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Could it be *Brucella melitensis*? Recognizing and managing a rare pathogen in periprosthetic infections

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Abstract

Periprosthetic joint infections caused by *Brucella melitensis* are rare and present significant diagnostic and therapeutic challenges, especially in endemic regions such as Anatolia. The indolent nature of *Brucella* infections often results in subclinical presentations, complicating early detection and management. This case series highlights the importance of recognizing *Brucella melitensis* as a potential pathogen in periprosthetic joint infection and explores the treatment options for this condition. Herein, we present five cases of *Brucella melitensis*-associated periprosthetic joint infections involving three hip replacements and two knee replacements. Diagnoses were confirmed through advanced diagnostic techniques, including prolonged cultures and serological testing, as routine methods often yielded negative results. Two patients underwent one-stage revision arthroplasty, two underwent two-stage revision arthroplasty, and one patient was managed conservatively with targeted antibiotics due to the absence of prosthetic loosening. All patients showed excellent functional recovery and infection eradication at follow-up, with normalized inflammatory markers and no evidence of recurrence. This case series emphasizes the importance of clinical suspicion and the use of advanced diagnostics in endemic areas for timely recognition of *Brucella*-associated periprosthetic joint infections. One-stage revision arthroplasty combined with prolonged antibiotic therapy demonstrated favorable outcomes and may serve as an effective treatment strategy.

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Introduction

Periprosthetic joint infections (PJIs) remain one of the most challenging complications of joint arthroplasty, often necessitating prolonged treatment and surgical intervention. Although common pathogens associated with PJIs include *Staphylococcus aureus* and coagulase-negative staphylococci, rare infections caused by *Brucella melitensis* pose unique diagnostic and therapeutic challenges, particularly in endemic regions such as Anatolia, Turkey.[1–10]

Brucella is a zoonotic pathogen primarily transmitted through contact with infected animals or consumption of unpasteurized dairy products[1,3,6,10–12] Infections caused by *Brucella* are characterized by nonspecific systemic symptoms such as fever, night sweats, and fatigue, with osteoarticular involvement being one of the most common complications. Despite the prevalence of *Brucella* in endemic areas, *Brucella*-associated PJIs are exceedingly rare and often present with atypical symptoms, including the absence of radiographic signs of prosthetic loosening.[3,7,9–14]

Diagnosing *Brucella*-associated PJIs is particularly challenging due to the fastidious nature of *Brucella* and low sensitivity of standard diagnostic tests. Routine synovial fluid cultures frequently yield negative results, and adjunct diagnostic modalities such as the Rose Bengal test, polymerase chain reaction (PCR), and prolonged culture incubation are often required for definitive diagnosis.[15] Additionally, biomarkers such as synovial fluid alpha-defensin, although promising for common PJIs, have been reported to fail in detecting *Brucella*-associated PJIs.[3]

Management strategies for *Brucella*-associated PJIs remain controversial. In cases without implant loosening, conservative treatment with doxycycline- and rifampicin-based regimens has demonstrated success.[9,16,17] However, surgical interventions, including one- and two-stage revision arthroplasty, are often required to achieve definitive infection control, especially in cases of chronic infection or implant instability.[3,9,16] One-stage arthroplasty exchange has shown promising success rates under appropriate patient selection criteria, particularly when stringent debridement and targeted antimicrobial therapy are employed.[7]

This case series aimed to highlight the critical need for heightened clinical suspicion and advanced diagnostic strategies for *B. melitensis*-associated PJIs in endemic regions, especially when routine culture results are inconclusive. Furthermore, it demonstrates the feasibility and effectiveness of tailored treatment approaches, including one-stage revision arthroplasty and targeted antibiotic regimens, in achieving successful clinical outcomes and eradicating infection in this challenging patient population.

Methods

This case series describes our experience with five patients diagnosed with *B. melitensis*-associated PJIs at our institution between 2020 and 2022. All patients had previously undergone total knee

arthroplasty (TKA) or total hip arthroplasty (THA) and later presented with chronic joint pain, swelling, or radiographic signs of implant loosening. Diagnosis was established using prolonged culture incubation, serological testing, and PCR analysis. Treatment strategies included long-term antibiotic therapy and, when necessary, one- or two-stage revision arthroplasty.

