

Genitourinary brucellosis: results of a multicentric study

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Abstract

This study reviewed the clinical, laboratory, therapeutic and prognostic data on genitourinary involvement of brucellosis in this largest case series reported. This multicentre study pooled adult patients with genitourinary brucellar involvement from 34 centres treated between 2000 and 2013. Diagnosis of the disease was established by conventional methods. Overall 390 patients with genitourinary brucellosis (352 male, 90.2%) were pooled. In male patients, the most frequent involved site was the scrotal area ($n = 327$, 83.8%), as epididymo-orchitis ($n = 204$, 58%), orchitis ($n = 112$, 31.8%) and epididymitis ($n = 11$, 3.1%). In female patients, pyelonephritis ($n = 33/38$, 86.8%) was significantly higher than in male patients ($n = 11/352$, 3.1%; $p < 0.0001$). The mean blood leukocyte count was $7530 \pm 3115/\text{mm}^3$. Routine laboratory analysis revealed mild to moderate increases for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The mean treatment duration and length of hospital stay were significantly higher when there were additional brucellar foci ($p < 0.05$). Surgical operations including orchiectomy and abscess drainage were performed in nine (2.3%) patients. Therapeutic failure was detected in six (1.5%), relapse occurred in four (1%), and persistent infertility related to brucellosis occurred in one patient. A localized scrotal infection in men or pyelonephritis in women in the absence of leucocytosis and with mild to moderate increases in inflammatory markers should signal the possibility of brucellar genitourinary disease.

Keywords: *Brucellae*, Brucellosis, epididymo-orchitis, genitourinary, orchitis

Original Submission: 22 December 2013; **Revised Submission:** 12 May 2014; **Accepted:** 12 May 2014

Editor: S. Cutler

Article published online: 16 May 2014

Clin Microbiol Infect 2014; **20**: O847–O853

10.1111/1469-0691.12680

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Introduction

Brucellosis is a major zoonotic disease in many parts of the world, especially in South and Central America, India, the Mediterranean and the Middle East [1]. The disease is an endemic zoonosis in Turkey, too. The reported incidence of brucellosis in Turkey by the Turkish Ministry of Health was 256.7 cases per million in 2004 [2]. Human brucellosis occurs as a systemic infectious disease with various clinical manifestations. The generalized symptoms, consisting of fever, night sweats and malaise, are not disease specific and can mimic many diseases, particularly tuberculosis, typhoid fever, infectious mononucleosis, Hodgkin's disease, HIV infection and malaria. *Brucellae* spread to tissues, rich in elements of reticulo-endothelial system by the haematogenous route and localizes mainly at the joints, central nervous system (CNS), cardiovascular system (CVS), respiratory system and genitourinary tract [3–8].

Brucellae can affect the genitourinary tract in different ways in male patients, while data are relatively lacking for female patients. Approximately 10% of brucellosis cases have genitourinary complications, with epididymo-orchitis being the most frequent [9]. However, reports from Turkey suggest a lower incidence (1–4.3%) [5–8]. *Brucella* epididymo-orchitis patients may present at urology clinics with testicular lesions resembling tumours or tuberculosis [10,11], renal [12] and testicular [13] abscesses, and prostatitis [14]. Few reports have focused on genitourinary brucellosis, with most being small case series [15–19]. This multicentre retrospective study provides the largest series reported, detailing clinical, laboratory, therapeutic and prognostic features of genitourinary brucellosis.

Methods

Study design and patient population

Only adult patients over the age of 15 years with genitourinary brucellosis were enrolled in this study. This retrospective

multicentre study pooled patients from 34 medical centres in Turkey. The diagnosis of genitourinary brucellosis was made by the clinicians at the participating centres. No control group was included in the study. Fatih Sultan Mehmet Training and Research Hospital's Review Board in Istanbul approved the study.

