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Original article

Prosthetic joint infections due to *Mycobacterium tuberculosis*: A retrospective study

Vanina Meyssonnier[a,d,*], Valérie Zeller[a,d], Stéphanie Malbos[a], Beate Heym[c,d], Luc Lhotellier[b,d], Nicole Desplaces[c,d], Simon Marmor[b,d], Jean-Marc Ziza[a,d]

[a] *Service de médecine interne et rhumatologie, groupe hospitalier Diaconesses CroixSaint-Simon, 125, rue d'Avron, 75960 cedex 20, Paris, France*
[b] *Service de chirurgie osseuses et traumatologique, groupe hospitalier Diaconesses Croix Saint-Simon, 75960 cedex 20, Paris, France*
[c] *Laboratoire de biologie médicale, groupe hospitalier Diaconesses Croix Saint-Simon, 75960 cedex 20, Paris, France*
[d] *Centre de référence des infections ostéo-articulaires complexes, groupe hospitalier Diaconesses Croix Saint-Simon, 75960 cedex 20, Paris, France*

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ABSTRACT

Objective: Tuberculous prosthetic joint infection (PJI) is uncommon and often diagnosed late. The objective here is to describe the management of tuberculous PJI at an osteoarticular infection referral center.
Methods: A single-center retrospective study of patients managed between 1987 and 2016 was performed.
Results: We identified 9 patients with a median age of 80 years. The hip was involved in all 9 patients. A known history of tuberculosis was noted in 2 patients and tuberculosis was present at other sites in 4 patients (lung, $n = 3$; urinary tract and scrotum, $n = 1$; and spine, $n = 1$). The diagnosis was established by routine intra-operative microbiological sampling, during ($n = 4$) or at a distance from ($n = 5$) hip arthroplasty. In the 8 patients with available follow-up data, mean antibiotic therapy duration was 16 months (range, 12–18 months). None of the 4 patients in whom the infection was diagnosed during arthroplasty required surgical revision because of the infection. Of the other 5 patients, 3 were managed by exchange arthroplasty and 1 by excision of the hip without subsequent prosthesis implantation; the remaining patient did not undergo revision surgery. The infection was eradicated in all 9 patients, after 15 months to 10 years.
Conclusion: Tuberculous PJI is uncommon. The prognosis is good with prolonged antibiotic therapy, although the optimal duration remains unclear. The surgical strategy should be discussed on a case-by-case basis. The prosthesis can be retained if the tuberculous infection is an unexpected finding during arthroplasty.

1. Introduction

Tuberculosis is a major public health burden with over 9 million newly diagnosed cases each year worldwide [1]. Osteoarticular forms account for 10% to 20% of all cases of extrapulmonary tuberculosis and affect the hip in nearly one quarter of cases [2]. Prosthetic joint infection (PJI) due to tuberculosis (TB-PJI) is uncommon, and no studies of large cohorts have been reported to date. The diagnosis is often challenging and delayed, as the clinical and radiological findings are often non-specific or misleading. In some patients, the diagnosis is established because samples for mycobacterial cultures and/or histological examination are taken during the primary arthroplasty due to a suggestive intra-operative appearance of the native joint. In this situation, TB is an unexpected finding that was not suspected before surgery. Another possible scenario is the development of TB-PJI several months or years after the arthroplasty [3]. The clinical presentation usually consists in non-specific local signs of chronic infection at the prosthetic joint (e.g., draining sinus tract or abscess). Samples specifically intended for mycobacteria detection may then be taken, due to suggestive macroscopic findings or, as is the case at our referral center, routinely during revision surgery for PJI. The objective of this study was to describe the epidemiological, clinical, and microbiological features of TB-PJI diagnosed at our center, their frequency among all PJI cases, their pharmacological and surgical management, and their outcomes.

2. Methods

The microbiology laboratory database at our referral center for complex osteoarticular infections (Diaconesses Croix Saint-Simon

* Corresponding author at: Groupe hospitalier Diaconesses Croix Saint-Simon, 125, rue d'Avron, 75960 cedex 20, Paris, France.
E-mail address: vanina.meyssonnier@gmail.com (V. Meyssonnier).

