CLINICAL ARTICLE

Total Knee Arthroplasty in Patients with Unsuspected Tuberculosis of the Joint: A Report of Four Cases and a Systematic Review of the Literature

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Objectives: To provide a case series and systematic review that explores the clinical manifestations, treatments, and methods for defining tuberculosis diagnoses in patients who have undergone total knee arthroplasty (TKA).

Methods: Four patients (three women, one man; average age, 59.5 ± 8.89 years; range, 48–69 years) underwent TKA and were subsequently treated for previously unsuspected knee tuberculosis between January 2013 and December 2019. We also reviewed published cases of tuberculous periprosthetic joint infections (TBPJIs) following TKA through databases of MEDLINE/PubMed, the Cochrane Library, and EMBASE. We reviewed studies that were published between January 1980 and December 2019.

Results: In our four cases, the preoperative diagnoses were osteoarthritis (n = 2), rheumatoid arthritis (one case), and Charcot's arthropathy (one case). The main clinical manifestations were knee swelling and pain, without fever, weakness, or weight loss. Comorbidities included multiple joints with rheumatoid arthritis or Charcot's arthropathy, diabetes mellitus, and uremia. One patient had a history of lumbar tuberculosis treated with debridement and intervertebral fusion. Preoperative elevated erythrocyte sedimentation rates (ESRs) were detected in all cases, and elevated C-reactive protein (CRP) levels were observed in three cases. The tuberculosis diagnoses were confirmed *via* histopathologic analysis (three cases) and second-generation sequencing (one case). Three patients received antituberculosis therapy for 1 year, without surgical intervention. Two-stage exchange arthroplasty was performed in one patient because of prosthesis loosening. Within an average follow-up period of 24.75 months, tuberculosis reactivation was not observed and overall functional improvement was demonstrated. Forty-four TBPJI cases were reported in the literature between January 1980 and December 2019. Most (59.09%) occurred within the first year after the index arthroplasty, and the diagnoses were confirmed by culturing *Mycobacterium tuberculosis* in 88.64% of cases. Favorable outcomes were achieved in 90.91% of the patients who did not undergo surgery, 71.43% of those treated with debridement, 93.33% undergoing revision arthroplasty, and in 90.91% of those undergoing resection and arthrodesis.

Conclusions: Clinical manifestations of knee tuberculosis and TBPJI are atypical. Thus, attention should be paid to finding the causes of increased ESRs and CRP levels, particularly in patients with weakened immune functioning, before performing TKA. Pathological examination is an effective method for diagnosing tuberculosis, although sending multiple specimens for pathological examination is necessary.

Key words: Arthroplasty; Infections; Knee; *Mycobacterium*; Tuberculosis

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Introduction

In 2016, the top 10 causes of death accounted for more than half (56.9 mn; 54%) of deaths worldwide. Tuberculosis was the tenth leading cause of death globally; it ranked seventh in low-income countries and fifth in lower middle-income countries. There were 1.3 mn tuberculosis-related deaths worldwide in 2016[1].

Globally, an estimated 10.0 mn (range, 9.0–11.1 mn) people experienced tuberculosis in 2018, with an incidence of 132 per 100,000 people[1], despite the total number of tuberculosis-related deaths decreasing by 11% between 2015 and 2018[2]. There were an estimated 1.2 mn (range, 1.1–1.3 mn) tuberculosis-related deaths among HIV-negative people in 2018 and an additional 251,000 deaths (range, 223,000–281,000) among HIV-positive people[3]. China accounted for 9% of all tuberculosis cases, worldwide, second only to India, which accounted for 27% of all cases[4].

Bone and joint tuberculosis is the third most common type of extra pulmonary tuberculosis, accounting for 10%–15% of such cases; it predominantly involves the spine and the large joints (sacroiliacs, hips, knees, etc.)[5, 6]. Compared with other types of bone and joint tuberculosis, the incidence of knee joint tuberculosis is lower and primarily occurs in underdeveloped countries. In addition, patients with weakened immunity have been found to be more susceptible to latent tuberculosis of the knee joint[7]. Because the clinical manifestations of joint tuberculosis are atypical and vary widely, accurate diagnoses during the early stages of disease remain difficult. In particular, patients with primary knee osteoarthritis, or other diseases, combined with early tuberculosis of the knee are easily misdiagnosed as having only the original disease[8]. If tuberculosis of the knee is treated as a non-infectious joint disease, using only joint replacement, there can be undesirable consequences.

A previous study analyzed 89 cases of relapsed joint tuberculosis after surgical treatment (mostly joint fusion surgeries). Among them, 45 patients (50.6%) did not receive antituberculosis chemotherapy because of misdiagnoses, and 32 (36.0%) received non-standard antituberculosis chemotherapy[9]. Su *et al.* summarized the information from eight patients with tuberculous knee arthritis, who received antituberculosis treatment received 2–20 months before their operations, 12 months after their operations, and during a 3.4–11-year follow-up period; only one patient relapsed[10]. Moreover, Kim *et al.* reported patients who were not considered to have clinical manifestations of active tuberculosis because their erythrocyte sedimentation rates (ESRs) and C-reactive protein (CRP) levels were normal; therefore, preoperative antituberculosis treatment was not given, resulting in three cases of tuberculosis recurrence within 2–3 months after surgery[11]. Although these patients were postoperatively diagnosed with tuberculosis and received antituberculosis treatment, the recurrence rate was still high. Therefore, preoperative antituberculosis treatment plays an important role in avoiding tuberculosis recurrence. However, there have been inconsistencies in the reported preoperative medication treatments and intervals. Su *et al.* reported eight patients with tuberculous arthritis who underwent knee replacement, three were medicated for 2 months and five were treated for 10–12 months[10]. The treatment plans for these patients involved treatment with three antituberculotic medications (rifampicin, ethambutol, isoniazid) for at least 12 months after surgery. The average time from tuberculosis diagnosis to total knee arthroplasty (TKA) was 25.7 months; only one patient with rheumatoid arthritis had tuberculosis recurrence within 14 months after surgery, and the joint fusion was cured[10]. Moreover, Ozturkmen *et al.* reported 12 patients with active tuberculosis who underwent TKA: three had two-stage knee replacements, with the interval between the stages phases ≤6 months and antituberculosis treatment before and after the operation; the other nine had one-phase knee replacements and preoperative antituberculosis treatments[12]. The treatment combined four antituberculotic medications for 2 months after the operation, followed by two antituberculotic medications for another 10 months. Among these patients, three had higher than normal ESRs and CRP levels 6 months after the operations; therefore, their treatments with antituberculosis medications were extended to 18 months. The average time from tuberculosis diagnosis to TKA, in that study, was 4.0 ± 1.5 months. During an average follow-up of 6.1 ± 1.8 years, none of the patients experienced tuberculosis relapse. The authors believed that even active tuberculosis was not a contraindication for TKA, and that there was no need to have a long interval between the tuberculosis diagnosis and the TKA.

TKA is performed for tuberculosis of the knee joint, and there is less recurrence when antituberculosis treatment is administered before surgery; otherwise, the recurrence rate would be higher[1]. However, only a few studies have focused on patients diagnosed with tuberculosis of the knee joint after TKA surgery.