Microbiological, serological, routine laboratory and radiological investigations

Blood, bone marrow, abscess and body fluid cultures were taken for diagnostic purposes. Blood and bone marrow specimens were cultivated using automated systems, mainly BACTEC™ 9240 (Becton-Dickinson, Sparks, MD, USA) and the Phoenix™ Diagnostic System (Becton-Dickinson Diagnostic Instrument System). Blood samples were cultivated for 14 days. Clinical specimens other than blood and bone marrow were inoculated onto sheep blood agar and chocolate agar. All isolates were defined by standard microbiological techniques such as motility, oxidase, catalase, glucose fermentation, production of H₂S and urease. *Brucella abortus* S99 antigen obtained from the Pendik Animal Diseases Research Institute (Istanbul, Turkey) was used for serum tube agglutination test (SAT). The Rose Bengal test (Pendik Animal Diseases Research Institute) and Coombs' agglutination (Coombs-SAT) test were used for serological analysis. Routine laboratory analyses for all patients, ultrasonography (USG) and other diagnostic imaging studies were performed according to the symptoms of the patients.

Definitions

Diagnosis of brucellosis. The diagnosis was based on clinical findings for brucellosis, including fever, night sweats, arthralgia, hepatomegaly and splenomegaly, positive SAT (titre \geq 1:160) or Rose Bengal test, and/or isolation of *Brucellae* from blood, other tissues, urine cultures or fluids [20].

Classification of brucellosis. Patients were subclassified into acute, subacute and chronic stages according to the duration of the disease, as less than 8 weeks, from 8 to 52 weeks and more than 1 year, respectively [21].

Epididymo-orchitis. A brucellosis patient with epididymal and testicular tenderness, and/or florid inflammation of the scrotum,

and enlargement and/or oedema on physical examination and/or on USG was classified as epididymo-orchitis [16].

Pyelonephritis. A brucellosis patient with upper urinary tract infection including fever, flank pain and costovertebral angle tenderness and/or isolation of *Brucellae* from the urine cultures or renal oedema and inflammation detected by USG was categorized as pyelonephritis.

Prostatitis. A brucellosis patient with symptoms and signs of prostatitis with oedema and inflammation of the prostate on USG or typical histological appearance in a prostate biopsy specimen was confirmed as prostatitis.

Acute kidney injury. An abrupt (within 48 h) and absolute increase in the serum creatinine concentration of ≥ 0.3 mg/dL from baseline, a percentage increase in the serum creatinine concentration of $\geq 50\%$, or oliguria of < 0.5 mL/kg per hour for more than 6 h, was classified in as acute kidney injury [22]. Patients with kidney damage and evidence of obstruction, diabetes mellitus, systemic lupus erythematosus, chronic renal failure or underlying renal diseases were excluded.

Glomerulonephritis. A patient with typical histological appearance compatible with glomerulonephritis on microscopic examination of a kidney biopsy specimen was recorded in this category.

Genitourinary involvement. This group comprised brucellosis patients with genitourinary or urinary involvement.

Therapeutic failure. The persistence or deterioration of symptoms and signs related to brucellosis and/or brucellar genitourinary involvement at the end of therapy was considered as a therapeutic failure [8].

Relapse. This was defined as reappearance of clinical signs and symptoms of brucellosis during the 12 months after the treatment [21].

Treatment

All patients were treated with various combinations of antibiotics after the diagnosis, such as doxycycline, rifampicin, ciprofloxacin, trimethoprim/sulfamethoxazole orally, and an aminoglycoside (streptomycin and gentamicin) and ceftriaxone parenterally, with the appropriate doses and durations at the participant centres. All patients were followed-up and examined daily by the same physicians during the hospitalization period. Patients were followed-up for at least 6 weeks after completion of therapy; cure, therapeutic failure, relapse and death (if it occurred) were recorded for each patient.

Data collection and statistical methods

A standard questionnaire was sent to the participant centres via the internet and data were collected by using a computer database. Demographic and epidemiological data, clinical and laboratory data including symptoms and signs, co-existent foci of brucellosis, underlying diseases, routine and other diagnostic laboratory test results, imaging findings and the results of organ biopsies, treatment and outcome data such as drug combinations used, duration of treatments, therapeutic failures, cure, relapse, surgical operations and length of stay (LOS) in the hospitals were retrieved from the patient charts and recorded for each patient by the local physicians at the participating centres. Patients were divided into two groups for comparative analysis; group one did not have focal infection and group two comprised those with additional involved sites.

The data analysis was performed with SPSS in the Windows V.16.0 program. Descriptive statistics were presented as frequencies, percentages for categorical variables and mean \pm standard deviation (range) for continuous variables. Numerical data were first tested for normality and then analysed using Student's *t*-test for parametric data; the Mann-Whitney *U*-test was used for variables for non-parametric data for group comparisons. Categorical data were analysed using the chi-square and Fisher's exact tests. All tests were two-tailed and statistical significance was assigned to *p* values less than 0.05.