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Hospital, Paris, France) was searched for patients managed for TB-PJI between January 1987 and December 2016. All patients thus identified were included retrospectively in the study. The diagnosis was documented by positive cultures for *Mycobacterium tuberculosis* or the presence of epithelioid or giant-cell granulomas in osteoarticular or periprosthetic soft-tissue samples. The following data were collected: demographic characteristics, medical history, clinical manifestations, whether TB was diagnosed based on cultures or tissue samples, sites of collection of positive samples, time from arthroplasty to diagnosis of TB-PJI, antibiotic susceptibility profile of the *M. tuberculosis* strain, modalities of pharmacological and/or surgical treatment, duration and tolerance of anti-TB drug therapy, and outcome.

2.1. *Identification of* M. tuberculosis

Cultures of bone and joint samples for *M. tuberculosis* were performed routinely in all patients with suspected PJI, using Löwenstein-Jensen medium with up to 3 months of incubation then, since 2016, a Mycobacteria Growth Indicator Tube (MGIT) with 45 days of incubation. In both cases, an auramine phenol stain was performed on the culture. When *M. tuberculosis* was recovered by culturing, antibiotic susceptibility testing was performed for the main anti-TB drugs, i.e., rifampicin, isoniazid, ethambutol, and pyrazinamide. Intraoperatively, a tissue sample for histological examination was collected in patients with suspected osteoarticular TB, a history of TB at the surgical site, a caseating soft-tissue abscess or an unusual macroscopic appearance, or chronic PJI with no preoperative microbiological documentation (negative cultures of samples taken by aspiration or during previous surgery). Patients with confirmed TB-PJI were evaluated for TB at other sites, notably the lungs, by a physical evaluation, chest radiographs and, if appropriate, computed tomography. Depending on the treatment phase, the anti-TB drug regimen consisted of isoniazid (3–5 mg/kg/d), rifampicin (10 mg/kg/d), ethambutol (15–20 mg/kg/d), and pyrazinamide (20–25 mg/kg/d up to 1500 mg/d). Total treatment duration varied with the extent of the lesions, response to treatment, and physician preference.

2.2. *Role of the funding source*

Not applicable.

3. Results

During the 28-year study period, 1760 cases of PJI were managed, of which 60% involved the hip, 37% the knee, and 3% the shoulder. Of these cases, only 9 (0.5%) were due to *M. tuberculosis*. The hip was involved in all 9 patients. Table 1 reports the epidemiological and clinical features, circumstances surrounding the diagnosis, and sample positive for *M. tuberculosis*. Of the 9 patients, 5 were aged 80 or older. A single patient had immunodepression related to glucocorticoid therapy for over 1 year to treat giant-cell arteritis (patient #4). In practice, the patients fell into two groups according to whether the diagnosis of TB-PJI was established during arthroplasty or later.

3.1. *Diagnosis during arthroplasty: patients #1 through #4*

In 4 patients, the diagnosis of TB-PJI was made by cultures and/or histological examination of osteoarticular samples taken during primary arthroplasty (Table 1). The reasons for obtaining mycobacterial samples were a friable appearance of the bone suggesting a tumor in patient # 1 and a chronic infection in patients #2 and # 4; the reason was unknown in patient #3. None of these 4 patients had any preoperative symptoms suggesting TB. No acid-fast bacteria were seen upon microscopic examination of the smears. Of the 3 patients in whom histological examination was performed, 2 had a giant-cell granuloma with caseating necrosis suggesting TB-PJI. In all 4 patients, the cultures recovered a *M. tuberculosis* strain that was susceptible to multiple antibiotics.In 1 patient (patient #2), who was from China and had a history of primary TB, the evaluation for other TB foci detected lung and urinary tract involvement.

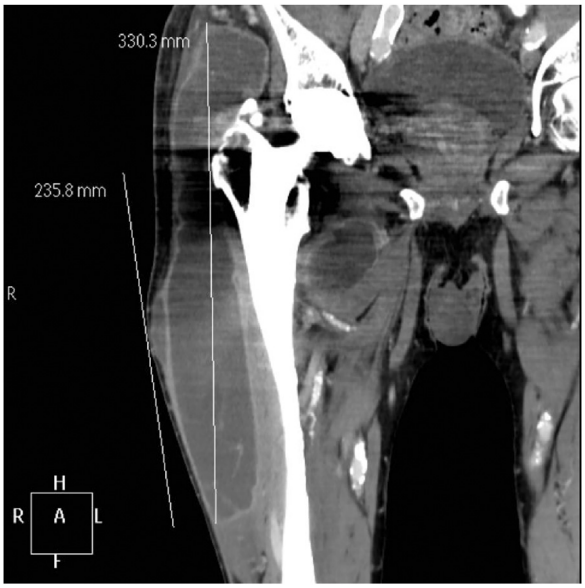

Fig. 1. Cold abscesses in the thigh on the side of a total hip prosthesis infected with *Mycobacterium tuberculosis* (patient #5).