The present study aimed to: (i) report the clinical treatment process and prognoses for four patients diagnosed with tuberculosis of the knee joint after undergoing TKA; and (ii) review and assess previous TBPJI reports to analyze the diagnoses and treatments and to summarize the risk factors, clinical manifestations, diagnostic methods, treatment options, and clinical effects of atypical tuberculosis of the knee joint.

Materials and Methods

Patient Information

Between January 2013 and December 2019, 12 patients were diagnosed with tuberculosis and underwent knee joint replacements in our hospital. Among them, four were misdiagnosed with non-infectious arthropathy before TKA; the knee joint tuberculosis diagnoses were made postoperatively. The patients included one man and three women (average age, 59.5 ± 8.89 [range, 48–69] years).

The four patients were residents of our county, and none had a family history of tuberculosis. The preoperative

diagnoses were rheumatoid arthritis (one case), osteoarthritis (two cases), and Charcot's arthropathy (one case). The main patient symptoms were knee joint swelling and pain, without systemic symptoms such as weight loss, fatigue, low fever, and night sweats. Their comorbidities included one case of polyarticular rheumatoid arthritis (due to long-term use of hormones), one case of polyarticular Charcot's arthropathy, one case of diabetes, one case of uremia (hemodialysis), and one case of lumbar spinal tuberculosis (cured 3 years before TKA). Preoperative CRP levels were elevated in three patients, the ESRs were elevated in all patients, and one patient was positive for rheumatoid factor. Moreover, preoperative X-rays showed osteoporosis in one case (rheumatoid arthritis) and bone destruction, subluxation of the knee joint, and soft tissue swelling in one case (Charcot's arthropathy). Other X-rays showed narrow joint spaces, subchondral bone hardening, and osteophyte formation.

Of the four patients who underwent routine knee replacements, three underwent surface replacements and one patient underwent rotating hinge knee arthroplasty (Charcot's arthropathy). Following clinical manifestations of infection, the post-TKA tuberculosis diagnoses were determined by pathological examinations, fluorescent quantitative polymerase chain reaction (PCR) detection, acid-fast staining of joint synovial fluid, and next-generation sequencing technology.

The patient with rheumatoid arthritis did not undergo pathological or joint synovial fluid examinations after TKA. However, the patient continued to experience postoperative swelling and the pain worsened. The patient's knee was punctured several times and the joint fluid cultured, but bacterial growth was not observed. Further, treatment with ceftriaxone and vancomycin had no obvious effect. One year after surgery, the prosthesis loosened and the patient's CRP level and ESR were both elevated. At that point, the patient was diagnosed with prosthetic infectious loosening and underwent debridement and insertion of a placeholder with bone cement containing vancomycin. Finally, postoperative joint fluid was sent for common bacterial culture, and the joint capsule and bone tissue were sent for pathological examinations.

A patient with Charcot's arthropathy continued to have elevated CRP levels, an elevated ESR, and joint effusion. After TKA, the patient underwent bacterial culture of the joint fluid and a soft tissue pathological examination.

One patient with osteoarthritis had a history of spinal tuberculosis surgery. After the TKA, the patient's synovium and bone tissue were sent for pathological examination. The patient with osteoarthritis and uremia underwent hemodialysis treatment but did not undergo a post-TKA pathological examination. The patient developed joint swelling and increased pain, 1 month after surgery. Therefore, the patient was sent for debridement and pathological examination, routine bacterial culture of joint fluid, acid-fast staining, and second-generation sequencing.

All patients diagnosed with tuberculosis of the knee joint, after TKA, were treated with a combination of four antituberculosis treatments (rifampin, isoniazid, ethambutol, and pyrazinamide) for 12 months; the patient with the loose prosthesis also underwent debridement and implantation with bone cement placeholders during the first stage and revision during the second stage.

The patients also underwent rechecks of their CRP levels, ESRs, and liver function indicators during the period that they were medicated. Follow-up observations of knee pain, swelling, and joint mobility of the patients also occurred, with joint scores and function scores calculated according to the Knee Society Score (KSS) criteria.

The protocol for this research project was approved by a suitably constituted Ethics Committee at the institution in which the work was undertaken; the study conformed to the provisions of the Declaration of Helsinki (as revised in Brazil in 2013).

Systematic Review

The inclusion criteria for studies included in this review were: (i) knee arthroplasty; (ii) preoperative diagnosis of non-tuberculous arthritis; (iii) TBPJI; and (iv) *M. tuberculosis* infection. The exclusion criteria included: (i) diagnosis of knee tuberculosis prior to knee arthroplasty; (ii) reviews or meta-analyses describing non-tuberculous mycobacterium infections; (iii) tuberculosis infections in other parts; and (iv) studies not published in English (Fig. 1).

All major databases were queried to perform a comprehensive literature review. The databases included MEDLINE/PubMed, the Cochrane Library, and EMBASE. We reviewed studies that were published between January 1980 and December 2019. The following key words were used along with the AND or OR Boolean operators: knee, tuberculosis, infection, mycobacterium, mycobacterial infection, replacement, and arthroplasty.

The initial database queries produced 191 reports; 162 articles were excluded, including those that were duplicates (43), reviews or meta-analyses (24), descriptions of general periprosthetic joint infections (25), descriptions of hip replacements (14), descriptions of non-tuberculous mycobacterium infections (all case reports, 14), articles on knee joint tuberculosis replacements (23), and non-English reports (19)[13–41]. We identified 44 cases of TBPJI described in the 29 selected articles.

The analysis index included: age, sex, clinical manifestations (joint pain, swelling, sinus and fever, weight loss, night sweats), preoperative diagnosis of TKA, concomitant diseases, and risk factors (to determine whether patients with TBPJI have factors that make them susceptible to infection); time from TKA to infection (to determine whether there is a time period for tuberculosis development); time from infection to diagnosis of tuberculosis of the knee joint (to determine whether the timing of tuberculosis infection diagnosis is associated with the treatment method and clinical prognosis); the method (e.g. bacterial culture, acid-fast staining, pathological examination, PCR examination, and next-generation sequencing) used to diagnose tuberculosis

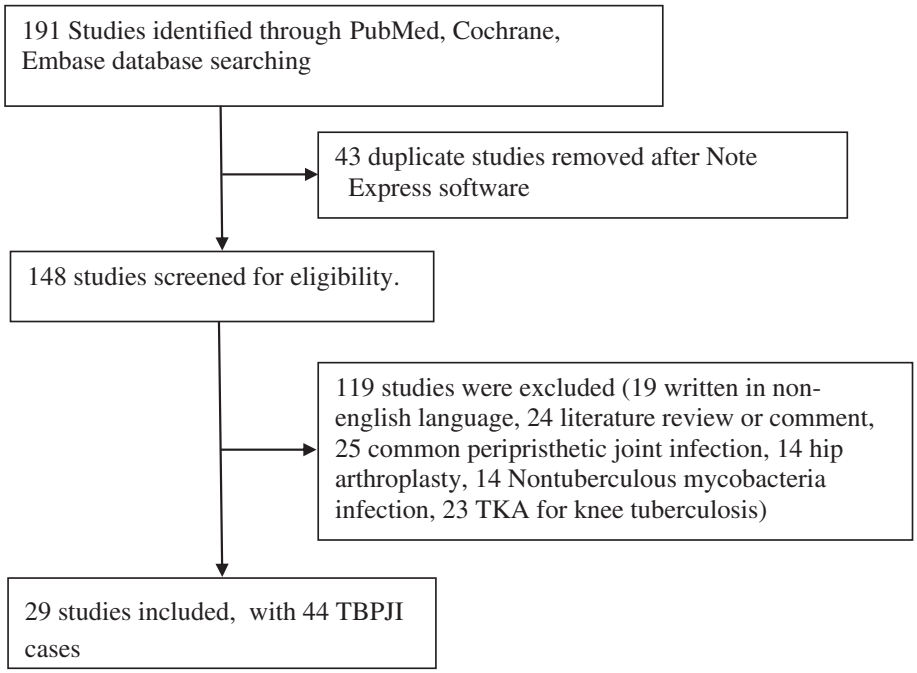

Fig. 1 Flow diagram, illustrating the identification, screening, and exclusion process. Finally, 29 studies were included in this study

(to analyze the value of these methods); types of anti-tuberculosis drugs used and treatment duration; whether surgery was used and the surgical methods used, if any; time from infection to diagnosis of tuberculosis; treatment methods used; and the follow-up duration and clinical results.