Results

Patient characteristics

Overall 390 patients with genitourinary brucellosis (352 male patients, 90.2%) were studied. The mean age of the patients was 39.66 ± 14.94 (range, 15–85) years. The clinical signs and symptoms of the patients were presented in Table 1. Fatigue (86.9%), night sweats (83.6%) and fever (82.3%) were the most frequent symptoms and fever (44.9%), hepatomegaly (23.8%) and splenomegaly (19%) were the most frequent signs found in the patients on admission. In addition to the major symptoms of brucellosis, the following genitourinary symptoms were observed in female patients: dysuria in 21 (55.3%) out of 38 patients, haematuria in 10 (26.3%) and genital discharge in four (10.5%). Testicular complaints included tenderness, swelling and hyperaemia in 345 (98%), dysuria in 71 (20.2%), urethral discharge in 20 (5.7%) and haematuria in 16 (4.5%) out of 352 males with genitourinary complaints.

The mean duration between the onset of symptoms and hospital admission was 15.9 ± 19.9 (range, 1–210) days. In other words, 375 (96.2%) patients presented to hospital within 2 months of the onset of symptoms. Previous history of

TABLE 1. Clinical symptoms and signs in genitourinary system brucellosis ($n = 390$)

Symptoms	n (%)
Fatigue	339 (86.9)
Night sweats	326 (83.6)
Fever	321 (82.3)
Loss of appetite	227 (58.2)
Arthralgia	215 (55.1)
Weight loss	212 (54.4)
Lower back pain	200 (51.3)
Dysuria	93 (23.8)
Testicular complaints in men ($n = 352$)	345 (98.0)
Signs	
Fever ($\geq 38^\circ\text{C}$)	175 (44.9)
Hepatomegaly	93 (23.8)
Splenomegaly	74 (19.0)
Haematuria	26 (6.7)
Genital discharge	24 (6.2)
Costovertebral angle tenderness	13 (3.3)
Scrotal signs in men ($n = 352$)	
Tenderness ^a	325 (92.3)
Swelling ^b	317 (90.1)
Hyperaemia ^c	284 (80.7)

^aRight testicle, 128; left testicle, 114; bilateral, 83.

^bRight testicle, 129; left testicle, 131; bilateral, 57.

^cRight testicle, 117; left testicle, 107; bilateral, 60.

brucellosis was recorded in 29 (7.4%) cases, with a mean of 16.7 ± 14.3 months. Eighteen out of these 29 patients (62%) had suitable treatment for their previous episode of brucellosis.

The concomitant diseases were as follows: diabetes mellitus in 17 (4.4%), urinary stones in 11 (2.8%), benign prostate hypertrophy in 10 (2.6%), hypertension in 8 (2.1%), acute kidney injury related to brucellosis in 7 (1.7%), chronic hepatitis in 3 (0.8%) and other disease in nine patients (2.3%) (cerebrovascular event, 1; drug addiction, 1; orchiectomy operation, 1; rheumatic disease, 1; coronary artery disease, 1; lumbar disc hernia, 1; facial paralysis, 1; cardiac failure, 1; chronic bronchitis, 1). Patients were neither immunosuppressed nor using immunosuppressive drugs.

Microbiological, serological, routine laboratory and radiological investigations

Serological results were as follows: Rose Bengal test, 91.6% (328/358); SAT, 94% (363/386); Coombs-SAT, 92.9% (91/98). Blood cultures were positive in 36.5% (91/249), bone marrow culture in 63.6% (7/11), urine culture in 1.5% (3/201) and genital discharge culture in 5.9% (2/34). Overall, 56 (54.4%) out of 103 isolates were typed as *Brucella melitensis*, and the remainder reported as *Brucella* spp. The results of routine laboratory analyses and USG findings in patients with genitourinary system brucellosis are presented in Tables 2 and 3, respectively.

