Brucella melitensis periprosthetic joint infection:

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Brucellosis, caused by a facultative intracellular gram-negative coccobacillus, is one of the most common zoonotic infections worldwide. Very rarely, brucellosis can cause periprosthetic joint infections (PJI). In this case-based literature review, we summarize the current medical literature regarding *Brucella* PJI, with the aim to raise awareness among clinicians, particularly in non-endemic areas. We report a case of a woman with a 3 weeks history of increasing hip pain, who was eventually diagnosed with *Brucella* PJI. We searched multiple databases to identify all case reports on *Brucella* PJI in humans published from February, 1983 to December, 2023. A total of 42 cases from 38 published articles were retrieved and summarized, along with our case. Mean age was 65.5 years, with sex ratio nearly one. Almost all patients presented with local symptoms and 56% with systemic symptoms. Only knee (n=30) and hip (n=13) prosthetic joint were involved. If performed, culture showed positive results on synovial fluid (74%), intra-operative tissue (79%), and/or blood (38%). Serological confirmation was obtained in 97%. Antimicrobial treatment consisted of a combination of doxycycline and rifampin in most cases, with in nearly half of the cases the addition of an aminoglycoside. The majority of patients (n=24) were surgically treated with a two stage exchange arthroplasty; although other options were successful as well. *Brucella* PJI is a rare but potentially severe manifestation of brucellosis. *Brucella* PJI must be considered in patients from endemic areas, especially when another causative agent has not been isolated. If culture results remain negative, PCR or serology should be performed. To date, there is no uniform recommendation for the duration of antimicrobial therapy nor the preferred surgical procedure. Relapse is possible even with adequate therapy.

Keywords: *Brucella*, periprosthetic joint infection, zoonosis.

INTRODUCTION

Brucellosis, caused by a facultative intracellular gram-negative coccobacillus, is the most common zoonotic infection worldwide[1,2]. The disease is endemic in several areas in particular the Mediterranean basin, Sub-Saharan Africa, Middle East and South America[2]. Transmission occurs through ingestion of unpasteurized milk products, inhalation of infected aerosol particles and after direct contact with infected animal fluids or tissue[3]. Occupational exposure occurs in veterinarians, abattoir workers, laboratory workers and dairy-industry professionals[1].

The genus *Brucella* consists of 12 currently recognized species (spp.), of which only four (*B. melitensis, B. suis, B. abortus and B. canis*) are known to cause human disease[1,4,5]. During the acute phase of infection, nonspecific flu-like symptoms can be observed due to hematogenous spread[6,7]. *Brucella* spp. have the capacity to survive and multiply for prolonged periods within host macrophages which explains their ability to cause chronic infections affecting all systems (e.g. the osteoarticular system, nervous system, genitourinary system, mucocutaneous system, cardiovascular system and pulmonary system)[5,8,9]. Osteoarticular complications are the most commonly reported, ranging from 10-85%, including sacroiliitis, spondylitis, peripheral arthritis, osteomyelitis and tenosynovitis[10]. Brucellosis can be diagnosed by conventional culture, serologic assays or PCR. Cultures can be performed on blood, bone marrow, joint fluid, pleural fluid, pus, cerebrospinal

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fluid or intra-operative specimens[8]. Blood cultures typically require a longer incubation period of 10 to 14 days, to avoid false negative results[3]. There are several serological tests, a standard tube agglutination test (SAT) remains the most common diagnostic tool to confirm Brucellosis. Titers of ≥1:160 in non-endemic areas or ≥ 1:320 in endemic areas along with a suggestive clinical presentation are pathognomonic[1,8,11]. A combination ELISA test (IgM and IgG) remains a good alternative for SAT[12]. Other highly sensitive screening tests include the Rose-Bengal (slide agglutination) test and the immunochromatographic lateral flow assay[13]. In recent years, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) is evolving into a fast, cost-effective and reliable method for identification of *Brucella* isolates at the genus and species level[14,15]. The treatment of brucellosis consists of a combination of antimicrobial drugs for a prolonged period of time (≥ 6weeks), with the use of antibiotics capable of invading macrophages and with high activity in the acidic intracellular environment, e.g. doxycycline and rifampin or an aminoglycoside (streptomycin or gentamicin)[1,8]. In specific severe complications (e.g. spondylitis, neurobrucellosis, or endocarditis) triple regimens are used. Therapy duration depends on disease manifestation ranging from 6 weeks up to 6 months in case of severe osteoarticular complication[1].