Results

Clinical Features of the Cases

Case Descriptions

Case 1. During surgery on the patient with Charcot's arthropathy, turbid synovial fluid, hypertrophy, congestion and edema, dark red and patchy exfoliation of the cartilage, exposed subchondral bone, sclerosis, and free bone fragments in the synovial tissue were observed (Fig. 2).

Case 2. In the patient with rheumatoid arthritis, synovial hyperemia and edema, extensive cartilage destruction, vascular wing formation, and fibrous adhesions were observed during the TKA operation. In this case, synovial hyperplasia and swelling were observed, along with evidence of infection, during post-TKA debridement. There was also free, sand-like bone at the interface between the bone cement and bone bed.

Case 3. During TKA for the patient with osteoarthritis and a history of spinal tuberculosis, we observed synovial hyperplasia, swelling of the subchondral bone of the medial compartment, chondrosclerosis, and surrounding osteophyte formation.

Case 4. During TKA for the patient with osteoarthritis and a history of uremia, we observed light yellow joint fluid, synovial swelling, the subchondral bone of the medial compartment, chondrosclerosis, and surrounding osteophyte formation.

Case Confirmation

None of the four patients in this study had samples submitted for culturing to test for the presence of *M. tuberculosis*. Two of the patients were diagnosed with knee joint tuberculosis following pathological examination of floral multinucleated giant cells and epithelioid cells, with positive auramine-O fluorescence staining. One patient demonstrated chronic inflammation of the synovial tissue, and *M. tuberculosis* was detected using a quantitative fluorescence PCR test. In the final patient, a joint puncture fluid smear was positive for acid-fast bacilli, and next-generation sequencing showed the presence of *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and *M. tuberculosis* complex.

Duration

The results of the present study showed that the time from knee joint replacement to a diagnosis of tuberculosis of the knee joint ranged from 8 to 360 days, with an average of 103.25 ± 171.61 (mean ± SD) days.

Within 3 months of receiving antituberculosis drugs, the patients' CRP levels and ESRs returned to normal. Three of the four patients were cured following antituberculosis drug therapy, without debridement; one patient was cured after two-stage repair. The follow-up period for the patients in this study ranged from 18 to 36 months, with an average of 24.75 ± 9.45 (mean ± SD) months. The average KSS was

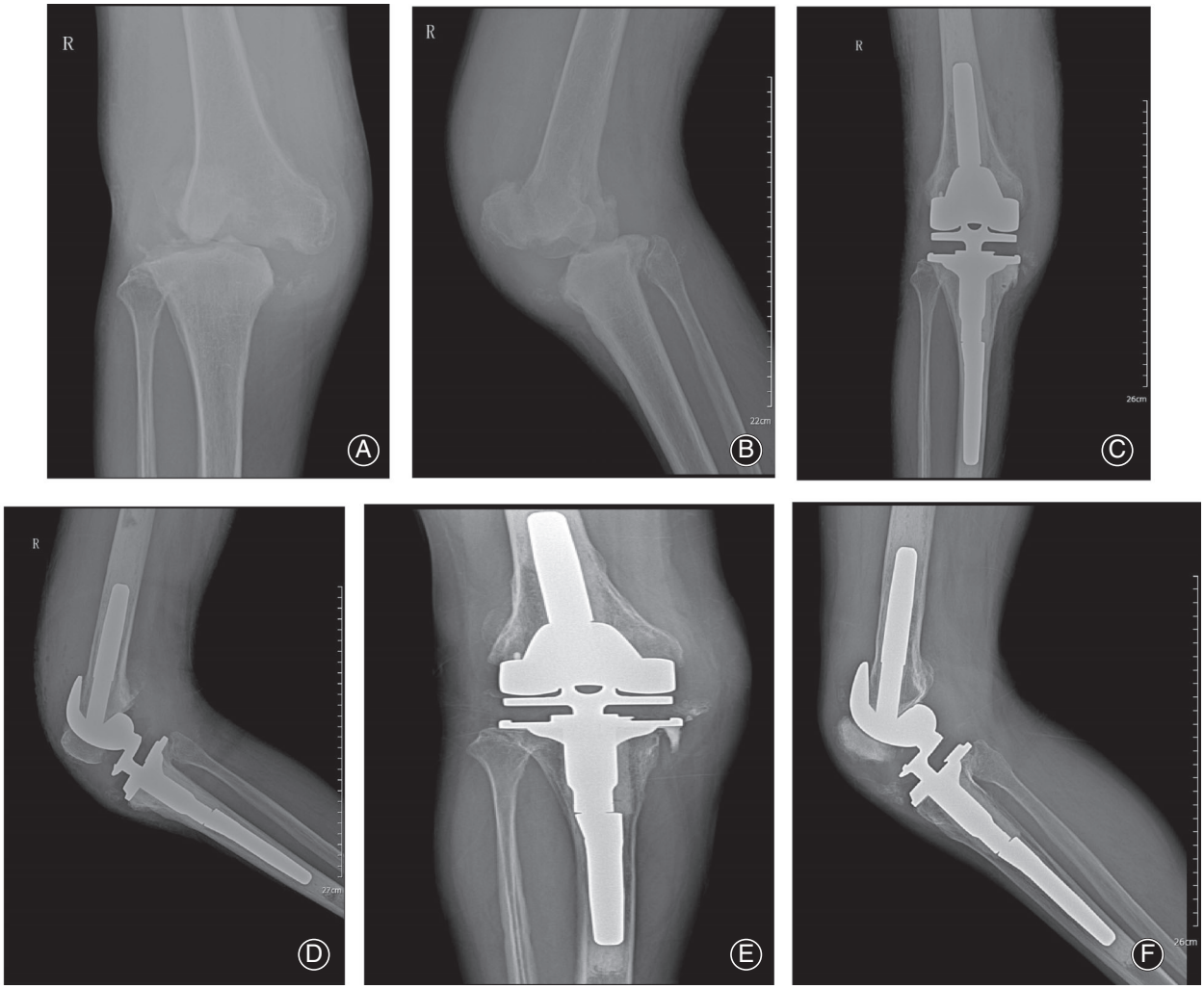

Fig. 2 A 48-year-old female with Charcot's joint disease in her right knee. During surgery on the patient with Charcot's arthropathy, turbid synovial fluid, hypertrophy, congestion and edema, dark red and patchy exfoliation of the cartilage, exposed subchondral bone, sclerosis, and free bone fragments in the synovial tissue were observed. (A, B): Preoperative X-ray of the right knee showing a swollen joint, bony destruction, and subluxation; (C, D) X-ray showing a normal, rotating hinged prosthesis after total knee arthroplasty (TKA); (E, F) X-ray showing the stable prosthesis and the absence of soft tissue swelling, 2 years after the index TKA.

