Early Onset Prosthetic Knee Joint Infection by Mycobacterium Fortuitum: A Case Report and Literature Review

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Prosthetic joint infection (PJI) is a devastating complication following total knee arthroplasty (TKA). Non-tuberculous mycobacteria (NTM) are considered a very rare cause of knee prosthetic joint infection with only a few of such cases reported in the literatures. Mycobacterium fortuitum is one of the NTM defined as rapidly growing mycobacteria (RGM).

In this case report, we present an infected TKA case by M. fortuitum with an early onset of symptoms only 3 weeks from the index operation. Although the literature suggests two-stage exchange arthroplasty for surgical treatment in this group of patients, we could successfully treat this patient with debridement and prosthetic retention with the proper prolonged course of antibiotics. At 6-month follow-up, the patient revealed excellent functional outcomes with no signs of recurrent infection detected.

Keywords: *Knee arthroplasty, Non-tuberculous mycobacteria, Rapidly growing mycobacteria, Prosthetic joint infection, Mycobacterium fortuitum*

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Introduction

Non-tuberculous mycobacteria (NTM) can cause prosthetic knee joint infections in rare cases. Runyon[(1)] classified NTM into four classes, of which, the first three groups are classified as "slowly growing mycobacteria" and the fourth group is classified as "rapidly growing mycobacteria" (RGM). The RGM have a unique characteristic of producing visible colonies in less than 1 week at 37°C or at room temperature on a variety of media. Mycobacterium fortuitum is one of the commonest of the RGM along with Mycobacterium abscessus and Mycobacterium chelonae. The RGM are often considered to be a saprophytic organism found commonly in the environment, such as nature water, tap water, dust, and soil. Contaminated water, water-based solutions and ice can be sources for nosocomial infections[(2)]. There are some reports of the outbreak of NTM prosthetic joint infection[(3)] but most cases are sporadic.

From extensively review of literatures, only 19 cases (20 knees) of prosthetic knee joint infections (PJI) causing by M. fortuitum have been reported. There is still gap of knowledge to provide the best management of PJI occurred in this group of patients due to its rarity. Almost all previous cases had successful treatment with prosthesis removal and prolonged course of antibiotics. Only 4 cases (5 knees) had prosthesis retention with chronic antibiotics suppression due to poor surgical candidate of the patients[(5,6,18)]. This article aims to report a case of early onset prosthetic knee joint infection caused by M. fortuitum successfully treated at our institution with debridement and prosthesis retention. She had good functional outcomes with no signs of recurrent infection detected at 6-month follow-up. The present study also includes literature review of all reported cases of M. fortuitum prosthetic knee infections so far. Informed consent was obtained from the patient for reporting her clinical data and clinical photographs.

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Case Report

A 70-year-old woman, with medical comorbidities including asthma, well-controlled diabetes, and hypertension, presented with chronic right knee pain. She was diagnosed with severe osteoarthritis of the right knee. Preoperative radiographs of her right knee (Figure 1) showed obliteration of the medial tibiofemoral joint space and some degrees of knee recurvatum on lateral view, but there was no obvious sign of radiographic infection. She had no history of intra-articular injection on her right knee.

At the first admission, the physical examination showed acute paronychia of her right big toes with swelling, redness, and a small amount of purulent pus discharge from one side of the nail. She took an over-the-counter antibiotic for 3 days before the admission. The TKA was canceled, and

the open and drainage with partial nail extraction from collected pus had negative results for aerobic organisms. After 2 weeks of oral antibiotics and daily wound care, the paronychia resolved with no signs of infection or inflammation detected.

The right total knee arthroplasty (TKA) surgery was rescheduled for again in the interval of 6 weeks from the previous admission. She underwent the right TKA (NexGen LPS-Flex, Legacy posterior stabilized knee, Warsaw, Zimmer) in November 2018 under simple spinal analgesia with continuous adductor canal block. on her right big toe was performed. The culture Preoperative and intraoperative assessments showed no signs of infection. The operative time was within two hours. The prophylactic intravenous antibiotic (cefazolin) was administered at half an hour before skin incision and was continued until 24 hours, postoperatively. The immediate postoperative period showed excellent clinical outcomes with no signs of surgical site infection or prolonged wound drainage. Figure 2 showed the immediate postoperative x-rays of her right knee.