Periprosthetic joint infections (PJI) caused by *Brucella* spp., is an extremely rare manifestation of brucellosis. To date, there is no uniform recommendation for the duration of antimicrobial therapy nor the preferred surgical procedure. *Brucella* infections are difficult to treat given their ability to survive in phagocytic cells. In addition, *Brucella* has the capacity to form biofilm, as described in in vitro' studies[16,17], although this phenomenon has not been described in vivo yet. We report a case of a woman with a 3 weeks history of increasing hip pain who was eventually diagnosed with *Brucella* PJI. We reviewed the literature with the purpose to clarify the uncertainties about the ideal medical and surgical treatment of this rare manifestation of brucellosis.

CASE REPORT

A 67-year-old female of Turkish origin presented to the emergency department with a 3 weeks history of increasing right sided pain, intermittent fever and weight loss. Physical examination revealed a painful hip at 90° flexion and internal rotation, local pain on palpation and a limping gait. No symptoms of local infection such as calor, rubor and tumor

were present. Her medical history included arterial hypertension (AH), type 2 diabetes mellitus (DM2), breast cancer treated with surgery plus adjuvant chemoradiotherapy and right sided coxarthrosis treated with a hybrid total hip arthroplasty (THA) 16 years-ago. The patient underwent a two-stage revision arthroplasty for a Streptococcus agalactiae PJI six and a half years after initial THA, with good outcome.

Blood analysis revealed a mild anemia (Hb 11.4g/dL), normal total white blood cell (WBC) count 6.380/mm^3 with normal distribution, hyponatremia (129 mmol/L), and elevated C-reactive protein (CRP) 80.9 mg/L (normal value ≤ 5 mg/L). Radiography of the right hip disclosed signs of cement creep, no fracture (Fig. 1).

Because of suspicion of infection with duration of symptoms less than 3 weeks, a DAIR (Debridement, Antibiotics and Implant Retention) procedure with exchange of the modular head and polyethylene liner of the cup as well as a cement-in-cement revision of the polished tapered cemented stem was performed, according to guidelines18. The synovial fluid analysis revealed a WBC count of 42.8 × 10^9/L (with 89.3 % polymorphonuclear cells (PMN)). According to local guidelines, patient was started empirically on an IV combination therapy with piperacillin-tazobactam and vancomycin postoperatively. However, as soon as cultures on intra-operative tissue and on synovial fluid were found positive for *Brucella melitensis*, the patient was switched to oral minocycline (200mg/day) and rifampin (900mg/day).

Further history taking revealed that the patient travelled regularly to her home country Turkey where she reported having consumed fresh unpasteurized milk products. All blood cultures remained negative. Antibiotics were continued for a total duration of 12 weeks, with good tolerance and compliance.

Six months after the DAIR procedure, the patient presented with recurrence of pain and an increased CRP. A new synovial fluid aspirate revealed a WBC count of 6.7*10**9/L with a predominance of PMN (85 %). Bloodcultures were negative, synovial fluid culture was positive with B. melitensis. The surgical plan consisted of a two-stage exchange with a 6-week interval.

Triple antibiotic therapy was started after first stage surgery and included gentamicin IV od 5mg/kg for 2 weeks, in combination with oral doxycycline 100mg bid and rifampicin 300mg tid. The latter two antibiotics were continued until 3 months after the

Fig. 1 — Conventional radiographs before, during and after the two-stage exchange arthroplasty.

second stage operation. Blood cultures and deep tissue cultures taken at the time of both surgeries remained negative. The patient was rehabilitated and remained pain-free (more than 17 months after the second stage surgery).

METHODS

Literature search

Three computer databases (Pubmed, Scopus and Google Scholar) were searched reviewing title, abstract and references to identify all case reports about *Brucella* PJI (Fig. 2). The following search string was used: Brucell* AND (prosth* OR replacement OR arthroplasty) AND (knee OR hip OR joint).

