Difficult-to-Detect Low-Grade Infections Responsible for Poor Outcomes in Total Knee Arthroplasty

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Abstract

In this article, we present the case of a patient with a stiff, painful knee after total knee arthroplasty, and with erythrocyte sedimentation rate, C-reactive protein level, and synovial fluid analysis within normal limits. Open biopsy for cultures showed *Propionibacterium acnes* prosthetic joint infection, which was successfully treated with 2-stage revision and intravenous antibiotics.

Take-Home Points

- Despite standardization of diagnostic criteria by the MSIS for the diagnosis of PJI, some low-grade inflections create a diagnostic challenge for clinicians.
- *P acnes* infection following TJA can be present despite patients having normal serum inflammatory marker levels and synovial fluid aspirations.
- Patients with a PJI with low virulence organisms can present with painful, arthrofibrotic joints that do not appear to be clinically infected.
- Biopsy for pathology and culture can aid in the diagnosis of suspected PJI in patients who fail to meet MSIS criteria.
- If detected and accurately diagnosed, PJI with *P acnes* can be successfully eradicated with IV antibiotics and 2-stage revision arthroplasty with a good functional outcome.

Total joint arthroplasty (TJA) is a routinely performed, highly efficacious procedure for patients with degenerative osteoarthritis.[1,2] In the United States in 2003, more than 450,000 total knee arthroplasties (TKAs) were performed, and this number is projected to increase by more than 673% by 2030, as America's population continues to age.[3] With the increase in primary TJAs has come an increase in revision TJAs. The most common cause of revision TJA is infection (25.2%), which has a rate of 1% to 4% after primary TJA.[1,4] Despite advancements in implant technology, preoperative preventive strategies, perioperative techniques, and postoperative management, a recent meta-analysis of patient follow-up data revealed that 15% to 20% of patients remained dissatisfied after TJA, despite having technically well-placed implants.[5,6]

Recent studies have suggested that prosthetic joint infection (PJI) may be underreported because of the difficulty in diagnosis, which may be one of the reasons why patients remain dissatisfied after TJA.[7] As a result, new efforts have been made to develop uniform criteria for PJI diagnosis.[8] In 2011, the Musculoskeletal Infection Society (MSIS) developed a new definition for the PJI diagnosis, based on clinical and laboratory criteria, in order to increase diagnostic accuracy. However, MSIS acknowledged that PJI may be present even if these criteria are not met, particularly in the case of low-grade infections, as patients may not present with clinical signs of infection and may have normal inflammatory markers and joint aspirates. The biofilm-forming bacteria *Propionibacterium acnes* and *Staphylococcus epidermidis* are 2 such low-virulence organisms—once commonly considered contaminants but now recognized as potential pathogens for postoperative joint infections.[9] In a review performed at a major orthopedic hospital, Bjerke-Kroll and colleagues[10] found that the rate of PJI with *P acnes* has been increasing linearly over the past 14 years. According to reports in the literature,[11-13] *P acnes* has been isolated in 2% to 4% of all cases of PJI, and Zappe and colleagues[13] found a *P acnes* PJI rate of 6% in a retrospective analysis performed at their institution. Given the high rate of *P acnes* colonization of the axilla, this organism is now increasingly recognized as a cause of infection after shoulder surgery, as found in a case series of 10 patients with *P acnes* PJI after total shoulder arthroplasty (TSA).[14] However, there is still limited

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data on the role of *P acnes* in lower extremity PJI.

Although patients with *P acnes* PJI can present with overt signs of infection, more often they lack systemic or local signs of infection, making the diagnosis difficult.[15] Surgeons may not consider PJI as a cause of TJA failure in patients who do not meet diagnostic criteria.[7] In a case series of patients with *P acnes* PJI after TSA, Millett and colleagues[14] concluded that erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are not always reliable indicators of infection with low-virulence organisms. Eighty percent of patients in their study had normal ESR and CRP level before surgery. Zappe and colleagues[13] reported on *P acnes* PJI diagnoses in 4 total hip arthroplasties (THAs), 3 TKAs, and 1 TSA. Of the 8 patients, 6 (75%) had borderline elevated CRP levels, and 4 (50%) had normal synovial fluid analysis and cultures from joint aspirations. In a study using electron microscopy and fluorescence in situ hybridization (FISH) labeling, Stoodley and colleagues[16] found, in 8 polyethylene liners removed from culture-negative THA patients for aseptic loosening, extensive biofilm colonization with *S epidermidis*.