Various treatment strategies were used (Table 1). Prolonged anti-TB drug therapy was given to 3 patients, whereas 1 patient (patient #4) was lost to follow-up after the diagnosis of TB-PJI. In the 2 patients with a caseating granuloma, the anti-TB drugs were started as soon as the histological results returned, i.e., 10 days after the arthroplasty procedure; the cultures confirmed the diagnosis subsequently in both patients. In another patient, the anti-TB drugs were started after 1 month, as the culture became positive only on day 24. In these 3 patients pharmacological therapy was used alone, and no surgical revision was needed due to the TB. The initial anti-TB drug regimen consisted of rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 to 7 months then rifampicin and isoniazid. Total duration of anti-TB drug therapy was 18 months. None of these 3 patients had any evidence of recurrent TB at last follow-up 7, 9, and 10 years after the diagnosis.

3.2. *Diagnosis at a distance from the arthroplasty: patients #5 through #9*

The symptoms that prompted sample collection to look for *M. tuberculosis* developed 2 to 20 years after the arthroplasty procedure (Table 1). The nature of the symptoms varied, but no patient experienced a prolonged fever or a deterioration in general health. In 2 patients, neither of whom had hip pain or hip prosthesis malfunction, an abscess or sinus tract developed in the periprosthetic soft tissues. Material aspirated from the lesion contained acid-fast bacteria visible by light microscopy and produced cultures positive for *M. tuberculosis*. One of these patients (patient #5) (Fig. 1) had a cold abscess in the thigh that was visible clearly by CT. The evaluation for other TB foci included a routine lung sample that was positive for *M. tuberculosis*. In the other patient (patient #6), a sinus tract developed over the prosthetic joint 2 months after the initiation of anti-TB drug therapy for pulmonary, genitouri-

Table 1
Features in the 9 patients with tuberculous prosthetic joint infection.

Patient	Age (years) /gender/country of origin	History of TB and/or immunodepression	Clinical signs	Extra-articular involvement	Reason for THA	Time from THA to TB diagnosis	Diagnostic sample: microbiological (M) or histological (H)	Anti-TB drug therapy duration (months)	Revision surgery	Relapse-free follow-up duration
1	80/M France	none	pain	none	hip OA	Intra-operative	M/H	18	no	7 years
2	69/M China	primary TB	pain	lungs, urinary tract	hip OA	Intra-operative	M	18	no	9 years
3	64/F France	none	pain	none	hip OA	Intra-operative	M/H	18	no	10 years
4	83/F Unknown	giant-cell arteritis	pain	none	femoral neck fracture	Intra-operative	M	lost to follow-up	no	lost to follow-up
5	86/M France	none	pain, soft-tissue abscesses	lungs, soft tissues	hip OA	3.5 years	M	15	no	15 months
6	59/M Portugal	none	sinus tract	lungs, spine, scrotum,	hip OA	13 years	M	12	one-stage exchange	3 years
7	84/M France	none	pain, sinus tract	none	hip OA	7 years	M	14	two-stage exchange	3 years
8	84/F France	bone	pain, sinus tract	none	hip OA	20 years	M	15	prosthesis already removed	2 years
9	56/M Congo	bone TB	pain, sinus tract	none	hip OA	2 years	H	12	one-stage exchange	18 months

nary, and spinal TB. In 2 other patients, a sinus tract persisted after revision surgery. The reason for revision was loosening managed by one-stage exchange arthroplasty in 1 patient (patient #7) and streptococcus and *Escherichia coli* PJI managed by removal of the prosthesis in the other patient (patient #8). The diagnosis was established by the culture of joint fluid collected by aspiration of the hip. The remaining patient (patient #9), who was from the Congo, had had ipsilateral TB of the hip treated 34 years earlier by arthrodesis and 6 months of anti-TB drugs. He was admitted to our center 2 years after total hip arthroplasty, due to the development of a sinus tract followed by an anterior abscess. Aspiration of the hip recovered a methicillin *Staphylococcus aureus* strain. One-stage complete exchange arthroplasty was performed. During the procedure, multiple caseating abscesses were found within the bone and soft tissues, suggesting TB. Histological examination of intra-operative samples showed caseating epithelioid and giant-cell granulomas. Standard cultures performed specifically to detect TB were negative.

