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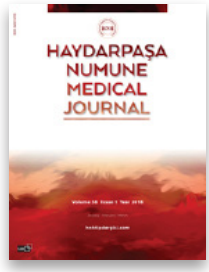

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REVIEW

If you Want to Find, you Must Think: Case Report and Literature Review of the Periprosthetic Knee Infection from *Brucella* Melitensis

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Abstract

In addition to the difficulty of diagnosis in periprosthetic joint infections (PJI) following total knee arthroplasty, the infectious agent is also often difficult to identify. Correct identification of the pathogen increases the chance of a successful treatment. Although rare, clinicians should keep Brucella infections in mind when a pathogen cannot be found in PJI cases. A 58-year-old female patient was diagnosed with a periprosthetic Brucella infection following bilateral total knee arthroplasty. All symptoms disappeared in the postoperative 1st year after a two-step revision arthroplasty. We aimed to draw attention to periprosthetic infections caused by Brucella and to perform a review of literature in this case report.

Keywords: *Brucella melitensis*; periprosthetic knee infection; total knee arthroplasty.

Brucellosis was defined by Sir David Bruce in 1860s and is also known as "undulant fever," "Mediterranean fever," or "Maltese fever"[1]. It is a zoonotic disease caused by Gram negative *Brucella* and can cause infections in both humans and animals[2,3]. Humans can be infected by *Brucella abortus*, *Brucella canis*, and *Brucella melitensis* and the infection can directly or indirectly spread through infected livestock, food, and other infected humans[4]. These pathogens can cause systemic infections or present as local findings of systemic infections such as arthritis or meningitis.

Periprosthetic joint infections (PJI) are a very rare form of Brucellosis but constitute a major complication of total hip and knee arthroplasties. In addition, it reports the incidence of many national centers as <2%[5,6]. More than 25% of the revision knee arthroplasties are performed due to PJIs[7]. Methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most commonly isolated microorganisms in PJIs[8] and are followed by streptococcus and enterococcus species in Europe[9]. Approximately 16–20% of the PJIs are culture-negative and empiric antibiotherapy may be necessary in such cases[9]. However, this should be avoided until a microbiological diagnosis can be confirmed except for severe sepsis cases.

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Although the type of pathogen depends on the patient, risk factors, comorbidities, and the characteristics of the pathogens, the timing of the infection is also important in causality. In cases of clinical suspicion of periprosthetic infections with negative blood and/or synovia cultures, *B. melitensis* must be ruled out in patients with a history of travel to high-risk areas, occupational exposure, or exposure to contaminated animal products since this pathogen is very rare and cultures require long incubation times. Hence, the systemic findings of Brucellosis must be questioned when the pathogen cannot be identified in periprosthetic infections.

Brucella infections are characterized by fever with chills, excessive sweating, headache, malaise, weight loss, back pain, and generalized body pain; however, in approximately 40% of the adults, the initial symptoms are unclear due to underlying rheumatological and degenerative diseases. This is one of the reasons *Brucella* infections are not initially included in the differential diagnosis of periprosthetic knee infections.

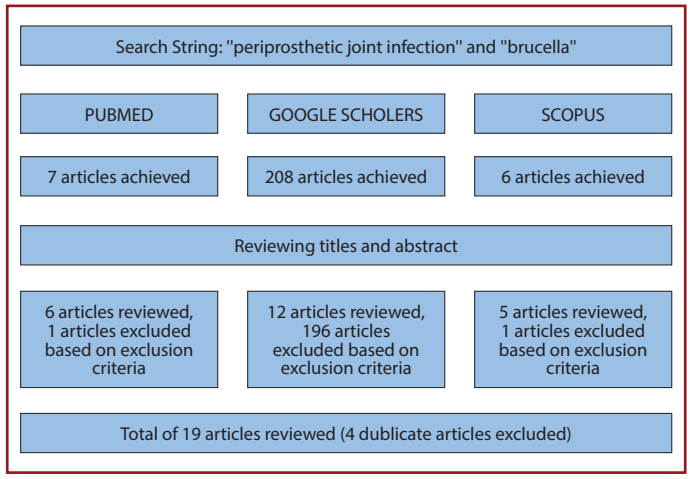

Figure 1. The flowchart details the method of retrieval of relevant articles for this study.