Study inclusion

Titles and abstract were independently screened by two reviewers (LV and LH). The inclusion criteria included (1) articles published from February, 1983 to December, 2023, (2) species (humans), (3) full text online available, (4) case reports regarding *Brucella* PJI.

Data extraction

The following data were extracted from the case reports included: (a) patient characteristics: sex, age, country of exposure and exposure risk, (b) clinical manifestations: local and systemic symptoms, involved prosthesis and time to symptoms after total joint arthroplasty (TJA), (c) diagnostic tools: biochemistry, culture, serology,
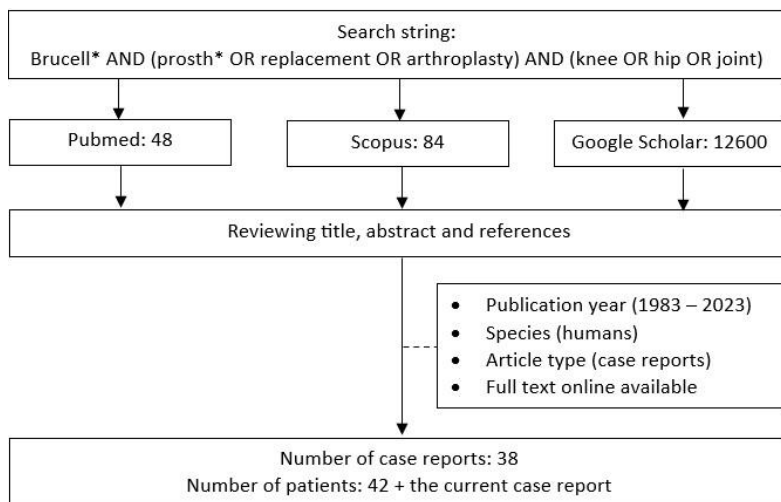

Fig. 2 — Flow-chart of the literature search.

radiology, (d) treatment: antimicrobial medication, surgery, implant free interval (e) outcome and follow-up: clinical resolution, reactivation of infection.

Descriptive statistics

Categorical variables are described as counts (n) and percentages (%). Continuous variables are reported as mean (+/- standard deviation, SD) or median (+ interquartile range (IQR)) where appropriate.

RESULTS

Patient characteristics

Including our case, a total of 43 cases were retrieved. 51 % patients were female, 44 % male, gender was not reported in 5 %. Median age was 65,5 years (range 24-78 years). As to the method of exposure, 19 patients (44 %) reported consumption of unpasteurized dairy products and 14 patients (33 %) had occupational exposure. As risk factors, underlying degenerative joint disease (65 %), diabetes mellitus (n=6) or inflammatory joint disease (n=2) were reported. None of the patients had an active malignancy or were otherwise immunocompromised (Table I).

Clinical manifestations

Almost all patients (n=42) presented with local symptoms (dolor (88 %), tumor (35 %), rubor (21 %), calor (14 %)); a sinus tract was reported in 21%. Twenty-four patients presented with systemic symptoms such as: fever (51 %) or night sweats (21 %). Median time to symptoms after TJA was 60 months, ranging from 0-198 months. A total of 30 knee and 13 hip PJI were described (Table II).

Diagnostic findings contributing to diagnosis

Laboratory testing results were reported in a limited number of cases. In those reported, median CRP was 44 mg/L (range 0,24-1010 mg/L), median erythrocyte sedimentation rate (ESR) was 67 mm/h (range 18-123 mm/h) and WBC count 6380 cells/m3 (range 250-10.200 cells/ m3). B. melitensis was the most common pathogenic species (29/43), followed by B. abortus and B. suis in four patients and one patient respectively. In nine cases, the species remained unidentified. Culture of joint fluid was positive in 25 out of 34 joint aspirations performed. In 26 patients, diagnosis was established by culture on intra-operative tissue material, whereas blood cultures were positive in five cases. In case serological testing was

Table I. — Literature review: patient characteristics.