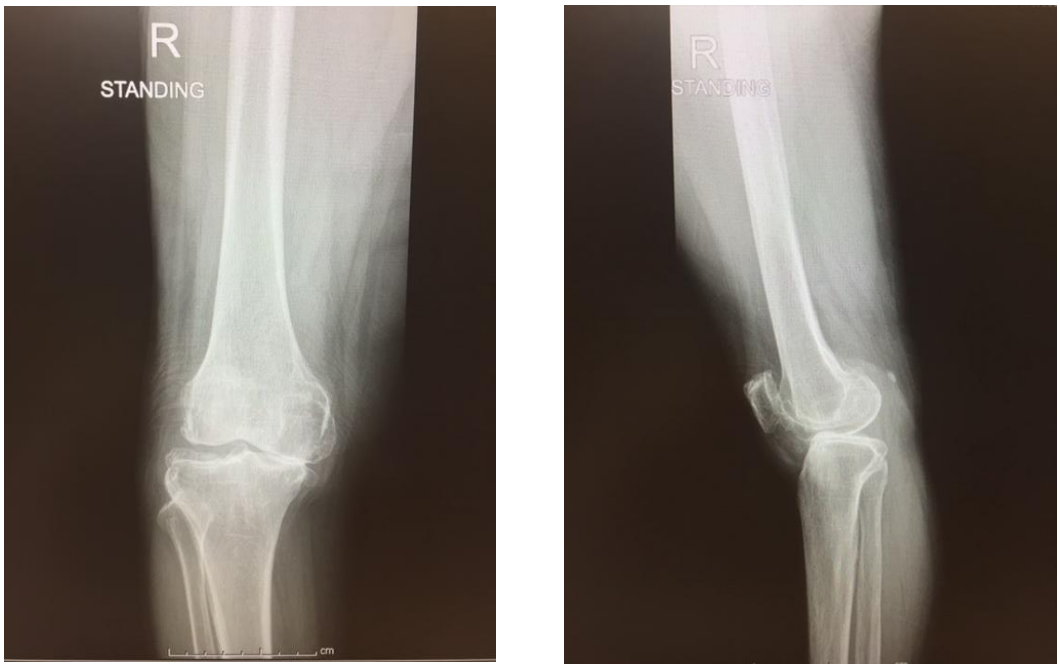

Fig. 1 Preoperative radiographs of the right knee

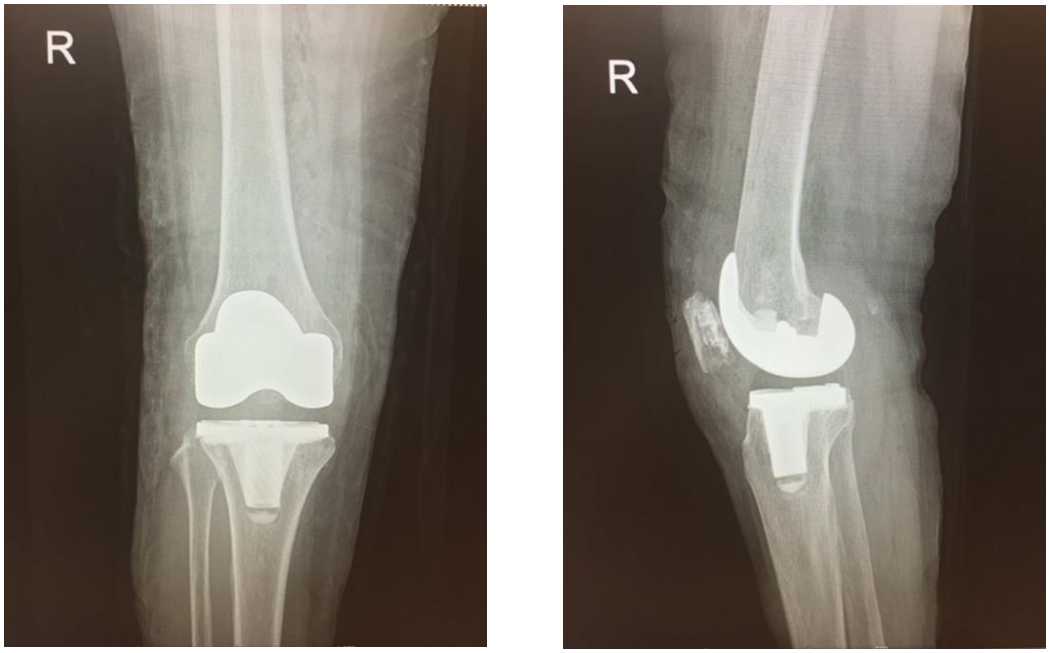

Fig. 2 Immediate postoperative radiographs of the right knee

At 3 weeks after the operation, the patient presented to another hospital with gradual onset of pain in her right knee with swelling and erythema around the surgical wound. The initial diagnosis was a stitch abscess. She was given an oral cephalexin and was advised for daily wound care. Two weeks later, she could not walk due to severe increasing pain on her right knee and presented to our hospital. The physical examination showed increased knee temperature with moderate effusion in the right knee. There