

Case Report

Conservative treatment of early-onset tubercular periprosthetic joint infection following total knee arthroplasty

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Abstract

Tubercular periprosthetic joint infections (PJI) are uncommon diseases in developed countries. Therefore, the systematic screening for *Mycobacterium tuberculosis* (TB) is not currently recommended before a total knee arthroplasty procedure. However, due to the new human migration flows and higher mycobacterial infection rates, tuberculosis could represent a rare but potential cause for PJI. Controversies about tubercular PJI diagnosis, management and treatment still exist due to a lack of clinical evidence. In the current report we present the case of an early-onset *M. tuberculosis* PJI of the knee and its successful conservative treatment with two years follow-up.

Key words: *Mycobacterium tuberculosis*; periprosthetic joint infection; total knee arthroplasty; revision surgery; extrapulmonary tuberculosis; musculoskeletal tuberculosis.

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Introduction

M. tuberculosis infections (TB) affect nearly 1.3 million people every year and remain a world-wide leading cause of death. Although the incidence of TB has always been lower in western European countries, it is now becoming an emerging problem due to the renewed human migration flows from endemic countries [1]. Skeletal and joint TB localization represent the 11% of extrapulmonary TB cases, half of which are vertebral located [2,3]. Tubercular periprosthetic joint infection (PJI) is an uncommon clinical condition, with less than fifty cases reported in the literature [4], affecting more likely knee arthroplasty than hip arthroplasty [5]. Tubercular PJI can be classified into early and late onset. Early-onset infections occur less than eight weeks after surgery, while late-onset infections are detected more than eight weeks after surgery [6]. Most authors consider the reactivation of a previous unrecognized (old or latent) tuberculosis infection as the primary pathogenetic mechanism, due to the local tissue damage related to arthroplasty surgery, which could mimic an early periprosthetic infection [6]. In other patients, the infection originates from a hematogenous dissemination of a distant tubercular pulmonary or

extrapulmonary focus. Patient immunosuppressed state could contribute to the systemic and local spread of the disease [6–8]. The diagnostic process of tubercular PJI is often difficult due to a nonspecific clinical presentation, that could lead to a delay in the diagnosis and treatment initiation. Moreover, the presence of concomitant secondary bacterial infections is often a confounding factor. Currently, the management of tubercular PJI has no clear guidelines. In the literature, some cases were successfully treated by a prolonged antitubercular chemotherapy alone [9]. However, other authors believe that a 2-stage revision with a long course of chemotherapy is necessary to fully eradicate the infection [10].

In the current report we present the case of an early-onset tubercular PJI in a patient without previous history of TB infection, treated successfully with antitubercular chemotherapy and irrigation and debridement.

Case Report

In November 2016 a 77-year-old male patient reported right knee pain non-responsive to painkiller treatment. The patient had a medical history of insulin-dependent diabetes, hypercholesterolemia, high blood

pressure and previous episodes of big toe gouty arthritis with hyperuricemia. X-rays and MRI showed a Grade II Kellgren - Lawrence osteoarthritis, joint effusion, aspecific synovitis and femur and tibia bone erosion (Figure 1) [11]. Therefore, the patient underwent arthroscopic debridement and lavage. During arthroscopy, an Outerbridge III-IV grade cartilage lesion was found in both tibia condyles and medial femur condyle, widespread synovial hyperemia and articular loose bodies [12,13]. However, the synovial fluid analysis did not allow to confirm the diagnosis of gouty arthritis.

