

Periprosthetic joint infection due to *Brucella* infection: A report of a rare presentation and review of the literature

Mahmoud Jabalameli¹, Abolfazl Bagherifard², Mohammad Taher Ghaderi³, Paniz Motaghi⁴, Hossein Akbari Aghdam³,

From ¹Professor, ²Associate Professor, ³Fellowship, ⁴Research Manager; Bone and Joint Reconstruction Research Center, Shafa Yahyaieian Orthopedic Hospital, Iran University of Medical Sciences, Tehran, Iran

ABSTRACT

Periprosthetic infection (PJI) is a serious complication of total knee arthroplasty (TKA). PJI due to Brucellosis is a very rare entity. In this report, we described the case of knee joint loosening after TKA in a 63-year-old female who arrived with complaints of a restricted range of motion, stiffness, and pain. The diagnosis was made based on clinical, radiological, and laboratory findings. She was treated with antibiotics and two-stage revision surgery. We also reviewed all similar cases in the English literature from the epidemiologic, diagnostic, and treatment aspects and brought suggestions for evaluations before TKA in endemic areas. Authors emphasize that Brucellosis must be considered among differential diagnoses for patients with PJI, especially in endemic areas. Serologic evaluations and long-term blood and joint aspirated fluid culture must be performed when the patient has a history of recurrent febrile illness, joint swelling, and exposure to animals or the consumption of unpasteurized dairy products. Early suspicion of Brucellosis improves the outcome and prevents medical staff from being infected. A double therapy with doxycycline and rifampin for 6 months and performing two-stage revision surgery is the treatment of choice.

Key words: *Brucella* joint infection, Brucellosis, Knee prosthesis infection, Prosthesis infection, Total knee arthroplasty

Over the past few years, the number of joint replacements for end-stage joint destruction has been gradually increased worldwide [1]. Total knee arthroplasty (TKA) is one of the most common joint replacement surgeries. Periprosthetic joint infection (PJI) is a deleterious complication after this surgery. PJI may result in the loosening that requires revision arthroplasty [2]. The occurrence of *Brucella* infection after TKA is a very rare condition. In our country, the incidence of Brucellosis has been recently increased, thus the PJI with *Brucella* must be more accurately considered among differential diagnoses [3]. Besides, the most common complication of Brucellosis is musculoskeletal involvement such as osteoarticular infection and arthritis [3]. In 2016, we diagnosed a case of PJI due to Brucellosis in a 68-year-old woman who was referred to an infectious disease specialist with complaints of pain and discharge from knee prosthesis 8 months after TKA. In this case, the diagnosis of PJI was made according to Parvizi *et al.* criterion [4]. Unfortunately, because we were clinically not suspected of the diagnosis of Brucellosis, safety laboratory precautions were not implemented while examining


the specimen, the physician, and laboratory technician became infected [5]. Although the occurrence of PJI due to Brucellosis is a very rare entity [6], early diagnoses of this rare presentation lead to a better outcome and avoid unwitting infection of laboratory staff.

Here, we report the second case of PJI due to Brucellosis who was diagnosed at our institute. Furthermore, a review of all cases of *Brucella* species PJI in the English literature from the epidemiologic, diagnostic, and treatment aspects was done.

CASE REPORT

A 63-year-old female housewife underwent a total knee arthroplasty for the treatment of right knee degenerative osteoarthritis. Two years after the surgery, she was referred to an infectious specialist with complaints of uncontrolled fever and intermittent knee pain on the operated side.

Laboratory evaluations showed normal cell blood count (CBC) with slight elevation in the erythrocyte sedimentation rate (ESR) (69 mm/h) and C-reactive protein (CRP) (2+). Further evaluations did not reveal any source of infection; however, she received triple antibiotic therapy comprising vancomycin, meropenem, and

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Correspondence to: Paniz Motaghi, Shafa Yahyaieian Research Committee, Mojahedin Eslam St, District 12, Tehran, Iran. E-mail: paniz.motaqi@gmail.com

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rifampin.

At first, the symptoms were relieved; but 10 months later, she arrived back with a complaint of intermittent pain, fever (39°C), chill, and a swollen knee. On examination, the vital signs were stable with a blood pressure of 120/73, heart rate of 79/min, and respiratory rate of 21/min. This time, she was treated by teicoplanin and rifampin under the supervision of an infectious disease specialist.

