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Case report

Miliary tuberculosis with delayed-onset total knee arthroplasty *Mycobacteria tuberculosis* infection successfully treated with medical therapy alone: A case report and literature review

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ABSTRACT

Tuberculosis (TB) affecting a prosthetic knee is an unusual and diagnostically challenging presentation of this disease. This study reported a case of an 80-year-old man with a left total knee arthroplasty (TKA) performed eight years before his presentation. He presented with left knee swelling and pain for one month. Knee X-rays showed a normal joint space with no loosening of his prosthesis. His chest X-ray showed miliary disease, and microbiological studies of his sputum and synovial fluid aspirate grew *Mycobacteria tuberculosis* complex. He was successfully medically treated with anti-tuberculous therapy alone for one year. His knee hardware was retained, and he did not require debridement, resection, or revision. It is believed that this is the first reported case of miliary TB with delayed-onset TKA prosthetic joint infection (PJI) in which the prosthesis was successfully retained. Thirty-eight published TB TKA PJI cases in medical literature were also reviewed.

1. Introduction

Miliary tuberculosis is a severe form of tuberculosis (TB) characterized by wide dissemination [1]. Total knee arthroplasty (TKA) prosthetic joint infection (PJI) due to *Mycobacterium tuberculosis* (MTB) is a rare presentation of TB [2]. Thirty-eight reported cases were found in the medical literature: 11 (29%) of them were successfully treated with medical therapy alone, the remaining required different surgical modalities or died [3]. Delayed-onset TB PJI may occur many years after the original arthroplasty and is therefore often seen in the elderly with multiple comorbidities, in whom surgical options may not always be feasible [4]. This study presents a case of miliary TB presenting with TKA PJI that was successfully treated with anti-tuberculous medications alone without any surgical intervention, and reviewed published cases in the medical literature with TB TKA PJI.

1.1. Case report

This case is of an 80-year-old gentleman with type 2 diabetes mellitus, a remote history of partially resected benign prostatic hyperplasia, and who had severe osteoarthritis of both knees, which prompted an elective right and left TKA 15 and eight years ago, respectively, without any postoperative complications.

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He presented to the hospital in April 2015 with left knee pain and swelling for one month. His illness began five months before with daily undocumented fever, but without night sweats, chills, or rigors. Although his appetite was good, he unintentionally lost nine kilograms over the preceding three months. His energy level was good, and he normally walked with a cane. One month prior to presentation he developed left knee pain and swelling, which slowly progressed until he became unable to walk and he had complete loss of knee function with inability to bend it. His right knee was completely normal. He also noticed a new chronic cough with a little brownish sputum that had not changed over the previous five months, without hemoptysis, shortness of breath or chest pain. He was a retired shop vendor who lived in Riyadh. He had no previous known contact with any person with TB, no animal contact of any kind, and had never consumed raw milk products.

Clinically he appeared well: he was not cachectic, his weight was 53 kg, body mass index (BMI) 19 kg/m^2, temperature 37.5 °C, blood pressure 125/85 mm Hg, pulse rate 75 beats/min, respiratory rate 12 breaths/min, oxygen saturation 95% on room air, and glucocheck six millimoles per liter. His left knee was swollen, red, warm, and very tender over the lateral aspect, there was no active movement, and severe pain on any attempt of passive movement. His chest exam showed reduced chest expansion bilaterally, with diffuse inspiratory crackles. His cardiovascular exam was normal. His abdomen was soft, non-tender, and had no organomegaly.

His initial laboratory results on presentation were: erythrocyte sedimentation rate (ESR) 73 mm/h (normal 0–35); C-reactive protein (CRP) 230 mg/l (normal >10 positive, <10 negative); alanine transaminase (ALT) 30 units/l (normal 20–65 units/l); aspartate aminotransferase (AST) 26 units/l (normal 12–37 units/l); albumin (alb) 20 g/l (normal 30–50 g/l); bilirubin 4.4 mcmol/l (normal three to 17 mcmol/l); alkaline phosphatase (ALP) 150 units/l (normal 50–140 units/l); and human immunodeficiency virus (HIV-1 and HIV-2 antigens/antibodies) serology was nonreactive. X-rays of his knees showed normal prostheses, no osteopenia, no soft tissue swelling, no joint space narrowing, no cysts, no osteolysis or any loosening of the prosthesis (Figure 1). Chest X-ray (CXR) showed bilateral nodular opacities with a diffuse miliary pattern (Figure 2).