This study was approved by the institutional review board (IRB) of our hospital (Approval No: 1133/06.09.2024). All patient details have been fully de-identified, and no identifiable information has been included. The reporting of this study conforms to the Case Report (CARE) guidelines.[18] Written informed consent for publication was not required, as per ethical guidelines, as patient data were completely de-identified.

Case presentations

Case 1: Two-stage revision arthroplasty following culture-negative diagnosis

In late 2020, a woman in her late 60s presented with a 3-month history of pain, redness, and swelling in her knee, 5 years after undergoing TKA for osteoarthritis at Umraniye Training and Research Hospital. Initial laboratory work-up revealed elevated C-reactive protein (CRP; 2 mg/dL) level with a normal leukocyte count, and the initial synovial aspiration was inconclusive. The patient declined immediate surgery and was managed with empirical antibiotics and a knee brace.

One week later, due to persistent effusion and worsening pain, a repeat synovial aspiration confirmed PJI with a high granulocyte count. She underwent two-stage revision arthroplasty, beginning with implant removal and placement of a vancomycin- and gentamicin-loaded spacer. Intraoperative cultures revealed the presence of *B. melitensis* 8 days later, leading to a 12-week course of doxycycline and rifampicin, supplemented with 2 weeks of intravenous gentamicin. Revision TKA was performed 6 weeks after prosthesis removal. At the 19-month follow-up, the patient remained pain-free and walked independently, with normal inflammatory markers and stable radiographs (Figure 1).

Summary of other cases

A man in his early 60s, who previously underwent THA, presented to Umraniye Training and Research Hospital with progressive hip pain and swelling for 4 months (Case 2). Laboratory findings showed elevated CRP (3.5 mg/dL) level, but imaging revealed no implant loosening. Synovial

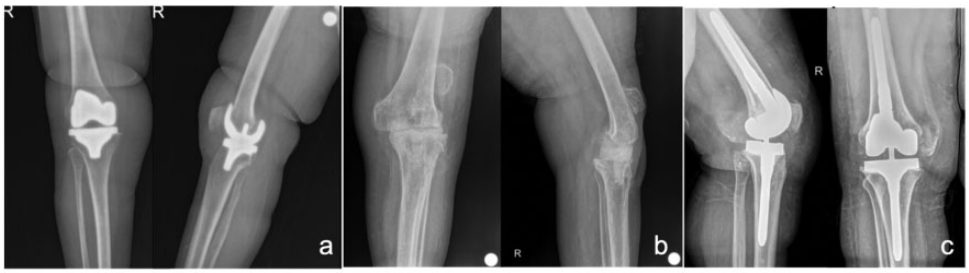

Figure 1. (a) Preoperative X-ray of Case 1 showing TKA with no evident signs of loosening, despite clinical symptoms of pain, redness, and swelling. (b) Postoperative X-ray of Case 1 demonstrating the placement of a vancomycin- and gentamicin-loaded spacer (OGMKS66®) following removal of the infected prosthesis and (c) final follow-up X-ray of Case 1 at 19 months showing a well-fixed revision TKA prosthesis with no signs of loosening or infection recurrence. TKA: total knee arthroplasty.

aspiration confirmed PJI, and intraoperative cultures revealed the presence of *B. melitensis*. He underwent two-stage revision THA, with a vancomycin- and gentamicin-loaded spacer (OGMHS®), followed by implantation of a Wagner SL Revision® stem. At the 18-month follow-up, he remained asymptomatic, with stable implant positioning and normal inflammatory markers (Figure 2).

A man in his mid-60s, who underwent TKA 8 years ago, was evaluated at Kartal Dr. Lütfi Kırdar City Hospital for persistent knee pain lasting 2 months (Case 3). Imaging revealed implant loosening, and one-stage revision TKA using a NexGen® Legacy® Constrained Condylar Knee was performed. Intraoperative cultures revealed the presence of *B. melitensis*. He received doxycycline and rifampicin for 12 weeks. At the 12-month follow-up, the patient was symptom-free, with a well-fixed implant and normalized inflammatory markers (Figure 3).