After 14 months, the patient again complained of fever, knee pain, and severe joint swelling, so she was admitted for the third time after her TKA surgery and this time rifampin, clindamycin, and tavanex were administered. After discharge, she was referred from another center to our department of orthopedic surgery. On examination, erythema and swelling around her knee joint and restricted range of motion (ROM) were observed.

ESR and CRP were elevated (53 mm/hr and CRP 21 mg/L). A whole-body bone scan was obtained and manifested an increased radiotracer uptake in her right knee. Radiographic findings were suggestive of the loosening of the prosthesis (Fig. 1). Knee aspiration was performed under sterile conditions and the specimen was sent for analysis and culture. Leukocytosis was not seen and no bacteria were grown on routine media after 48 h.

According to the clinical and radiologic findings and high ESR and CRP, a two-stage revision arthroplasty was scheduled for her. We entirely debrided synovial tissue and other surrounding tissues in the joint and synovial fluid, synovial tissue, and bone was sent for microbiological evaluations, and long-term incubation was requested to rule out *Brucella* infection. After the sterilization of the femoral component, it was placed with the cement on the femoral side and a new polyethylene spacer was inserted in the tibial side with the cement (Fig. 2a). The wound was closed using routine techniques. This time we warned laboratory technicians about the possibility of *Brucellosis*. As expected, the long-term culture was positive for *Brucella*. The serologic test for *Brucellosis* on the specimen was also positive.

Double anti-*Brucella* therapy using a combination of oral rifampin and oral doxycycline was administered for 6 months. As soon as the antibiotic therapy was completed and we achieved

a negative serologic test result, the second stage of total knee revision was performed. During the operation, temporary components were extracted and replaced by permanent ones (Fig. 2b). All cultures of intraoperative specimens were negative after prolonged incubation. She had an uneventful post-operative course without any sign of recurrence. At the end of the two-year follow-up period, she was asymptomatic and had a good knee joint function.

DISCUSSION

Brucellosis is a zoonotic infection caused by the bacterial genus *Brucella*. The main risk factors of *Brucellosis* are the consumption of unpasteurized dairy products and less commonly contact with raw meat or working in farmlands. Infection after total knee replacement is a serious complication and is associated with a high incidence of morbidity [6]. PJI due to *Brucella* spp. is an extremely rare condition that can result in septic loosening and require revision treatment.

Since the first case of knee PJI due to *Brucella* infection, 25 other patients (including the current case) have been reported in the English literature, with a presentation of knee pain and swelling years after TKA surgery, that did not respond to wide spectrum antibiotic therapy and ended with either positive tissue culture or serologic test suggesting *Brucella* infection. In the current case report, we included all cases published in PubMed and Scopus and tried to evaluate their similar features. Three main categories of data were extracted from articles: (a) Risk factors and geographical distribution, (b) diagnostic criteria, and (c) treatment strategy and outcome. All information is summarized in Tables 1-3 [6-26].

This infectious disease is globally distributed, two of the most endemic regions are the Mediterranean basin and Greece [27]. A similar distribution is seen among reported cases of PJI due to *Brucellosis*; 17 cases of all 26 patients were found in middle east countries, with Turkey and Iran accounting for 23% and 15% of them, respectively.

In 2016, we diagnosed a case of PJI due to *Brucellosis* in a 68-year-old woman who was referred to an infectious disease specialist with complaints of pain and discharge from knee prosthesis 8 months after TKA. Despite the negative culture of aspirated fluid,

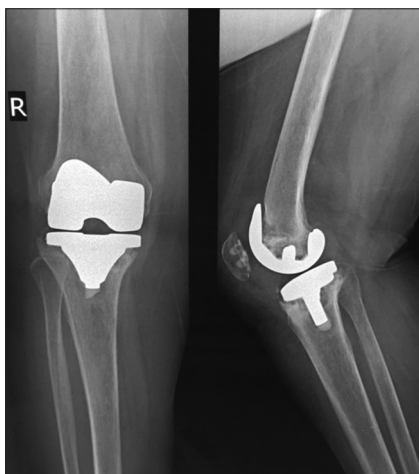


Figure 1: Anteroposterior and lateral radiographic view of the involved knee – evidence of loosening of the prosthesis