He was admitted to an Airborne Infection Isolation Room (AIIR). Knee aspiration of thick yellow fluid was sent for bacterial culture, which had no aerobic or anaerobic bacterial growth. Acid-Fast Bacilli (AFB) smear was negative, but 16 days later the TB culture grew *Mycobacteria tuberculosis* complex (MTB) with a positive polymerase chain reaction (PCR) by GeneXpert® directly from the Mycobacterial Growth Indicator Tube (MGIT). Three sputum AFB smears and PCR were positive for MTB; rifampin resistance by the *rpo-B* target was not detected. Ultimately, his sputum culture also grew MTB, Interferon gamma release assay (IGRA) in the form of TB- QuantiFERON® was positive, and his tuberculin skin test (TST) was 15 mm induration (neither test was performed prior to his current presentation).

Upon diagnosis he was started on anti-tuberculous therapy (ATT): isoniazid (INH) 300 mg, rifampin (RMP) 600 mg, ethambutol (EMB) 800 mg, and pyrazinamide (PZA) 1200 mg. The medical decision was made not to undergo any surgical intervention to retain his knee hardware, and to monitor his medical response. One month later his sputum AFB smear became negative but ultimately grew MTB, his cough improved, knee swelling and tenderness improved, weight increased to 54 kg, and the inflammatory markers improved (ESR 59 mm/h, CRP 129 mg/l). His ALT and AST remained normal, so he was discharged on the same medications.

He returned to clinic one month later with ongoing improvement in his knee swelling and function. The susceptibility results of MTB had returned by then, which showed it to be susceptible to all first-line drugs (isoniazid, streptomycin, rifampin, ethambutol). The PZA and EMB were stopped at the two-month mark and he continued on INH and RMP for a total duration of one year.

During his follow-up he continued to improve clinically with weight gain, resolution of cough, and decreased knee swelling. At one-year follow-up from the day his ATT was started, his weight was up to 62 kg, his knee swelling, pain, and tenderness had all completely disappeared, and he gained back his full range of knee motion (0 90°) without pain. His ESR was 26 mm/h, CRP 5.4 mg/l, and CXR was clear. INH and RMP were both stopped. At the six-month and 12-month follow-ups after treatment completion, he remained well with no clinical signs of relapsed disease.

2. Discussion

Primary tubercular osteoarthritis is considered a common presentation of musculoskeletal TB, with the knee being affected 20% of the time [5], but in a prosthetic knee joint the reported data demonstrate it as an uncommon entity [2]. The current study presents the first reported case of TB complicating TKA as part of disseminated miliary disease only medically treated.

Tuberculosis affecting a prosthetic joint has been documented to be rare, but if affected it has a tendency towards weightbearing joints, notably the knee and hip. In a previous retrospective study looking at 2543 prosthetic joint infections, only one of the affected cases were due to TB [6]. The risk of reactivation of TB in patients undergoing joint arthroplasty for quiescent TB native septic arthritis varies between 0 and 31%, with the highest being TKA [7].

Tuberculosis can invade the prosthetic joint by three proposed mechanisms: [1] active interarticular TB presents at that time of surgery; [2] hematogenous seeding from a reactivated focus elsewhere — either pulmonary or extra-pulmonary; and [3] reactivation of latent osteoarticular TB following arthroplasty. The current patient had no previous history to suggest prior infection, or contact with people diagnosed with TB; however, he had not been tested for latent TB infection (LTBI) in the past. Since his TKA, this was his first presentation of knee pain and swelling, which reflects the most common early manifestations of knee TB disease. The presence of constitutional symptoms, positive sputum AFB smears, miliary pattern on CXR, TB cultures from both sputum and synovial fluid, a positive IGRA and TST, as was evident in the current report, favors hematogenous spread due to disseminated miliary TB.

