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Management of *Mycobacterium tuberculosis* Prosthetic Joint Infection: 2 Cases and Literature Review

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Prosthetic joint infection caused by *Mycobacterium tuberculosis* (TBPJI) is uncommon but can be encountered in immunocompromised patients or those from tuberculosis-endemic regions. A lack of clinical suspicion and experience with TBPJI often leads to a delay in diagnosis. We report 2 cases of TBPJI in a Hungarian-Canadian and Iranian-Canadian immigrant, respectively. Both were treated with concurrent surgical and medical therapy. We also performed a literature review on TBPJI case reports, outlining their diagnosis and management.

Keywords. extrapulmonary TB; *Mycobacterium tuberculosis*; prosthetic joint infection; PJI.

Tuberculosis remains a major global health problem with an estimated 10 million incident cases worldwide in 2019 [1]. In Canada, 1796 cases of active tuberculosis were reported in 2017, with an incidence of 4.9 per 100 000 population [2]. Most cases were from foreign-born (71.8%) and Canadian-born Indigenous populations (17.4%) [2].

In 2017, extrapulmonary tuberculosis accounted for 21.4% of all tuberculosis cases reported in Canada [2]. In 2010, osteoarticular tuberculosis (eg, Pott disease, tuberculous arthritis) accounted for 2.5% of all tuberculosis cases reported in Canada [3], a proportion essentially unchanged for years and similar to that of neighboring countries (eg, United States) [4, 5].

Prosthetic joint infections caused by *Mycobacterium tuberculosis* (TBPJI) are rare [6, 7]. Similar to native joint tuberculous arthritis, the varied clinical and radiographic presentation of TBPJI, as well as lack of consideration by clinicians, often leads to delays in diagnosis and subsequent disease progression [8–10].

To date, there are no established, evidence-based recommendations on the diagnosis and management of TBPJI. We report 2 cases of TBPJI and review the current literature on this topic.

CASE 1

A 71-year-old immunocompetent, nondiabetic woman had progressive left hip pain since 2013; initial workup demonstrated normal inflammatory markers, no metabolic bone diseases, and no underlying malignancy by whole-body computed tomography. Her medical history included cardiac bypass surgery.

In April 2017, increasing difficulty ambulating and radiographic signs of severe arthropathy with acetabular erosion prompted surgical intervention. Preoperatively, her C-reactive protein level was elevated (141.6 mg/L), but image-guided hip aspiration for routine bacterial culture was negative.

Intraoperative findings revealed a necrotic femoral head with acetabular erosion, raising concerns for severe inflammatory arthropathy vs occult/past infection; a cement spacer was therefore inserted rather than total hip arthroplasty until infection was ruled out. Intraoperative samples for routine bacterial cultures were ultimately negative. Histopathology demonstrated scattered multinucleated giant cells with granulomatous reaction (Figure 1), though fungal and bacterial (including acid-fast) stains were negative.

She was well until 2 months postoperatively, when a sinus tract developed with serosanguinous discharge from her left hip. A repeat hip aspirate was again negative for bacterial growth. A Mantoux skin test done was positive at 32 mm. An additional hip aspirate was positive for acid-fast bacilli (AFB), later identified as *Mycobacterium tuberculosis* complex at a provincial reference laboratory by mycobacterial culture and in-house–developed nucleic acid amplification testing (NAAT)/polymerase chain reaction (PCR). Recent chest computed tomography revealed old granulomatous disease.

She was referred to Infectious Diseases for management. Further history revealed possible childhood exposure to active pulmonary tuberculosis from her stepmother when the patient emigrated from Hungary to Austria in 1987, before permanently residing in Canada in 1989.
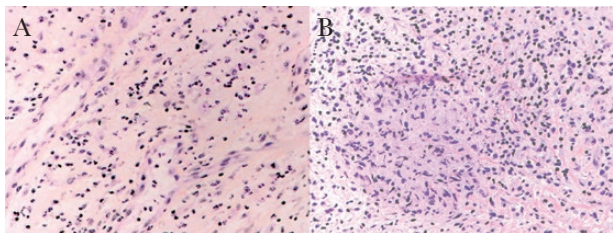
Figure 1. Histopathology of left acetabulum tissue from case-patient 1. *A*, Acute neutrophilic inflammation (hematoxylin and eosin [H&E] stain, ×400). *B*, Granulomatous reaction with scattered multinucleated giant cells (H&E stain, ×400).

The patient was treated with isoniazid, rifampin, and ethambutol. Pyrazinamide was avoided due to age and the increased risk for drug-induced hepatitis. Her isolate was pan-susceptible to first-line agents; she continued triple therapy for 2 months followed by isoniazid and rifampin for an additional 10 months. She responded well to antimycobacterial therapy (AMT) alone without any adverse reactions. In September 2018 (2 months after completing AMT), she underwent a revision total hip arthroplasty to improve mobility (from a cement spacer) and remains clinically well postoperatively.