A man in his mid-60s, with a history of THA performed 8 years ago, reported a 2-month history of gradually worsening hip pain (Case 4). He was treated at Kartal Dr. Lütfi Kırdar City Hospital, where imaging revealed acetabular loosening. One-stage revision arthroplasty was performed, replacing the acetabular

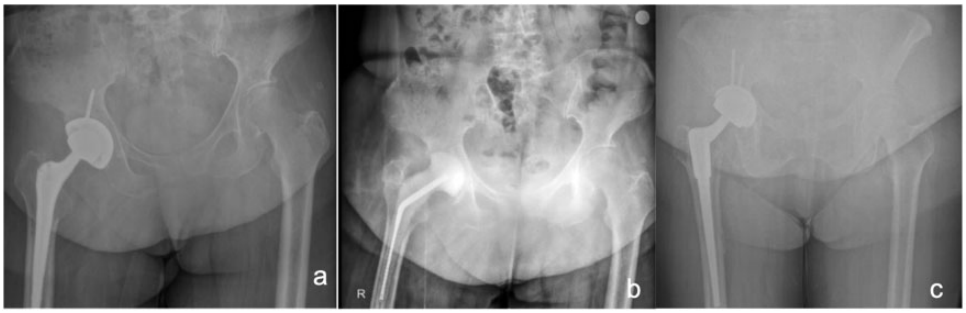

Figure 2. (a) Preoperative X-ray of Case 2 showing THA with no visible signs of loosening, despite clinical symptoms of pain and swelling in the right hip. (b) Postoperative X-ray of Case 2 showing the placement of a vancomycin- and gentamicin-loaded spacer (OGMHS®) following removal of the infected hip prosthesis and (c) final follow-up X-ray of Case 2 at 18 months showing a well-fixed revision THA prosthesis (Wagner SL Revision® Stem) with no evidence of loosening or infection recurrence. THA: total hip arthroplasty.

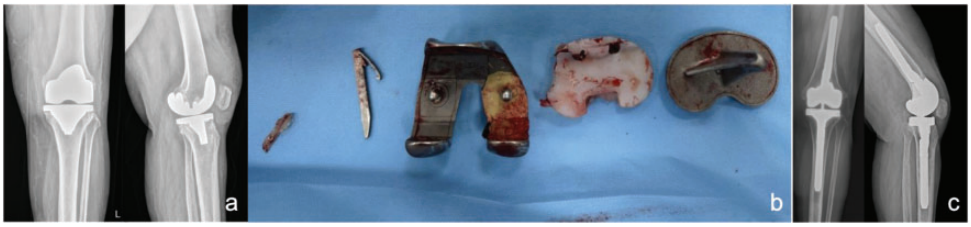

Figure 3. (a) Preoperative X-ray of Case 3 demonstrating radiographic signs of implant loosening in left total knee arthroplasty, prompting surgical intervention. (b) Intraoperative X-ray of Case 3 showing the ex-components with no sign of infection and complete bone resolution during one-stage revision surgery and (c) final follow-up X-ray of Case 3 at 12 months showing a stable, well-fixed prosthesis with no evidence of infection recurrence.

component with a G7® Acetabular System. Postoperative cultures confirmed the presence of *B. melitensis* infection. The patient completed a 12-week course of doxycycline and rifampicin and remained pain-free at 12 months, with imaging confirming a stable prosthesis (Figure 4).

In another case, a man in his early 60s with a 6-year history of TKA presented to Kartal Dr. Lütfi Kırdar City Hospital complaining of knee pain and swelling that had progressed over 4 months (Case 5). Unlike the other cases, imaging did not reveal implant loosening. Management consisted solely of 12 weeks of oral doxycycline and rifampicin. At the 10-month follow-up, the patient remained asymptomatic, and imaging showed a stable prosthesis and normalized inflammatory markers, indicating successful infection control without surgery (Figure 5). A detailed summary of all five cases is presented in Table 1.

Figure 5. Clinical image of the patient in Case 5 showing signs of swelling and limited range of motion in the right knee, consistent with symptoms of periprosthetic joint infections.