Genitourinary and other foci of infection

The most frequent involved site was the scrotal area ($n = 327$, 83.8% of all patients and 93% of male patients), as epididy-

TABLE 2. Laboratory findings of brucellosis cases with genitourinary system involvement on admission ($n = 390$)

	Mean \pm SD	Normal
Leucocyte count ($\times 10^3/\text{L}$)	7530 ± 3115	4000–11 000
Haemoglobin (g/dL)	12.7 ± 1.9	14–18 for men 12–16 for women
Platelet ($\times 10^3/\text{L}$)	$235\ 400 \pm 91\ 606$	150 000–450 000
Erythrocyte sedimentation rate (mm/hr)	35.3 ± 20.7	≤ 15 for men ≤ 20 for women
C-reactive protein (mg/L)	28.2 ± 39.9	0–8
Alanine aminotransferase (IU/L)	53.6 ± 89.5	17–63
Aspartate aminotransferase (IU/L)	51.2 ± 77.2	15–41
Alkaline phosphatase (IU/L) ($n = 271$)	147 ± 115	41–133
Creatine phosphokinase (U/L) ($n = 172$)	168 ± 256	60–400
Lactate dehydrogenase (U/L) ($n = 236$)	332 ± 407	140–280
Blood urea nitrogen (mg/dL) ($n = 360$)	28.7 ± 16.6	7–20
Creatinine (mg/dL) ($n = 360$)	0.80 ± 0.74	0.7–1.2

TABLE 3. The results of ultrasonographic evaluation of patients with genitourinary system brucellosis

Abdominal findings ($n = 271$)	Number	Per cent
Hepatomegaly	82	30.3
Splenomegaly	72	26.6
Peritoneal fluid	11	4.1
Renal involvement (damage)	5	1.8
Abscess	3 ^a	1.1
Others	2 ^b	0.7
Scrotal/genitourinary findings ($n = 348$)		
Inflammation	315	90.5
Oedema	286	82.2
Testicular involvement	279 ^c	80.2
Genital mass	25	7.2
Genital abscess	21	6.0
Others	28 ^d	8.0

^aTubo-ovarian, 1; abdominal, 1; splenic, 1.

^bAbdominal lymphadenopathy, 1; pyonephrosis, 1.

^cRight testicle, 151 (54.1%); left testicle, 90 (33.3%); bilateral, 38 (13.6%).

^dEpididymitis, 17; prostatitis, 3; varicocele, 4; tubo-ovarian abscess, 1; localized fluid, 3.

mo-orchitis ($n = 204$, 58%), orchitis ($n = 112$, 31.8%) and epididymitis ($n = 11$, 3.1%), (Table 4). Clinical, laboratory and radiological evaluations revealed additional brucellar focus or foci in 110 patients (28.2%). The distribution of additional organ involvements were as follows: sacroiliitis, 52 (13.3%); spondylodiscitis, 34 (8.7%); clinical hepatitis, 14 (3.6%) (>5 times upper limit of normal for aminotransferases); peripheral arthritis, 21 (5.4%); meningoencephalitis, 6 (1.5%); others, 9 (2.3%). On the other hand, pyelonephritis in female patients (33/38, 86.8%) was significantly higher than in male patients (11/352, 3.1%) ($p < 0.0001$; OR (95% CI), 204.6 (67–624.7)).

Treatment

Antibiotic combinations were as follows: doxycycline and rifampicin ($n = 229$, 63.6%); doxycycline, rifampicin and an aminoglycoside ($n = 46$, 12.8%); doxycycline and an aminoglycoside ($n = 44$, 12.2%); doxycycline, rifampicin and

TABLE 4. Final clinical diagnosis of genitourinary system brucellosis cases according to gender

Diagnosis	Number	Per cent
Male patients (n = 352)		
Orchitis	112 ^a	31.8
Epididymitis	11 ^b	3.1
Epididymo-orchitis	204 ^c	58
Pyelonephritis	11	3.1
Abscess formation	6 ^d	1.7
Prostatitis	5	1.4
Glomerulonephritis	1	0.3
Female patients (n = 38)		
Pyelonephritis	33	86.8
Glomerulonephritis	2	5.3
Fallopian tube abscess	2	5.3
Tubo-ovarian abscess	1	2.6

^aTesticular abscess (additional diagnosis), 1.
^bUrethritis (additional diagnosis), 1.
^cTesticular abscess (additional diagnosis); 1, prostatitis (additional diagnosis), 1.
^dTesticular abscess, 5; scrotal abscess, 1.

trimethoprim/sulfamethoxazole (n = 13, 3.6%); ceftriaxone, doxycycline and rifampicin (n = 17, 4.7%); doxycycline, rifampicin and ciprofloxacin (n = 16, 4.4%); and others (n = 25, 6.9%). Surgery was performed in nine patients (2.3%) and orchiectomy was performed in six (1.5%) patients. Abscess drainage was performed in two cases (one was in the paravertebral area) and lumbar stabilization was established in one case.