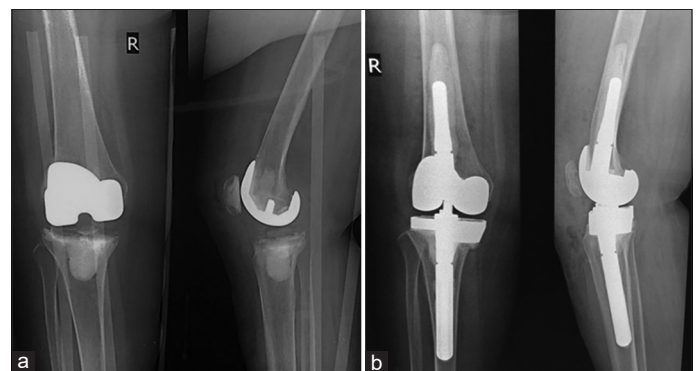


Figure 2: Anteroposterior and lateral view of the involved knee. After the (a) first step and (b) second step of revision surgery

Table 1: Risk factors and geographical distribution of the knee PJI cases due to Brucellosis

Year	1 st author [Reference number]	Reference number	Country exposure (endemic)	Risk factor
1991	Agarwal [6]	7	Saudi Arabia	Na
1997	Iglesias [7]	8	Spain	Na
1997	Orti [8]	9	Spain	Contact with goat
1997	Malizos [9]	10	Greece	Shepherd
2003	Weil [10]	11	Israel	Unpasteurized dairy products
2003	Weil [10]	11	Israel	Unpasteurized dairy products
2006	Marchese [11]	12	Italy	Unpasteurized dairy products
2007	Marbach [12]	13	Italy	Unpasteurized dairy products
2008	Tassinari [13]	14	Italy	Na
2008	Atay [14]	15	Turkey	Unpasteurized dairy products
2009	Dauty [15]	16	Portugal	Unpasteurized dairy products
2010	Erdogan [16]	17	Turkey	Unpasteurized dairy products
2011	Wunschel [17]	18	Turkey	Unpasteurized dairy products
2012	Oner [5]	6	Turkey	Na
2014	Karaaslan [18]	19	Turkey	Na
2016	Jabalameli [4]	5	Iran	Na
2016	Lewis [19]	20	Thailand	Contact with goats
2016	Sazegar [2]	2	Iran	Na
2016	Klassove [20]	21	Israel	Contact with raw meat
2017	Flury [21]	22	Turkey	Unpasteurized dairy products
2017	Mortazavi [1]	1	Iran	Non-pasteurized dairy products
2017	Turvey [22]	23	Canada	Consumed raw meat
2018	Maalouf [23]	24	Lebanon	Unpasteurized dairy products
2019	Balkhair [24]	25	Oman	Unpasteurized dairy products
2019	Hamdi [25]	26	Saudi Arabia	Unpasteurized dairy products
This case			Iran	Unpasteurized dairy products

she was treated with antibiotics, but the discharge did not stop. One year later, she was referred to our institute with complaints of severe stiffness, pain, and discharge from the fistula. Pre-operative evaluations, including knee aspiration fluid examination and blood culture, were negative after 48 h, and ESR and CRP were within normal ranges. At last, because no reason for her painful joint was found and joint loosening was observed in radiography, diagnosis of PJI was made according to Parvizi *et al.* [4]. definition and diagnostic criteria, and a revision arthroplasty was performed. Synovial fluid and prosthesis culture were requested.

Our center is a revision referral center; we routinely keep all synovial fluid and joint cultures for a long time. After long-term incubation of the intraoperative specimens, cultures returned positive for Brucella infection and she received combined antibiotic therapy through rifampin and doxycycline for 6 months. Unfortunately, because we were clinically not suspected of the diagnosis of Brucellosis, safety laboratory precautions were not implemented while examining the specimen, the physician, and laboratory technician became infected [5].

Clinical presentations of Brucellosis are non-specific, thus there is a high chance of misdiagnosing these patients [26]. Symptoms include chills, fever, malaise, sweating, hepatomegaly, and splenomegaly. It may also involve the musculoskeletal system and leads to joint swelling and infection [3].

