethambutol; GAT, gatifloxacin; IMP, imipenem; INH, isoniazid; LEV, levofloxacin; MOX, moxifloxacin; MMP, meropenem; RIF, rifampin; TCL, tetracycline; TMP-SMX, trimethoprim-sulfamethoxazole.
syndromes, most notably with surgical site infections that occur after augmentation mammoplasty or median sternotomy (26). Therefore, it is recommended that tap water and tap water-derived fluids should be avoided in the operating room and for the cleaning of medical and surgical instruments (27). However, intraoperative contamination could not explain the late onset of prosthetic knee joint NTM infection (18, 20). According to the immune status of these patients, direct inoculation of NTM during postoperative period is the most possible way for prosthetic knee joint infection. In the present case, no environmental source was confirmed to be associated with this NTM infection. Either intra-articular steroid injection or intraoperative contamination may be the possible means for inoculation of NTM into her knee joint.

The choice of antibiotics therapy to treat prosthetic knee joint infection caused by NTM should be guided by antimicrobial susceptibility testing, because there is inter- and intraspecies variability in antimicrobial susceptibility patterns (27). According to these reported cases, empirical antibiotics should cover RGM, especially *M. fortuitum* before identification results of NTM. Prolonged antibiotics treatment is necessary for complete remission of NTM infection before re-implantation but the optimal duration of antibiotic therapy is unknown. Due to variable severity of infection, it may be more suitable to use an inflammation marker to guide the duration of antibiotic therapy. In the present case, ESR was used to guide the antibiotic therapy and it seems to be a suitable marker to determine the timing for re-implantation.

In our review, most of the patients who underwent re-implantation of infected prosthesis were cured of infection and did not experience relapse after they completed antibiotic therapy. Although two cases were cured without removal of the prosthesis, they needed long-term antibiotics suppression to keep them free of symptoms. The failure to clear infection without removal of the infected hardware could be associated with the ability of *Mycobacteria* to form architecturally complex mature biofilm (28-30). If resection is not feasible, it is possible to successfully suppress these infections, as long as a safe, effective, and preferably orally administered regimen is available.

In conclusion, NTM should be considered in the list of possible pathogens for prosthetic knee joint infection. Co-infection with two kinds of RGB is possible. Special mycobacterial culture is required for diagnosis and repeated culture may be done to rule out co-infection with other NTM species for unfavorable treatment course. Removal of prosthesis and prolonged adequate antibiotics treatment before re-implantation of prosthesis are the key points for therapy of NTM prosthetic knee joint infection.

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References