Outcome analysis

Therapeutic failure was recorded in six (1.5%) patients. Failure was recorded when there was worsening of the clinical picture (n = 4), persistence of raised ESR and CRP (n = 1), abscess formation (n = 2) or worsening of USG findings (n = 1). All of these patients except one responded well to antibiotic modifications. A drainage operation was needed in a male patient due to development of a testicular abscess during follow-up. Four (1%) cases relapsed after the end of antibiotic treatment, and infertility related to brucellosis persisted in one patient. Symptoms of genitourinary brucellosis reappeared in two out of four relapsed cases. Patients with solitary genitourinary involvement (n = 279) had a LOS in hospital of 9.6 ± 5.6 (1–30) days for the doxycycline and rifampicin combination, whilst it was 14.1 ± 6.0 (2–30) days for the doxycycline, rifampicin and streptomycin regimen (p 0.001). Six out of 38 (15.8%) female patients were pregnant (6–32 weeks of gestation). Gestation ended with spontaneous abortion in two, preterm labour in one and term birth in three. No death was observed for this cohort.

Comparison of treatment and outcome data for genitourinary system brucellosis patients without other coexistent focal disease and with other involved sites is presented in Table 5. Both the mean treatment duration and LOS in hospital was significantly higher in the presence of additional foci of

TABLE 5. Comparison of genitourinary system brucellosis patients without other coexistent focal disease (group 1) and those with another involved site (group 2)

	Group 1 (n = 279)	Group 2 (n = 111)	p-Value
Mean treatment duration \pm SD, days (range)	47.2 \pm 11.7 (42–90)	63.0 \pm 38.9 (42–240)	<0.0001
Mean LOS \pm SD, days (range)	10.0 \pm 5.7 (1–30)	13.2 \pm 8.5 (1–60)	0.001
Failure, n (%)	4 (1.4)	2 (1.8)	1.0
Relapse, n (%)	3 (1.1)	2 (1.8)	0.626
Surgical intervention (needed), n (%)	6 (2.2) ^a	2 (1.8) ^b	1.0

LOS, length of hospital stay.
^aAll genital surgery.
^bSpinal surgery, 1; orchiectomy, 1.

infection (63 vs. 47.2 days, p < 0.0001 and 13.2 vs. 10 days, p 0.001, respectively).

Discussion

Epididymo-orchitis as a consequence of brucellosis was observed in one-tenth of patients [9]. Genitourinary involvement in human brucellosis raises the possibility of sexual dissemination [23]. Misdiagnosis leading to irrational therapies in this syndrome may result in serious genitourinary complications, including abscess formation [24], infarction [25], atrophy [26], suppurative necrosis [27], failure of spermatogenic function, infertility and testicular loss in a significant portion of cases [28]. In this study, 90% of the patients were male and 93% of them experienced epididymitis and/or orchitis. Female patients were more likely to have pyelonephritis compared with male patients (86.8% vs. 3.1%). However, when the brucellosis cases with pyelonephritis were taken as a whole, one-fourth of the cases were in male patients. Thus, pyelonephritis related to brucellosis is not necessarily a female disease. Added to that, glomerulonephritis was also seen infrequently in both sexes. This datum appeared to be one of the most interesting findings of this study because pyelonephritis has been rarely reported in the past. In fact, nephritis was believed to be a frequent complication of endocarditis in brucellosis patients [29]. However, none of our patients had coexistent endocarditis. Fallopian tube and tubo-ovarian abscesses were seen in 8% of the women affected while prostatitis (1.4%) and testicular/scrotal (1.7%) abscess formation were occasionally recorded in male patients.

