

Case Report

Late onset periprosthetic joint infection of the knee caused by *Streptococcus anginosus*. Case presentation and literature review

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Abstract

Periprosthetic joint infection (PJI) is one of the most dramatic complications of joint arthroplasty. Although streptococcal bone and joint infections are less common than staphylococcal cases, their role as causative agents of bone and joint remains significant accounting for at least 10% of PJIs. *Streptococcus anginosus* group (SAG) bacteria are usually found in the normal flora of the urogenital tract, intestinal tract and oropharynx and could cause pyogenic infections to affect brain, lungs and liver. SAG bacteria are uncommonly reported as a cause of osteomyelitis and the involvement of a joint represent a rare event. *S. anginosus* has been anecdotal related to implant devices infections such as vascular prosthesis or orthopedic implants, however, PJI of the knee has never been fully reported before. We describe the case of a late onset periprosthetic knee infection due to *Streptococcus anginosus* successfully treated by a two-stage revision arthroplasty and postoperative parenteral Vancomycin, (2 g per day) and Levofloxacin (750 mg per day) for 4 weeks and then oral Levofloxacin for a further 2 weeks.

Key words: Periprosthetic joint infection; total knee arthroplasty; *Streptococcus anginosus*; *Streptococcus milleri* group; streptococci.

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Introduction

Periprosthetic joint infection (PJI) is one of the most dramatic complications of joint arthroplasty leading to high patient morbidity, social and health-care costs, requiring advanced management from both surgical and medical perspective [1–3]. Although streptococcal bone and joint infections are less common than staphylococcal cases, their role as causative agents of bone and joint remains significant accounting for at least 10% of PJIs [4].

Streptococcus anginosus group (SAG) bacteria, formerly known as *Streptococcus milleri* group encounters three species: *Streptococcus anginosus*, *Streptococcus intermedius* and *Streptococcus constellatus*. These species are usually found in the normal flora of the urogenital tract, intestinal tract and oropharynx, and when they are involved as pathogens their main clinical manifestation is the formation of abscesses in several body parts [5]. Pyogenic infections due to SAG bacteremia were reported to affect brain, lungs and liver [6,7]. SAG infections have also been

described in children and patients with immunodeficiency conditions such as elderly patients or HIV patients [8,9]. SAG bacteria are uncommonly reported as a cause of osteomyelitis and the involvement of a joint represent a rare event [10]. *Streptococcus anginosus* has been anecdotal related to implant devices infections such as vascular prosthesis or orthopedic implants, however, PJI of the knee has never been fully reported before [10–12]. We describe the case of a late onset periprosthetic knee infection due to *Streptococcus anginosus* successfully treated by a two-stage revision arthroplasty with two years of follow up.

Case Report

In October 2017, a 72 years-old male presented at our institution complaining pain and effusion of the left knee. The patient had undergone a primary left total knee arthroplasty (ATTUNE® Knee System, DePuy Synthes, Warsaw, Indiana) at an outside institution in 2015. He had a prior history of left knee meniscectomy

and a prostatectomy procedure. The patient suffered from hypertension, gout and recurrent urinary tract infections. Body mass Index was 34 kg/m². The pain was activity-related, and the patient could walk only with the aid of a cane. Clinical evaluation revealed substantial knee effusion without signs of wound dehiscence. No other signs of local inflammation were detected. Body temperature was 36.8 °C and no fever was reported in the previous days. Active and passive range of motion was 0° – 100°, and the knee was stable at physical examination [13]. The Knee Society Score (KSS) questionnaire was used to assess the global residual function of the knee according to pain, range of movement and its stability. At the moment of the clinical evaluation was 57/00 points [14]. Radiographs (AP and LL views) showed signs of periprosthetic loosening around the medial tibial plateau (Figure 1).

Figure 1. Preoperative radiograph of the knee.



Radiographs showed a well-positioned TKA with signs of periprosthetic osteolysis around the medial tibial plateau.

Figure 2. Radiograph after the first stage of revision arthroplasty.



An antibiotic-loaded cemented spacer, fixed with two metallic rods, maintained the knee in extension position.

The erythrocyte sedimentation rate (ESR) was 129 mm/hr (normal range, 0 to 30 mm/hr), and the C-reactive protein (CRP) level was 9.45 mg/dL (normal range, < 0.35 mg/dL).

According to Musculoskeletal Infection Society (MSIS) and Infectious Diseases Society (IDSA) criteria for PJI diagnosis [15], joint aspiration was performed. It revealed 4,150 white blood cells per mL, 90.4% of which were segmented neutrophils. Two synovial fluid cultures were positive for *Streptococcus anginosus*, which was found susceptible to levofloxacin, clindamycin, and vancomycin. We performed a radiolabeled autologous white blood cells (WBC) scintigraphy in order to detect additional foci of infections, which demonstrated increased uptake only around the left knee.