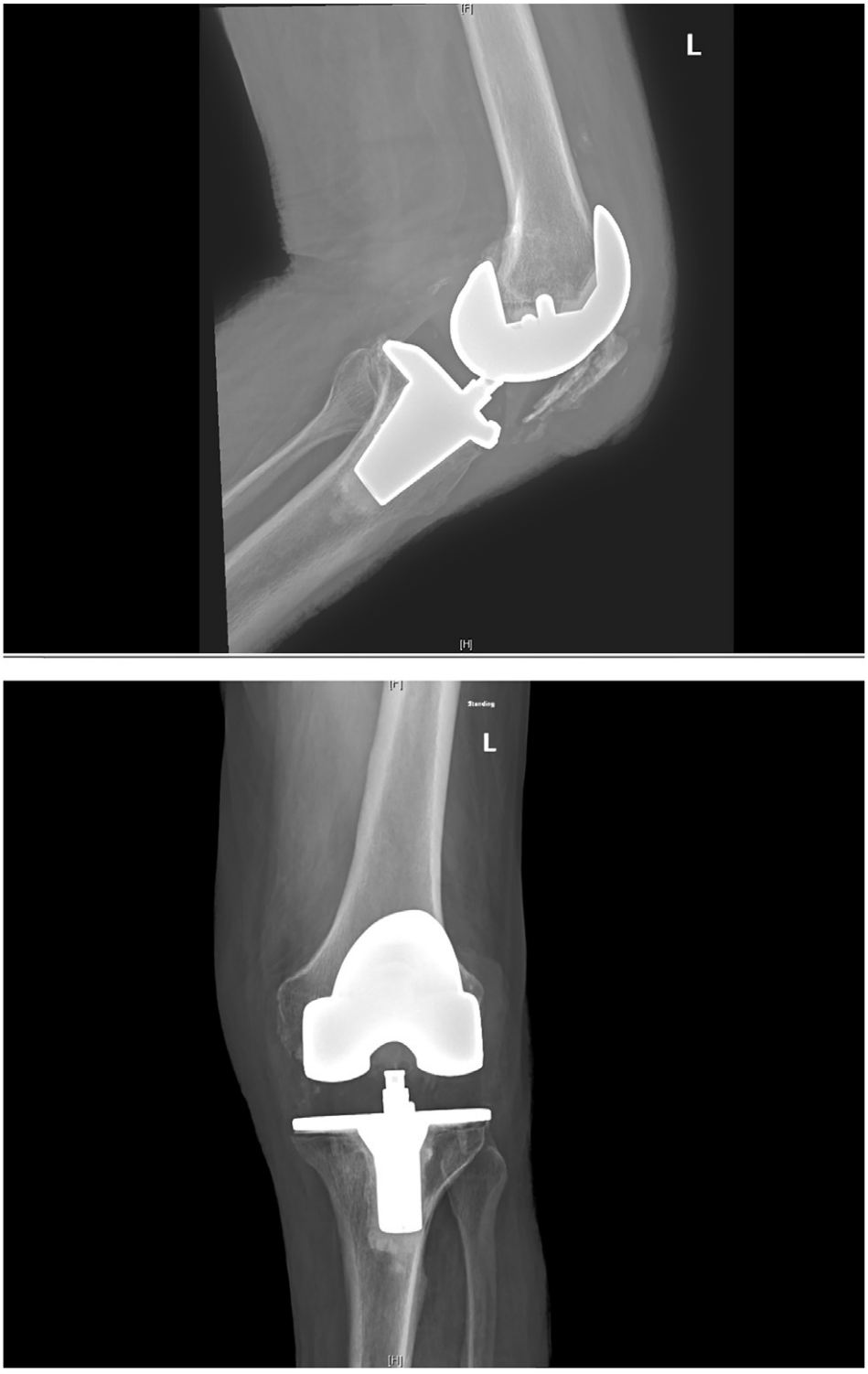

Figure 1. X-ray of left knee showing a normal prosthesis at presentation.