This case report emphasizes that a *Brucella* infection should be ruled out in a patient with complaints of increased heat and pain in both knees following bilateral total knee arthroplasty in light of clinical findings and laboratory results.

Table 1. Demographic information in the studies

	Journal	Country	Year	Age	Gender	Location	Exposure risk
Ortega et al.[31]	The journal of arthroplasty	Spain	2002	63	Male	Hip	Cattle owner
Weil et al.[32]	Clinical infectious diseases	Israel	2003	67	Male	Knee	Unpasteurized milk or goat cheese
Weil et al.[32]	Clinical infectious diseases	Israel	2003	64	Male	Knee	Unpasteurized milk or goat cheese
Weil et al.[32]	Clinical infectious diseases	Israel	2003	38	Male	Hip	Unpasteurized milk or goat cheese
Kasim et al.[14]	Scand J Infect Dis	Lebanon	2004	47	Female	Hip	Home-made cheese
Cairo et al.[33]	J Bone Joint Surg Am	Spain	2006	50	Male	Hip	Working with cattle
Cairo et al.[33]	J Bone Joint Surg Am	Spain	2006	71	Male	Hip	Contact with cattle
Ruiz-iban et al.[34]	Journal Of Orthopaedic Surgery	Spain	2006	66	Female	Hip	Contact with cattle
Ruiz-iban et al.[34]	Journal Of Orthopaedic Surgery	Spain	2006	71	Male	Hip	Agricultural laborer
Marbach et al.[35]	Revue Medicale Suisse	Sicily	2007	67	N/A	Knee	Non reported
Tena et al.[30]	Diagnostic Microbiology And Inf Disease	Spain	2007	51	Male	Hip	Farmer
Tassinari et al.[29]	Musculoskeletal Surgery	Italy	2008	68	Male	Knee	Systemic infection
Dauty et al.[36]	Joint bone spine	France	2009	65	Female	Knee	Unpasteurized goat cheese
Erdogan et al.[26]	Knee Surg Sports Traumatol Arthrosc	Türkiye	2010	63	Female	Knee	Unpasteurized milk products
Nichols et al.[37]	Infection Control & Hospital Epidemiology	Mexico	2014	67	Female	Hip	Non reported
Lowe et al.[38]	Emerging Infectious Diseases	India	2015	N/A	N/A	Hip	Non reported
Carothers et al.[28]	Am J Orthop	Usa	2015	67	Female	Hip	Consistent febrile illness
Lewis et al.[18]	Travel Med. And Inf. Disease	Thailand	2016	51	Male	Knee	Travel
Flury et al.[39]	J Bone Jt Infect.	Türkiye	2017	75	Male	Knee	Unpasteurized milk products
Mortazavi et al.[40]	Arch Bone Jt Surg.	Iran	2017	28	Male	Knee	Unpasteurized milk products
Maalouf et al.[41]	J Med Libanais	Lebanon	2018	63	Female	Knee	Home-made cheese
Balkhair et al.[42]	Case Rep Infect Dis	Oman	2019	57	Female	Knee	Unpasteurized milk products
This case		Türkiye	2020	58	Female	Knee	Unpasteurized milk products

Materials and Methods

Case Report

A 58-year-old female patient had undergone bilateral total knee arthroplasty due to pain, limitation in the range of motion and Stage 4 osteoarthritis findings in X-rays in both knees 6 years ago. There was no prolonged wound drainage or infection in the early post-operative period. Sedimentation rate, CRP levels, and X-rays were regularly evaluated in the postoperative 2nd, 6th months, 1st, 2nd, and 5th-year follow-ups. Her postoperative 1st-year KSS score was 75, KSS function score was 80, and Oxford Knee score was 34. There were no findings of loosening or PJI. The patient presented to the orthopedics clinic with complaints of bilateral pain and swelling which started at the right knee followed by the left knee 6 years after the operation. Aspiration of the knee joint was performed under sterile conditions, and samples were sent for culture. Reagent strip test was +1 for leukocyte esterase. Cultures returned negative. Joint aspiration was repeated after 30 days. A vancomycin-resistant linezolid-sensitive unidentified Gram-negative bacteria was reported. Although the pathogen could not be identified, a diagnosis of periprosthetic infection was made, and a two-step revision arthroplasty was scheduled due to the loosening observed in the X-ray. Both prostheses were removed, and tissue cultures were obtained. Bone cement with linezolid was applied to both knees. A pathogen could not be identified in cultures obtained during the removal of prostheses. The patient history revealed night sweats accompanying knee pain, fever, and loss of appetite. In addition, the patient stated that she had recently consumed home-made cheese produced from non-pasteurized milk.