Variables		Number and percentages (%)
Sex (n=41)	Male	n=19 (44 %)
	Female	n=22 (51 %)
	Not reported	n=2 (5 %)
Age (n=42)	Median	65,5 years (IQR: 10)
	Age range	24-78 years
Risk factors	Unpasteurized dairy products	n=19 (44 %)
	Farmer	n=14 (33 %)
	Previously treated Brucellosis	n=6 (14 %)
	Unknown	n=10 (23 %)
Country of exposure	Turkey	n=8 (19 %)
	Spain	n=8 (19 %)
	Iran	n=5 (12 %)
	Israel	n=4 (9 %)
	Italy	n=3 (7 %)
	Saudi Arabia, Greece, Liban*	n=6 (14 %)
	Other countries**	n=9 (21 %)
Comorbidity	Degenerative joint disease	n=28 (65 %)
	Inflammatory joint disease	n=2 (5 %)
	DM	n=6 (14 %)
	AH	n=3 (7 %)
	Obesity	n=2 (5 %)
	None reported	n=10 (23 %)
* Two patients from every country of exposure: Saudi Arabia, Greece, Liban **One patient from each country: Afghanistan, Oman, Ireland, Mexico, Portugal, Thailand, India, Canada, USA.		

Table II. — Clinical manifestations.

Variables		Number and percentages (%)
Local Symptoms	Present: Dolor Tumor Rubor Calor Sinus tract Not reported	n=42 (98 %) n=38 (88 %) n=15 (35 %) n=9 (21 %) n=6 (14 %) n=9 (21 %) n=1 (2 %)
Systemic symptoms	Present: Fever Night sweats Absent Not reported	n=24 (56 %) n=22 (51%) n=9 (21%) n=14 (34 %) n=5 (12 %)
Involved prothesis	TKA Unilateral Bilateral THA	n=30 (70 %) n= 23 (53 %) n= 7 (16 %) n=13 (30 %)
Time to symptom after TJA	Median Time range Not reported	60 months (n=41) (IQR= 78) 0-198 months (n=41) n=2

performed, 30 of 31 cases were positive. Radiographic signs of loosening were present in 28 cases (Table III).

Treatment and outcome

Details on medical and surgical treatment are summarized in Table IV. Surgical treatment was performed in 32 patients. Twenty-four patients underwent two-stage exchange, four patients underwent one-stage exchange and three patients a DAIR procedure. For the two-stage exchange procedures, the median implant interval was 8 weeks (IQR=10), ranging from 2.5 to 24 weeks.

Most patients were treated with combination therapy consisting of doxycycline and rifampicin (n=33), for a median duration of 16 weeks, in some cases combined with an aminoglycoside. In the small minority, trimethoprim-sulfamethoxazole (TMP-SMX) (n=5) or a quinolone (n=2) were administered. The median duration of follow-up for 37 patients with available data was 24 months ranging from 3 months to 120 months; all these patients had favourable outcomes, without uniform specification.

DISCUSSION

PJI caused by *Brucella spp*. is extremely rare. A total of 42 cases from 38 published articles were retrieved and summarized, along with our case. If a method of transmission is known, it usually occurs through consumption of unpasteurized dairy products (19/43, as in our patient) or contact with livestock (14/43). Most patients in the literature review present with local symptoms (98 %) and systemic symptoms (56

%) as in our case; these symptoms are non-specific. The interval between arthroplasty and *Brucella* PJI is variable: our patient presented 9.5 years after initial THA, with literature data ranging from 0-198 months, depending on the timing of the exposure. In one case, the diagnosis was made during elective hip arthroplasty surgery for aseptic necrosis leading to the wide time range[19].

Only hip (n=13, as in our case) and knee (n=30, of whom 7 bilateral) prosthetic joints were involved in this series. This probably reflects the fact that these are the most frequently implanted prostheses[20], but also in native brucellar arthritis knee and hip joints are more commonly affected, as with other causes of joint infection[21].

Blood cultures, joint aspiration and surgical revision with intra-operative tissue samples are all part of the diagnostic algorithm in patients with a suspicion of PJI[18]. In our patient, cultures on intra-operative tissue and synovial fluid were found positive for *Brucella melitensis* while blood cultures remained negative. Remarkably, blood cultures were only performed (or reported) in 13 cases in the series. A negative blood culture does not seem to rule out *Brucella* PJI, as only 38 % of all performed cultures showed positive results; this may however depend on the technique used, culture medium and duration of incubation. Synovial fluid and tissue cultures have an acceptable diagnostic yield: if performed, positive results were obtained in 74 % and 79 % of all cases. However, notwithstanding the diagnostic contributions of these tests, the risk of airborne

Table III. — Diagnostic findings contributing to diagnosis (Laboratory, culture, serology and radiography).