85.25 ± 9.91 (mean ± SD) at the last follow-up, and the average function score was 84.75 ± 11.70 (mean ± SD) points.

Two patients were diagnosed with tuberculosis of the knee joint on postoperative days 8 and 10, and were treated with a combination of four antituberculosis drugs for 12 months; thereafter, they were followed for an additional 21 and 24 months.

Complications and Treatment

During the follow-up period, none of the patients demonstrated recurrence, joint swelling, or pain, and they demonstrated joint mobility of 0°–120°.

The patient with osteoarthritis complicated with uremia and requiring hemodialysis continued to experience swelling and pain after the operation. A joint fluid smear showed acid-fast bacilli, 35 days after surgery; the next-generation sequencing results were positive for *P. aeruginosa*, *B. cepacia*, and *M. tuberculosis* complex. The patient was treated with levofloxacin for 6 weeks, and a combination of the four antituberculosis drugs for 12 months. During the follow-up, the patient did not demonstrate joint swelling, and had joint mobility of 5°–110°.

The patient with rheumatoid arthritis had persistent swelling and pain after the first TKA. Further, the patient's ESR and CRP levels continued to rise, but the results of bacterial cultures from multiple punctures were negative (no tuberculosis cultures were performed). At the same time, broad-spectrum antibiotics were ineffective. After 1 year, the patient's prosthesis loosened.

At that point, the patient underwent implantation of a prosthesis using bone cement containing vancomycin, according to the infectious loosening debridement protocol. The pathological report for this patient revealed tuberculosis; therefore, the patient was immediately started on a combination of four antituberculosis drugs for 12 months. A rotating hinge prosthesis was placed during the second stage of the revision, and antituberculosis treatment was continued for an additional 9 months. During a 3-year follow-up period, the patient did not demonstrate joint swelling or tuberculosis recurrence; the joint mobility was 10°–70°.

Another patient was diagnosed with osteoarthritis and underwent a joint replacement; there was no intraoperative evidence of caseous necrosis. Postoperative pathology indicated the presence of chronic inflammation of the synovial tissue, but no neutrophils were observed. The Polymerase Chain Reaction (PCR) results for the synovial tissue specimens were positive for *M. tuberculosis*. Eventually, this patient was diagnosed with tuberculosis of the knee joint and was treated with a combination of the four antituberculosis drugs for 12 months. After >2 years of follow-up, there was no evidence of tuberculosis recurrence and the knee joint function remained good (Fig. 3).

Systematic Review

Case Information. A total of 29 reports were reviewed in this study, including a total of 44 reported cases of TBPJI (Table 1). Most of the 29 studies were case reports, with one article reporting six cases of TBPJI.

Of the 44 patients with TBPJI, 16 were males and 28 were females. Their ages ranged from 34 to 86 years, with an average age of 70.14 ± 12.57 years. There were two patients in the 30–39-year-old group, two in the 40–49-year-old group, two in the 50–59-year-old group, seven in the 60–69-year-old group, 20 in the 70–79-year-old group, and 11 in the ≥80-year-old group. The clinical manifestations of the patients were similar to those for patients with general periprosthetic joint infections; there were no specific clinical manifestations.

Clinical Manifestation and Concomitant Diseases. Chang[20] and Uhel[31] reported patients with tuberculosis of the knee and hip, respectively, without specifying their clinical manifestations. Among the remaining 33 patients with TBPJI, 29 (29/33; 87.88%) experienced pain, 25 (75.76%) experienced swollen joints, nine (27.27%) had sinus formation, four (12.12%) had masses around their affected knees, and six (18.18%) had fevers. Fifteen patients did not have preoperative diagnoses; however, of the 29 with preoperative diagnoses, 18 (62.07%) had osteoarthritis, six (20.69%) had rheumatoid arthritis, three (10.34%) had traumatic arthritis, one (3.44%) had sequelae of suppurative arthritis, and one (3.44%) had a loose TKA prosthesis.

The other concomitant diseases and risk factors demonstrated by the included patients were: tuberculosis in other parts (n = 14) and tuberculosis of the knee (17/29, 58.62%); diabetes (5/29, 17.24%); systemic or local hormone use (5/29, 17.24%); two with malignant tumors[24]; one with AIDS[26];

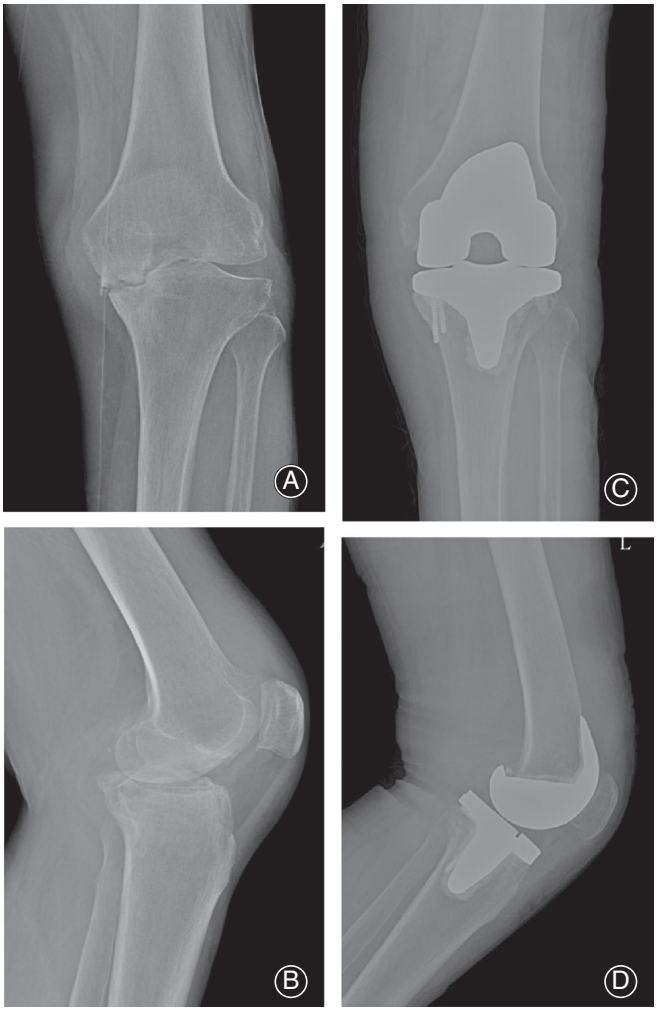

Fig. 3 A 63-year-old female who had undergone debridement, fusion, and fixation for lumbar tuberculosis 2 years earlier. This patient was diagnosed with osteoarthritis and underwent a joint replacement; there was no intraoperative evidence of caseous necrosis. Postoperative pathology indicated the presence of chronic inflammation of the synovial tissue, but no neutrophils were observed. The PCR results for the synovial tissue specimens were positive for *M. tuberculosis*. Eventually, this patient was diagnosed with tuberculosis of the knee joint and was treated with a combination of the four antituberculosis drugs for 12 months. After >2 years of follow-up, there was no evidence of tuberculosis recurrence and the knee joint function remained good. (A, B): Pre-total knee arthroplasty (TKA) X-ray showing disappearance of the medial space in the left knee and the irregular articular surface of the medial femoral condyle; (C, D) Post-TKA X-ray shows a well-positioned prosthesis; (E, F) Two years after the TKA, the position of the knee prosthesis remained good, without any evidence of translucent lines or soft tissue swelling.