Therefore, in February 2018, the patient was admitted for a two-stage revision arthroplasty for periprosthetic joint infection. After the explant of the

femoral and tibial component, irrigation and debridement were performed, and a thorough synovectomy was completed. Then, a static antibiotic-loaded cement spacer was implanted (Figure 2). Cementation technique included 5 bags of 40 mg of cement with 1g Gentamicin and 1g Clindamycin each (COPAL® G+C, Heraeus Medical GMBH, Germany). Six intraoperative specimens were obtained for culture. Five out of six samples were positive for *Streptococcus anginosus* and susceptibility tests confirmed the results obtained in the first place. After consultation with the infectious-disease specialist of our Institution, postoperative parenteral Vancomycin, (2 g per day) and Levofloxacin (750 mg per day) was administered for 4 weeks. Then orally Levofloxacin was continued for a further 2 weeks.

The postoperative period was uneventful. Six weeks after the surgery, the inflammatory markers had normalized (ESR - 5 mm/hr and CRP - 4.2 mg/L) and the patient displayed no clinical signs of infection for the following 4 weeks.

Then, 10 weeks after the first stage, the patient underwent the definitive reimplantation. The spacer was removed, and 6 intraoperative specimens were sampled. After accurate lavage and debridement, a rotational hinged revision TKA with high-dose antibiotic-loaded cement was implanted (Nexgen® Complete Knee Solution, ZimmerBiomet, Warsaw, IN, USA) (Figure 3). There were used two 40 mg bags of cement with 1g Gentamicin and 1g Clindamycin each (COPAL® G+C, Heraeus Medical GMBH, Germany). Skin incision healed completely in 15 days. Intraoperative cultures were negative for any pathogen at this time.

Two years after the reimplantation walked without the aid of canes and had returned to his normal activity level. The range of motion of the right knee was 0° - 120° and the KSS score was 85. The patient had no clinical signs or symptoms of infection, and radiographs showed well-fixed implants.

Discussion

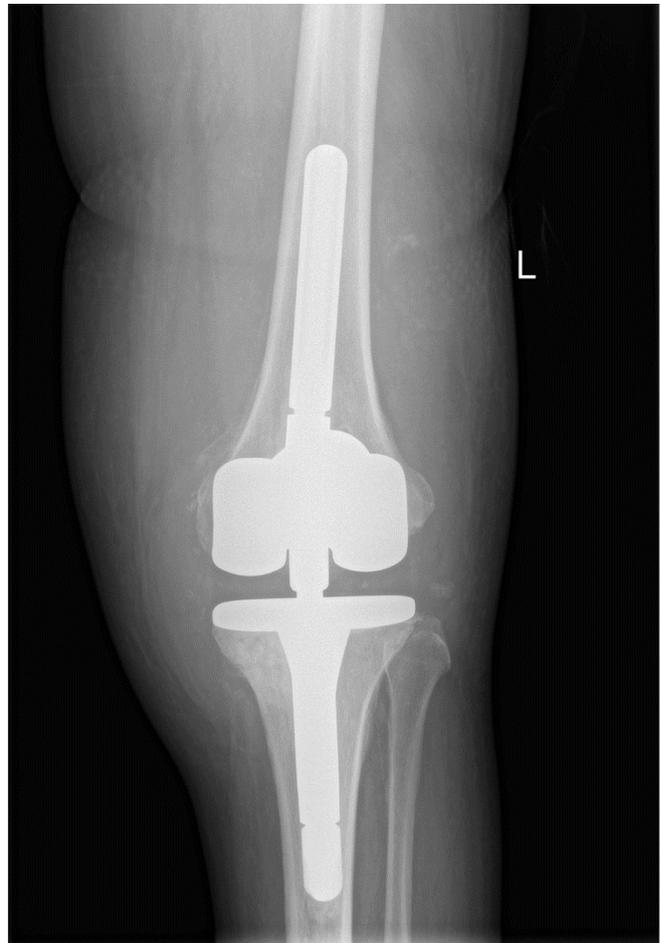
Periprosthetic joint infections can negatively affect the clinical outcome of both primary and revision total joint arthroplasty [1,16–19]. *Streptococcus* species cause between 4 to 16% of periprosthetic joint infections, which are most often related to hematogenous bacterial seeding of the prosthesis from oral or urogenital sources. Streptococcal PJIs are mostly caused by beta-hemolytic streptococci such as *Streptococcus agalactiae* and *Streptococcus dysgalactiae* and by viridans group streptococci such a

Streptococcus mitis. *Streptococcus anginosus* group bacteria, are classified as viridans streptococci, however, have clinically distinct characteristics from other viridians due to capability to cause aggressive pyogenic infections in various body districts and rarely attack bone and joints [5,6,10].

Streptococcus intermedius tends to be isolated as a sole pathogen, whereas *Streptococcus anginosus* and *Streptococcus constellatus* are associated with polymicrobial infections [7].

Streptococcus anginosus osteomyelitis and periprosthetic joint infections are poorly reported in the literature. Seng *et al.* analyzed the prevalence of bone and joint infections due to streptococcal species in a retrospective single-center survey, during a period of 5 years. They found that SAG bacteria caused 22 out of the 100 streptococcal infections (22%) and *Streptococcus anginosus* was the causative pathogen in

Figure 3. Radiograph after the second stage of revision arthroplasty.