Variables		Number and percentages (%)
Routine laboratory	Median CRP	44 mg/L (n=23) (IQR: 45.4)
	Range CRP	0,24- 1010 mg/L
	Median ESR	67 mm/h (n=25) (IQR: 38.5)
	Range ESR	18- 123 mm/h
	Median WBC	6380 cells/m³ (n=15) (IQR= 3.7)
	Range WBC	4.250-10.200 cells/m³
Culture results	Species	
	B. melitensis	n=29 (67 %)
	B. abortus	n=4 (9 %)
	B. suis	n=1 (2 %)
	Brucella sp.	n=9 (21 %)
	Joint fluid	
	Positive	n=25 (58 %)
	Negative	n=9 (21 %)
	Not reported	n=9 (21 %)
	Intra-operative tissue	
	Positive	n= 26 (60 %)
	Not reported	n= 17 (40 %)
	Blood cultures	
	Positive	n=5 (12 %)
	Negative	n=8 (19 %)
	Not reported	n= 30 (70 %)
Serology	Positive	n=30 (70 %)
	Negative	n=1 (2 %)
	Not performed	n=12 (28 %)
Implant loosening on X-ray	Yes	n=28 (65 %)
	No	n=15 (35 %)

transmission to operating room and laboratory personnel remains high, as *Brucella* is a biosafety level three organism[22]. Caution should therefore be taken, certainly in patients from endemic regions. The series demonstrates that the diagnosis can be challenging, as in several cases, multiple surgical revisions were performed before the diagnosis was made. Therefore, if culture remains negative, and the epidemiological context is appropriate, the microbiologist and/or infectiologist should be consulted, and a PCR-based assay or serology should be considered[23]. Serological tests for *Brucella* PJI seem to be the most reliable and safe diagnostic test. In our case, serology was not performed because of culture positivity.

Literature data confirm the lack of consensus on the ideal surgical treatment for *Brucella* PJI: good outcomes are described with all types of surgery, although there may be reporting bias. In general, a thorough DAIR can be performed in patients with acute PJI (symptom duration < 3weeks), in the presence of good quality of bone and soft tissue, stable prosthesis and an 'absence of a difficult-to-treat' causative pathogen[18].

In accordance with current guidelines, our patient first underwent a DAIR procedure, with directed antibiotic therapy (minocycline/rifampicin) for 12 weeks. The relapse that occurred 3 months after the stop of antibiotics is not surprising as, according to literature, about 10 % of patients with brucellosis experience a recurrence, 90 % of whom occur within one year after discontinuing antimicrobial drug treatment[24]. Moreover, for patients in endemic regions as in the case of our patient (frequently traveling to her home country), it is impossible to differentiate between a relapse (from residual bacteria in the prosthetic material in situ) or a reinfection.

From our literature review, we retain three cases successfully treated with a single DAIR procedure[25-27]. In the first case, a triple antibiotic regimen was given for the first month, followed by 5 months of bitherapy; in the other two cases, a DAIR was performed arthroscopically (despite radiographical loosening in one case), with favourable outcome. Notwithstanding the reporting of these successful outcomes, arthroscopic DAIR is currently generally discouraged due to insufficient debridement, lack of replacement of mobile parts, and higher relapse risk[28].

A two-stage exchange was performed in 24 cases

Table IV. — Treatment and outcome.