Of these 5 patients, 4 initially received rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 to 6 months, followed by rifampicin and isoniazid for 8 to 12 months, for a total treatment duration of 12 to 15 months. One patient (patient #6) had a *M. tuberculosis* strain that was resistant to isoniazid and streptomycin and received rifampicin, ethambutol, and pyrazinamide for 12 months in all, starting 6 months before surgery. All the other patients started the treatment after surgery if performed. The anti-TB drugs were well tolerated.

Four patients required surgery (patients #6 through #9). In 3 patients, the procedure consisted in exchange arthroplasty, performed in a single stage (patients #6 and #9) or in two stages (patient #7). Results were negative from cultures to detect mycobacteria in samples taken during one-stage exchange arthroplasty (patient #6) or the second stage of two-stage exchange arthroplasty (patient #7) after 6 months of anti-TB drug therapy. In the remaining patient (patient #8), hip resection was performed but could not be followed by secondary arthroplasty, given the severity of the joint destruction. None of these patients had any evidence of relapsing TB at last follow-up after 18 to 36 months.

Finally, patient #5 did not require surgical treatment, as the outcome was favorable with anti-TB drug therapy alone. This patient was lost to follow-up at the end of the course of anti-TB drugs.

4. Discussion

TB-PIJ is an uncommon condition, with fewer than 75 cases reported between 1973 and 2017, most of which were included in one of three literature reviews. The hip is involved in 55%, and the knee in 40%, of cases, whereas the shoulder and wrist are only very rarely affected [3,4,5]. This very low incidence of TB-PIJ contrasts with the far higher incidence of clinical TB in France, where, despite a 10-fold decrease since 1970, about 5000 new cases are diagnosed each year (INVS 2014 data). The incidence of clinical TB is about twice as high in the district that includes Paris than elsewhere in the country. The number of arthroplasty procedures performed in France increases steadily year on year, in part due to the aging of the population, and arthroplasty is also being performed in ever older patients. The incidence of clinical TB decreases between 40 and 69 years of age then increases in patients aged 70 years or older [6,7]. A history of childhood TB is more common among older individuals, in whom immunosenescence also increases the likelihood of TB reactivation, explaining the higher risk of TB after 70 years of age [8,9]. PJI occurs at a median age of 70 years, with a cumulative incidence of about 1% to 3% per prosthesis-year [10,11]. *M. tuberculosis* may, however, adhere less strongly to foreign material compared to other microorganisms responsible for PJI, such as *Staphylococcus. aureus* [12], potentially explaining the low incidence of TB-PJI. Thus, at our center, although mycobacteria were sought routinely in all osteoarticular samples, only 9 cases of TB-PJI were diagnosed between 1987 and 2016. These 9 patients accounted for 0.5% of all patients managed at our center for PJI during the study period. Since 2017, given the low prevalence of osteoarticular TB, the decision to look for mycobacteria is taken before arthroplasty revision surgery, based on the history of the disease, medical history of the patient, and intra-operative appearance of the bone and joint. TB should be considered if an abnormal appearance of the bone is noted during prosthesis implantation, particularly when there are multiple and/or large periarticular abscesses, as well as if the patient has a history of TB of the operated joint or of chronic PJI with negative joint samples.

The hip was the only joint involved with TB-PJI in our patients. At our center, 35% of all PJIs involve total knee prostheses, which are also the site of nearly half the cases of TB-PJI reported in the literature. We have no clear explanation for this result. However, whereas TB of the native knee is more common in adults, TB of the hip may predominate in children, suggesting a role for the reactivation of TB acquired during childhood [2].

We observed two different clinical presentations. In one presentation, TB-PJI was diagnosed based on samples collected during arthroplasty, due to an appearance of the bone that seemed inconsistent with osteoarthritis or a traumatic fracture. None of the 4 patients with this presentation had experienced a deterioration in general health or any symptoms suggesting clinical TB. A single patient, who was from China, had a known history of primary TB during childhood. Implantation of a prosthesis into an apparently healthy joint may promote the local reactivation of TB. The potential role for trauma in the development of osteoarticular TB has been suggested in the literature, via the concept of *locus minoris resistentiae* (vulnerable zone), with reactivation of a latent TB focus at the site of the injury. The injury may consist in an impact, an injection, or a surgical procedure [13,14]. Thus, in patients with this presentation, the intra-operative appearance of the tissues should prompt the surgeon to collect samples designed specifically for mycobacterial cultures and histological studies. The suspicion of TB acquired intraoperatively may be strengthened if a chest radiograph shows residual changes suggesting TB in the remote past and/or if the patient has evidence of immunodepression and/or is taking an immunosuppressant, such as one of the TNFα antagonists, which are known to promote TB reactivation. In this group of patients, as well as in the patients who received a TB diagnosis within 6 weeks after arthroplasty in the study by Spinner et al. [3], revision surgery was unnecessary. The bone resection performed to implant the prosthesis probably contributed to the favorable outcome.