Discussion

Brucella-associated PJIs pose substantial diagnostic challenges due to their indolent course, frequent culture negativity, and absence of systemic symptoms, making

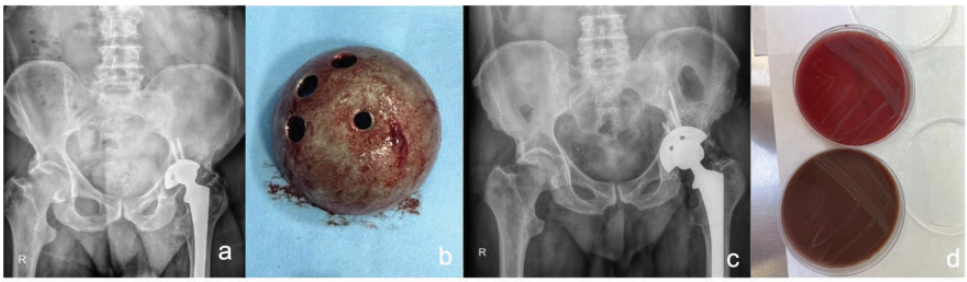

Figure 4. (a) Preoperative X-ray of Case 4 showing subtle signs of implant loosening in the left hip after total hip arthroplasty, prompting one-stage revision surgery. (b) Intraoperative X-ray of Case 4 demonstrating the previous acetebular cup with complete bone resolution around it during revision surgery. (c) Final follow-up X-ray of Case 4 at 12 months showing a well-fixed implant with no signs of infection recurrence and (d) bacterial growth on blood agar (top) and chocolate agar (bottom), confirming a positive culture for *Brucella melitensis*. The colonies appeared small, nonhemolytic, translucent, and smooth after prolonged incubation (on 16th day).

Table 1. Summary of *Brucella melitensis*-associated PJI cases.

Case no.	Age (years)	Sex	Joint affected	Prosthesis type	Time since arthroplasty (years)	Symptoms	CRP level	Radiographic loosening	Treatment	Antibiotic regimen	Outcome	Last clinical status
1	Late 60s	Female	Knee	TKA	5	Pain, swelling, redness	2 mg/dL	No	Two-stage revision surgery	Doxycycline + rifampicin + gentamicin	Full recovery, no recurrence	Pain-free, independent ambulation, full knee ROM
2	Early 60s	Male	Hip	THA	6	Pain, swelling	3.5 mg/dL	No	Two-stage revision surgery	Doxycycline + rifampicin + gentamicin	Full recovery, no recurrence	Pain-free, independent ambulation, full hip ROM
3	Mid-60s	Male	Knee	TKA	8	Persistent pain	1.8 mg/dL	Yes	One-stage revision surgery	Doxycycline + rifampicin	Full recovery, no recurrence	Pain-free, full knee ROM, stable implant
4	Mid-60s	Male	Hip	THA	8	Persistent pain	1.8 mg/dL	Yes	One-stage revision surgery	Doxycycline + rifampicin	Full recovery, no recurrence	Pain-free, full hip ROM, stable implant
5	Early 60s	Male	Knee	TKA	6	Pain, swelling	3.2 mg/dL	No	Antibiotics only	Doxycycline + rifampicin	Full recovery, no recurrence	Pain-free, full knee ROM, no infection recurrence

CRP: C-reactive protein; ROM: range of motion; THA: total hip arthroplasty; TKA: total knee arthroplasty; PJI: periprosthetic joint infection.
Detailed overview of five cases of *Brucella melitensis*-associated PJIs, including patient demographics, clinical presentation, diagnostic findings, treatment approaches, and outcomes.

early detection challenging. The low sensitivity of routine microbiological cultures often delays diagnosis, necessitating a targeted approach incorporating serology, prolonged culture incubation, and PCR testing in high-risk cases.[19] Our case series highlights these diagnostic complexities, as *Brucella*-associated PJI was not initially suspected in any patient but was ultimately confirmed through adjunctive microbiological techniques following persistent culture-negative results. These findings reinforce the importance of heightened clinical suspicion and a systematic diagnostic work-up, particularly in regions where brucellosis is endemic.

