Brucella Prosthetic Joint Infection: A Report of 3 Cases and a Review of the Literature

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We report 3 cases of Brucella melitensis infection of prosthetic hips and knees, and we summarize data about 4 cases reported in the literature. Six of the 7 affected patients were men. The median duration from prosthesis implantation to the onset of symptoms was 38.7 months. Five patients had only local symptoms. Preoperative joint aspirates yielded negative culture results for 3 patients, and blood culture results were negative for 6 patients. Excisional arthroplasty was the initial intervention for 3 patients. Three others responded well to medical therapy alone. One patient had relapse while receiving tetracycline and underwent total hip replacement. All patients were treated with combined antibiotic therapy for 6 weeks to 19 months. All had favorable long-term responses. The 3 patients we treated underwent a 2-staged resection arthroplasty. Antibiotics alone can be used to treat Brucella prosthetic joint infection, but loosening of the joint and clinical or microbiological failure must be treated with a 2-staged excisional arthroplasty and 3 months of treatment with doxycycline and rifampicin.

Brucellosis, a zoonosis of worldwide distribution, is a systemic infection caused by Brucella species that can involve many organs and tissues [1]. Osteoarticular disease is the most common complication of brucellosis and has been described in 10%–85% of patients [2, 3]. Arthritis involving large joints and the sacroiliac joints is the most prevalent and important clinical form of osteoarticular involvement; spondylitis, bursitis, tenosynovitis, and osteomyelitis have been also described [2–10].

Prosthetic joint infection (PJI) is a serious complication of total joint arthroplasty, with coagulase-negative staphylococci and Staphylococcus aureus accounting for >50% of cases [11, 12]. The infecting organism can be introduced either during surgery or through hematogenous seeding. Brucella PJI, however, is rare. Only 4 cases of PJI associated with Brucella species have been reported in the medical literature [13–16]. We describe our experience with 3 patients who had Brucella PJI and review data about 4 additional cases published in the literature.

PATIENTS AND METHODS

The first case of Brucella PJI at the Hadassah University Hospital (Jerusalem, Israel) was identified in 1997, and 2 additional cases were diagnosed subsequently. By means of manual and computerized (MEDLINE database) literature searches, data regarding all published cases of Brucella PJI were collected. The laboratory testing of these cases included use of a standard tube agglutination test with Brucella abortus antigens, and blood and synovial fluid specimens were cultured using blood culture bottles (BacT/Alert; Organon Teknika). All specimens were processed using conventional bacteriological techniques and incubated for ≥21 days.
Figure 1. Radiograph of the hip of patient 1 disclosing loosening of the femoral component and a clear radiolucent line around the femoral implant.

CASE REPORTS

Patient 1. A 38-year-old man was admitted to the Hadassah University Hospital for revision of left total hip replacement because of increased pain, which was accompanied by loosening of the prosthesis. Four years before hospital admission, at another hospital, total hip arthroplasty had been performed for rapidly destructive coxarthrosis attributed to psoriatic arthritis. This had been manifested by fever and disabling joint pain, which was unsuccessfully treated with methotrexate and corticosteroids. No skin lesions were present.

Physical examination revealed limitation of hip joint movement. The peripheral WBC count was 8600 cells/mm³, and the erythrocyte sedimentation rate (ESR) was 20 mm/h. Radiography of the hip disclosed loosening of the femoral component with mild subsidence and a clear radiolucent line around the femoral implant. Some new bone formation and sclerotic changes were visible around the acetabulum (figure 1). A ⁹⁹Tc-Technetium bone scan revealed moderately increased uptake in the femur and the acetabulum. Cultures of joint fluid aspirate were sterile. Revision surgery revealed abundant necrotic tissue together with marked loosening of the prosthesis. Excision arthroplasty was performed. All cultures of samples obtained during surgery yielded Brucella melitensis. The serum Brucella antibody titer was 1:1600. Doxycycline (200 mg/day) and rifampin (600 mg/day) were administered for 6 weeks, followed by a second-stage surgical revision and an additional 6 weeks of combined antibiotic therapy.

Retrospective evaluation suggested that what was originally diagnosed as psoriatic arthritis was probably Brucella osteomyelitis on the basis of the clinical presentation of systemic febrile illness, polyarthralgia, a history of ingestion of unpasteurized dairy products, and a noncaseating granulomatous inflammatory process revealed by synovial biopsy. Physical examination performed a year after the second-stage revision revealed a painless hip with complete restoration of motion.