These findings pointed to a PJI caused by *Brucella*. The patient was consulted with the infectious diseases department. *Brucella* agglutination test was performed and returned 1/320 positive. The patient was given 2 × 300 mg oral rifampicin and 2 × 100 mg doxycycline for the treatment of B. *melitensis*-associated periprosthetic joint infection. Eight weeks later, the patient was admitted for the second stage of revision arthroplasty. Agglutination tests from the serum samples returned 1/640 positive. Tis-

Table 2. Data on the studies

	Synovial culture	Species	Radiographic changes	Surgery	Outcomes
Ortega et al.[31]	No	*B. melitensis*	Loosening of femoral component	Yes/2 stage	No reinfection
Weil et al.[32]	Positive	*B. melitensis*	Loosening of femoral component	Yes/2 stage	No reinfection
Weil et al.[32]	Negative	*B. melitensis*	Loosening of both components	Yes/2 stage	No reinfection
Weil et al.[32]	Negative	*B. melitensis*	Loosening of femoral component	Yes/2 stage	No reinfection
Kasim et al.[14]	No	*B. abortus*	Loosening	Yes/1 stage	No reinfection
Cairo et al.[33]	No	*B. melitensis*	No loosening	No	No reinfection
Cairo et al.[33]	No	*B. melitensis*	Loosening	Yes/1 stage	No reinfection
Ruiz-iban et al.[34]	Positive	*B. abortus*	Radiolucent lines	Yes/2 stage	No reinfection
Ruiz-iban et al.[34]	No	*B. melitensis*	No loosening	Yes/debridement	No reinfection
Marbach et al.[35]	No	*Brucella spp.*	Loosening	Yes/2 stage	No reinfection
Tena et al.[30]	Positive	*B. melitensis*	Loosening	Yes/2 stage	No reinfection
Tassinari et al.[29]	Positive	*B. melitensis*	Loosening of tibial component	No	No reinfection
Dauty et al.[36]	Negative	*B. melitensis*	Loosening of tibial component	Yes/2 stage	No reinfection
Erdogan et al.[26]	Positive	*B. melitensis*	No loosening	No	No reinfection
Nichols et al.[37]	No	*B. abortus*	Loosening	Yes/2 stage	No reinfection
Lowe et al.[38]	Positive	*B. melitensis*	Non reported	None	Lost to follow up
Carothers et al.[28]	Negative	*B. abortus*	Loosening	Yes/2 stage	No reinfection
Lewis et al.[18]	Positive	*B. melitensis*	No loosening	No	No reinfection
Flury et al.[39]	Positive	*B. melitensis*	Loosening	Yes/2 stage	No reinfection
Mortazavi et al.[40]	Negative	*B. melitensis*	Loosening	Yes/2 stage	No reinfection
Maalouf et al.[41]	Negative	*Brucella spp.*	Loosening	Yes/2 stage	No reinfection
Balkhair et al.[42]	Negative	*B. melitensis*	No loosening	No	No reinfection
This case	Negative	*B. melitensis*	Loosening	Yes/2 stage	No reinfection

B. melitensis: Brucella melitensis, B. abortus: Brucella abortus.

sue cultures were negative. Bilateral revision arthroplasty was carried out without waiting for negative agglutination test results. There was no prolonged wound drainage or infection in the post-operative period. Treatment for the periprosthetic infection was continued for 6 months. *Brucella* agglutination test results returned negative after the end of treatment. The patient was pain free in both knees and did not have any symptoms of infection.