CASE 2

A 50-year-old man was seen for worsening mobility and inability to work due to prosthetic hip infection in 2016. His past history included left hip osteomyelitis as a child, complicated by osteoarthritis requiring multiple surgeries. He underwent total hip arthroplasty in 2013 at age 47. Preoperative imaging showed a grossly deformed femoral head, neck, and intertrochanteric region. During arthroplasty, tissue samples sent for routine bacterial cultures and histopathology for standard (ie, bacterial, fungal) stains were negative. In 2014, he underwent a washout with head/liner exchange and 6 weeks of ceftriaxone, vancomycin, and rifampin for culture-negative prosthetic joint infection (intraoperative samples negative for routine bacterial cultures). For reasons unexplained, he continued rifampin monotherapy until reassessment in June 2016 for increased swelling and sinus drainage from his surgical wound. A superficial wound swab grew *Peptostreptococcus* spp, which was interpreted as a contaminant.

He underwent single-stage revision arthroplasty with operative cultures yielding no bacterial growth. Suspecting an indolent infection, additional specimens were sent for AFB and returned positive with confirmed *M tuberculosis* complex by NAAT/PCR and mycobacterial culture. Histopathology demonstrated necrotizing granulomas and presence of AFB. Sputum acid-fast staining was negative; the patient denied any respiratory symptoms. Recent chest radiography showed healed granulomatous disease.

Infectious Diseases was consulted for management. The patient was born in Iran but lived in Afghanistan and Uzbekistan during childhood before permanently residing in Canada. Of interest, his wife was treated for tuberculous mastitis in 2010; the patient received a 9-month course of isoniazid for latent tuberculosis treatment in 2011.

He was treated with isoniazid, rifampin, ethambutol, and pyrazinamide (isolate was pan-susceptible to first-line agents) for 2 months, followed by isoniazid and rifampin for an additional 10 months. He responded well to AMT with only mild transient thrombocytopenia and lymphopenia during therapy. Six months after completion of AMT and following rehabilitation, he successfully returned to work with full capacity and remained clinically well.

REVIEW OF THE LITERATURE

We undertook a comprehensive search of English-language articles from inception to February 2021 through Embase, Ovid Medline, PubMed, and Google Scholar, using keywords "*Mycobacterium tuberculosis*" and "prosthetic joint infection" including medical subject heading (MeSH) terms (Supplementary Files 1 and 2). Nonhuman infections were excluded. Native joint septic arthritis, infections not involving prosthetic joints, infections by pathogens other than *M tuberculosis*, and non-English articles were excluded. Our search expanded by reviewing citations from included studies. We identified a total of 107 cases of TBPJI from 50 published articles (Supplementary Table 1) [7, 11–59].

Median age was 71 years (interquartile range [IQR], 60.3–79 years), with male-to-female ratio approaching 1:1. The most common were hip (52%) and knee (43%) infections; other affected joints were also reported. Patients initially received arthroplasty for osteoarthritis (70%), inflammatory arthritis (9.5%), or fracture involving the joint (12.3%).

Twenty-two (20.6%) cases reported underlying comorbidities (Table 1). Twenty-nine (27.1%) cases reported prior tuberculous infections, including pulmonary (n = 10), osteoarticular (n = 13), and latent infection (n = 2). Only 3 cases documented prior treatment. Ten patients reported having lived in or traveled to endemic countries. Only 1 case confirmed prior household exposure to tuberculosis.

Clinical presentations varied and were nonspecific. Localized (eg, pain, swelling) and constitutional (eg, fever, night sweats, weight loss) symptoms were described, including development of sinus drainage (n = 33) or abscesses (n = 14). Symptom onset following arthroplasty ranged from 10 days to 38 years (median, 2 years); 4 cases had a presumptive diagnosis of TBPJI made intraoperatively.

Diagnosis was confirmed from joint aspirate or tissue sent for 1 or more of the following: AFB staining (n = 19), mycobacterial culture (n = 91), NAAT/PCR (n = 23), or histopathology

Table 1. Summary of Cases and Patient Characteristics From Literature Review, by Medical/Surgical Management