TABLE 1 Cases of tubercular prosthetic joint infection reported in the literature

Author	Age/ sex	comorbidity	preoperative diagnosis	Time from TKA to infection	Clinical manifestation	Time from Infection to diagnosis	Diagnostic method	Medical therapy (duration in Month)	surgery	Outcome at Follow-up
Wray [13]	63/M	Pulmonary TB	OA	postoperatively	Pain, swollen	NR	histo	H, R (12)	None	good 18 months
Carrega [14]	80/F	NR	OA	postoperatively	Pain, sinus	NR	histo, culture, AFS	H, R (14), E (2)	Staged revision	Died at 7 months
Veloci[15]	62/M	steroid	OA	postoperatively	pain, swollen	3 years	histo, culture	H, R (18), PZA (2)	None	Good 19 months
Tekin Koruk[16]	55/M	NR	OA	15 days	pain, swollen, fever, Lose weight	1 month	Histo, culture	H, R (12), Z, E (2)	None	good 18 months
Uppal[17]	72F	NR	TKA loosening	1 month	Posteromedial mass of knee sinus	3 years	histo	H, R, Z, E (18)	Debridement	NR
Kadakia[18]	85/F	Pulmonary TB	fracture	1 month	sinus	3 months	culture, AFS, CN-S	H, R, Z, E (6)	None	NR
Lee[19]	79/F	NR	OA	2 months	Pain, swollen	2 months	histo	H, R, Z, E (12)	Debridement	good 13 months
Marmor[20]	66/M	Disseminated TB	OA	2 months	Pain, swollen, fever	4 months	histo, culture	H, R, Z (6)	Staged revision	good 60 months
Tokumoto[21]	71/F	Hip TB, 46 years ago	OA, Latent TB	2 months	pain, swollen	NR	histo, culture, SAU	H, E (18)	Removal of prostheses	good 96 months
de Haan[22]	75/F	Knee TB, 61 years ago	OA	3 months	pain, swollen	1 month	culture	H, R, Z, E (9)	Debridement	good 36 months
Khater[23]	75/F	Popliteal mass, debridement	Sequela of Septic Arthritis	3 months	pain, swollen, sinus	1 month	culture	H, E (18), R, Z (NR)	Removal of prostheses	NR
Marmor[20]	65/F	Urinary TB	OA	3 months	pain, swollen	6 months	histo, culture	H, R, Z (6)	Staged revision	good 84 months
Marmor M[20]	77/F	diabetes	OA	4 months	abscess	1 month	histo, culture	H, R, Z (8)	Debridement	good 18 months
Chang CH[24]	70/F	hypertension	NR	4 months		2.5 months	culture	H, R, Z, E (8), H, R (4)	Staged revision	good 917 months
von Keudell[25]	84/M	Pulmonary TB 61 years ago	RA	5 months	pain, swollen, sinus	<1 month	histo, culture, AFS	H, R, Z, E (12), H, R	Staged revision	good 924 months
Marschall[26]	48/M	AIDS, ulmonary TB, Tubercular meningitis	OA	6 months	pain, swollen	3 months	PCR, culture	H, A, E (1), MOX (0.5), R (0.5)	None	Died during therapy
Al Soub[27]	61/M	hypertension, diabetes	OA	6 months	pain, swollen	2 months	histo, culture, SEP	E, Z (13), Mox (13)	Staged revision	good 20 months
Harwin[28]	60/F	LTBI treated 25 years ago	OA	7 months	Medial mass of knee, sinus	2 years	Histo, culture	H, R (21), Z, E (12)	Staged revision	good 24 months
Chang[24]	72/F	Parkinsonism, pulmonary TB, Prostate Ca, Pituitary adenoma	NR	7 months		2.5 months	culture	H, R, Z (12)	Staged revision	good 24 months
Chang[24]	81/F	HTN, HCV, Thyroid Ca, Prostate Ca	NR	8 months		8 months	culture	H, R, Z, E (14)	Staged revision	good 27 months
Al-Shaikh[29]	73/F	NR	OA	8 months	pain, swollen	5 months	histo, culture, SAU	H, R, Z (21), E (9)	Removal of prostheses	good 12 months
Veloci[15]	34/F	NR	RA	8 months	Lateral mass of knee	4 years	histo, culture	H, R (18), Z, E (2)	None	good 24 months
Klein[30]	36/F	Genital TB 11 years ago steroid	RA or OA	11 months	pain, swollen	1 month	histo, culture	H, R, Z, E (19), MOX, AMK (19)	Staged revision	good 36 months

Chang[24]	80/M	Pulmonary TB parkinsonism	NR	11 months		3 months	culture	E, TBN, STREP	Debridement	Chronic infection
Wang[31]	72/M	Pulmonary TB	OA	1 year	pain	3 months	histo, culture	H, R, Z, E (1)	Debridement	Died for Other reason
Wolfgang[32]	61/M	NR	OA	1 year	pain, swollen	3 months	histo, culture	H, R (24), Z (2)	Staged revision	good 12 months
Elzein[33]	72/M	HTN	NR	14 months	pain, swollen, sinus, fever	5 months	culture	H, R (24), Z (2), H, R (10)	Staged revision	good 26 months
Chang[24]	72/F	diabetes	NR	2 years		1.5 months	culture	H, R (24), Z (14)	Staged revision	good 34 months
Chang[24]	73/F	HTN	NR	29 months		3 months	culture	H, R, Z (15)	Staged revision	good 111 months
Kandnari[34]	55/F	NR	RA	3 years	pain, swollen	NR	culture	H, R, Z, E (10)	None	NR
Uhel[35]	84/F	NR	NR	3 years		NR	culture	H, R (16) Z, E (2)	None	NR
Zeiger[36]	40/F	NR	NR	4 years	pain, swollen	NR	culture	NR	Removal of prostheses	NR
Barry[37]	80/M	Diabetes Pulmonary TB	OA	4 years	pain, swollen, fever, lose weight	1 month	PCR, culture IGRA	H, R, Z, E (2), H, R (10)	None	good 12 months
Spinner[38]	70/F	steroid	RA	5 years	pain, swollen, sinus	2 months	Culture CN-S	H, E (12)	Removal of prostheses	good 30 months
Carrega[14]	72/F	diabetes	NR	7 years	pain, swollen, sinus	NR	histo, culture	H, R (12), E (2)	Staged revision	good 12 months
Uhel[35]	79/M	Pulmonary TB, pericarditis TB, Liver TB	NR	7 years	NR	NR	Culture AFS	H, R (16), E (4), Z (2)	Removal of prostheses	good 12 months
Uhel[35]	82/F	NR	NR	9 years	NR	NR	Culture AFS	H, R (19), Z (0.5)	Removal of prostheses	good 6 months
Uhel[35]	86/M	NR	NR	9 years	NR	NR	PCR	H, R, OFX (11), E (4)	Removal of prostheses	good 3 months
Uhel[35]	84/M	Pulmonary TB 35 years ago Liver, spleen TB	NR	11 years		NR	PCR, culture	H, R (13), E (2)	Debridement	Died during therapy
Neogi[39]	73/F	NR	OA	14 years	pain, swollen	2 months	histo, PCR	H, R (18), Z (7), E (4)	None	good 36 months
Uhel[35]	85/F	NR	NR	14 years		NR	culture	H, R (16), Z (1), E (2)	Removal of prostheses	good 2 months
Lusk[40]	75/F	Diabetes hemodialysis	Traumatic arthritis	16 years	pain, swollen	NR	histo, culture	H, Z, E (6), R (1)	Removal of prostheses	Died during therapy
Tokumoto[21]	70/F	steroid	traumatic	38 years	pain, swollen	3 months	histo, culture	H, R (12)	Removal of prostheses	good 324 months
Egües Dubuc[41]	77/F	Anti-TNF steroid	RA	NR	pain, swollen, fever, mass	1 year	PCR	H, R, Z	None	NR

