

ORIGINAL PAPER

Brucella epididymo-orchitis: A single-center experience with a review of the literature

Rawa Bapir^{1,2,3}, Ahmed Mohammed Abdalqadir², Esmaeel Aghaways⁴, Hemn Hussein Bayz⁵, Hiwa O. Abdullah^{1,3}, Shaho F. Ahmed¹, Berun A. Abdalla^{1,3}, Jihad Ibrahim Hama⁶, Bryar Othman Muhammed⁵, Karokh Fadhil Hamahusseini^{1,7}, Farman Mohammed Faraj², Fahmi Hussein Kakamad^{1,3,4}

¹ Smart Health Tower, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq;

² Department of Urology, Sulaimani Surgical Teaching Hospital, Sulaimani, Iraq;

³ Kscien Organization, Hamdi Street, Azadi Mall, Sulaimani, Kurdistan, Iraq;

⁴ College of Medicine, University of Sulaimani, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq;

⁵ Smart Health Tower Raparin, Rania, Sulaimani, Kurdistan, Iraq;

⁶ Research Center, University of Halabja, Halabja, Iraq;

⁷ Kurdistan Center for Gastroenterology and Hepatology, Sulaimani, Kurdistan, Iraq.

Summary *Brucella epididymo-orchitis (BEO) is a rare complication of brucellosis. Despite the high incidence of brucellosis in developing countries, few case series on BEO are available. This study focuses on the clinical presentations, diagnosis, and treatment of BEO with a review of the literature. This study included consecutive BEO patients diagnosed and treated at Smart Health Tower between 2021 and 2023. The required data were retrospectively collected from patients' profiles. The BEO diagnosis was established through scrotal Doppler ultrasound in cases with a positive Rose Bengal test and positive IgG and IgM results for brucellosis, in addition to scrotal pain and swelling. This study included 11 cases whose ages ranged from 22 to 55 years. Most of the cases presented with testicular pain (72.7%), followed by fever (63.6%) and arthralgia (63.6%). The right side (54.5%) was slightly more affected than the left side (45.5%). The major abnormal laboratory finding was an elevated C-reactive protein (82%). The treatment was conservative, in which a combination of gentamicin, doxycycline, and rifampicin was administered to the patients for about 6-8 weeks. One case underwent an orchiectomy due to the abscess formation. All the patients responded well to the treatment, with no recurrence. In the Middle East, brucellosis remains a concerning infectious disease. Early diagnosis, aimed at preventing abscess formation and other complications, takes first priority to avoid invasive interventions.*

KEY WORDS: Brucellosis; Brucella; Orchitis; Genitourinary infection; Orchiectomy; Zoonosis.

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INTRODUCTION

Brucellosis, known as Malta fever, is a zoonotic multiorgan disease caused by infection with *Brucella* species. The major sources of infection are dogs, sheep, cattle, goats, swine, camels, and reindeer. Human infection can occur through direct contact, inhalation of the microbe, consumption of contaminated meat, or ingestion of unpasteurized milk (1, 2). Millions of people globally are at risk

of infection, particularly in developing countries where there is inadequate control over animal infections. While the prevalence of brucellosis in developed countries is currently minimal, isolated cases do arise within occupational cohorts at risk, such as farmers, veterinarians, and laboratory and slaughterhouse personnel (3). Brucellosis is linked to a range of genitourinary infections in males, such as *brucellar epididymo-orchitis* (BEO), cystitis, prostatitis, interstitial nephritis, pyelonephritis, exudative glomerulonephritis, the formation of renal and testicular abscesses, and seminal vesiculitis (3). BEO is an infrequent complication of brucellosis, occurring in 5.7% of cases, and it is commonly unilateral. The prevailing symptoms encompass fever, scrotal pain, and swelling, chills or rigors, malaise, generalized discomfort, fatigue, and headache. The incidence and nature of complications are contingent upon the specific strain of the infecting *Brucella*, the patient's age, and the duration of the illness (1, 3, 4). It typically affects young and middle-aged individuals, and failure to prompt diagnosis or inadequate management can lead to various complications, such as testicular abscess, necrotizing orchitis, atrophy, infarction, suppurative necrosis, infertility, tumor, and aspermia (5, 6).