were crusts along the surgical wound with a small pocket of abscess at the upper edge of the wound and a sinus tract drainage with purulent pus discharge from the tract of the redivac drain placement which was communicating with the knee joint (Figure 3).

3A **3B**

Fig. 3 Clinical photographs of the right knee at 5 weeks after the right TKA
3A: Anterior view of the right knee shows crusts and abscess along the surgical wound.
3B: Sinus tract drainage is visible from the tract of the redivac drain placement.

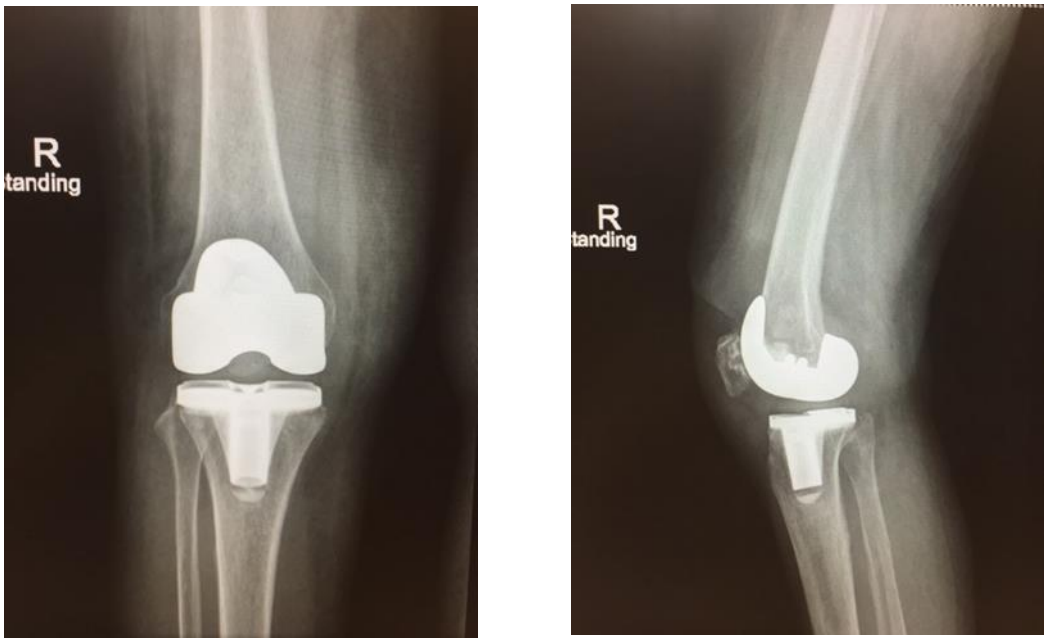

Fig. 4 Five-week postoperative radiographs of the right knee show well-fixed prosthesis with no osteolysis at both tibial and femoral components