Time to onset of symptoms postoperatively plays an important role in the management of these patients. According to a previous case report published by Harwin et al., two modes of presentation were identified for unsuspected TB PJI based on the onset of symptoms and time to diagnosis. Early-onset presentation, which occurs six to eight weeks after surgery, and late-onset presentation, which usually manifests after eight weeks from the time of surgery [5]. The onset of presentation helps in drawing

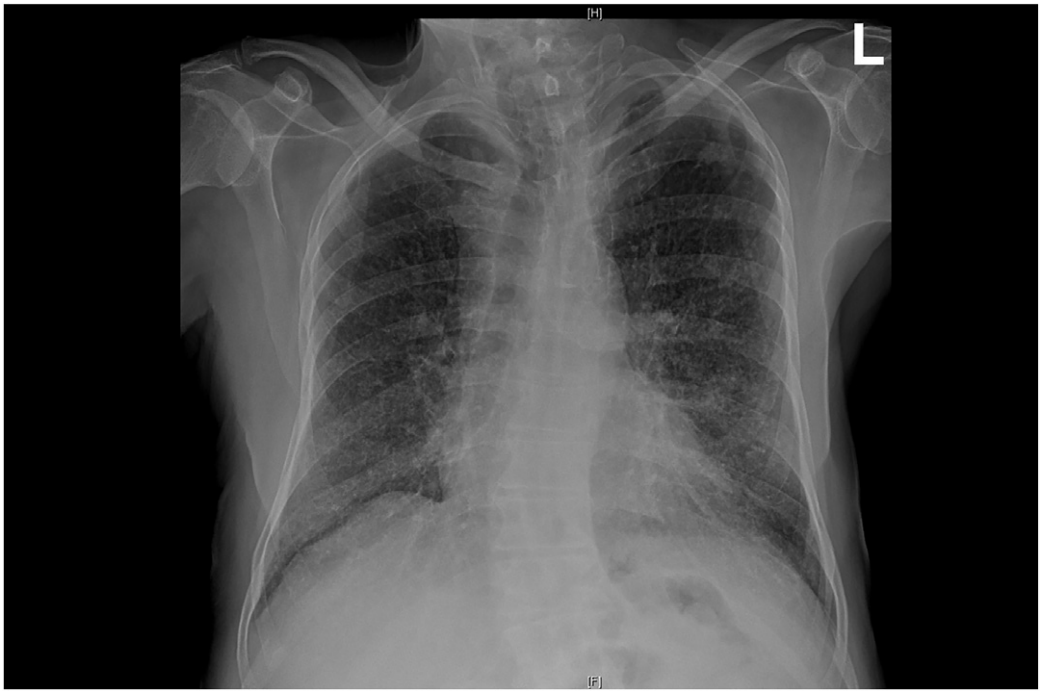

Figure 2. Chest X-ray showing bilateral diffuse miliary shadowing.

up a management plan: most cases in the early-onset period require only standard anti-tubercular therapy, while late-onset cases require an additional surgical intervention in the form of two-stage re-implantation surgery, debridement and irrigation, prosthesis removal, or arthrodesis.

Sultan et al. suggested that TKA TB PJI would resolve by ATT alone if the implant is well-fixed and in the absence of clinical and radiological signs of loosening, as MTB is a non-biofilm forming organism [8]. This case supports such a notion with an 8-year delayed-onset of illness associated with miliary disease, managed conservatively with medical therapy alone, and retention of arthroplasty with a successful outcome. It is believed that this is the first report of such a case.

Although a history of previous TB is an important causative recurring factor in TB PJI, half of patients' document prior history and <30% have an abnormal CXR [9]. The current patient was among those who demonstrated an abnormal CXR with a miliary pattern. Owing to the rarity of TB affecting the prosthetic knee joint, diagnosis can be challenging. The diagnostic modalities – including radiographs, ESR and bone scanning – are noted to be of limited value in PJI. Microscopy and culture of tissue samples is the diagnostic gold standard with a yield exceeding 90%, and positive AFB smear in 20–40%. The combination of direct synovial smears, culture, and histopathology may confirm the diagnosis in >90% of such cases. PCR serves as a test of high sensitivity in the early diagnosis of tuberculous arthritis.

Based on previously conducted literature reviews [4], there are no clear guidelines that exist for optimal management of TB disease in the prosthetic knee joint. The duration of treatment ranges from 6 to 36 months and the need for surgery seems to be common [9]. The current patient received a total of 12 months of standard ATT in the absence of any surgical intervention with complete cure.