In March 2017 the patient reported worsening of knee pain, on X-Ray and MRI the bone erosion area had increased with a Grade III Kellgren-Lawrence osteoarthritis. According to the physical examination, ROM was 0 - 110, knee tests showed a stable joint, KOOS score was 67/100, therefore an all cemented total “cruciate-retaining” knee replacement was carried out (NexGen, Zimmer Biomet) (Figure 2) [14,15]. Ten days after surgery, the patient suffered a deep wound dehiscence with few clear secretions. Blood tests and synovial fluid analysis were not suggestive for infection (Table 1), but the case was treated as an acute periprosthetic knee infection according to Musculoskeletal Infection Society (MSIS) criteria [16,17]. Five intraoperative tissue and fluid samples were sent for culture. Surgical debridement and polyethylene exchange with component retention and irrigation with a large volume of saline solution were performed. Then the patient received an empirical antibiotic therapy with Levofloxacin 500 mg/die. Although after microbiology and histology examination the infecting organism was not identified, it was planned to continue the antibiotic therapy for a total of 4 weeks.

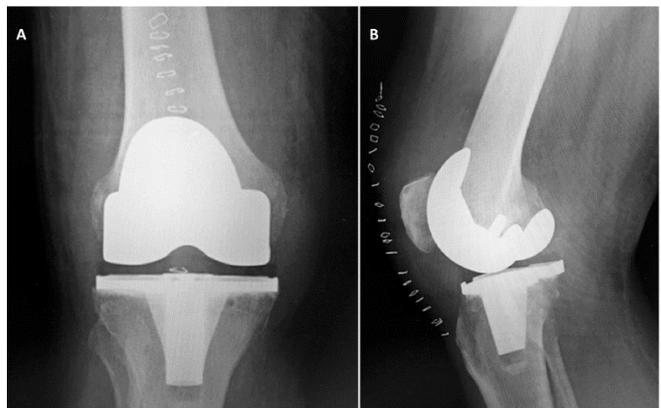
In the following two weeks, the patient reported worsening of knee pain and two fistulae appeared around the wound, secreting a moderate quantity of clear and yellowish fluid. According to the infectiologist from our department, Quantiferon testing and molecular biology analysis of the synovial fluid was performed focusing on *mycobacteria*. QuantiFERON-TB Gold® Plus test was positive, while IUTM and BACTEC culture and microscope B.A.A.R.

Figure 1. MRI of the knee, coronal view, T1-weighted scan.



Preoperative MRI of the knee shows subchondral bone erosion of the medial compartment.

Figure 2. X-ray of the knee, A) AP and B) LL view.



Postoperative radiographic findings show a CR total knee arthroplasty.

Table 1. Inflammatory markers trend modification from the first to the last observation.

	November 2016	March 2017	April 2017	July 2017	July 2019
WBC (4800 - 10800)	4970	3210	3120	3980	5820
ESR (2 - 30 mm/h)	48	56	65	56	43
CRP (0 - 0.5 mg/dl)	0.26	0.53	1.14	0.76	0.3

resulted negative. PCR Real-time analysis performed on purulent fluid and synovial aspirate, showed *Mycobacterium tuberculosis* complex DNA. Therefore, antitubercular chemotherapy with oral Ethambutol 800 mg/die, Rifampicin 600 mg/die, Isoniazid 300 mg/die, Pyridoxine 300 mg/die was administered to the patient. X-rays and metal artefact reduction CT did not reveal any sign of periprosthetic loosening. The patient was then discharged and evaluated weekly. After one month, the patient reported lower knee pain and suspended oral painkillers, reporting significant functional improvement. Full healing of fistulae was obtained after seven months (Figure 3). At the last follow-up, in July 2019, the patient showed a KOOS of 78/100, and X-rays did not show significant signs of periprosthetic loosening compared to previous examinations.