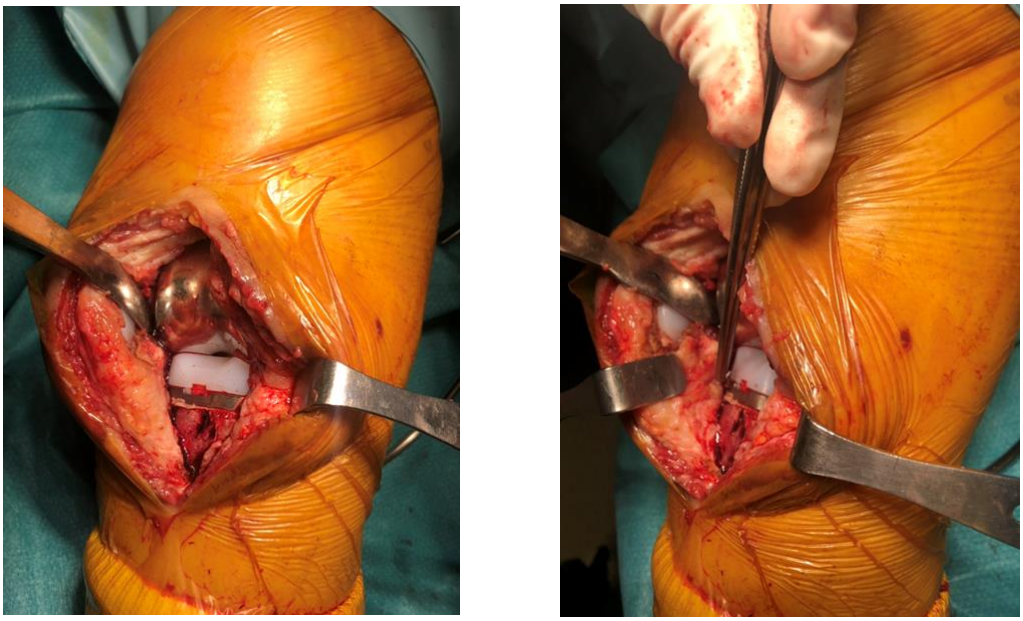

Fig. 5 Intraoperative pictures show pus was found inside the joint mainly on the lateral gutter around the tip of the forceps

Fig. 6 Clinical photograph shows a sinus tract drainage after the first debridement

The blood test showed an elevated C-reactive protein (CRP) level of 90 mg/L and an elevated erythrocyte sedimentation rate (ESR) level of 93 mm/hr. She had leukocytosis with white blood cell count 12,900 cells/μL with 75% neutrophil predominate from the complete blood count (CBC). The radiographs of the right knee showed well-fixed prosthesis with no osteolysis at both tibial and femoral components (Figure 4). She underwent debridement, polyethylene exchange, and prosthesis retention on the same day that she came to our institute. Small amount of pus was found inside the joint mainly on the lateral gutter (Figure 5) with generalized synovitis. The sinus tract previously mentioned from the physical examination was confirmed intraoperatively to communicate with the joint via the superolateral gutter. There was no component loosening. We used 15 L of irrigation solutions including saline and three antiseptic solutions (Povidone iodine, hydrogen peroxide, and Dakin's solution). Initial results of all 7 specimens from the intraoperative gram strain and culture were negative but found increased number of neutrophils microscopically. The empirical antibiotic with intravenous fosfomycin was chosen for this patient.