Literature Review

The current literature has been systematically evaluated by us. The articles published in the past 20 years by the two authors were investigated separately by the words "periprosthetic joint infection" and "*Brucella*" using two different computer databases (PubMed and Google Scholars). The results were then reviewed by the two authors (Fig. 1). No other studies could be found by repeating the search.

The data resulting from the literature review are shown in Tables 1 and 2.

Results

In the control follow-up which was 2 years after the operation, there was no relapse, the patient had no active complaints and could ambulate without support and had no wound problems. Her CRP was 3.5 µg/L, sedimentation rate was 19 mm/h, and *Brucella* agglutination (Wright) test was negative. The KSS score, KSS function score, and Oxford Knee Score was 70, 75, and 35, respectively, in the right knee and 72, 75, and 37, respectively, in the left knee.

Discussion

Brucellosis, which is rare in non-endemic countries, is a zoonotic disease caused by *Brucella* spp with "undulant fever" as a frequent symptom and can affect both humans and livestock[2,3,10]. *B. abortus*, *B. canis*, and *B. melitensis* subtypes[11,12] in addition to *Brucella* ceti and *Brucella pinnipedialis* isolated from marine mammals can cause infection in humans[13].

Brucella infections can cause arthritis, meningitis, or systemic infections or present with osteraticular findings such as sacroileitis, arthritis, spondylodiscitis, bursitis, tenosynovitis, or osteomyelitis[12,14-16]. Direct contact with infected animals or consumption of dairy products (raw milk, fresh cheese, etc.) can be the sources of infection[17]. Travel to endemic countries or immigrants from such countries are source of infection in developed countries[18-20]. Our patient presented with findings of arthritis in both knees. The patient was evaluated with a diagnosis of periprosthetic joint infection. A detailed history revealed fever, weight loss, and nocturnal sweating in addition to findings of arthritis. In addition, the patient stated that she had recently consumed fresh cheese produced using non-pasteurized milk. These findings led us to the diagnosis of a periprosthetic infection caused by *Brucella* species.

Brucellosis is the most common zoonotic infection globally, and at least 500,000 new cases are reported every year[21]. *Brucella* species cause infections in the Middle East, Mediterranean (Portugal, Spain, and Greece), South and Central America[22]. A total of 189,226 cases of Brucellosis have been officially reported between 1980 and 2005, approximately, 90,000 of which were reported between 2000 and 2005[23]. However, these are only officially declared cases. Brucellosis has not been eradicated in Türkiye and the population is still at risk[24].

Although periprosthetic infection rates are below 2% in many national centers, it is still the most important complication of TKA and THA[5,6]. Bozic et al.[7] have stated that 25% of the revision arthroplasties in America are performed due to PJI. Microbiological identification of the pathogen is important for the treatment of periprosthetic infections. Commonly isolated microorganisms in periprosthetic infections are methicillin-resistant *S. aureus*, methicillin-sensitive *S. aureus*, and *S. epidermidis*[8]. Aggarwal et al.[9] state that streptococcal and enterococcal PJI are more prevalent in America compared to Europe and the incidence of culture-negative periprosthetic infections is 16–20% in America and Europe. Synovial fluid cultures from both knees returned negative in our patient.

There is no consensus on the optimal treatment of *Brucella*-related PJI. A number of studies state that these infections can be treated using antibiotics if there is no loosening[25-27]. The most frequently reported treatment regimen consists of rifampicin, doxycycline, and streptomycin for 6 weeks–26 months (average 6 months)[10,26,28-30]. Our patient was given rifampicin and doxycycline for 6 months. The two-step revision arthroplasty was performed in this period due to loosening without waiting for the agglutination test to become negative.

Conclusion

PJI are still a major problem in arthroplasties. Identification of the pathogen is very important for the early diagnosis and treatment of these infections. *Brucella* infection should be kept in mind in cases of PJI with negative cultures.

Periprosthetic Brucella infections in non-endemic areas are very rare. Contact with livestock and consumption of con-

taminated food must be questioned while obtaining the medical history. In addition, travel to endemic areas and contact with immigrants and contaminated food should also be questioned.

If you want to find a *Brucella* infection, you have to look for it.

Peer-review: Externally peer-reviewed.

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