To confirm the diagnosis of Brucellosis, it is necessary to isolate the organism from blood culture and perform serologic tests [28]. Septic and reactive forms are two pathogenic mechanisms of Brucella that affect joints. The septic form seems more probable as Brucella spreads through the bloodstream, as in other bacterial arthritis [29]. Agarwal described the first case with a PJI caused by Brucella in 1991 [7]. Weil in 2003 presented a report of three patients, one of them was infected, TKA was done, and the diagnosis was made by tissue culture during surgical debridement. After 6 weeks of combined antibiotic therapy against Brucella, second-stage surgical revision was done, and additional combined antibiotic treatment continued for 6 weeks [11]. Among all 26 reviewed patients of Brucella-related PJI, 24 patients (92%) had tenderness, 11 (42%) had swollen knees, and 5 (19%) had limited ROM. PJI in 14 patients (54%) was also associated with systemic presentations, including intermittent fever, chills, malaise, fatigue, and night sweat. The mean interval between the TKA surgery and symptoms was 64.7 ± 5.1 months (ranging from 2.5 to 168 months). The amount of ESR was missing in 13 patients; however, it was elevated in 11 cases out of the rest of them. In twenty patients, a serologic test was performed and revealed positive results except for one patient, whose test was negative, with a titer of $<1:40$. The culture of aspirated fluid from the infected joint was positive for Brucella in 18 patients and

Table 2: Diagnostic features of the knee PJI cases due to Brucellosis

Year	1 st author [Reference number]	Local presentation	Systemic presentation	Interval TKA to symptom	Serology	Aspiration	Tissue culture	ESR	Radiologic findings
1991	Agarwal [7]	Superficial infection, Abscess	No	2.5 m	+ (2560)	+	+	Na	No loosening
1997	Iglesias [8]	Swelling, Knee pain	Yes	48 m	+	+	Na	Na	No loosening
1997	Orti [9]	Knee pain	No	14 m	+	+	+	57	No loosening
1997	Malizos [10]	Synovitis, knee pain	Yes	5 m	+	+	+	Na	No loosening
2003	Weil [11]	Swollen, painful, warm knee	No	36 m	+ (1600)	+	- (A. baumannii)	Na	Loosening of both femoral And tibial components
2003	Weil [11]	Knee pain	Yes (fever)	168 m	+ (1600)	+	+	76	Bone scanning revealed increased uptake in the lumbar spine, the right sacroiliac joint, and the left knee. Plain knee radiography 7 revealed mild loosening of the femoral component.
2006	Marchese [12]	Keen pain, swelling	No	108 m	Na	+	+	Na	Loosening
2007	Marbach [13]	Knee pain	No	48 w	Na	-	+	Na	Loosening
2008	Tassinari [14]	Knee pain	No	24m	+ (800)	+	+	81	Small area of resorption on tibial component No loosening
2008	Atay [15]	Knee pain	No	48 m	+	Na	+	Na	No loosening
2009	Dauty [16]	Discharge,	Yes	Na	Na	-	+	60	Loosening of tibial plateau
2010	Erdogan [17]	Knee pain,	Yes (chills, Fever)	24 m	+	+	+	43	No loosening
2011	Wunschel [18]	Knee pain	No	60 m	+	+	Na	Na	Loosening
2012	Oner [6]	Knee pain	Yes	96 m	+	+	Na	Na	Loosening
2014	Karaaslan [19]	Swelling, knee pain	Yes (Fever)	24 m	+	+	Na	Na	Loosening
2016	Jabalameli [5]	Knee pain, and stiffness, discharge	No	12 m	Na	-	+	20	Loosening
2016	Lewis [20]	Swelling, knee pain, fever	Yes	60 m	+	+	Na	Na	No loosening
2016	Sazegar [2]	Knee pain, limited ROM, swelling, warm	No	60 m	+	Na	Na	105	Components loosening
2016	Klassove [21]	Knee pain	No	144 m before presentation in the left knee and 48 m before presentation in the right knee.	IgG 1:640 IgM 1:1920.		+	80	Increased uptake in the left knee around the implant
2017	Flury [22]	Knee pain	No	144 m	+ (240)	+	+	Na	Loosening of the prosthesis With migration of the tibial component

(Contd...)

Table 2:(Continued)

Year	1 st author [Reference number]	Local presentation	Systemic presentation	Interval TKA to symptom	Serology	Aspiration	Tissue culture	ESR	Radiologic findings
2017	Mortazavi [1]	Pain, swelling, and limitations in the ROM	Yes (fatigue, low-grade fever and night sweats.)	48 m	+ (1280)	+	+	51	Effusion and soft tissue swelling but the prosthesis was stable and had no evidence of loosening after 18 months of conservative treatment, loosening occurred
2017	Turvey [23]	Knee pain, unable to bear weight, effusion, limited ROM	Yes (intermittent fevers)	132 m	-(1/40)	Na	+	67	Loosening and subsidence of the tibial component With lucency seen in the proximal tibia.
2018	Maalouf [24]	Tenderness, swelling, and redness, unable to bear weight.	Yes (night sweats and chills)	24 m	+(5120.)	Na	+	Na	Loosening of the tibial prosthesis and evidence of osteomyelitis
2019	Balkhair [25]	Knee pain, swelling, moderate effusion	Yes (indolent fever, night sweats, and malaise)	120 m	Na	+	+	109	Bilateral increased radiotracer uptake around both knee joint prostheses compatible with periprosthetic joint infection
2019	Hamdi [26]	Knee pain, swelling, and limited ROM	Yes (intermittent fever and weight loss)	144 m	Na	-	+	112	Component loosening
This case		Tenderness, erythema, and swelling around her knee joint ROM was restricted	Intermittent fever, night sweat	24 m	+	+	+	106	Increased radiotracer around involved knee, prosthesis loosening