Later on, she experienced gradual onset of pain in her right knee again at 1 week after the debridement with wound drainage at the sinus tract (Figure 6). She underwent the second debridement of her right knee. The intraoperative findings were small amount of serosanguinous fluid with a pocket of subcutaneous tissue necrosis around the sinus tract at the superolateral gutter. At this juncture, we were not only collected the intraoperative swab cultures and tissue cultures but we also collected synovial fluid in the blood culture vials. We requested to extend the normal culture time which was about 5 days to 2 weeks to improve yield in culture-negative prosthetic joint infection[8]. Then we performed meticulous debridement especially at the pocket around the superolateral gutter.

All 3 specimens of synovial fluid culture in blood culture vials were positive for M. fortuitum but the intraoperative swab and tissue culture remained negative result. The broth microdilution method confirmed the antibiotic susceptibility with Amikacin (MIC 2 µg/mL), Clarithromycin (MIC 0.5 µg/mL), and Ciprofloxacin (MIC 0.5 µg/mL) (Table 1). Antimicrobial therapy was selected based on the susceptibility data and clinical experience from our infectious specialists consisted of intravenous amikacin, oral clarithromycin, and oral levofloxacin. After completing of 2-month course of intravenous antibiotic, the patient complained hearing loss, otalgia, and tinnitus which were ototoxicity side effects from amikacin. She continued receiving oral clarithromycin and levofloxacin but stop intravenous amikacin. The ototoxic side effects got better as time passes after the cessation of amikacin.

At the last follow-up about 6 months after the debridement, she had no fever and there was no signs of inflammation or recurrent infection. She had no pain on her right knee and could walk without assistive devices. She could walk upstairs by herself to her bedroom on the second floor. The range of motion of her right knee was 5-120 degrees. Both inflammatory markers, ESR and CRP, were normalized in this follow-up (28 mm/hr and 1 mg/L, respectively).

Table 1 The susceptibility data of *M. fortuitum* in this study by broth microdilution method

Drugs	S/I/R	MIC	Unit
Cefoxitin	S	16	µg/mL
Amikacin	S	2	µg/mL
Clarithromycin	S	0.5	µg/mL
Tigecycline	-	0.5	mcg/mL
Linezolid	-	<1	µg/mL
Trimethoprim-sulfamethoxazole	-	1	µg/mL
Moxifloxacin	-	0.5	µg/mL
Ceftriaxone	-	<4	µg/mL
Cefepime	-	4	µg/mL
Imipenem	-	<2	µg/mL
Ciprofloxacin	S	0.5	µg/mL
Minocycline	-	<1	µg/mL
Amoxicillin/Clavulanic acid	-	4	µg/mL
Tobramycin	-	<1	µg/mL
Doxycycline	-	0.25	µg/mL

Discussion

Mycobacterium fortuitum is classified as one of rapidly growing mycobacteria (RGM) in group IV of Runyon's classification. The clinically significant and most commonly isolated RGM species consists of M. fortuitum, M. abscessus, M. chelonae, and M. mucogenicum[25]. It is a low-virulence organism commonly found ubiquitously in the nature[2]. These organisms can form biofilms and are relatively resistant to standard disinfectants such as chlorine, organomercurials, and alkaline glutaraldehydes[12].

In 1938, Cruz[4] isolated the original organism of M. fortuitum from a post injection abscess. M. fortuitum infection can present with a variety of clinical manifestations, especially cutaneous infections and abscesses [9], pulmonary infections[10], corneal infections[11] and catheter-related infections[2]. Postsurgical wound infections have also been reported after the use of contaminated solutions, instrumentations, and implants. There are case reports of postsurgical wound infection of RGM in the field of cosmetic surgery[15], cardiothoracic surgery[16], and general surgery from iatrogenic causes[21]. The diseases

caused by RGM can occur in both apparently normal hosts and the immunocompromised hosts[19].