Patient 2. A 61-year-old Arab man underwent total knee arthroplasty (TKA) for treatment of degenerative joint disease of the right knee 3 years before the present admission to the hospital. Thirty years before undergoing TKA, the patient had experienced right hip arthritis of unknown origin that resulted in spontaneous hip fusion. A year after undergoing TKA, the patient presented with a right popliteal abscess that had no communication to the joint. Culture of a sample of pus from the drained abscess yielded methicillin-susceptible Staphylococcus epidermidis. Cefazolin was administered intravenously for 6 weeks. Two years later, the patient presented with a swollen, painful, warm right knee, with marked loosening of both femoral and tibial components visible on radiographs. Culture of joint aspirate yielded Acinetobacter baumanii; the infection was unsuccessfully treated with imipenem. Because of continued swelling and pain, excision arthroplasty, marked by extensive tibial bone loss, was performed. All cultures of samples obtained during surgery yielded B. melitensis. The serum Brucella antibody titer was 1:1600. Doxycycline (200 mg/day) and rifampin (600 mg/day) were administered for 6 weeks, followed by a second-stage surgical revision and an additional 6 weeks of combined antibiotic treatment. A year later, the patient was still free of joint pain.

Patient 3. A 67-year-old Arab man was admitted to Hadassah University Hospital with fever, right-side pelvic pain, and lower back pain. Sixteen years before hospital admission, the patient had undergone bilateral proximal valgus tibial osteotomy. Two years later, TKA had been performed because of progressive left-knee pain compatible with severe degenerative changes seen on radiographs. During examination, the patient appeared to be ill, his temperature was elevated (38.2°C), and there was mild tenderness over the right sacroiliac joint. The peripheral WBC count was 4500 cells/mm³, and the ESR was 76 mm/h. No gross abnormality appeared on either plain radiographs or CT scans of the pelvis, sacroiliac joints, and dorsal
A few days after admission to the hospital, the patient developed severe pain in his left knee. Plain knee radiography revealed mild loosening of the femoral component. A year later, the patient remained free of knee pain.

All 3 of our patients had consumed unpasteurized milk or goat cheese during the months before admission to the hospital.

RESULTS

The demographic characteristics of the 7 patients with *Brucella* PJI are summarized in table 1. The first 4 patients (patients 1–4) were described in the literature, and the next 3 (patients 4–7) are those described above, who were treated at Hadassah University Hospital. Six of the patients were men. The mean age of the 7 patients was 54 years, which is compatible with the age at which patients typically undergo joint replacement. All patients either had consumed unpasteurized milk or goat cheese or had occupational exposure. Six came from areas where brucellosis is endemic.

Among these patients, there were 5 total knee replacements and 2 total hip replacements (table 2). The median time from prosthesis implantation to onset of symptoms was 38.7 months; the interval between the primary arthroplasty and the onset of PJI in our series, however, was 2.5–14 years, in contrast to the interval of 2–14 months in the published cases. All patients experienced symptoms for several months before diagnosis. Most patients had underlying degenerative joint disease, which necessitated joint replacement. Five of the 7 patients had only local symptoms at presentation, including pain (all patients), swelling (3 patients), warmth (3 patients), redness (1 patient), and sinus tract formation (1 patient). Only 2 patients developed fever and other systemic signs. The initial prosthesis was cemented in 3 patients; for the other 4, this information was not available.

All patients had normal WBC counts and mildly elevated ESRs (mean, 54 mm/h; range, 30–76 mm/h). Radiography demonstrated loosening of the prosthesis in 4 of the 7 patients (57% of implants). Preoperative joint aspirate specimens yielded negative Gram stain and culture results for 2 of 3 of our patients, and the correct diagnosis was not made until the time of surgery. One of the 4 patients described in the literature also had negative results of preoperative joint aspirate culture, and diagnosis was made on the basis of history of occupational exposure and strongly positive results of serological tests. Blood cultures yielded *Brucella* species in only 1 case [15]. Six of 7 isolates were *B. melitensis*; *B. abortus* was isolated from only a single patient. The results of serological tests were strongly positive for all patients for whom the test was performed. Excisional arthroplasty was the initial intervention for 3 (43%) of the 7 patients. Three patients who did not undergo excisional arthroplasty responded well to medical therapy. One patient (patient 1), who was treated twice with tetracycline alone (a 6-week course and a 6-month course), had relapse and underwent revision total hip replacement. The 3 patients treated at our institution underwent staged revision arthroplasty. The first stage consisted of removing the infected prosthesis and debriding the remaining cement and necrotic tissue. The median interval between resection arthroplasty and the second stage, including revision reimplantation, was 6 weeks. Reimplanted prostheses were cemented (all with gentamicin-impregnated bone cement) in all patients for whom this information was available. Antibiotic therapy was administered to all patients. Four of the 7 patients received doxycycline and rifampin, 2 patients were given streptomycin and doxycycline, and 1 patient was treated with rifampin and trimethoprim-sulfamethoxazole. All were treated for a prolonged duration (6 weeks to 19 months). The median duration of follow-up for 5 patients with available data was 8 months. All patients recovered without any relapses of infection in either the new or the remaining prosthesis.