TKA: Total knee arthroplasty, ESR: Erythrocyte sedimentation rate, ROM: Range of motion

negative in 4 patients. During surgeries, the specimens were taken for 20 patients; *Brucella* was isolated in media after prolonged incubation. According to our review of the literature, cultures of intraoperative tissue samples provide the best yield.

In radiography, 16 joints showed prosthesis loosening. An increased in radiotracers was occurred in four patients. The pathogenesis of septic loosening of the prosthetic joint is unknown. There are two mechanisms suggested in the English literature: Reactive and septic forms. However, the latter seems more common in reported cases [29].

For Brucellosis treatment, combination antimicrobial therapy is usually favored over monotherapy because high relapse rates have been reported with monotherapy. In the absence of prosthesis, oral doxycycline is prescribed for six weeks either with streptomycin (for 2–3 weeks) or rifampin (for 6 weeks). Despite the remaining controversy surrounding the best treatment approach for *Brucella* spp. PJIs, the current consensus is that dual or triple antibiotic therapy may be superior, particularly if the prosthesis is retained. However, there is no agreement on the duration of treatment [22-25]. While *Brucella* PJI without radiological loosening is thought to be completely treated through conservative approach and solely with double or

triple therapy, surgeons emphasize that performing two-step revision surgery for removal and replacing prosthesis component is mandatory when prosthesis loosening occurs [23,25]. We also agree that two-stage revision is required for the treatment of patients with prosthetic loosening. Despite the good outcome achieved in eight patients who did not have prosthesis loosening by sole antibiotic therapy, one-stage revision surgery, or arthroscopic debridement was done (Tables 2 and 3). We claim that all cases of PJI due to Brucellosis would involve bone tissue; hence, all patients should undergo two-stage revision surgery regardless of the joint loosening.

According to our review of the literature, the best medication therapy for cases with prosthesis involvement to be given between two stages of surgery would be a combination of doxycycline and rifampin for at least 6 weeks combined with an aminoglycoside (usually streptomycin). However, we believe dual therapy by rifampin and doxycycline for 6 months can achieve a great outcome without recurrence. Other researchers have applied a wide range of protocols that are summarized in Table 3 that consist of doxycycline and rifampin for at least 6 weeks and relapse of infectious only occurred in few cases that required continuing the medical treatment for a longer period. Overall, relapse is uncommon, even with