AFS, acid-fast staining method; AIDS, acquired immune deficiency syndrome; AMK, amikacin; anti-TNF, anti tumor necrosis factor; CN-S, coagulase negative staphylococcus,; Disseminated TB, positive isolation of TB from blood culture; E, Ethambuto; F, female; H, Isoniazid; Histo, histopathological examination; HTN, hypertension; IGRA R, Interferon gamma release assay; LTBI, latent tuberculosis infection; M, male; MOX, moxifloxacin; NR, not reported; OFX, ofloxacin; PCR, polymerase chain reaction; R, Rifampicin; SAU, *Staphylococcus aureus*; SEP, *Staphylococcus epidermidis*; STR, streptomycin; TB, tuberculosis; TBN, prothionamide; Z, Pyrazinamide.

and one requiring hemodialysis due to renal failure[36]. In addition, 26 of 44 patients (59.09%) had at least one risk factor (tuberculosis, rheumatoid arthritis, glucocorticoid, diabetes, tumor, dialysis, and AIDS).

Duration Between Surgery and TBPJI Diagnoses. Among the 44 patients, there was a wide range of times between surgery and TBPJI diagnoses, ranging from immediately after TKA (characterized by persistent pain, swelling, restricted mobility, etc.) to 38 years after surgery. The average time between the TKA and the occurrence of infection was 44.69 ± 81.22 months. The majority of cases (26; 59.09%) occurred within 1 year after surgery, with an average time of 4.88 ± 3.78 months. The average time from infection to the TBPJI diagnosis was 7.31 ± 11.68 months (range, 1–48 months). The reason for the delayed diagnoses was most commonly the failure to immediately suspect tuberculosis; tuberculosis was considered only after the cultivation and identification of common bacteria.

Tissue Culture. Of the 44 patients with TBPJIs, 39 (88.64%) were identified as positive following joint fluid or tissue culture, 21 (47.73%) following positive pathological examinations, six (13.64%) following positive PCR tests, and five (11.36%) following positive acid-fast staining results.

Treatment With Antituberculosis Drugs. Furthermore, of the 44 patients, 11 (25%) were treated with antituberculosis drugs, alone. Ten of those were cured (cure rate, 90.91%); only the patient with AIDS died during treatment[26]. Seven (15.91%) patients underwent debridement and spacer replacement. Of these, one patient died during treatment[14] and another experienced chronic infection (treatment success rate, 71.43%). Moreover, of these 44 patients, 15 (34.09%) prostheses were successfully retained, 15 (34.09%) required second-stage renovation, and 11 (25%) required joint fusions after prosthesis removal (one of whom died during treatment)[34]. None of the patients underwent primary revision. The average time from infection to diagnosis, for cases treated only with antituberculosis drugs, was 13.25 ± 17.19 months (range, 1–48 months), the average time from debridement to diagnoses of tuberculosis of the knee was 7.67 ± 12.70 months (range, 1–36 months), and the average time between a patient undergoing revision surgery and the diagnosis of tuberculosis of the knee was 4.88 ± 5.85 months (range, 1–24 months). In addition, 11 patients underwent fusion surgeries, while the time from treatment to diagnosis in the other four patients was 2.75 ± 1.48 months (range, 1–5 months).

The administered antituberculosis drug treatment mostly involved a combination of four drugs (rifampicin, isoniazid, ethambutol, and pyrazinamide). Under normal circumstances, the drug combination was continued for 12 months. If the ESRs and CRP levels remained elevated within 6 months of the operation, the medication period was extended to 18 months. However, other medication options were also reported, including continuing the four-drug combination for 2 months, followed by a two-drug combination (rifampicin and isoniazid) for 10 months. Some reports also described the addition of ofloxacin or moxifloxacin. For mixed infections, other antibiotics can be added, depending on the results of bacterial cultures and drug sensitivity determinations.

Discussion

Causes of Missed or Misdiagnosed Joint Tuberculosis

In general, the incidence of bone and joint tuberculosis is low. Thus, tuberculosis is rarely considered during the first consultation. Additionally, the clinical manifestations of joint tuberculosis are often atypical, with most patients not having systemic manifestations, such as fever, night sweats, or weight loss. Moreover, tuberculosis of the knee joint primarily manifests as knee joint pain, swelling, and restricted mobility, but not fever, similar to the typical manifestation of osteoarthritis. Finally, differential diagnoses are more difficult in patients with rheumatoid arthritis. All cases in this study showed pain and swelling, except for the patient with Charcot's arthropathy. The clinical manifestations of TBPJI in the patients included in our review were: pain (87.88%), swelling (75.76%), sinus tract formation (27.27%), and mass formation around the knee joint (12.12%); only 18.18% experienced fever. After TKA, routine examination of the joint fluid and culturing of the fluid for common aerobic bacteria were common, while tubercle bacilli cultures were not generally used. Pathological examinations of the synovium and bone tissue were not performed in cases without obvious abnormalities; thus, the opportunity for diagnostic confirmation was lost. Moreover, in cases that included general pathological examinations, the pathological results of some cases had no typical manifestations, such as caseous necrosis and epithelioid degeneration, and only showed "chronic inflammation." In the absence of further, specific tests, such as acid-fast staining and PCR, there was the possibility for a misdiagnosis or missed diagnosis.

A previous study described an 85-year-old patient who fell and fractured the tibial plateau and underwent therapeutic joint replacement[18]. The results of the patient's postoperative bone pathology analysis did not show caseous necrosis, epithelioid cells, or Langhans giant cells. However, the patient's surgical incision did not heal, and a sinus developed. One month later, the patient developed a stubborn, productive cough. Taking into consideration a chest radiograph that showed preoperative parietal lobe scarring, the sputum and sinus pus were subjected to laboratory tests that showed that both were positive for acid-fast bacteria. Bone tissue samples, obtained during the TKA, were also positive for acid-fast bacteria. Another study described a 60-year-old female patient who was preoperatively diagnosed with osteoarthritis[28]. During surgery, moderate synovial hyperplasia, edema, cellulose ooze, and vascular wing formation were observed. Thus, this patient was diagnosed with rheumatoid arthritis and underwent therapeutic joint replacement

surgery. The results of the postoperative pathological analyses, for this patient, showed cellulose-like degeneration and non-specific inflammation. However, 5 months after the operation, a mass appeared on the medial side of the patient's knee. After 1 year of observation, the mass broke and the prosthesis loosened. A cheese-like substance was seen in the mass and tubercle bacilli were cultured. Therefore, this case was a missed diagnosis of knee tuberculosis.