Characteristic	All Patients (N = 107[a])	AMT Only (n = 21)	Surgery Only (n = 4)	AMT + DAIR (n = 27[b])	AMT + Staged Revision[c] (n = 36[b])	AMT + Hardware Removal (n = 22[b])
Age, y, median (IQR)	71 (60.3–79)	65.5 (60–77.5)	59.5 (46–73.8)	73.5 (67.8–80)	69 (56–77)	71.5 (60.3–75)
Female sex	52	7	3	15	18	11
Risk factor						
Diabetes mellitus	12	2	1	2	5	3
Steroid use	6	0	0	2	1	2
Anti-TNF use	2	2	0	0	0	0
HIV/AIDS	1	1	0	0	0	0
Chemotherapy	1	0	0	0	0	1
Preoperative diagnosis						
Osteoarthritis	51/73 (70)	13/17 (76.5)	3/3	10/16 (62.5)	21/28 (75)	8/13 (61.5)
Inflammatory arthritis	7/73 (9.5)	4/17 (23.5)	0/3	2/16 (12.5)	0/28	1/13 (7.7)
Fracture	9/73 (12.3)	0/17	0/3	4/16 (25)	4/28 (14.3)	1/13 (7.7)
Other	6/73 (8.2)	0/17	0/3	0/16	3/28 (10.7)	3/13 (23.1)
Arthroplasty						
Hip	56	8	3	12	22	13
Knee	46	13	1	14	12	7
Other	5	0	0	1	2	2
Other bacteria isolated from joint aspirate	26	0	1	5	12	9
AMT duration, mo, median (IQR)	12 (11.3–18)	15 (12–18)	NA	12 (9–15.5)	13 (11–15.8)	12 (12–15.8)
Outcome						
Clinical resolution	81/102 (79.4)	18/20 (90)	0/3	21/27 (77.8)	29/35 (82.9)	17/21 (81)
Functional loss[d]	6/102 (5.9)	1/20 (5)	1/3 (33.3)	0/27	2/35 (5.7)	2/21 (9.5)
Clinical failure[e]	4/102 (3.9)	0/20	0/3	3/27 (11.1)	1/35 (2.9)	0/21
Overall mortality	11/102 (10.8)	1/20 (5)	2/3 (66.7)	3/27 (11.1)	3/35 (8.5)	2/21 (9.5)
TB-related death	4/102 (3.9)	1/20 (5)	0/3	1/27 (3.7)	1/35 (2.9)	0/21
Additional surgery required	5/102 (4.9)	0/20	0/3	4/27 (14.8)	1/35 (2.9)	0/21

Data are presented as No. or as no./No. (%) unless otherwise indicated.

Abbreviations: AMT, antimycobacterial therapy; DAIR, debridement and implant retention; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; TB, *Mycobacterium tuberculosis*; TNF, tumor necrosis factor.

[a]Two patients received no interventions (1 was lost to follow-up, 1 had a postmortem diagnosis of prosthetic joint infection caused by *Mycobacterium tuberculosis*).

[b]Five cases received 2 surgical interventions: DAIR + 2-stage revision (n = 2); DAIR + hardware removal (n = 2); and 2-stage revision + hardware removal (n = 1).

[c]Staged revision includes 1-stage and 2-stage revision arthroplasty.

[d]Functional loss defined here as limitations or inability to use affected joint to carry out activities or functions of daily living (in relation to unaffected joint).

[e]Clinical failure includes chronic joint infection, relapse of infection, etc.

(n = 32). Twenty patients had a tuberculin skin test done (16 positive; 4 negative). One or multiple bacterial pathogens were isolated in at least 26 cases prior to confirmation of TBPJI, including *Staphylococcus aureus* (n = 10), coagulase-negative staphylococci (n = 10), *Corynebacterium* spp (n = 3), and *Pseudomonas aeruginosa* (n = 3).

Table 1 summarizes patient characteristics and outcomes based on the treatment modality received. Excluding patients receiving no interventions, almost all patients (96%) received AMT. The 4 cases receiving surgery only (2 hardware removal, 2 staged revisions) have no explanation available for omission of AMT, although 2 patients died shortly from unrelated causes and 1 was lost to follow-up. For the 21 medically managed cases, 2 were clinically unstable to undergo surgery, and 8 had stable prosthesis or recent surgical intervention for the joint.

Choice of AMT combinations varied depending on clinician and drug adverse events; generally, a combination of first-line antimycobacterials was used unless drug resistance was detected. Duration ranged from 6 months to 3 years, including 1 case considering lifelong suppression (drug not specified) following debridement and implant retention surgery [55]. Slightly longer courses (median, 15 months [IQR, 12–18 months]) appeared to be used in those receiving AMT only, compared to those undergoing combined medical/surgical management (eg, median, 12 months [IQR, 12–15.8 months]).

The follow-up period ranged from immediately completing AMT to 20 years. Most cases (81 of 102 [79.4%]) had clinical resolution. Four of 11 deaths were attributed to tuberculosis, including disseminated or pulmonary tuberculosis (n = 2), multidrug resistance (n = 1), and 1 case of postmortem-confirmed TBPJI without receiving treatment. Five unrelated deaths were due to preexisting conditions (eg, cancer, cirrhosis); 2 cases did not report cause of death.