Table 3: Treatment strategy for knee PJI cases due to Brucellosis

Year	1 st author [reference number]	Medical (AB)	Surgical	Implant free interval	Outcome	Relapse (in 2 years)
1991	Agarwal [7]	Dox/Rif 76w	None	0	Good	-
1997	Iglesias [8]	Dox/Rif 6.5w; then Strep (3w)/Dox 12w	None	0	Good	
1997	Orti [9]	Strep/Dox/Rif 6w	None	0	Good	
1997	Malizos [10]	Strep (3w)/Dox 20w, then Bact 8w	None	0	Good	-
2003	Weil [11]	Dox+Rif (6w)	2 stage revision	6 w	Good	-
2003	Weil [11]	Dox+Rif (6w)	2 stage revision	6 w	Good	-
2006	Marchese [12]	Strep/Dox 4w, then Dox/Rif/Levo 32 w	Implant removal	-	Good	
2007	Marbach [13]	Dox/Rif 12 w	2 stage revision	12 w	Good	
2008	Tassinari [14]	Dox/Rif 8w	None	0	Good	-
2008	Atay [15]	Dox/Rif 6wk	Debridement, antibiotics, irrigation and retention. (arthroscopy)	0	Good	
2009	Dauty [16]	Dox/Rif 12 w	2 stage revision	6	Good	-
2010	Erdogan [17]	Dox/Rif 16 w	None	0	Good	
2011	Wunschel [18]	Dox/Rif 24 w	1 stage revision	0	Good	
2012	Oner [6]	Dox/Rif 16 w	2 stage revision	20w	Good	
2014	Karaaslan [19]	Dox/Rif 12 w	2 stage revision	12 w	Good	
2016	Jabalameli [5]	Dox/Rif 24w	2 stage revision	24 w	Good	
2016	Lewis [20]	Gen (2 w)/Dox/Rif 24 w	None	0	Good	
2016	Sazegar [2]	Dox/Rif 8 w	2 stage revision	8 w	Good	
2016	Klassove [21]	Gen (3 w)/Dox and Rif 12 w	2 stage revision	8 w	Good	+
2017	Flury [22]	Dox/Rif/Pen 24 w	2 stage revision	2.5 w	Good	
2017	Mortazavi [1]	Dox/Rif/YMP-SMX 24 w	2 stage revision	16 w	Good	
2017	Turvey [23]	Gen (2w)/Dox and Rif (12 w)	2 stage revision	Na	Good	-
2018	Maalouf [24]	Gen/Rif/Dox 16 w	2 stage revision	na	Good	-
2019	Balkhair [25]	Gen (1w)/Dox and Rif 24w	1 stage revision	0	Good	-
2019	Hamdi [26]	Rif (24 w) + Rif/Strep (48 w)	2 stage revision	8 w	Good	-
	This case	Rif/Dox 24 w	2 stage revision	24 w	Good	-

W: Week, Rif: Rifampin, Dox: Doxycycline, Strep: Streptomycin, Pen: Penicillin, Gen: Gentamycin, Levo: Levofloxacin, Bact: Bactomycin

shorter treatment durations, and is typically caused by failure to complete treatment or lack of source control rather than antibiotic resistance [23]. Fluri in 2016 reported a case of TKA infected by *Brucella*. Their treatment protocol consists of combined antibiotic therapy 1 week before the second stage of revision surgery and 3 months after that was applied for their patients. They also reviewed 30 cases of PJI caused by *Brucellosis* that 18 of them were infected TKA. In these cases, if the infection by *Brucellosis* was suspected, the serological tests for *Brucellosis* were evaluated, and the cultures incubated for a longer period to detect the *Brucella* spp. [22].

At last, PJI due to *Brucella*, although rare, can occur especially in endemic areas. In these areas, serologic tests for *Brucella* infection should be included in pre-operative laboratory evaluations, and also physicians should consider *Brucellosis* and perform serologic evaluations in patients who arrive with a painful or swollen prosthetic knee joint. We necessitate the importance of considering the history of using dairy products, and the occurrence of joint loosening in cases of PJI, as two key criteria suggesting *Brucella* joint infection. Since the laboratory cultures of *Brucella* spp. are often unsuccessful due to their slow rate of growth and require special media with high CO₂ tension, a negative culture cannot rule out this diagnosis. Thus,

the routine test of Wright, Coombs Wright, and 2-Mercaptoethanol (2ME) tests are recommended in all prosthetic joints that are suspected of infection [29-31].

As *Brucellosis* is the most common laboratory-acquired infection that can easily transmit, while examining the infected specimen through aerosolization [32,33], when suspecting *Brucella* joint infection, safety laboratory precautions must be implemented, especially in regions of high endemicity. For all exposed individuals, prophylactic treatment through doxycycline and rifampin for three weeks and follow-up serologic testing is recommended. In patients with an epidemiological risk, *Brucellosis* should be included in the list of potential causes of an infected prosthetic joint. Furthermore, considering a diagnosis of *Brucella*-related PJI would prevent medical staff from being infected while working with body fluids either during surgeries or performing laboratory tests.

CONCLUSION

Brucella-related PJI is a late complication of knee joint arthroplasty, with a mean onset of 64 months after the procedure. We must include this entity in the differential diagnosis of infected

prosthetic joints who arrive with worsening pain and restricted range of motion who are resistant to primary antibiotic therapy. For similar clinical manifestations, we recommend physicians perform serologic evaluations and long-term blood and joint aspirated fluid culture, especially when the patient has a history of recurrent febrile illness, joint swelling, and either occupational exposure to animals or the consumption of unpasteurized milk or cheese. We suggest that practitioners should apply a double therapy with doxycycline and rifampin for 6 months to avoid relapse and perform two-stage revision surgery in the occurrence of prosthesis loosening.

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