A hinge revision TKA, with tibial stem and antibiotic-loaded cement was placed.

two periprosthetic joint infections [10]. Joint involved and treatment procedures were not specified.

Lora-Tamayo *et al.*, in a multicenter retrospective study, analyzed the epidemiology of 462 streptococcal PJIs treated with implant retention. SAG infections were 6.9% and *Streptococcus anginosus* was detected in 3.7% of cases (17 out of 462). However, patients characteristics, joint involved and antibiologic treatment were not described [20]. Renz *et al.* in a large case series of streptococcal periprosthetic infections, mentioned two cases of PJI due to *Streptococcus anginosus* [23]. One of the patients with chronic hip infection underwent removal of the implant with the persistence of the pathogen and consequent death. The other case was not described but apparently received a suppression therapy with amoxicillin after a non-specified surgical treatment, with a successful outcome. We, therefore, believe that the case we described, represents the first periprosthetic joint infection due to *Streptococcus anginosus* fully reported in the English medical literature.

We treated the case as a hematogenous PJI considering the late clinical presentation and the species involved, which typically colonize oropharynx and urogenital tract. Moreover, the patient reported a history of recurrent infections of the urinary tract, which we believe could represent the source of the implant seeding. Taking into account the multi-district pyogenic potential of SAG bacteria, we performed a Technetium bone scan, in order to detect additional foci of infections and to prevent the re-infection after revision surgery, which demonstrated increased uptake only around the left knee.

The choice of the revision strategy was determined considering the unusual aetiology of the pathogen organism. Both 1-stage and 2-stage exchange revision arthroplasty provided good clinical outcome and clearing of infection rates over 84%, when the implant is placed with antibiotic-loaded bone cement [17]. Streptococcal PJIs are typically related with poor outcomes and higher rates of re-infection after revision surgery. The reported treatment success of streptococcal PJI varies from 58 to 83% [20–24]. Therefore, using a 2-Stage exchange revision, over a 1-stage exchange revision, have a potential advantage particularly when the causative pathogen is a difficult-to-treat bacteria or in the hypothesis of polymicrobial infections, as it often happens concomitant to a *Streptococcus anginosus* infection.

Streptococcus anginosus is susceptible to penicillin in almost 100% of cases [6]. However, for streptococci, potentially longer intravenous therapy is necessary

(typically four weeks), as oral beta-lactams may not reach sufficient tissue concentrations [1]. Therefore, antibiotic therapy with Vancomycin and Levofloxacin i.v. were administered for 4 weeks, and then orally continued for a further 2 weeks.

Determining when to perform the reimplantation stage of a 2- stage exchange revision is a very challenging decision for the surgeon and thus is commonly based on several factors such as serological markers, aspiration results, or an antibiotic holiday period. An antibiotic holiday period is thus frequently used to monitor how a patient clinically responds to the discontinuation of antibiotics: the rationale of the practice is that clinical improvement of the patient would indicate infection eradication, while deterioration suggests possible recurrence or persistence of infection. Klouche *et al.* used a 6-week antibiotic holiday period, observing a 97.8% infection cure rate for 2-stage exchanges in hips [23]. According to other authors, the duration of an antibiotic-free period does not appear to significantly affect PJI rate after reimplantation; on the other hand, many patients fail during the antibiotic-free period [24,25]. Although there's a lack of evidence in support or against the use of an antibiotic holiday before reimplantation, we decided to observe "an antibiotic-free period" of 4 weeks.

The patient had normalization of ESR and CRP with substantial clinical improvement, rapid recovery and healing of the incision wound, and no sign of knee effusion. Intraoperative samples were negative for *Streptococcus anginosus* or other pathogens, and therefore we decided to do not administer antibiotics in the post-operative period. Another issue of debate in streptococcal PJI is the role of long-term antimicrobial suppression. Renz *et al.* reported that prolonged oral antibiotic therapy after surgical treatment of streptococcal PJIs was associated with significantly better treatment outcome [23]. Consecutive patients with streptococcal PJI receiving antimicrobial suppression for > 6 months were prospectively included and compared to a retrospective control group without suppression. They found that suppressive antimicrobial treatment was associated with a higher success rate compared with no suppression (93% vs. 57%, $p = 0.002$).

Conclusions

We reported a case of periprosthetic knee infection due to *Streptococcus anginosus*. SAG bacteria are pyogenic pathogen which can occasionally seed vascular or other metallic implants and tends to develop

polymicrobial infections. According to our knowledge, this is the first fully documented case of PJI management due to *Streptococcus anginosus*. The treatment of streptococcal PJIs could be challenging because the tendency to poorer clinical outcome and lower clearance of infection rate. Therefore two-stage exchange revision represents a reasonable treatment choice when the causative pathogen is a difficult-to-treat bacteria or in the hypothesis of polymicrobial infections, as it often happens concomitant to a *Streptococcus anginosus* infection. Further studies are needed in order to provide sufficient evidence about the need for “drug holiday” prior to reimplantation in two-stage exchange revision and the efficacy of long-term antimicrobial suppression in streptococcal PJIs.

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