DISCUSSION

Mycobacterium tuberculosis is an acid-fast, aerobic bacillus with humans as its only known reservoir [60]. It has a wide spectrum of clinical manifestations, including pulmonary, disseminated, and osteoarticular tuberculosis [61].

Prosthetic joint infections caused by *M tuberculosis* are uncommon [6, 7]. One explanation is that the population more often undergoing joint replacement surgery (ie, higher income or socioeconomic status) [62] is less likely affected by tuberculosis, which largely impacts marginalized persons or those from tuberculosis-endemic countries, though this trend may change as access to health care improves with time [63].

Based on our literature review, the nonspecific clinical presentation and variable timeline for symptom onset following arthroplasty suggest the need for a detailed history by the clinician suspecting TBPJI. This includes outlining any relevant risk factors including immunocompromised status, travel to or living in endemic regions, or prior active or latent tuberculosis infection, as well as an exposure history that raises suspicion and need to obtain samples for microbiologic testing of TBPJI [6, 64]. Although the tuberculin skin test was used in cases (19%) from our literature review, it should not be relied upon to diagnose or exclude active infection [3, 65].

Clinicians should consider atypical pathogens (eg, fungal, *M tuberculosis*) when patients with PJI fail a trial of empiric antibiotics with negative synovial or tissue cultures for common bacteria. However, 24% of cases in our literature review had other bacteria isolated, further delaying diagnosis of TBPJI. Possible coinfections with intracellular bacteria (eg, *Salmonella* spp, *Listeria* spp) via survival within macrophages through a cell-mediated response (Th1) was proposed in case reports/series [66–68]; however, a population-based study found no associated infection risk with intracellular pathogens in patients with active tuberculosis vs the general population [69]. Additionally, we searched for *M tuberculosis* and coinfection with bacteria reported in our literature review; few case reports were found [70, 71]. The relation between tuberculosis and other bacteria causing PJI may be of interest for future research.

As with native joint tuberculous arthritis and extrapulmonary tuberculosis, diagnostic confirmation of TBPJI is challenged by poor diagnostic yield and low sensitivity (19%) of AFB smear microscopy on extrapulmonary samples, which are often paucibacillary [3, 65]. As such, synovial fluid (sensitivity, 64%–79%) or tissue (sensitivity, 94%) for mycobacterial culture is often required [3], although the incorporation of NAAT/PCR testing (if available) offers rapid identification of *M tuberculosis* [72], as in our 2 presented cases. The advent of next-generation sequencing offers greater versatility in diagnosis of tuberculosis, drug resistance detection, and typing of *M tuberculosis* [73]. In England, whole-genome sequencing available as part of routine testing for tuberculosis along with rapid molecular diagnostics (NAAT/PCR) allows for effective public health outbreak investigation and earlier genotypic susceptibilities [73]. Certainly, considering use of whole-genome sequencing depends on cost-effectiveness in comparison to standard culture and molecular testing methods, availability of trained personnel and local infrastructure, and local prevalence of tuberculosis.

The patient characteristics, stratified by treatment modality (Table 1), appeared to be similar between groups. Duration of AMT (median, 12 months [IQR, 11.3–18 months]) may have been extrapolated from guidelines for native joint tuberculous arthritis [6, 74], where 6–12 months of isoniazid- and rifampin-based regimen is recommended, with longer durations preferred for complicated cases [3]. The optimal AMT duration for TBPJI remains to be determined, although based on our literature review, slightly longer courses were used in patients receiving AMT alone vs combined medical/surgical management. Though not explicitly mentioned, clinicians likely preferred longer courses to achieve remission in patients where hardware retention is part of the management strategy.

Comparing outcomes between treatment groups, rate of clinical resolution seemed to be higher in patients on AMT only. Approximately 40% of patients on AMT alone were assessed by their surgeon to have stable prosthesis (ie, better prognosis) without further surgical intervention needed. Conversely, patients requiring surgery likely had severe hardware-related complications contributing to less favorable outcomes. Although overall clinical success appeared similar between groups receiving combined medical/surgical management, patients undergoing debridement and implant retention surgery were more likely (15%) to require definitive surgery afterward (ie, staged revision, hardware removal) to achieve clinical remission and regain function/mobility. As choice of optimal medical and/or combined surgical management remains tentatively a case-by-case decision in consultation with Infectious Diseases and Orthopedics, larger observational studies comparing treatment strategies may be conducive to developing best practices for TBPJI.

CONCLUSIONS

TBPJI is a rare manifestation of tuberculosis, but clinical suspicion should be raised in those with epidemiologic and clinical risk factors for active tuberculosis infection, which may include failure to respond to prior antibiotics for treatment of PJI. Though medical therapy alone has shown promising outcomes based on our literature review, further studies comparing treatment strategies (AMT and/or surgical management) are required to better define groups of patients who require either or both as their optimal management for TBPJI.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online.

Notes

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