Reviewing published case reports on exclusively TB TKA PJI (Table 1) between 1980 and 2018 published in the English language using PubMed, 38 cases were found with a wide range of follow-up from one month to 10 years (mean 1.8 years). Five cases (13%) affected the knee and lungs alone, one case (2.6%) affected the lungs, liver and pericardium, and 25 cases (65.8%) were localized PJI. Five cases (13.2%) ultimately died. Eleven (29%) did not have any surgical intervention and did not die. Twenty-five cases (65.8%) required some type of intervention: one (2.6%) arthroplasty, eight (21%) resection arthroplasty, one (2.6%) staged exchange, seven (18%) debridement, three (7.9%) revision arthroplasty, one (2.6%) debridement and delayed arthrodesis, and four cases (10.5%) underwent two-stage revision arthroplasty.

3. Conclusion

It is believed that this is the first reported case of disseminated miliary TB with delayed-onset TKA *Mycobacteria tuberculosis* PJI successfully treated with medical therapy alone. In high-prevalence areas with TB, clinicians should be aware of the possibility of

Table 1
Cases reported in medical literature of total knee arthroplasty tuberculosis prosthetic joint infection with author name and year published, patients' age and sex, time of onset of disease from total knee arthroplasty, diagnostic method, other sites of disease, type of medical treatment with duration, surgical intervention, and outcome at follow-up duration.

Author and year	Sex, age in years	Time from TKA to disease	Diagnostic method	Other sites of disease	Medical treatment (months)	Surgical intervention	Outcome at follow-up
Besser, 1980 [10]	M, 65	<1 month	Synovial tissue histopathology	None	NM	None	Good 1 year
Bryan, 1982 [11]	F, 72	8 years	Synovial fluid culture	Elbow	INH/RMP/PZA [9]	Arthrodesis	Good 3 years
Zeiger, 1984 [26]	F, 40	4 years	Synovial tissue culture	None	NM	Resection arthroplasty	Good 2.5 months
Wolfgang, 1985 [12]	M, 61	13 months	Synovial fluid culture	None	INH/RMP [9]	Staged exchange	Good 1 year
Wray, 1987 [13]	M, 62	<1 month	Synovial tissue histopathology and culture	Pulmonary	INH/RMP/EMB [16]	None	Good 5 years
Wray, 1987 [13]	M, 63	<1 month	Synovial tissue histopathology and sputum culture	Pulmonary	INH/RMP [16]	None	Good 1.5 years
Eskola, 1988 [14]	M, 47	18 months	Synovial fluid culture	None	INH/RMP/EMB [16]	Debridement	Good 2 years
Gale, 1991 [15]	M, 67	<1 month	Synovial tissue histopathology, sputum culture	Pulmonary	INH/RMP [16], EMB [11]	None	Good 10 years
Spinner, 1996 [16]	M, 79	10 years	NM	None	NM	Revision arthroplasty	NM
Lusk, 1995 [17]	F, 75	15 years	Synovial tissue histopathology and culture	None	INH/PZA [11], RMP [1], EMB [10]	Resection arthroplasty	Died at 6 months
Tokumoto, 1995 [18]	F, 71	20 months	Synovial aspirate culture	None	INH/EMB [22]	Resection arthroplasty	NM
Tokumoto, 1995 [18]	F, 70	38 years	Synovial aspirate culture	None	INH/RMP [16]	Resection arthroplasty	Good 2 years
Spinner, 1996 [19]	F, 70	4 years	Synovial tissue culture	None	INH/RMP/EMB [16]	Debridement	Good 2 years
Al Shaikh, 2003 [20]	F, 73	8 months	Synovial tissue culture	None	INH/RMP/PZA [16] EMB [13]	Debridement, delayed arthrodesis	Good 1 years
Marmor, 2004 [21]	M, 66	2 months	Synovial aspirate and blood cultures	Disseminated	INH/RMP/PZA [11]	Two-stage revision arthroplasty	Good 5 years
Marmor, 2004 [21]	F, 65	3 months	Synovial aspirate culture	Urinary tract	INH/RMP/PZA [11]	Two-stage revision arthroplasty	Good 7 years
Marmor, 2004 [21]	F, 77	4 months	Synovial aspirate culture	None	INH/EMB/PZA [12]	Debridement	Good 1 years
Kadakia, 2007 [22]	F, 85	1 month	Synovial aspirate AFB smear	Lungs	NM	None	Good NM
Khater, 2007 [23]	F, 75	3 months	Synovial tissue histopathology and culture	None	INH/EMB [22] RMP (NM)	Resection arthroplasty	Good 18 months
Wang, 2007 [3]	M, 72	3 years	Synovial tissue culture	lungs	NH/RMP/EMB/PZA [1]	Debridement	Dead
De Haan, 2008 [24]	F, 75	3 months	Synovial tissue culture	None	INH/RMP/EMB/PZA [13]	Debridement	Good NM
Marschall, 2008 [5]	M, 48	9 months	Synovial aspirate culture	Lungs, brain	INH/EMB/PZA [1], MOX (0.5), RMP (0.5)	None	Dead
Lee, 2009 [7]	F, 79	2 months	Synovial tissue histopathology	None	INH/RMP/EMB/PZA [16]	Debridement	Good 13 months
Neogi, 2009 [9]	F, 73	14 years	Synovial tissue PCR	NM	INH/RMP [22], EMB [4], PZA [27]	None	Good 3 years
Klein, 2012 [25]	F, 36	11 months	Synovial tissue culture	None	INH/RMP/EMB/PZA/MOX [23]	Two-stage revision arthroplasty	Good 3 years
Carrega, 2013 [6]	F, 80	<1 month	Synovial tissue histology and culture	None	INH/RMP [18], PZA [2]	Two-stage revision arthroplasty	Dead
Harwin, 2013 [27]	F, 60	7 months	Synovial tissue culture	None	INH/RMP [24], EMB/PZA [16]	Revision arthroplasty	Good 2 years
Tekin Koruk, 2013 [28]	M, 55	20 days	Synovial aspirate culture	None	INH/RMP [16], EMB/PZA [2]	None	Good 18 months
Seng, 2016 [29]	NM	NM	NM	NM	NM	NM	NM
von Keudell, 2016 [30]	M, 84	5 months	NM	None	INH/RMP (> 15), EMB/PZA [16]	Revision arthroplasty (partial)	Good 15 months
Uhel, 2018 [4]	F, 84	3 years	Synovial fluid culture	None	INH/RMP [16], EMB/PZA [2]	None	Good, NM
Uhel, 2018	F, 82	9 years	Synovial tissue culture	None	INH/RMP [19], PZA (0.5)	Resection	Good