Furthermore, the disease can mimic testicular tumors and tends to recur more than once, which makes it more challenging (1, 7). Despite the higher incidence and morbidities of brucellosis in developing countries, few case series on BEO are available in the literature (5, 8-13). The current study is a single-center experience focusing on the clinical manifestations, diagnosis, and treatment outcomes of BEO, with a literature review of the published case series. The references have been inspected for credibility based on the most up-to-date criteria (14).

METHODS

Study design

This study was a single-center case series involving con-

secutive BEO patients diagnosed and treated at the urology clinic of *Smart Health Tower* (SHT) between January 2021 and January 2023. Patients provided explicit consent to partake and to authorize the publication of any related data in this study. The study was ethically evaluated by the scientific committee of SHT.

Data collection

After data de-identification, the required data were retrospectively collected from patients' profiles within the urology clinic's database. The extracted information included patient demographics, occupation, clinical presentations, laboratory findings [*erythrocyte sedimentation rate* (ESR), *C-reactive protein* (CRP), complete blood count, liver function tests, *Rose Bengal test* (RBT), anti-*Brucella* antibodies (IgG and IgM) by the *enzyme-linked immunosorbent assay* (ELISA), and urine culture], *ultrasound* (U/S) examination, strategy and outcome of treatment, and follow-up.

Diagnosis strategy

The diagnosis of brucellosis was established based on clinical symptoms consistent with brucellosis, a positive RBT, and positive anti-*Brucella* antibodies (IgG and IgM) on the ELISA. The BEO was diagnosed when patients had pain and swelling of the scrotum with enlarged testicles and/or epididymis during the physical examination. The BEO diagnosis was confirmed by scrotal Doppler U/S in cases with a positive RBT and positive IgG and IgM results for brucellosis. The U/S features of BEO were testicular vascularity, enlargement, non-homogenous echotexture, and heterogeneous or hypoechogenicity.

Eligibility criteria

All the confirmed cases of BEO who were diagnosed and

managed in SHT between 2021 and 2023 were enrolled in this study.

Statistical analysis

The arrangement and coding of the data were performed using Microsoft Excel 2019. For qualitative data analysis (descriptive statistics), the *Statistical Package for the Social Sciences* (SPSS) Version 25 was utilized. The data were presented as means, frequencies, and percentages.

Literature review

Overall, 15 studies with 393 cases were reviewed in this series, of which most were conducted in Turkey (53.3%), followed by Iran (20%) and one study per Kuwait, Saudi Arabia, Greece, and Spain (3-5, 8-13, 15-20). The raw data of each reviewed study is shown in Table 1. The mean age of the cases was 34.5 ± 2.71 , and most of them (76.6%) were at risk of infection as they either had close contact with animals or used raw meat and unpasteurized milk products. The right and left sides were affected nearly equally, and bilateral involvement has been reported in 51 cases (13%). The major reported symptoms were fever (79.4%), pain (77.9%) and swelling (70%) of the testicles or scrotum, and sweating (57%) (Table 2). The three most commonly reported abnormal laboratory findings were high ESR (63%), CRP (57.3%), and WBC (29.8%). In all cases, the diagnosis was primarily based on clinical findings, with confirmatory tests including *Brucella* antigen tests (97.5%), Doppler U/S (63.6%), and positive blood cultures (23.2%). Doppler U/S found 7 cases (1.8%) of testicular abscesses. The majority of cases (95.4%) underwent conservative treatment with antibiotics, while orchiectomy and drainage procedures were conducted in 2.8% and 0.3% of cases, respectively. A good outcome was achieved in 97.7% of patients, whereas nine cases (2.3%) failed to respond to the treatment.

Table 1.
Raw data of each reviewed series on BEO, or *Brucella* orchitis.