Reports of PJI cases misdiagnosed as aseptic loosening also suggest that screening and diagnostic tools are not sensitive enough to detect all infections and that PJI likely is underdiagnosed. In a prospective cohort study, Portillo and colleagues[17] categorized patients who were undergoing revision surgery after TJA by cause of failure: aseptic loosening, mechanical failure, or PJI based on current MSIS guidelines. Intraoperative cultures were taken during the revisions. *P acnes* was isolated in 2 (3%) of the 63 cases classified as PJI and in 12 (19%) of the 63 classified as aseptic loosening. Tsukayama and colleagues[18] reported an 11% rate of positive intraoperative cultures for *P acnes* during revision surgery in cases that the operating surgeon considered aseptic, based on white blood cell (WBC) count, ESR, and CRP level. Rasouli and colleagues[19] used an Ibis biosensor to perform polymerase chain reaction (PCR) on synovial fluid from 44 patients who underwent aseptic revision of TKA failures. The authors detected a pathogen in 17 (38%) of the 44 presumed aseptic patients and

Table. **Summary of Clinical and Laboratory Findings on Presentation to Our Office 2 Years After Primary Total Knee Arthroplasty, at Time of Open Biopsy, at Stages 1 and 2 of 2-Stage Revision, and at 1-Year Follow-Up**

Sex	Male
Age	69 y
Index surgery	Left total knee arthroplasty
Symptoms	Pain, stiffness
Date of:	
Index surgery	5/25/12
Presentation	6/5/14
Stage 1 of 2-stage revision	11/4/14
Stage 2 of 2-stage revision	1/6/15
Functional capacity	
Before revision (presentation, 2014)	1 city block, with cane, limited by pain; on disability
After revision (1-year follow-up, 2016)	Pain no longer limits ambulation; returned to work
Flexion	
Before revision (presentation, 2014)	10°-30°
After revision (1-year follow-up, 2016)	5°-90°
Follow-up after revision	13 mo
Synovial cell count (presentation, 2014)	422 cells/μL
Synovial % PMNs (presentation, 2014)	42%
Open biopsy results	
Frozen section	<5 neutrophils per high-power field
Culture organism	*Propionibacterium acnes* ×5
Culture time to growth	12.2 d (10, 12, 12, 13, 14)
Culture sensitivity	Oxacillin
Antibiotic used for treatment, duration	Oxacillin, 6 wk
Erythrocyte sedimentation rate	
Presentation (2014)	9 mm/h
Before stage 2 of revision (2015)	25 mm/h
C-reactive protein level	
Presentation (2014)	0.29 mg/dL
Before stage 2 of revision (2015)	0.68 mg/dL
White blood cell count	
Presentation (2012)	7.5×10^3/μL
Before stage 2 of revision (2015)	7.1×10^3/μL

Abbreviation: PMN, polymorphonuclear neutrophil.

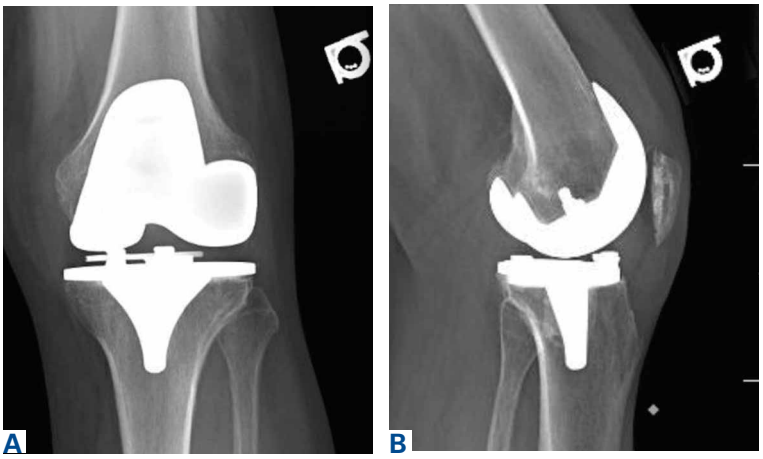

Figure 1. (A) Anteroposterior and (B) lateral radiographs of left the knee, on presentation to our office in 2014, show well-seated femoral and tibial implants in excellent alignment.