For prosthetic knee joint infections caused by M. fortuitum, there are only 19 cases (20 knees) reported from the literatures (Table 2)[17,18]. The exact prevalence and incidence are still unknown. The difficulty in diagnosis of M. fortuitum and other RGM comes from several reasons. These pathogens can cause an early onset of clinical manifestations like other bacterial infections. A high index of suspicion is important when results of the bacterial culture or acid-fast stains are negative. Most clinical laboratories discard routine culture media after 48-72 hours but the growth of RGM requires five or more days to form visible colonies. Special mycobacterial culture (e.g., Lowen-stein-Jensen) should be requested or hold the culture time to two weeks will be the solution for this problem. M. fortuitum can form non-pigmented colonies on MacConkey agar[20]. The positive 3-day phenolphthalein sulfatase (aryl sulfatase) test and a positive nitrite reduction test are used for distinguishing M. fortuitum from other RGM[20]. The accurate and reproducible methods in species-specific identification of mycobacteria are 16S rRNA gene sequencing method[13] and PCR restriction analysis[14]. As a result of the widespread use of these species identification methods, more than 50 new mycobacterium species have been discovered[24].

All three positive cultures in this case were synovial fluid in blood vials culture from the second debridement. Other 10 specimens (7 from the first debridement and 3 from the second debridement) from intraoperative swab cultures and tissue cultures were all negative. Specimens collected in blood vials can exactly improve the sensitivity of the organism detection (sensitivity 90%-92%) and were being preferred to intraoperative swab cultures (sensitivity 68%-76%) and tissue cultures (sensitivity 77%-82%)[8]. Multiple and repeated culture may have a role as the co-infection with two kinds of RGM in the same patient has been reported[27].

Rapid onset of infection following knee arthroplasty defined as infections less than 3 months after the surgery. We should suspect high-virulence pathogens such as Staphylococcus aureus or gram-negative bacilli as causative agents. The mode of entry is usually from intraoperative contamination or postoperative wound dehiscence[7]. However, RGM is also recognized as a cause of an early onset of infection results from intraoperative contamination with RGM from tap water or tap-water derived fluids used during prosthesis implantation[28]. We should have a high index of suspicious especially in the case with a negative routine culture or refractory to antibiotics[18].

Treatment in this group of patients is difficult and challenging at the same time. The organisms do not respond to traditional antituberculous agents and most antibiotics. Because of limited number of patients, the optimal treatment regimen is not available. Identifying species of RGM is mandatory because each specie has different antimicrobial susceptibility profile. Fortunately, M. fortuitum was susceptible to more antibiotics than M. chelonae and M. abscessus[19]. Antibiotics that were reported to have good susceptibility for M. fortuitum include amikacin[25], clarithromycin[22], ciprofloxacin[25], imipenem[26], and trimethoprim sulfamethoxazole[25]. Single-drug therapy is not recommended because M. fortuitum has a rRNA methylase gene (erm gene) that can cause macrolide resistance so combination of 2-3 antibiotics is preferred[23].

The combination of resection arthroplasty and at least 6-month course of antimicrobial therapy is the most successful treatment strategy in almost all cases[5]. Nevertheless, there were 4 patients (5 knees) who were successfully treated with retained prosthesis and prolonged antibiotic therapy due to severe medical comorbidities[5,6,18]. The main factor to suppress the infection in the retained prosthesis patients is the availability of safe and effective oral antibiotics especially in M. fortuitum, which is considered to be antibiotics-susceptible specie.

In this study, the patient had early onset of infection with the onset of symptoms at 3 weeks postoperatively. There is no evidence to support the association between the event of acute paronychia on her right big toe and the prosthetic joint infection because of negative culture from the toe and 6-week interval which should be enough time to define complete remission before the right total knee arthroplasty. The treatment options have been discussed with the medical team and the patient. Debridement and prosthesis retention were the treatment of choice because the components were well-fixed and duration of symptoms was less than 2 weeks. However, after the laboratory results showed M. fortuitum infection, we collaborate with infectious specialists as difficulty in antibiotics selection from multidrug resistance and drug-related adverse events can occur. A combination of antibiotics (IV amikacin, oral clarithromycin, and oral levofloxacin) was selected according to the susceptibility profile in Table 1. Closed monitoring and prolonged course of 6 months or lifelong antibiotics suppression are the key for successful treatment.