Author (year)	Country	No. Case	Risk factors		Age (mean)	Major Symptoms									Symptoms Duration (mean/day)	Affected site			
			Animal contact	RMMPPI		Fever	Chills	TSS	TSP	Sweating	Arthralgia	Dysuria	Anorexia	Headache		R	L	Both	
Alarbid et al (2023) (8)	Kuwait	11	8	0	32.5	10	0	0	0	0	0	0	0	0	0	N/A	N/A	N/A	N/A
Khodadadi et al (2023) (5)	Iran	50	11	15	38.1	32	31	30	45	30	17	0	12	3	11.26	10	14	26	
Gozdas et al (2020) (9)	Turkey	25	14	15	36	16	0	25	25	12	14	4	12	0	20	N/A	N/A	2	
Naz et al (2016) (15)	Turkey	21	14	16	44.6	14	0	13	21	7	10	0	2	0	N/A	10	10	1	
Aydemir et al (2015) (4)	Turkey	6	2	0	39	3	1	4	5	1	2	2	0	0	22*	3	2	1	
Savasci et al (2014) (10)	Turkey	28	N/A	N/A	31	9	8	28	28	10	1	8	8	0	N/A	11	16	1	
Gonen et al (2013) (16)	Turkey	14	6	11	41**	12	0	N/A	N/A	10	4	0	0	0	≤ 30	8	6	0	
Sofian et al (2013) (17)	Iran	40	19	20	40	37	0	N/A	N/A	36	20	13	0	0	≤ 30	12	16	12	
Güneş et al (2010) (18)	Turkey	15	5	10	27	14	3	15	15	12	8	0	0	0	<14>42	9	5	1	
Celen et al (2009) (3)	Turkey	27	2	25	28.2	24	16	21	27	19	20	6	13	10	N/A	N/A	N/A	2	
Roushan et al (2009) (13)	Iran	53	37	4	35.5	43	0	54	54	40	12	0	0	0	29	30	22	1	
Colmenero et al (2007) (19)	Spain	48	9	11	36.6	48	42	48	48	40	0	2	0	0	52.5	21	25	2	
Papatsoris et al (2002) (20)	Greece	17	17	8	30.1	13	0	0	0	0	0	4	0	0	N/A	N/A	N/A	N/A	
Kadikoylu et al (2002) (11)	Turkey	12	12	N/A	30	12	0	12	12	6	0	0	3	0	N/A	N/A	N/A	N/A	
Memish et al (2001) (12)	Saudi Arabia	26	N/A	10	N/A	25	14	26	26	1	6	4	3	4	<14>42	15	9	2	

RMMPPI: Raw meat or milk product ingestion; N/A: non-available; TSS: testicular or scrotal swelling; TSP: testicular or scrotal pain; R: right; L: left; CRP: C-reactive protein; WBC: white blood cell; ESR: erythrocyte sedimentation rate, ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline Phosphatase; U/S: Ultrasound; CSV: conservative; OT: orchiectomy; UNK: unknown.
* The duration is for only 4 cases. ** Median age.