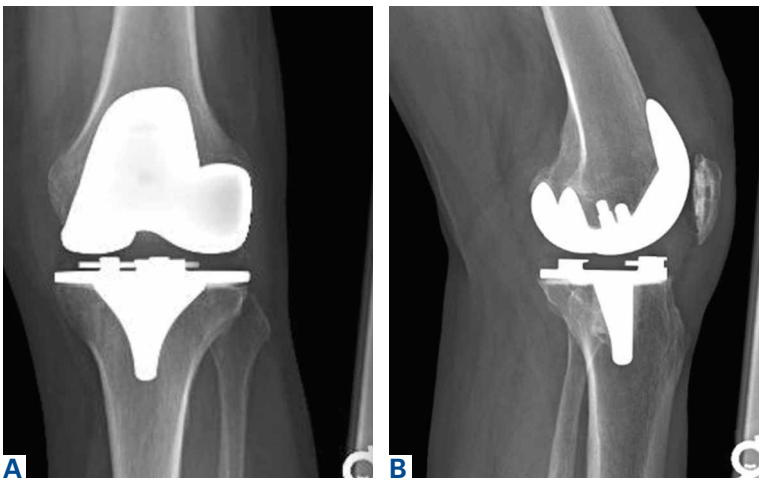

Figure 2. (A) Anteroposterior and (B) lateral radiographs of the left knee immediately after total knee arthroplasty in 2012 show well-seated femoral and tibial implants in excellent alignment.

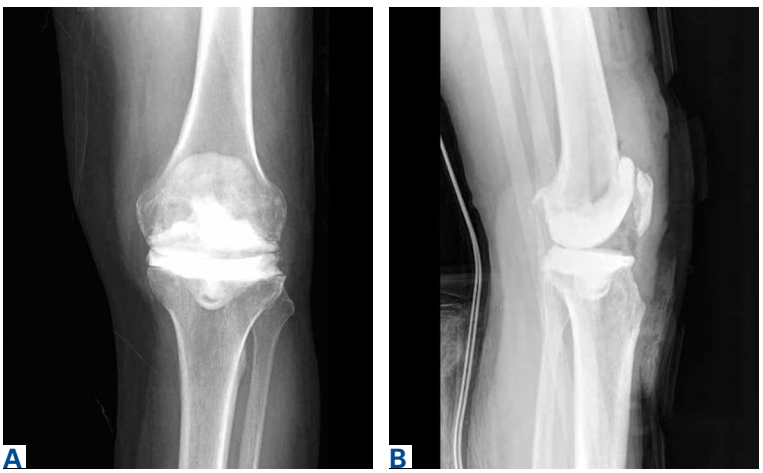

Figure 3. (A) Anteroposterior and (B) lateral radiographs of the left knee after stage 1 of a 2-stage revision in 2014 show antibiotic cement spacer in joint space.

concluded some aseptic loosening cases are actually chronic low-grade organism PJIs not diagnosed according to current PJI criteria.

In this article, we present the case of a patient with a stiff, painful knee after TKA and with ESR, CRP level, and synovial fluid analysis within normal limits. Open biopsy for cultures showed *P acnes* PJI, which was successfully treated with 2-stage revision. The patient provided written informed consent for print and electronic publication of this case report.