Determining the mechanism of *Brucella*-associated PJIs remains a significant challenge, as infection may occur via primary hematogenous seeding before implantation or through late hematogenous spread due to reactivation. *Brucella* is known for its ability to persist intracellularly, leading to chronic or latent infections that may remain undetected for years. Previous studies have reported delayed *Brucella* infections, including a case where a prosthetic joint infection manifested 14 years after systemic brucellosis treatment.[19] Similarly, our case series demonstrated long intervals between arthroplasty and symptom onset (ranging from 5 to 8 years), suggesting that these infections were not perioperative but instead resulted from reactivation of dormant bacteria under favorable conditions, such as immunosuppression or local tissue changes. This hypothesis is reinforced by the absence of acute systemic symptoms in most cases, a characteristic feature of chronic *Brucella* infections. However, considering the limitations in tracing the exact timeline of infection, both perioperative inoculation and late hematogenous seeding remain viable explanations. Future studies incorporating molecular typing and epidemiological surveillance may help differentiate these mechanisms and better define the pathogenesis of *Brucella*-associated PJIs.[20]

In endemic regions, *Brucella* testing should be incorporated early in the diagnostic work-up for culture-negative PJIs, particularly in patients presenting with chronic, low-grade symptoms or an atypical clinical course wherein no common bacterial pathogen has been identified.[2] In our case series, Case 2 exemplified this scenario, as the patient initially presented with hip pain and swelling without systemic manifestations. Despite normal laboratory markers, subsequent synovial aspiration and prolonged culture incubation ($\geq$14 days) revealed the presence of *B. melitensis*, illustrating the need for early *Brucella* screening in suspected cases. Considering the high prevalence of *Brucella* in endemic areas, serological testing—including *Brucella* agglutination tests, enzyme-linked immunosorbent assay, and Rose Bengal testing—should be performed as part of the initial diagnostic pathway.[21] Additionally, synovial fluid and intraoperative tissue cultures should be incubated for at least 14 days to enhance *Brucella* detection rates.[8] PCR testing should be considered in culture-negative PJI cases, particularly in patients with prior antibiotic exposure, as bacterial growth may be suppressed in standard cultures.[22]

In nonendemic regions, routine *Brucella* testing is not recommended for all PJIs. Instead, a selective diagnostic approach should be used, focusing on high-risk individuals, including patients with a history of travel to endemic regions, occupational exposure (e.g. veterinarians, livestock handlers, and farmers), or unexplained culture-negative PJIs despite comprehensive diagnostic work-up.[23] In these cases, serological testing and PCR should be initiated only if routine cultures fail to detect an identifiable organism. The decision to pursue targeted *Brucella* testing should also account for exposure to unpasteurized dairy products

and prior treatment for systemic brucellosis, as observed in Case 5, wherein the patient presented with chronic knee pain and swelling without radiographic signs of implant loosening. The infection was managed conservatively, and *Brucella* was identified only through targeted serological and PCR testing, highlighting the importance of selective testing in nonendemic settings.

A structured diagnostic approach ensures timely and accurate detection while minimizing unnecessary testing. Standard PJI work-up includes CRP, erythrocyte sedimentation rate, and white blood cell count, alongside synovial fluid analysis, Gram staining, and routine aerobic/anaerobic cultures.[24] Imaging studies, including X-rays for implant loosening assessment and magnetic resonance imaging or computed tomography for deep infection evaluation, are known to complement microbiological testing.[25] If routine cultures remain negative, *Brucella*-specific testing should be immediately initiated in endemic regions, whereas in nonendemic regions, it should be reserved for high-risk individuals with persistent negative cultures.

The value of intraoperative sampling is emphasized in Cases 3 and 4, where *Brucella* was only identified postoperatively following one-stage revision arthroplasty. This underscores the need for intraoperative tissue cultures in patients with unexplained implant loosening and negative preoperative cultures. In Case 1, the initial synovial aspiration was negative; however, repeated evaluation and prolonged culture incubation ultimately revealed the presence of *B. melitensis* 8 days postoperatively, reinforcing the importance of multiple sample collection and prolonged incubation periods.