Constitutional symptoms related to brucellosis, such as night sweats, fatigue and fever, were seen in more than four-fifths of the cases. The most frequent symptoms for male patients with brucellosis were testicular complaints in 98% of

the cases. Accordingly, the physical examination revealed tenderness, swelling and hyperaemia in more than 80% of these male patients. Other specific findings related to genitourinary system, such as dysuria, haematuria, genital discharge and costovertebral tenderness, were seen in less than one-fourth of all patients in descending order. Thus, the results of this study show that the testes are the primary targets for male patients with brucellosis. Interestingly, when laboratory data were evaluated, the inflammatory markers did not raise much suspicion of an infection. For example, the mean value of white blood cells was within the normal range in this study. There were initial reports from relatively small case series in accordance with this datum [19] and it may help differentiate brucellar disease with genitourinary involvement from other pyogenic infections. Accordingly, we observed mild to moderate increases for erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, liver enzymes and alkaline phosphatase values in our study. Moreover, abdominal findings detected by USG were not decisive. Interestingly, in 4% of the cases a minimal amount of free intraperitoneal fluid, which disappeared with treatment, was detected. This was probably due to lymphatic involvement obstructing the drainage. The most frequent findings were liver and spleen enlargements, observed in less than one-third of the patients. Accordingly, the clinicians recorded hepatomegaly and splenomegaly with manual examination in one-fifth of the cases. In contrast, findings of scrotal USG were associated with epididymitis and/or orchitis in more than 80% of male patients. Unilateral testicular involvement was seen in most of the cases while both testes were involved in 13.6%.

Human brucellosis poses a therapeutic dilemma owing to the intracellular localization of the bacterium within the host's reticuloendothelial cells, a site relatively inaccessible to antibiotics. Therefore, the proper combination of antibiotics for an adequate duration is warranted to improve outcome and prevent relapses [30]. In this study, 1.5% of the patients failed to respond to therapy and required antibiotic modification. Subsequently, the infection was eradicated with modified antibiotic combinations. Accordingly, 7.4% of our cases were relapses of previous brucellosis with an additional 1% of our study patients showing relapse after antibiotic treatment. Half of these clinical relapses experienced genitourinary brucellosis, but responded well to further antibiotic regimens. One of the male patients was reported to experience secondary infertility as a sequela.

In this study, 136 other focal involvements were detected in 110 (28.2%) out of 390 patients with genitourinary brucellosis, most frequently within the skeletal system. In these patients the mean duration of treatment was almost 2 weeks higher. In

addition, LOS was significantly longer in patients with additional brucellar foci. Thus, the treatment of genitourinary brucellosis seems to be hampered by the presence of other focal complications. Although various antibiotic combinations were used in this study, doxycycline and rifampicin was the most common regimen used, and adding streptomycin to this regimen extended LOS from 10 days to 2 weeks on average. This is likely to reflect the reluctance of clinicians to discharge patients until completion of parenteral streptomycin treatment. Therapeutic regimens used in this study generally provided satisfactory results. Additional surgery was performed in nine (2.3%) cases. Orchiectomy, the most frequent procedure, was followed by abscess drainage and lumbar stabilization in a patient with coexistent spondylodiscitis. Early diagnosis with prompt initiation of antibiotics in these patients may decrease the need for surgery as in other forms of brucellosis [31].

Genitourinary brucellosis in female patients is known to be associated with intrauterine infection, foetal death, premature delivery, abortion and low birth weight, particularly within the first and second trimesters [32–34]. In addition, surviving newborns may experience serious sequelae [35,36]. One-sixth of female patients in this study were pregnant and all with gestational ages less than 32 weeks. Half of them experienced a problematic course, two ended with spontaneous abortion and one with preterm labour. Thus, although data seem to be relatively lacking on this issue, early diagnosis and initiation of antibiotics is likely to be of paramount importance for the foetus and newborn in this subgroup of patients [37].

Diagnosis of genitourinary brucellosis requires a detailed history, a meticulous physical examination and a detailed laboratory and radiological evaluation. According to data collated from this largest known case series to date, localized infection related to the testicular area and its surroundings in men or pyelonephritis in women in the absence of leucocytosis and with mild to moderate increases for inflammatory markers should alert clinicians to potential genitourinary brucellosis. Coexistent arthritis or arthralgia and accompanying mild to moderate increases in liver function tests and ALP in a patient with probable genitourinary infection may strengthen the suspicion of brucellosis even in non-endemic areas. The diagnosis supported by microbiological and serological tests should be used to differentiate patients with genitourinary infection.

Transparency Declaration

We declare that we have no conflicts of interest.

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