Case Report

A 69-year-old man with a past medical history of hypertension underwent left primary TKA in 2012. In 2014, he presented to our office complaining of chronic left knee pain and stiffness that had developed insidiously over the first 3 months after surgery and never improved, despite rigorous physical therapy (**Table**). With use of an assistive device, he could ambulate for a maximum of 1 city block, and he was on disability from his job as an electrician. On presentation in 2014, radiographs of the left knee showed a well-seated, well-aligned TKA without any radiographic changes relative to the immediate postoperative radiographs (**Figures 1A-1B, 2A-2B**). Physical examination revealed no erythema or swelling of the joint. Skin was intact and incision well-healed. Left knee passive range of motion (ROM) was 10° to 30° of flexion and painful. A full infectious work-up was performed. Inflammatory markers were within normal limits: serum WBC count, 5.2 × 10^3/μL (normal, 4.0-10.5 × 10^3/uL); ESR, 9 mm/h (normal, <20 mm/h); and CRP, 0.29 mg/dL (normal, <0.8 mg/dL). Synovial fluid aspiration was performed for fluid analysis and cultures. Analysis revealed 422 WBCs/μL with 42% polymorphonuclear neutrophils (PMNs). MSIS criteria for using synovial fluid to diagnose PJI are >3000 WBC cells/uL with >65% PMNs. Cultures from synovial fluid were negative at 8 days of incubation.

Despite not meeting MSIS diagnostic criteria, the patient elected to undergo open biopsy for synovial culture as a last resort. During surgery, there was no purulence in the joint, and frozen section showed <5 neutrophils per high-power field. All cultures from 5 separate synovial tissue samples grew *P acnes*, confirming the PJI diagnosis. Cultures turned positive after being incubated an average of 12.2 days (range, 10-14 days). Sensitivities showed the organism was responsive to oxacillin. The risks and benefits of 2-stage revision surgery were dis-

cussed with the patient at the next office visit, and he decided on 2-stage revision. On November 4, 2014, he underwent open synovectomy, irrigation and débridement with iodine and Dakin solution, hardware removal, and cement antibiotic spacer placement without complication (**Figures 3A, 3B**). Intravenous (IV) oxacillin was administered for 6 weeks, as directed by an infectious disease specialist, and the patient was monitored, both clinically and by ESR and CRP level, for signs of infection.

Just before stage 2 revision on January 6, 2015, preoperative inflammatory markers were within normal limits. During surgery, additional cultures were taken from synovial tissue. At 15 days, these cultures showed no growth, confirming eradication of the infection. The patient underwent reimplantation without complication and had an uneventful postoperative course with no wound-healing issues (**Figures 4A, 4B**). At 1-month, 3-month, 6-month, and 1-year follow-up, he endorsed significantly improved pain and symptoms. ROM at 1-year follow-up was improved to 5° to 90° of flexion. The patient was ambulating pain-free, without an assistive device, and he had returned to work. He reported being satisfied with having undergone the 2-stage revision.

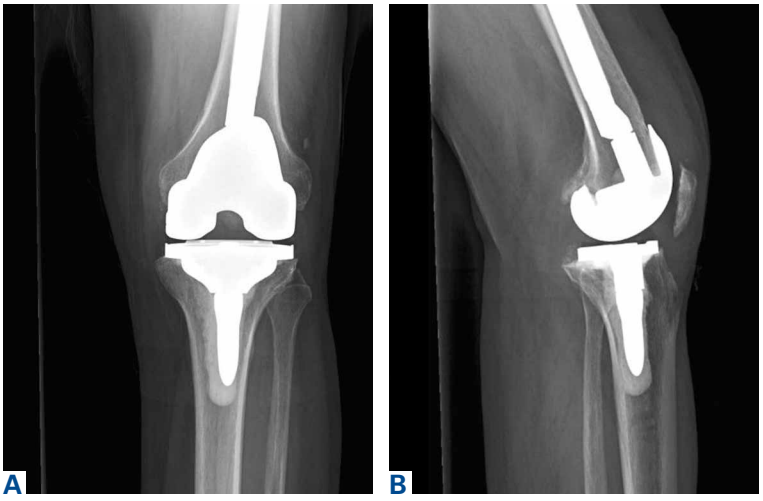

Figure 4. (A) Anteroposterior and (B) lateral radiographs of the left knee after stage 2 of a 2-stage revision in 2015 show well-seated femoral and tibial revision components in excellent alignment.

Discussion

Because PJIs with low-virulence organisms can present with normal levels of inflammatory markers and negative fluid analysis and culture from joint aspirations, they pose a diagnostic challenge for arthroplasty surgeons. In this case report, there was a low index of suspicion for PJI based on radiographic, physical examination, and laboratory findings. Our patient did not meet MSIS diagnostic criteria for PJI before undergoing open biopsy. Initial cultures from joint aspiration of synovial fluid were negative, and inflammatory markers were within normal limits. However, all 5 synovial tissue biopsy specimens that were cultured confirmed a low-grade periprosthetic infection with *P acnes*—likely the reason for the poor outcome. This case supports Zappe and colleagues[13] and Millett and colleagues,[14] who found that a subset of patients with a low-grade organism PJI had normal to mildly elevated inflammatory markers and negative fluid analysis and cultures from joint aspirations.