A definitive diagnosis of *Brucella*-associated PJI requires either a positive culture, PCR detection, or serological confirmation with rising antibody titers in paired samples.[2] Intraoperative tissue samples provide additional diagnostic yield, particularly in cases where *Brucella* is suspected but not confirmed preoperatively.[22] To facilitate clinical decision-making, we prepared a diagnostic flowchart (Figure 6) summarizing the stepwise approach to *Brucella*-associated PJI detection in endemic versus nonendemic regions, incorporating standard testing, epidemiological risk assessment, and microbiological work-up.

Once *Brucella*-associated PJI is confirmed, timely initiation of targeted antibiotic therapy is critical. Current guidelines recommend a 12-week regimen of doxycycline and rifampicin, with surgical intervention depending on implant stability.[25] In our series, four of the five patients required revision surgery, with two undergoing one-stage revision surgery (Cases 3 and 4) and two requiring a two-stage approach with interim antibiotic-loaded spacers (Cases 1 and 2). The decision between one-stage and two-stage revision surgery was based on implant stability and severity of infection, consistent with current recommendations for managing chronic PJIs.

Management of *Brucella*-associated PJIs depends on prosthetic stability and clinical presentation. Conservative antibiotic therapy, primarily with doxycycline and rifampicin, has proven effective for stable implants.[9,16] However, surgical intervention becomes necessary in cases of mechanical loosening, as observed in three cases in this series. One-stage revision surgery was performed successfully in two knee PJI cases, demonstrating excellent outcomes and supporting its feasibility as an alternative to two-stage revision surgery in selected patients.[3,7,21–23] Emerging evidence suggests that stringent debridement and targeted antibiotic therapy are critical to the success of this approach.[6,10,12,13,26]

This case series also highlights the importance of a multidisciplinary approach, involving orthopedic surgeons, infectious disease specialists, and microbiologists, in