CRP	Abnormal Laboratory findings									Diagnosis tools			Abscess	Treatment			Outcome	Recurrence
	WBC	ESR	ALT	AST	ALP	Anemia	Blood culture	Urine culture	Brucella antigen test	Positive Blood Culture	U/S	CSV		OT	Drainage			
N/A	N/A	N/A	N/A	N/A	N/A	0	11	N/A	11	11	0	0	UNK	UNK	UNK	All Good	0	
30	13	30	15	9	16	0	0	1	50	0	50	0	50	0	0	All Good	0	
22	4	12	12	6	N/A	8	1	N/A	25	1	21	1	25	0	1	All Good	0	
17	3	11	N/A	N/A	N/A	6	8	N/A	21	8	18	0	21	1	0	2 failures	2	
6	2	3	N/A	N/A	N/A	0	2	0	6	2	5	0	6	0	0	All Good	0	
20	18	19	14	11	N/A	1	5	N/A	28	5	28	2	21	7	0	4 failures	0	
14	3	13	8	7	N/A	1	4	0	14	4	1	0	14	0	0	All good	1	
27	10	29	N/A	N/A	N/A	22	N/A	N/A	40	0	0	1	40	0	0	All good	0	
15	6	10	7	8	N/A	1	0	N/A	15	0	0	1	15	1	0	All good	0	
26	10	25	9	8	5	0	10	0	27	10	27	0	27	0	0	All good	1	
N/A	19	41	N/A	N/A	N/A	N/A	8	0	53	8	53	1	53	2	0	6 Failures	1	
48	7	30	N/A	N/A	N/A	N/A	27	0	39	27	18	1	48	0	0	1 Failure	3	
N/A	6	13	N/A	N/A	N/A	N/A	9	0	17	9	17	0	17	0	0	All good	0	
N/A	10	4	N/A	N/A	N/A	0	2	N/A	12	2	12	0	12	0	0	All good	2	
N/A	6	8	N/A	N/A	2	0	4	0	25	4	0	0	26	0	0	All good	1	

During the follow-up periods, which were different for each study, 11 cases (2.8%) of recurrence have been documented (Table 2).

RESULTS

This study included 11 cases whose ages ranged from 22 to 55 years, with a median and mean age of 31 and 35.3 ± 12.12, respectively. More than half of the cases were workers (55%), and the remaining were shepherds (27%), a butcher, and a student. The majority of the cases

presented with testicular pain (72.7%), followed by fever (63.6%), arthralgia (63.6%), sweating (45.5%), and scrotal swelling (45.5%). Regarding the laterality, the right side (54.5%) was slightly more affected than the left side (45.5%). Abnormal laboratory findings were elevated CRP (82%), anemia (27.3%), elevated WBC (18.2%), low WBC (9%), and elevated alanine transaminase (ALT) (9%). In addition, RBT and IgG and IgM antibodies for *Brucella* were positive in all the cases. The treatment strategy was conservative, in which a combination of gentamicin, doxycycline, and rifampicin was administered to all

Table 2. Summary of the published series on BEO, or Brucella orchitis.

Variables	Frequency/Percentage
Country of studies	
Turkey	8 (53.3%)
Iran	3 (20%)
Kuwait	1 (6.7%)
Saudi Arabia	1 (6.7%)
Greece	1 (6.7%)
Spain	1 (6.7%)
Demographic data	
Age (mean of means) ± SD	34.5 ± 2.71
Risk factors	
Contact with animal	156 (39.7%)
Raw meat or milk product ingestion	145 (36.9%)
Affected site	
Right side	129 (32.8%)
Left side	125 (31.8%)
Bilateral	51 (13%)
N/A	124 (31.5%)
Major symptoms*	
Fever	312 (79.4%)
Testicular or scrotal pain	306 (77.9%)
Testicular or scrotal swelling	276 (70%)
Sweating	224 (57%)
Chills	115 (29.3%)
Arthralgia	114 (29%)
Anorexia	53 (13.5)
Dysuria	43 (11%)
Headache	17 (4.3%)

Variables	Frequency/Percentage
Abnormal Laboratory findings*	
High ESR	248 (63%)
High CRP	225 (57.3%)
High WBC	117 (29.8%)
Positive blood culture	91 (23.2%)
High ALT	65 (16.5%)
High AST	49 (12.5%)
High ALP	23 (6%)
Anemia	39 (10%)
Positive urine culture	1 (0.3%)
Diagnostic tools	
Brucella antigen tests	383 (97.5%)
Scrotal Doppler ultrasound	250 (63.6%)
Positive blood culture	91 (23.2%)
Testicular abscess	7 (1.8%)
Treatment	
Conservative (antibiotics)	375 (95.4%)
Orchiectomy	11 (2.8%)
Drainage	1 (0.3%)
Unknown	11 (2.8%)
Outcome	
Good	384 (97.7%)
Failure	9 (2.3%)
Follow-up	
Recurrence	11 (2.8%)

*Other symptoms and laboratory findings have been reported in the reviewed studies, but this study reviewed the most common of them.