### Table 1. Demographic characteristics of patients with *Brucella* prosthetic joint infection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year of presentation</th>
<th>Age in years, sex</th>
<th>Occupation</th>
<th>Country (ethnicity)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1983</td>
<td>54, M</td>
<td>Dairy farmer</td>
<td>United States</td>
<td>Jones et al. [14]</td>
</tr>
<tr>
<td>2</td>
<td>1989</td>
<td>24, F</td>
<td>NA</td>
<td>Saudi Arabia</td>
<td>Agarwal et al. [13]</td>
</tr>
<tr>
<td>3</td>
<td>1997</td>
<td>74, M</td>
<td>Shepherd</td>
<td>Greece</td>
<td>Malizos et al. [15]</td>
</tr>
<tr>
<td>4</td>
<td>1997</td>
<td>60, M</td>
<td>Worked with goats</td>
<td>Spain</td>
<td>Orti et al. [16]</td>
</tr>
<tr>
<td>5</td>
<td>2002</td>
<td>38, M</td>
<td>Artist</td>
<td>Israel (Jewish)</td>
<td>Present report</td>
</tr>
<tr>
<td>6</td>
<td>2002</td>
<td>64, M</td>
<td>Retired</td>
<td>Israel (Arab)</td>
<td>Present report</td>
</tr>
<tr>
<td>7</td>
<td>2002</td>
<td>67, M</td>
<td>Retired</td>
<td>Israel (Arab)</td>
<td>Present report</td>
</tr>
</tbody>
</table>

**NOTE.** NA, not available.
DISCUSSION

The overall incidences of infection of the total hip and knee arthroplasty sites during the first 2 and 10 years after operation are ~5.9 and ~2.3 infections per 1000 joint-years, respectively [12]. The majority of infections (65%) are caused by aerobic gram-positive cocci, most commonly S. aureus, coagulase-negative staphylococci, and enterococci. Aerobic gram-negative bacilli, including Escherichia coli, Proteus mirabilis, and Pseudomonas aeruginosa, are far less frequent causes of infection (6% total). Anaerobes account for 4% of infections. Fungal and mycobacterial infections of prosthetic joints are unusual. Rare microbial causes of PJI have been reported. Only 4 cases of Brucella PJI [13–16] and 1 case of osteomyelitis involving prosthetic extra-articular hardware [17] have been reported.

Brucellosis is a disease with protean manifestations, which can be either acute or chronic. It is a systemic infection in which any organ in the body can be involved [1]. Osteoarticular complications are common in brucellosis, having been reported in 10%–85% of cases [2–10]. The spectrum of bone and joint complications includes arthritis, spondylitis, osteomyelitis, tenosynovitis, and bursitis. Sacroilitis was the most commonly reported complication in several studies [7, 8], whereas large, weight-bearing joints were the most commonly involved joints in other series [10]. Spondylitis, predominantly that involving the lumbar spine, is more common among elderly patients, and, on rare occasions, it can be associated with paraspinal abscesses [4, 9].

Our review of 7 cases of Brucella PJI (4 reported in the literature and 3 diagnosed and treated at our institution, Hadassah University Hospital) revealed that the disease occurs most commonly in adults aged 24–74 years. Most patients were men who lived in areas where brucellosis is endemic. All patients at our institution were infected through ingestion of unpasteurized dairy products, as deduced from the epidemiological context, whereas the patients described in the literature had occupational exposure to Brucella species. Brucella PJI involved mainly the knee joint. There were unremarkable underlying diseases. Most patients presented with an indolent onset of symptoms. The median duration from prosthesis implantation to onset of symptoms was 38.7 months. Among patients at our institution, this period lasted 2.5–14 years, whereas, for the published cases, the range was 2–14 months. The major obstacle to establishing a clinical diagnosis of Brucella PJI was the nonspecific and subtle nature of the symptoms and signs. Only 2 patients had systemic symptoms and signs. Abnormal blood test results were usually mild and nonspecific. Radiographic findings for all patients at our institution demonstrated loosening of the prosthesis, and bone loss ranged from mild to severe. The results of cultures of preoperative needle aspirates of the joint were positive for >80% patients with PJI [18]. Culture of synovial fluid samples from Brucella joint effusions recovers the bacteria in ~50% of cases [8]; we found a similar rate in our study, emphasizing the fact that a negative joint culture result does not rule out osteoarticular brucellosis. All patients had high titers of specific antibodies (>1:160). Two patients at our institution (patients 5 and 6) had Brucella PJI diagnosed only during revision surgery. In patient 5, insidious, untreated Brucella PJI had been incorrectly attributed to psoriatic arthritis and resulted in native joint destruction and a failed hip arthroplasty. In patient 6, a variety of coexisting infecting organisms masked the diagnosis of Brucella PJI.