Discussion

Periprosthetic joint infections represent one of the most common complication following joint arthroplasty, both after primary or revision surgery [18–21]. However tubercular PJI is a rare clinical condition in developed countries. Therefore, in absence of medical history of TB infection, preoperative screening for *mycobacteria* is not routinely performed in patients undergoing joint arthroplasty. Tubercular PJI could be the result of local reactivation of quiescent infections (group A) or hematogenous spread from an extrapulmonary or a pulmonary focus (groups B and C), as suggested by Harwin *et al.* [6]. Reactivation occurs long time after an apparent symptom which is often not recalled by the patient. Therefore, as frequently described in literature, early diagnosis of tubercular PJI is difficult. Clinical presentation is mainly characterized by absence of systemic symptoms and normal chest X-ray examination [9]. In our case patient did not report any suspicious history of TB close contact and systemic symptoms (fever, anorexia, weight loss). Moreover, chest X-ray and serum lab tests were normal. Possibly, the concomitant diagnosis of hyperuricemia with positive history of gout, could have hidden initial symptoms. Postoperatively, he complained with severe knee pain, wound dehiscence with two fistulae, without any systemic symptom. The presence of the sinus tract represents a strong sufficient criterion for early periprosthetic joint infection diagnosis. In case of an early onset PJI, the procedure of irrigation and debridement is indicated according to MSIS guidelines, with the aim to collect samples for histological and microbiological analysis. However, intraoperative culture samples were negative for any pathogen, and the

IUTM/BACTEC cultures and microscope B.A.A.R. analysis were also negative.

According to Tokumoto *et al.* there are, in fact, three possible reasons of tubercular PJI delayed diagnosis: i) missed diagnosis of tubercular articular infection before knee replacement; ii) inability to confirm the diagnosis even if clinically suspected; iii) concomitant infection with more common bacteria (*i.e. Staphylococcal species*) that could hide TB infection. In our case, we faced two of these three conditions [22]. Blood testing and synovial analysis with traditional indicators have poor specificity, acting as markers of general inflammatory activity rather than indicating that the patient has a tubercular infection. The use of QuantiFERON-TB Gold represented a useful tool, leading us to confirm a strong diagnostic suspect. However, it cannot distinguish between latent and active infection, and thus its specificity in acute settings is limited [23]. Polymerase chain reaction (PCR) has recently changed the approach in tuberculosis diagnosis, allowing a rapid and specific detection of tubercular DNA complex even in tissue sample or purulent fluids [24]. In fact, in our case the ultimate diagnosis was obtained through molecular biology

Figure 3. Secreting sinus tracts.



The image shows the operated knee, with a healing wound and two fistulae.

analysis of the purulent fluid from the sinus tract. Similarly, Neogi *et al.* reported the case of a 73-year-old patient who developed late *M. tuberculosis* PJI after knee arthroplasty, diagnosed with PCR in synovial tissue detected after negative synovial tissue and joint fluid cultures [9]. The treatment of tubercular PJI is controversial due to lack of evidence-based management guidelines. Medical treatment with retention of prosthesis, with or without joint irrigation and debridement (I&D), is only possible in early-onset infections, when clinical and imaging findings are consistent with the absence of prosthetic loosening, and when a sensitivity to anti-tuberculosis medications is demonstrated [6]. Several studies showed that tubercular infection is associated with poor biofilm formation and low adherence to metal implants [25]. We considered our case as an early-onset tubercular PJI and we treated it with medical therapy alone. However, we think that surgical debridement and polyethylene exchange performed forty days before diagnosis could have played an additional role in final good outcome results. On the other hand, when diagnosis is delayed, TB infection may cause bone lysis and septic loosening that would lead to poor outcomes if treated without implant removal. Therefore, for late-onset infections, two-stage replacement arthroplasty is the first choice of treatment and has shown satisfactory results even when previous I&D procedure have failed [10]. Arthrodesis can be a useful option in selected patients, with persistent infection, failed revision surgeries and medical comorbidities contraindicating further invasive procedures [26].

Conclusion

Due to the lack of evidence and consensus about diagnosis, management and treatment of tubercular PJI further high level studies are warranted. Identifying patients at high risk of tubercular exposition prior to knee replacement surgery it is not easy but may prevent catastrophic results. Early inclusion of *Mycobacteria* as a possible cause of total knee replacement failure may provide good outcomes without the need of implant removal. Moreover, molecular biology techniques, as PCR and Next Generation Sequencing, represent an essential tool in order to achieve rapid and effective diagnosis in culture-negative PJI [24].

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