Table 3.
Baseline characteristics of the BEO patients.

Variables	Frequency/Percentage
Demographics	
Age range (median, mean \pm SD), years	20-55 (31, 35.3 \pm 12.12)
Occupation	
Worker	6 (55%)
Shepherd	3 (27%)
Butcher	1 (9%)
Student	1 (9%)
Clinical presentations	
Testicular pain	8 (72.7%)
Fever	7 (63.6%)
Arthralgia	7 (63.6%)
Sweating	5 (45.5%)
Scrotal swelling	5 (45.5%)
Right	3 (27.3%)
Left	2 (18.2%)
Splenomegaly	4 (36.4%)
Chills	4 (36.4%)
Affected site	
Right Side	6 (54.5%)
Left Side	5 (45.5%)
Laboratory findings	
Elevated CRP (> 5 mg/dL)	9 (82%)
Anemia (< 13 g/dL)	3 (27.3%)
Elevated WBC (> 11000)	2 (18.2%)
low WBC (< 4000)	1 (9%)
Elevated ALT (> 50 IU/L)	1 (9%)
Positive Rose Bengal test	11 (100%)
Positive IgG and IgM for Brucella	11 (100%)
Ultrasonography findings	
Vascularity	10 (91%)
Testicular enlargement	7 (63.6%)
Heterogenous texture	6 (54.5%)
Heterogenous echogenicity	4 (36.4%)
Unretrieved	1 (9%)
Diagnosis	
Epididymo-orchitis	6 (54.5%)
Orchitis	5 (45.5%)
Treatment therapy (Duration)	
Gentamicin + Doxycycline + Rifampicin (6-8 w)	11 (100%)
Secondary treatment	
Orchiectomy	1 (9%)

the cases for about 6-8 weeks (Table 3). One case underwent orchiectomy as a secondary treatment due to the abscess formation. All the patients responded well to the treatment. After more than 2 years of follow-up for the first case and one year for the newest case, no recurrence has yet been reported.

DISCUSSION

Brucellosis represents an endemic multisystemic infectious disease within specific geographical areas such as the Middle East, the Arabian Peninsula, the Mediterranean region, and India. Its prevalence is significantly greater in rural environments in comparison to urban settings (1). The disease is commonly reported in developing countries; however, it can also be seen in developed countries due to immigration and travel (19). It has been reported that the preponderance of the cases is affected during the spring and summer, which may be caused by consuming milk

products and fresh cheese more commonly in the spring (3). The review of the literature revealed that the majority of the cases were reported in Turkey, followed by Iran, which supported the previous claim. In addition, two reviewed studies were conducted in developed countries like Greece and Spain (19, 20). The major risk factors for BEO are direct contact with animals, inhalation of infectious aerosols, and ingestion of raw meat or unpasteurized milk products (1, 7). Among the 393 reviewed cases, 76.6% were at risk of infection (3-5, 8-13, 15-20). In the present study, three cases were shepherds and one was a butcher, whereas for the remaining seven cases, it was unknown whether they had a risk factor for infection or not.

Scholars reported a higher susceptibility to infection among young males. *Savasci et al.* conducted a retrospective analysis of 28 cases of BEO, revealing that the majority of cases occurred between the second and third decades of life, with an average age of 31 years (10). In accordance with that finding, the mean ages of the reviewed and present cases were 34.5 and 35.3 years, respectively. This raises a noteworthy concern, as brucellosis could potentially exert adverse effects on the reproductive outcomes of sexually active young adults (9).

In around 20-40% of cases, *Brucella* orchitis is considered to stem directly from epididymitis (1). A study by *Baykan et al.* found that approximately 67% of 24 male cases showed involvement of both the epididymis and testes (21). While *Celen et al.* reported a bilateral testis involvement rate of less than 10%, *Baykan et al.* recorded a relatively higher rate of 21% (3, 21). The bilateral involvement in the reviewed literature was 13%, which is more compatible with *Celen et al.* than *Baykan et al.* In the present series, there was no bilateral involvement, and epididymo-orchitis was found in about 55% of the cases.