Recommendations for prevention of this infection from iatrogenic causes include adequate sterilization of surgical instruments, suture materials, and prosthetic implants. Autoclaving of the surgical instrument is the best method[21]. In addition, one should avoid tap water and tap-water

derived fluids at scrubbing in the operating room, as well as at cleaning of the surgical instruments as much as possible[28].

At the final follow-up at 6 months, the patient had satisfactory clinical outcomes. She could walk without any assistive devices and could walk upstairs by herself. The range of motion of her right knee was 5-120. Both inflammatory markers, ESR and CRP, were normalized. Of all 4 cases who had successful results from prosthesis retention, only 1 patient had follow-up time more than 1 year[5]. This study also presents the excellent outcomes in short-term results of 6 months.

Conclusion

M. fortuitum infection following knee arthroplasty is rare. Management is challenging from difficulties in diagnosis which needed a high index of suspicious and an effective treatment strategy was not established.

This paper suggests that extensive debridement with prosthesis retention and an appropriate combination of effective antibiotics is one of the interesting treatment options in the early-onset M. fortuitum prosthetic knee infection.

Table 2 Reported cases of prosthetic knee joint infection by *M. fortuitum*

Case No./(ref)	Age /Sex	Underlying diseases	Duration (days)[a]	Specific ATB regimens	Type of surgery	Outcome/follow-up
1/18	68/F	Gout	60	IV FOX, AMK then oral CIP, SMX/TMP and DOX	Two-stage exchange	Cured 12 months of follow-up
2/18	58/F	-	30	IV FOX and AMK then oral CLA, CIP and ETB	Two-stage exchange	Not available data at 12 months follow-up
3/18	77/F	HT	60	IV FOX, AMK then oral CLA, CIP	Two-stage exchange	Cured 12 months of follow-up
4/18	56/F	-	30	IV AMK then oral CLA, CIP	Two-stage exchange	Cured 12 months of follow-up
5/18	69/F	DM, CKD	180	IV LVX, AMK then oral CLA, CIP	Two-stage exchange	Failure
6/18	80/F	DM, HT	19	IV IMI, CIP, AMK then oral CIP, DO	Debridement, retention of prosthesis	Not available data at 12 months follow-up
7/18	51/M	Gout	90	IV AMK then oral CLA, CIP	Resection arthroplasty	Not available data at 12 months follow-up
8/18	76/F	HT	90	IV FOX, CIP then oral CLA, CIP	Resection arthroplasty	Cured 12 months of follow-up
9/27	72/F	DJD	112	IV AMK then oral DOX, CIP, CLA	Two-stage exchange	Cured 10 months of follow-up
10/6	68/M (bilat)	DM, CVI	5,460, 5,824	CLA, LNZ	Arthrocentesis only, poor surgical candidate	Joint retention with chronic suppression, Cured 8 months of follow-up
11/29	68/M	-	63	MER, MOX	Two-stage exchange	Not available data at 12 months follow-up
12/30	70/M	DJD	18	CLA, CIP, DOX	Two-stage exchange	Cured 7 months of follow-up
13/30	60/M	DJD	45	CLA, CIP, DOX	Two-stage exchange	Cured 2 months of follow-up

Table 2 (continued) Reported cases of prosthetic knee joint infection by *M. fortuitum*

Case No./(ref)	Age /Sex	Underlying diseases	Duration (days)[a]	Specific ATB regimens	Type of surgery	Outcome/follow-up
14/31	70/F	-	60	IV MER, oral CIP, AMK	First-stage revision and reimplant with autoclaved components	Good functional outcomes at 9 months of follow-up with no need of second-stage reimplantation
15/32	30/F	JRA	14	CFT, AMK, DOX	Two-stage exchange then knee arthrodesis	Infection persisted after two-stage exchange, cured but required arthrodesis at 1.5 years
16/33	44/F	DJD, CKD, PVD	28	IMI, DOX, AZ	Two-stage exchange	Cured 18 months of follow-up
17/34	62/F	DJD	28	AMK, TET, INH	REA with arthrodesis	Cured but required arthrodesis 7 months of follow-up
18/5	76/M	DJD	2,576	MOX, SMX/TMP, AZ	Debridement, retention of prosthesis	Good function outcomes at 6 months of follow-up
19/5	66/F	DJD	91	LVX, SMX/TMP	Debridement, retention of prosthesis	Good function outcomes at 47 months of follow-up