Hardware-involved orthopedic infections are often caused by bacteria that form a biofilm, which can be difficult to culture. Biofilm matrix binds cells into aggregates, which grow only a single colony on culture media, decreasing positive yield. Therefore, synovial fluid cultures are often negative, because of the low number of planktonic cells removed by aspirate. Using FISH and PCR, Stoodley and colleagues[16] found biofilm on hardware removed for "culture-negative aseptic loosening." This is especially important for low-grade organism infections that lack a strong inflammatory response in the joint and that may be missed with traditional screening. This may be one reason our patient's synovial fluid cultures and inflammatory markers were negative.

Another reason these low-grade infections can be missed is that *P acnes* is notoriously difficult to culture—it may take up to 15 days to grow in a special medium.[20] Intraoperative cultures may be read as false-negative if not incubated the right amount of time. In many hospitals, aerobic and anaerobic cultures are discarded if there is no growth after 3 to 5 days. In our patient's case, the earliest that cultures turned positive was on day 10—which is consistent with other reports, including one by Butler-Wu and colleagues,[15] who suggested a minimum incubation of 13 days for optimal recovery of organisms. Our case highlights the importance of lengthening incubation to allow for growth of low-virulent organisms. Given the different types of management used for PJI and aseptic loosening, it is imperative that surgeons take cultures during revision TJA and that cultures are held up to 14 days to allow enough time for low-virulence organisms to grow.

Fortunately, PJI with low-virulence organisms can be treated successfully. Treating *P acnes* PJI with exchange arthroplasty and IV antibiotics has documented success rates as high as 92%.[21] Again, we emphasize the importance of obtaining

intraoperative cultures to determine antibiotic sensitivities, which can guide treatment. Our patient's infection was eradicated with 2-stage revision and IV antibiotics, and his symptoms, ROM, and function improved significantly.

Diagnosing PJI after TJA can be challenging, as there is no definitive test that is sensitive, specific, rapid, and minimally invasive. Researchers have looked for novel serum or synovial fluid biomarkers that may be elevated in PJI. Synovial interleukin 6 (IL-6) and synovial α-defensin show great promise. In 2 separate studies, elevated IL-6 levels strongly correlated with infection.[22,23] Jacovides and colleagues[23] found that a synovial IL-6 level higher than 4270 pg/mL had a 100% positive predictive value and a 91% negative predictive value for diagnosing PJI. In some trials, synovial α-defensin has shown up to 100% sensitivity and specificity for PJI diagnosis. Most notably, in a trial by Frangiamore and colleagues,[24] α-defensin levels were elevated to statistically significant levels in *P acnes* PJI, indicating this test may help in diagnosing PJI with low-virulence organisms. Finally, PCR has also shown promise in detecting low-grade joint infections. PCR uses 16 primers that allow not only for the identification of pan-genomic bacterial markers, specific bacterial organisms, and *Candida,* but also for the presence of antibiotic resistance markers. Use of pan-genomic PCR also allows for detection of a wider variety of pathogens, including organisms commonly missed by conventional culture methods.[25]

Early intervention can significantly improve outcomes in PJI. Therefore, we recommend maintaining a high index of suspicion for low-virulence PJI in patients with chronic pain and decreased functionality after TJA with well-placed implants, despite their not meeting current MSIS diagnostic criteria for PJI. As new microbiological tools for detecting PJI with low-grade organisms are developed, use of these technologies can be incorporated into the diagnosis algorithm. Screening tools more sensitive in detecting low-grade organisms can help avoid the morbidity associated with interoperative synovial biopsies for culture and can allow for more efficient surgical planning. These tools, along with increased clinical awareness of potential PJIs, ultimately will lead to earlier detection, accurate diagnosis, and optimal treatment.

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This paper will be judged for the Resident Writer's Award.