Generally, patients with TBPJI demonstrate weakened immune systems due to their being elderly, having autoimmune diseases (e.g. rheumatoid arthritis), using hormones, having undergone cancer chemotherapy, having AIDS, etc., making them susceptible to infection[26]. The average age of our four patients was 59.5 years, and the 44 patients with TBPJI reported in the literature had an average age of 70.14 years. Risk factors that affected immunity included tuberculosis in other body sites and histories of tuberculosis in knee joints (48.28%), diabetes (17.24%), systemic or local hormone injections(17.24%), malignant tumors (two cases), AIDS (one case), and renal failure with hemodialysis (one case). Moreover, 26 patients (59.09%) had at least one risk factor (e.g. tuberculosis, rheumatoid arthritis, hormone therapy, diabetes, tumor, dialysis, or AIDS).

The comorbidities of our four patients included rheumatoid arthritis (taking oral hormones), uremic dialysis, Charcot's arthropathy, and diabetes; therefore, they had a certain degree of weakened immunosuppression and were susceptible to tuberculosis infections. Thus, for such patients, clinicians must be alert to the possibility of tuberculosis infections.

Mechanism of Tuberculosis Infection after TKA

In general, most of the pathogens causing periprosthetic joint infections are transmitted through surgical contamination. The infections were discovered during the late postoperative period because most were blood-borne infections. However, where do the tubercle bacteria come from? A high proportion of patients with autoimmune diseases have latent tuberculosis and treatment with anti-tumor necrosis factor (anti-TNF) will induce tuberculosis activity. Some studies have reported that the proportion of patients with rheumatoid arthritis who have tuberculosis infections is 8.7/10 mn, while among patients receiving anti-TNF therapy, this proportion increases to 49/10 mn[42, 43].

Garziera *et al*. described 176 patients with autoimmune diseases[44], and the conversion rate for positive tuberculin skin test results was 29.5%. Liu *et al*. used interferon-gamma release assays (IGRAs) to detect latent tuberculosis in patients with inflammatory joint disease, and the positive rate was 22.9% (22/96)[45].

TBPJI was defined, in this study, as occurring in patients who did not have preoperative tuberculosis infections; the periprosthetic joint infection occurred after TKA, and the tuberculosis infection was diagnosed using various methods. Again, where did the tuberculosis infection come from? On one hand, these patients had some degree of weakened immune responses and may have been infected with *M. tuberculosis* sometime after undergoing TKA. On the other hand, the postoperative infections may have been recurrent latent infections; this has been an accepted hypothesis in most studies. *M. tuberculosis* can exist in granulomas for decades, and it can survive for a patient's lifetime without causing clinical symptoms. De Haan described a 75-year-old female patient who experienced joint pain and swelling 3 months after TKA; *M. tuberculosis* was cultured in the joint fluid. The patient had tuberculosis of the knee at the age of 14 years, so the author believed that the onset was a relapse of the original tuberculosis 61 years later[21]. If a patient has a weakened immune system, tuberculosis can recur. Some studies have shown that *M. tuberculosis* in granulomas can be hematogenously spread to distant sites and that surgical trauma is conducive to colonization by these organisms[46, 47]. Marmor reported a patient with osteoarthritis who demonstrated joint swelling, pain, and fever, 2 months after TKA; *M. tuberculosis* was cultured in the patient's joint fluid and blood[15]. Barry described a patient with diabetes and osteoarthritis who developed joint swelling, pain, fever, weight loss, and a productive cough 4 years after TKA. An examination revealed diffuse miliary nodules in the lungs, and tubercle bacilli were cultured in both the joint fluid and sputum[36].

Similarly, for localized, latent tuberculosis, surgical trauma destroys the resting granuloma and causes tuberculosis recurrence[13, 18, 39]. Thus, these patients should not be diagnosed as having initial tuberculosis infections, post-TKA; rather, they should be diagnosed with post-TKA tuberculosis recurrence. Klein *et al*. described a 36-year-old female patient who had experienced fallopian tuberculosis 11 years earlier and who was cured after a 1-year course of oral antituberculosis drugs[30]. The patient reported pain in her right knee for 10 years and anti-inflammatory analgesics and local hormone injections were ineffective for treating the pain. The patient was preoperatively diagnosed with osteoarthritis or rheumatoid arthritis, and epithelioid granulomas and multinucleated giant cells were seen in a post-TKA synovial tissue pathology analysis. The working diagnosis for this patient was tuberculosis arthritis. However, the patient failed antituberculosis treatment for non-medical reasons. Finally, pain and swelling recurred 11 months after surgery, a subcutaneous abscess formed on the medial knee, and the prosthesis loosened. After debridement surgery, the pathological report described an epithelioid granuloma, and *M. tuberculosis* was cultured. In a case reported by Tekin, in addition to joint pain, fever, night sweats, and weight loss before TKA surgery, granuloma formation was reported in the postoperative pathology. Fifteen days after surgery, the patient's original symptoms worsened, and *M. tuberculosis* was cultured[16]. Von Keudell described an 84-year-old woman with rheumatoid arthritis who had experienced tuberculosis 61 years previously and was cured using drugs. The patient's pathology report, after TKA, showed granulomatous inflammation and negative tuberculosis PCR.

However, a sinus tract formed at the incision 5 months after the TKA, and the cultured pus demonstrated *M. tuberculosis*[25].

The original definition of TBPJI was a non-tuberculous lesion before surgery with a subsequent tuberculosis infection after TKA. The pathology of these cases, after TKA, showed tuberculous lesions, and the researchers described these cases as TBPJI. Besser, Bryan, Eskola, and Gale also reported such cases, and the authors classified these cases as missed diagnoses of tuberculosis arthritis; our four patients, described in this study, also met this diagnosis[48–51]. These two concepts are similar. After patients underwent TKA surgery, they later experienced tuberculosis infections around the joint prostheses, and antituberculosis drug therapies were not administered before surgery.

Diagnosis of Joint Tuberculosis and TBPJI

The routine examination of preoperative ESRs and CRP concentrations is of great significance in screening for inflammatory diseases, especially those resulting from bacterial infections. The sensitivities of ESRs and CRP levels for diagnosing periprosthetic joint infections are 85% and 88%, respectively. The extent of ESR and CRP level increases may reflect the infection severity and the bacterial virulence. The ESR and CRP increases associated with *Staphylococcus aureus* infections were higher than those associated with coagulase-negative staphylococcal and Gram-negative bacterial infections, and the values in culture-negative patients were lower[52]. When these two indicators increase before an operation, clinicians should carefully determine the cause, and rule out infectious diseases. Our four patients showed elevated ESRs and three showed elevated CRP levels. Uhel *et al.* reported that the average CRP level in six cases of TBPJI was 80 mg/L (range, 14–183)[34].

IGRA are specific serological indexes for diagnosing tuberculosis, with a sensitivity of 81.4% and a specificity of 96.7%. However, IGRA cannot distinguish between active and latent tuberculosis[53, 54].