In general, BEO patients have acute symptoms for about two weeks at the time of presentation (22). The primary manifestations of brucellosis can be fever, chills, sweating, nausea, vomiting, myalgia, arthritis, and osteoarticular involvement. In addition to previous symptoms, scrotal pain and swelling may be indicators of BEO (1). Among the 15 reviewed studies, the prevalent reported symptoms were fever (79.4%), scrotal pain (77.9%), scrotal swelling (70%), and sweating (57%). In line with the literature, the most common presentations in our cases were testicular pain (72.7%), fever (63.6%), arthralgia (63.6%), sweating (45.5%), and scrotal swelling (45.5%).

Regarding the incidence of BEO in patients with brucellosis, it has been reported to occur in 2% to 20% of the cases (1). In their study, *Celen et al.* documented 27 (18.8%) cases of BEO within a cohort of 143 patients with brucellosis. Meanwhile, *Papatsoris et al.* identified 25 (2.5%) BEO cases among a group of 995 cases with brucellosis (3, 20). To distinguish BEO from non-specific epididymo-orchitis, several factors have been reported to be considered, such as animal contact history, consumption of raw milk or cheese, gradual onset, extended duration, distinctive undulant fever, mild local inflammation, and the lack of lower urinary tract symptoms alongside insignificant leukocytosis (22). On the contrary, *Celen et al.* mentioned WBC as an important indicator of BEO (3). All the cases in the reviewed studies and in the present study had more than one of the distinguishing factors.

A high WBC was reported in 29.8% of the reviewed cases and 18.2% of the present cases, which may not support the observation of *Celen et al.* (3).

Distinguishing between BEO and non-specific epididymo-orchitis is crucial, as treatment delay raises the chance of contralateral involvement, tissue necrosis, and systemic symptoms. Thus, in regions where brucellosis is endemic, having a suspicion alone justifies commencing therapy while waiting for definitive lab test results (8, 21). Another challenge in the diagnosis of BEO is mimicking the disease as a testicular tumor, epididymitis, trauma, hematocele, or torsion of the testis (1, 4). *Aydemir et al.* reported a case of BEO that was diagnosed as a testicular tumor based on a U/S examination and later confirmed to be BEO by conducting tumor markers, *magnetic resonance imaging* (MRI), and tube agglutination tests. In another study, *Bapir et al.* (1) reported a misdiagnosed case of BEO that appeared as a tumor in both Doppler U/S and MRI. Then, the diagnosis was corrected using tumor markers and an RBT test.

The diagnosis of *Brucella* orchitis can be established by considering a combination of serology, ultrasonography, and the existence of typical symptoms such as fever, testicular pain, enlargement, and inflammation (1). The primary diagnostic approach for brucellosis is the serum agglutination test, and a positive result is defined as a titer ratio exceeding 1:160 when accompanied by distinct clinical symptoms. Nevertheless, in cases of prolonged brucellosis, agglutination test titers might be absent or below 1:160 (1). In such instances, the disease can be detected better by using other serologic tests like Coombs' anti-Brucella test, immunocapture agglutination test, 2-mercaptoethanol agglutination test, or ELISA, as the immune response to the infection causes an initial increase in IgM antibodies followed by a switch to increasing IgG antibodies within a few weeks of infection (19). In total, 97.5% of the cases in the reviewed studies were diagnosed based on the various *Brucella* antigen tests. Due to the mentioned drawback of the serum agglutination test, all the cases in the present study were diagnosed by RBT and ELISA tests.