Variables		Number and percentages (%)
Surgical treatment	None	n=9 (21 %)
	DAIR	n=3 (7 %)
	Girdlestone resection arthroplasty	n=1 (2 %)
	One-stage exchange	n=4 (9 %)
	Two-stage exchange	n=24 (56 %)
	DAIR followed by two stage exchange	n=1 (2 %)
	Unknown	n=1 (2 %)
Implant free interval in two-stage exchange (weeks)	Range interval	2.5-24 weeks (n=19)
Antimicrobial treatment and duration (weeks)	Doxy/Rif	n=33 (77 %)
	Time range	6-48weeks
	Median duration	16 weeks
	+ Gen	n= (9/33)
	Time range	1-4 weeks
	Median duration	2 weeks
	+ Strep	n= (7/33)
	Time range	11 days-52 weeks
	Median duration	3 weeks
	Doxy/strep	n=2 (5 %)
	Time range	88-106 weeks
	Median duration	97 weeks
	Alternative regimens	
	Doxy/Rif/Gen/TMP-SMX	n=1 (2 %) (77 weeks)
	Doxy/Rif/Strep/TMP-SMX/Cef	n=1 (2 %) (12 weeks)
	Doxy/Strep/TMP-SMX	n=1 (2 %) (20 weeks)
	Rif/TMP-SMX	n=1 (2 %) (76 weeks)
	Doxy/Rif/Strep/Levo	n=1 (2 %) (28 weeks)
	Doxy/Rif/Gen/TMP - SMX/Cipro/Cef	n=1 (2 %) (56 weeks)
	Unknown	n=2 (5 %)
Good outcome	Yes	n=37 (86 %)
	Unknown	n=6 (14 %)
Follow up after diagnosis (months)	Median	24 months (n=37) (IQR= 24)
	Range	6-120 months

Doxy, doxycycline; Rif, rifampicin; Gen, gentamicin; Strep, streptomycin; TMP-SMX, trimethoprim-sulfamethoxazole (TMP-SMX); Cef, ceftriaxone; Levo, levofloxacin; Cipro, ciprofloxacin.

(including in our case as a final option) and seems to be the most widely accepted surgical treatment for *Brucella* PJI. Although there is a wide implant-free interval, ranging from 2.5 to 24 weeks, good outcomes were described in all cases. From these data as well as the literature, a short implant-free interval with continuation of antibiotic treatment between the two stages seems also acceptable.

In contrast to current treatment guidelines for PJI, several articles suggest that without radiographical loosening, antimicrobial treatment without any surgical intervention may be sufficient for *Brucella* PJI. According to our research, nine patients without radiographical loosening but with positive synovial fluid cultures were successfully treated with antibiotics alone. This must be interpreted with caution because

treatment duration with antibiotics was rather long (median 27 weeks) in the majority, along with limited follow-up (< 1year (n=5)) after discontinuation of antibiotics. Why these patients were not treated surgically was not reported.

Antibiotic treatment in this series mainly consisted of a combination of doxycycline and rifampicin in most patients, with a median treatment duration of 16 weeks and combined with an aminoglycoside in nearly half of the cases (as in the final treatment of the current case). Alternative regimens with trimethoprim-sulfamethoxazole (TMP-SMX) and quinolones were used in the minority as rescue therapy. In six of the reported cases, the patient had been successfully treated for systemic brucellosis 2 to 24 months prior to *Brucella* PJI. Thus, even with

initially correct treatment, vigilance for recurrence remains necessary. We recommend that serology and molecular techniques should become the first step of the standard diagnostic algorithm for patients in or returning from endemic areas with a clinical suspicion for *Brucella* PJI. If serology is positive, surgical and laboratory staff can be informed so that appropriate precautions can be taken to avoid transmission. Accidentally exposed individuals, should receive prophylactic treatment consisting of doxycycline and rifampin for 3 weeks in combination with serological follow up[18].

Brucella associated PJI remains rare. Targeted diagnostics and therapy can only be initiated upon recognition; thus, awareness is paramount. Although common sense and extrapolation from other PJI suggests that the optimal treatment of this disease manifestation consists of surgery combined with antimicrobial therapy, this could not be confirmed based on data available from the literature. Therefore, a prudent approach seems advisable, and further research necessary in order to determine if treatment with antibiotics alone can be considered in selected cases.

Author contributions: LH was responsible for the conceptualization. LV and LH screened the literature and wrote the original manuscript. GFV, MD, SG, EV and ID were responsible for critical revision. All authors reviewed the manuscript.

Competing interests: The authors declare that they have no conflict of interest.

Ethical statement: Written informed consent was acquired from the patient and approval of the Research Ethics Committee UZ/KU Leuven (MP024043) was obtained.

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