The specificity of *M. tuberculosis* cultures for diagnosing tuberculosis is high, but there are contradictory reports on its sensitivity. Zeng *et al.* reported negative tuberculosis culture results from nine patients with tuberculous arthropathy, treated with TKA[55]. Similarly, Su *et al.* described 16 cases in which the culture results for *M. tuberculosis* and other aerobic and anaerobic bacteria were negative[10]. Ozturkmen stated that tuberculosis can be diagnosed using pathology results, without the need for bacterial cultures[12]. On the other hand, there are also reports of high sensitivities for diagnosing tuberculosis associated with positive *M. tuberculosis* cultures. Chang *et al.* reported seven cases of hip joint TBPJI and six cases of knee joint TBPJI that were diagnosed based on positive *M. tuberculosis* culture results; the longest culture time was 12 weeks[23]. The sensitivity of synovial tissue culture for diagnosing this disease was higher than that for synovial fluid cultures. Among the 44 cases of TBPJI reported in the literature, 88.64% were diagnosed by positive joint fluid or tissue culture results. Although *M. tuberculosis* growth is slow, their culture remains an effective method for diagnosing tuberculosis.

Histopathological examinations also have good accuracy for the diagnosis of tuberculosis, and examinations that are indicative of the presence of the disease are characterized by the presence of granulomas and epithelioid tissue cells surrounded by lymphocytes, with or without the presence of caseous necrosis or foreign body giant cells. Guo *et al.* confirmed 36 cases of knee joint tuberculosis using synovial pathological examinations[56]. Some tuberculosis lesions do not have caseous tissue and typical tuberculous pus; thus, multiple samples need to be examined. In the one case of Charcot's arthropathy, in our case series, the ESR and the CRP level increased continuously before the operation, and were considered to be the result of an inflammatory disease. All the synovial tissues removed in the first debridement were sent for examination, and the specimens were taken by pathological technicians who reported nonspecific chronic inflammation. During the second operation, five samples of edema and dark red synovial tissue were selected by the surgeons, and granulomas containing epithelioid cells were found in two samples. In another case, only one tissue was examined, and pathological changes typical of tuberculosis were not found. The diagnosis was confirmed using positive quantitative fluorescence PCR detection of *M. tuberculosis*. Therefore, multiple pathological specimens with abnormal appearances should be selected for examination; the European Bone and Joint Infection Society suggests that tissue samples from at least three different parts should be taken to improve the examination accuracy[57].

PCR can be used to quickly diagnose bone and joint tuberculosis, with high sensitivity and specificity[58]. Titov *et al.* compared the value of several methods in the diagnosis of joint tuberculosis[59]. In seven cases of joint tuberculosis with typical clinical and X-ray manifestations, four synovial fluid samples and four synovial tissue samples were positive for *M. tuberculosis*, using PCR. The results showed that PCR and pathological examinations had the highest accuracies for detecting the disease.

The expert *M. tuberculosis*/rifampicin (Xpert MTB/RIF) technique can simultaneously detect *M. tuberculosis*-specific nucleic acids and rifampicin resistance and can be completed within 90 min. Shen *et al.* recently conducted a meta-analysis and found that the sensitivity and specificity of Xpert MTB/RIF were 81% and 99%, respectively[60].

Second-generation sequencing is a relatively new technique for identifying pathogens, and is more advantageous for multi-bacterial infections. In a case of knee joint infection, Huang *et al.* identified the pathogen as *M. tuberculosis* complex using metagenomic next-generation sequencing[61]. Using this technique, one case in our study was diagnosed as a multi-bacterial mixed infection that included *M. tuberculosis*.

Missed Tuberculosis Diagnoses After TKA and Treatment of TBPJI

Among the 44 cases of TBPJI included in the present literature review, antituberculosis drug treatment, alone, was used to treat 25% of the cases, with a success rate of 90.91%. Debridement treatment, with reserved prostheses, was used in 15.91% of the cases (success rate, 71.43%); the overall total success rate following implant retention was 34.09%. Revision arthroplasties were performed in 34.09% of the cases, with a 93.33% success rate, and the rate of joint fusions was 25%. The average time from infection to diagnosis was 13.25 ± 17.19 months (range, 1–4 years) in patients treated with anti-tuberculosis drugs, alone; 7.67 ± 12.70 months (1–-3 years) in patients undergoing debridement surgery, 4.88 ± 5.85 months (1–24 months) in patients undergoing revision surgery, and 2.75 ± 1.48 months (1–5 months) in patients undergoing fusion surgery. We were unable to determine if an early diagnosis helped with prosthesis retention, but patients with delayed diagnoses may still be cured using only drug treatment. As most of the literature cases involved case reports, the treatment method was determined by the physician, resulting in inconsistent surgical indications. In the six cases of TBPJI reported by Chang, the average time from infection to diagnosis was only 4 months (range, 1.5–-8 months)[24]. However, the author did not indicate whether the prostheses were loose or not. Five cases underwent successful revision arthroplasty and one case, complicated with severe Parkinson's disease, remained in a state of chronic infection after debridement. Uhel *et al.* reported six cases of TBPJI (from multiple centers) and also did not indicate whether the prostheses were loose[34]. Three cases were treated with resection and arthrodesis of the knee. Veloci reported a case of TBPJI in which the time from infection to diagnosis was approximately 3 years; here, drug therapy alone remained successful in treating the infection[15].

According to the literature reports, treatment with antituberculosis drugs alone had a high success rate, and debridement treatment with implant retention was used for patients with severe pain, swelling, and a stable prosthesis. Even if a sinus is formed, current reports suggest that the prosthesis can still be retained if it is not loose[40]. *M. tuberculosis* cells differ form *S. aureus* cells in that their ability to adhere to and form biofilms on metal surfaces is comparatively weak, making drug treatment more likely to be effective.

Cases of first-stage revisions have not been reported in the literature; two-stage revision arthroplasty, however, is a commonly reported strategy. Chang *et al.* recommended using antituberculosis drugs for at least 10 months after debridement and implant spacers[24]. After the infection symptoms and inflammation index have completely subsided, the prosthesis can be implanted during the second stage; otherwise, patients needed debridement and implant spacers again. In the Chang *et al.* study, four patients underwent two debridement sessions and one underwent three debridements. All patients received antituberculosis drug therapy for 12 months, with an average follow-up period of 44.6 months; all patients developed good joint function. Thus, thorough debridement and a standardized drug treatment is important.

For patients with severe infections, poor general health, poor local soft-tissue conditions, and poor responses to drug treatment, joint fusion is a good choice. Mixed infections are difficult problems in the treatment of TBPJIs. Two cases of joint fusion were reportedly performed in patients with mixed infections that included *S. aureus*[23, 30].

Conclusions

In conclusion, the incidence of osteoarticular tuberculosis and TBPJI is low and their manifestations are atypical, making them easy to misdiagnose. Attention should be paid to finding the causes of increased ESRs and CRP levels that occur before an operation, and the possibility of tuberculosis should be considered in patients with weakened immune systems. Pathological examination is an effective method for diagnosing tuberculosis; however, multiple specimens need to be submitted for examination. Positive *M. tuberculosis* cultures have high sensitivity and specificity for making diagnoses. Regarding treatment, antituberculosis drug treatment is preferred, and debridement and prosthesis retention are needed. For patients with prosthesis loosening, two-stage repair can be adopted.

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