Table 1 *(continued)*

Author and year	Sex, age in years	Time from TKA to disease	Diagnostic method	Other sites of disease	Medical treatment (months)	Surgical intervention	Outcome at follow-up
[4]						arthroplasty	6 months
Uhel, 2018 [4]	F, 85	14 years	Synovial fluid culture	None	INH/RMP [16], EMB [2], PZA [1]	Resection arthroplasty	Good 2 months
Uhel, 2018 [4]	M, 86	9 years	Synovial fluid PCR	None	INH/RMP/OFX [11], EMB [4]	Resection arthroplasty	Good 3 months
Uhel, 2018 [4]	M, 84	11 years	Synovial tissue PCR and culture	Liver, spleen	INH/RMP [13]. EMB [2]	Debridement	Dead
Uhel, 2018 [4]	M, 79	7 years	Synovial fluid culture	Pericardiac, pulmonary, liver	INH/RMP [16] EMB [4] PZA [2]	None	Good 1 year
Veloci, 2018 [31]	F, 34	3 years	Synovial fluid culture	None	INH/RMP [22] EMB/PZA [2]	None	Good, 2 years
Veloci, 2018 [32]	M 62	3 years	Synovial fluid culture and histopathology	None	INH/RMP [22] PZA [2]	None	Good 1 months

TKA, total knee arthroplasty; M, male; F, female; NM, not mentioned; OFX, ofloxacin; MOX, moxifloxacin; INH, isoniazid; RMP, rifampin; PZA, pyrazinamide; EMB, ethambutol; PCR, polymerase chain reaction.

TKA PJI with this organism and should have a high index of suspicion when accompanying systemic symptoms; therefore, the appropriate microbiological studies for MTB must be performed. Although this patient presented many years following his TKA, he was completely cured without the need of any surgical intervention. In an appropriate setting this may be an optimal treatment option for similar cases; however, this can only be validated with properly designed clinical trials attempting to compare the two treatment modalities to reach a solid conclusion once and for all.

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None. Written consent was obtained.

Declaration of Competing Interest

All Authors have no declared conflict of interest.

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