Management of Brucella osteomyelitis and PJI is controversial with regard to selection of antibiotics, duration of treatment, and the role of surgery. In 1986, the World Health Organization recommended use of doxycycline (200 mg/day) in combination with rifampicin (600–900 mg/day po) for 6 weeks as the treatment of choice [19, 20]. Subsequent studies that compared doxycycline plus rifampicin with doxycycline plus streptomycin concluded that the latter combination was more efficacious, especially for patients with such complications as spondylitis [21, 22]. Although there was initial enthusiasm about trimethoprim-sulfamethoxazole for treatment of brucellosis, subsequent comparative studies revealed an unacceptably high rate of relapse [23]. Similarly, use of quinolone an-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infected joint</th>
<th>PJ age</th>
<th>Underlying disease or risk factor</th>
<th>Type of symptom</th>
<th>Previous infection in PJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hip</td>
<td>5 months</td>
<td>None</td>
<td>Systemic</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Knee</td>
<td>2 months</td>
<td>Juvenile rheumatoid arthritis</td>
<td>Local</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Knee</td>
<td>4 months</td>
<td>None</td>
<td>Local</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Knee</td>
<td>14 months</td>
<td>Idiopathic osteonecrosis of internal condyle of femur</td>
<td>Local</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Hip</td>
<td>4 years</td>
<td>Misdiagnosis of psoriatic arthritis</td>
<td>Local</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Knee</td>
<td>2.5 years</td>
<td>Hip fusion</td>
<td>Local</td>
<td>Popliteal abscess, Acinetobacter septic arthritis</td>
</tr>
<tr>
<td>7</td>
<td>Knee</td>
<td>14 years</td>
<td>Degenerative joint disease</td>
<td>Systemic</td>
<td>None</td>
</tr>
</tbody>
</table>
tibiotics has been disappointing, despite in vitro activity and good penetration into cells [24]. Consequently, quinolones are best reserved for adjunctive therapy [25]. The toxicity associated with prolonged aminoglycoside use and the shortage of streptomycin in our country (Israel) led us to treat our patients with doxycycline and rifampin. The total duration of antibiotic therapy necessary for eradication of infection is also unknown. In the present study, treatment duration ranged from 6 weeks to 19 months. Treatment for a minimum of 6 weeks has been most consistently successful for eradication of infection, which should be confirmed by culture before reimplantation of the prosthesis.

The optimal surgical approach to PJI is unknown because of the lack of large-scale, randomized, prospective studies [26–30]. In 3 patients with Brucella PJI described in the literature, the prosthesis was salvaged, a procedure usually reserved for patients with PJI who have no sepsis, whose prosthesis is not loose, and whose symptoms are of relatively acute onset [31]. The 3 patients with Brucella PJI from our institution underwent 2-staged exchange arthroplasty, which is the preferred therapeutic procedure for PJI at Hadassah University Hospital [32]. The protocol incorporates standardized antimicrobial therapy with a 2-stage surgical procedure. Removal of the prosthesis and cement is followed by a 6-week course of antibiotic therapy selected on the basis of the findings of quantitative in vitro susceptibility studies. Reimplantation is performed at the conclusion of the 6-week antibiotic course. The optimal time for reimplantation of prostheses for patients with Brucella PJI is unknown, because the disease is notoriously indolent and there is no consistent test for successful eradication. In the present study, the average time to reimplantation was similar to the time to reimplantation for patients with PJIs due to other organisms at our institution, with favorable results. Other investigators [33] have recommended that, for cases of PJI due to unusual or virulent organisms, there should be a longer period between resection and reimplantation. In the case of fastidious microorganisms, such as Brucella species, it is rational to wait for culture results before reimplantation. The 2-stage procedure also allows preparation of the nonstandard medical equipment and prostheses required for revision surgery. Use of methylmethacrylate cement impregnated with an antimicrobial agent has not been subjected to controlled trials and is not approved by the US Food and Drug Administration, but this practice is common [34]. With this protocol, a 90%–96% success rate has been achieved for infection at the site of total hip replacement, and a 97% success rate has been obtained for infection at the site of total knee replacement.

In conclusion, in countries where brucellosis is endemic, Brucella species should be sought in cases of PJI that occur after total joint arthroplasty. These infections seem to be insidious; they are easily masked by other coexisting infections, so they might be overlooked as a result of their subtle nature. It should also be remembered that a negative joint culture result does not rule out osteoarticular brucellosis. A combined medical and surgical approach that includes doxycycline and rifampicin therapy and confirmation of an infection-free period after the initial surgical approach appears to provide the best chance of a successful reimplantation. The optimal duration of antibiotic therapy and time to reimplantation remain unknown but may be similar to those for PJIs due to other microorganisms.

References


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