The other clinical presentation was observed in 5 of our 9 patients. Symptom onset was at a distance from the arthroplasty. Two patients were from countries where TB is endemic (the Congo and Portugal, respectively). One patient had a history of osteoarticular TB at the same site more than 30 years earlier. Another was under treatment for pulmonary, genitourinary, and spinal TB when the development of a sinus tract over the prosthetic hip suggested TB-PJI. The investigations done to look for other TB foci after the diagnosis of TB-PJI led to the diagnosis of pulmonary TB in another patient. The signs of TB-PJI were non-specific (abscess, sinus tract, radiological loosening), and none of the patients had constitutional symptoms (fever or decline in general health). The radiological signs of PJI are not specific for a given micro-organism, and the standard radiograph, as well as the C-reactive protein, may be normal in patients with TB-PJI [5]. Finally, co-infection with pyogenic microorganisms at the same site is not uncommon and may delay the diagnosis. This situation occurred in 2 of our patients, in whom the initial samples were used only for standard cultures,

which were unable to detect *M. tuberculosis* but showed pyogenic organisms, for which antibiotic therapy was given.

The diagnosis of TB-PIJ requires compliance with recommendations that multiple bacteriological samples be obtained and seeded onto specific media and that tissue samples be examined for caseating epithelioid and giant-cell granulomas [15]. In patients who do not respond to optimal antibiotic therapy, infection by a microorganism resistant to standard antibiotics, such as *M. tuberculosis*, should be considered [16].

In previously reported cases of TB-PJI diagnosed at a distance from arthroplasty, the surgical treatment usually consisted in permanent removal of the prosthesis or two-stage exchange arthroplasty [5]. Of our 5 patients in this situation, 3 underwent one- or two-stage exchange arthroplasty. In 1 patient, the diagnosis of TB-PJI was established only after removal of the prosthesis, and a new prosthesis was not implanted. Given the small number of patients and absence of a control group of patients who were not treated surgically, we cannot definitively state that surgery is required. The favorable outcome in our patients, most of whom had one-stage surgery, suggests that this procedure may be advisable. This possibility is supported by our finding that revision surgery was not required in any of the patients whose TB was diagnosed during arthroplasty. If the diagnosis of TB is made during primary or exchange arthroplasty, further revision surgery seems unnecessary.

All 9 patients in our study received anti-TB drugs for 12 months, or longer in patients with long-standing TB. This treatment was successful in the 7 patients with follow-up data after treatment discontinuation. The modalities of anti-TB drug therapy for TB-PJI are the same as for pulmonary TB: four drugs are combined initially, after which, provided the strain is susceptible, only rifampicin and isoniazid are continued. The optimal total treatment duration is unclear. Although our patients were treated for at least 12 months, we believe that a shorter course may deserve consideration. In patients who had osteoarticular TB without foreign material, 6 months of anti-TB drug therapy had a success rate of 87% to 99% [17–19]. Of 8 patients with TB-PJI who received anti-TB drugs for a total of 6 months, 5 responded, after more than 2 years of follow-up in 4 patients and 6 months in 1 patient; of the remaining 3 patients, 1 died and 2 had no follow-up data. Total treatment duration in the other patients ranged from 7 to 39 months, with a median of 15 months (interquartile range, 12–18 months) [8,9,20]. Data are scant on the effectiveness of the pharmacological and/or surgical treatments used. In addition, follow-up durations after treatment discontinuation vary widely, from a few months to several years [3–5]. Of our 7 patients with follow-up data after treatment discontinuation, none had experienced any signs of TB relapse at last follow-up. Overall, TB-PJI had a good prognosis. Nevertheless, the limitations of our study should be borne in mind. The number of patients was small, and the follow-up was less than 2 years in 3 patients, including 1 who was lost to follow-up after the diagnosis. A prospective multicenter study would be useful to define the optimal diagnostic and therapeutic strategy in patients with TB-PJI.

Disclosure of interest

The authors declare that they have no competing interes.

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