[a] Duration from prosthesis implantation to clinical diagnosis of PJI

Abbreviations: AMK, amikacin; ATB, antibiotics; AZ, azithromycin; CFT, cefoxitin; CIP, ciprofloxacin; CKD, chronic kidney disease; CLA, clarithromycin; CLD, chronic liver disease; CoNS, coagulase negative staphylococcus; CRP, C-reactive protein; CVI, chronic venous insufficiency; DJD, degenerative joint disease; DM, diabetes mellitus; DOX, doxycycline; ESR, erythrocyte sedimentation rate; ETB, ethambutol; F, female; FOX, cefoxitin; HT, hypertension; IMI, imipenem; INH, isoniazid; IV, intravenous; JRA, juvenile rheumatoid arthritis; LNZ, linezolid; LVX, levofloxacin; M, male; MER, meropenem; MOX, moxifloxacin; MSSA, methicillin sensitive *Staphylococcus aureus*; NA, not available; OFX, ofloxacin; PVD, peripheral vascular disease; PZA, pyrazinamide; REA, resection arthroplasty; RIF, rifampicin; WBC, white blood cell; SLE, systemic lupus erythematosus; SMX/TMP, sulfamethoxazole/trimethoprim; TET, tetracycline

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การติดเชื้อเร็วหลังการผ่าตัดข้อเข่าเทียมจากเชื้อมัยโคแบคทีเรียม ฟอร์ทูอิทุม : รายงานผู้ป่วยและทบทวนวรรณกรรม

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การติดเชื้อของข้อเทียมเป็นภาวะแทรกซ้อนที่ก่อให้เกิดความเสียหายอย่างมากหลังการผ่าตัดข้อเข่าเทียม การติดเชื้อมัยโคแบคทีเรียที่ไม่ใช่เชื้อวัณโรคพบได้น้อยมากในผู้ป่วยติดเชื้อหลังผ่าตัดข้อเข่าเทียม มีเพียงผู้ป่วยเพียงไม่กี่รายที่ได้รับการรายงานจากการสืบค้นวรรณกรรมทั้งหมดในปัจจุบัน ซึ่งเชื้อมัยโคแบคทีเรียม ฟอร์ทูอิทุมเป็นสมาชิกหนึ่งในกลุ่มมัยโคแบคทีเรียที่ไม่ใช่เชื้อวัณโรคและยังเป็นที่รู้จักในนามของเชื้อมัยโคแบคทีเรียที่เจริญเร็วอีกด้วย

ในรายงานผู้ป่วยฉบับนี้ ได้กล่าวถึงผู้ป่วยติดเชื้อหลังผ่าตัดข้อเข่าเทียมด้วยเชื้อมัยโคแบคทีเรียม ฟอร์ทูอิทุม โดยเริ่มมีอาการเพียง 3 สัปดาห์หลังการผ่าตัด จากการทบทวนวรรณกรรมที่ผ่านมา การรักษาผู้ป่วยในกลุ่มนี้แนะนำ two-stage exchange arthroplasty แต่คณะผู้วิจัยประสบความสำเร็จในการรักษาโดยผ่าตัดล้างข้อเข่าเทียมและเก็บข้อเทียมเดิมไว้ได้ร่วมกับมีการให้ยาปฏิชีวนะระยะยาวที่เหมาะสม ผลการรักษาที่ 6 เดือนหลังผ่าตัด ผู้ป่วยมีการใช้งานของข้อเทียมกลับมาดีเยี่ยมเป็นที่น่าพอใจและไม่พบอาการแสดงของการติดเชื้อซ้ำ