Abnormal blood investigation findings are often mild and not very specific. Prolonged infection might cause a slight drop in hemoglobin levels, and a moderate increase in ESR is commonly seen. Liver function tests may show a mild to moderate elevation in ALT and *aspartate aminotransferase* (AST) levels. A high CRP level is a noteworthy finding in most cases (3, 17). *Colmenero et al.* reported a positive blood culture in 65.8% of patients with brucellosis and stated the necessity of the method in diagnosing brucellosis. Furthermore, the positivity of blood culture in BEO cases has been reported to be 53-69% (22). The most significant laboratory findings in the reviewed studies were positive *Brucella* antigen tests (97.5%), high ESR (63%), and CRP (57.3%). In contrast to the previous findings, the blood culture was positive in only 23.2% of the 393 reviewed cases. In the present study, an elevated CRP was the dominant finding (82%), after positive RBT (100%) and ELISA (100%). No blood culture was conducted in this study because the diagnosis of brucellosis was based on RBT and ELISA.

Ultrasonography is usually vital for excluding the suspicion of an abscess or tumor rather than confirming the primary diagnosis. The frequent U/S features of BEO are tes-

ticular enlargement, hypervascularity, inhomogeneous echotexture, and heterogeneous or hypoechoic echogenicity. These features can also be seen in other etiologies of orchitis. Thus, the U/S examination cannot be relied on solely for the diagnosis of BEO (1, 9). All these features could be seen in the U/S examination of our cases, of which vascularity was the most prevalent finding (91%). It has been indicated that using medications like rifampicin, streptomycin, tetracycline, ciprofloxacin, doxycycline, and cotrimoxazole for at least six weeks has a significant impact on managing brucellosis (1). A suggested approach involves taking a daily combination of doxycycline (200 mg) and rifampicin (600 mg) for around six weeks. It's worth noting that using a single drug for treatment has a higher likelihood of failure compared to using a combination, so medical treatment should involve the use of two or three antibiotics together (1, 10, 21). The rate of treatment failure and the requirement for orchiectomy have been reported to vary from 0% to 40% and from 0% to 5.1%, respectively.

In accordance, the rates of treatment failure, recurrence, and orchiectomy among the reviewed cases were 2.3%, 2.8%, and 2.8% consecutively. All patients in this series were treated with antibiotic combinations. One orchiectomy (9%) was conducted due to abscess formation, and no recurrence was reported during the follow-up period.

CONCLUSIONS

In developing countries, especially in the Middle East, brucellosis remains a concerning infectious disease. As it is commonly diagnosed in young adults, it may have unfavorable effects on the reproductive activity of this group. An early diagnosis to prevent abscess formation and other complications is the first priority to avoid invasive interventions. RBT and ELISA, in addition to clinical presentations, may be sufficient for diagnosis.

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Correspondence

Rawa Bapir, MD

Dr.rawa@yahoo.com

Hiwa Abdullah, MD

hiewaom96@gmail.com

Shaho Ahmed, MD

shahomedi87@gmail.com

Berun Abdalla, MD

berun.anwer95@gmail.com

Smart Health Tower, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq

Esmael Aghaways, MD

esmael.aghaways@gmail.com

College of Medicine, University of Sulaimani, Madam Mitterrand Street,

Sulaimani, Kurdistan, Iraq

Hemn Bayz, MD

hemn.bayz@gmail.com

Smart Health Tower Raparin, Karux Str, Rania, Sulaimani, Kurdistan, Iraq

Jihad Hama, MD

jihad.hama@gmail.com

Bryar Muhammed, MD

bryar.muhammed@gmail.com

Research Center, University of Halabja, Halabja, Iraq

Karokh Hamahusseini, MD

karokh12@gmail.com

Kurdistan Center for Gastroenterology and Hepatology, Sulaimani, Kurdistan, Iraq

Farman Faraj, MD

farman.faraj@gmail.com

Ahmed Abdalqadir, MD

ahmed.abdalqadir@gmail.com

Department of Urology, Sulaimani Surgical Teaching Hospital, Sulaimani, Iraq

Fahmi Hussein Kakamad, MD (Corresponding Author)

fahmi.hussein@univsul.edu.iq

College of Medicine, University of Sulaimani

Doctor City, Building 11, Apartment 50

Madam Mitterrand Street, HC8V+F66, 46000 Sulaymaniyah, Kurdistan, Iraq

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