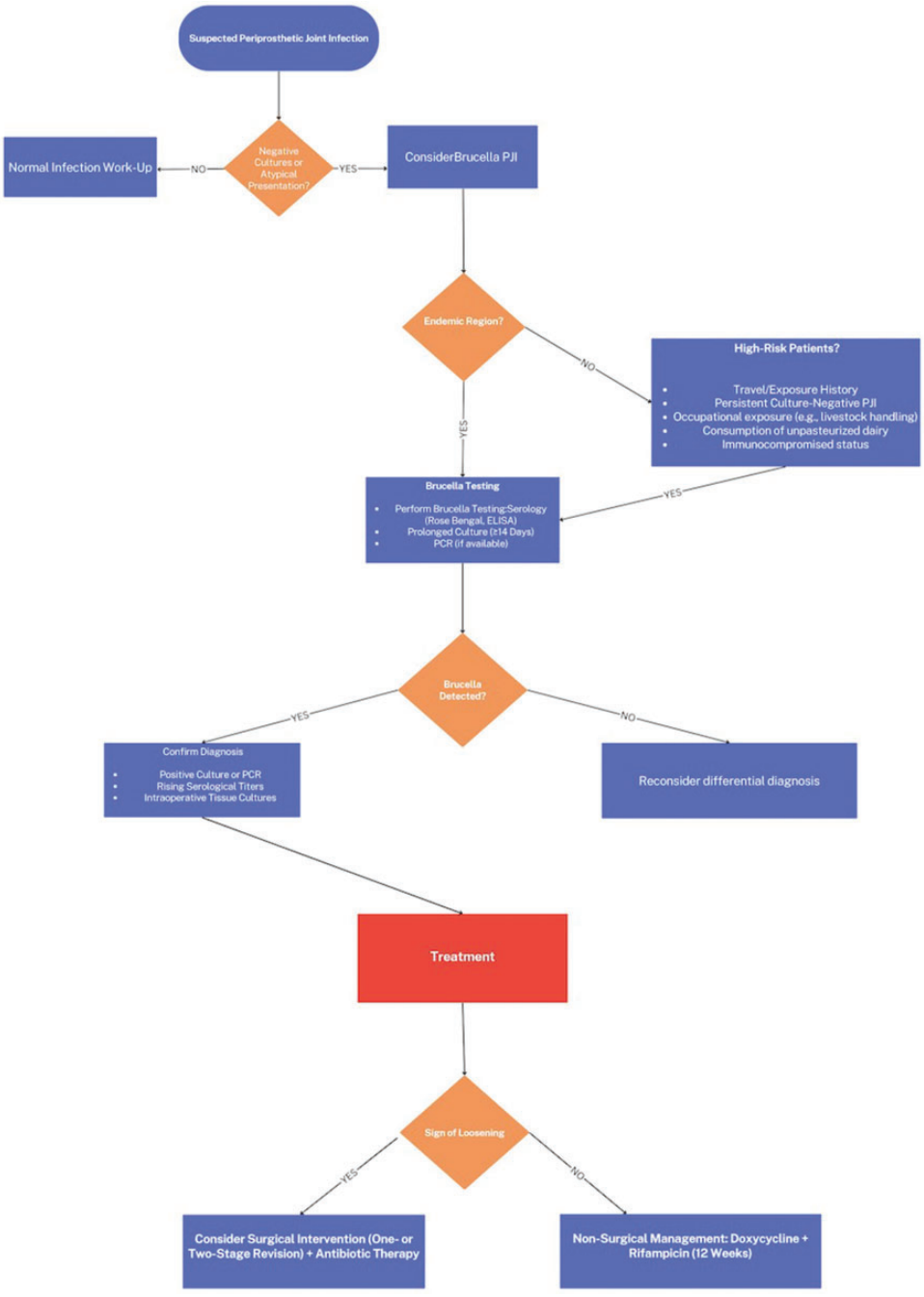

Figure 6. A flowchart illustrating the diagnostic and treatment pathway for *Brucella*-related PJI, particularly in cases with culture-negative or atypical presentations. If routine infection work-up is negative, *Brucella*-associated PJIs should be considered, especially in patients from endemic regions (Mediterranean Basin, Middle East, North and East Africa, South and Central Asia, Latin America) or those with high-risk factors. PJIs: periprosthetic joint infections; ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction.

managing these complex infections.[10,12,14,26] All five patients achieved excellent clinical and functional outcomes, with symptom resolution, normalization of inflammatory markers, and no evidence of recurrence. Follow-up imaging confirmed stable implant fixation. Notably, the two patients treated with one-stage revision surgery for knee PJIs showed full restoration of joint function and experienced pain-free mobility, emphasizing the potential of this approach in localized infections.[7,8]

This case series underscores the importance of maintaining heightened clinical suspicion for *Brucella*-associated PJIs in endemic regions, even in the absence of systemic symptoms or radiographic signs of loosening. Early serological screening and prolonged culture incubation are critical for timely and accurate diagnosis[7,26,27] Although conservative management remains viable in select cases, surgical intervention—especially one-stage revision surgery—offers a streamlined and effective option for eradicating infection and restoring joint function. Further studies are warranted to validate these findings and explore the broader applicability of one-stage revision surgery in managing *Brucella*-associated PJIs.[13,14,21,26]

Conclusion

Clinicians in endemic regions must maintain heightened suspicion for *B. melitensis* as a causative agent of PJIs, particularly in patients with chronic joint symptoms and exposure risks. Prolonged culture incubation and routine serological testing are critical for accurate diagnosis. *Brucella*-associated PJIs were effectively treated with one-stage revision surgery in our patients. This approach is particularly relevant for patients in endemic regions, offering a streamlined alternative to traditional two-stage revision surgery as well as benefits from economical and quality-of-life perspectives.

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None.

Author contributions

Mehmet Süleyman Abul: Concept and design of the study, data collection, and drafting of the manuscript; Muhammed Enes Karataş: Data collection, data analysis, and manuscript revision; Ömer Faruk Sevim: Drafting of the article, critical revisions of the manuscript; Furkan Başak: Manuscript review, data validation, and statistical analysis.

Availability of data and materials

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

Consent for publication

Written informed consent for publication was not required, as per ethical guidelines, as patient data were completely de-identified.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

This study was approved by Umraniye Training and Research Hospital (2213/06.08.2024) and Kartal Dr. Lütfi Kırdar City Hospital (1133/06.09.2024).

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