

The clinical and laboratory characteristics, treatments, and outcomes of patients with *Brucella* epididymo-orchitis (BEO) compared to those without BEO*

Hasan NAZ^{1**}, Pınar KORKMAZ², Figen ÇEVİK², Nevil AYKIN²

¹Department of Clinical Microbiology and Infectious Diseases, Kocaeli State Hospital, Kocaeli, Turkey

²Department of Clinical Microbiology and Infectious Diseases, Eskişehir Yunus Emre State Hospital, Eskişehir, Turkey

Received: 08.06.2014 • Accepted/Published Online: 22.11.2015 • Final Version: 17.11.2016

Background/aim: We aim to describe the clinical and laboratory characteristics, treatment, and outcomes of 21 patients with *Brucella* epididymo-orchitis (BEO) from Eskişehir Yunus Emre State Hospital, Turkey.

Materials and methods: A total of 21 patients with BEO who were diagnosed and followed in the Infectious Diseases Clinic between June 2001 and June 2013 were evaluated retrospectively.

Results: One hundred and twenty-eight of 192 patients evaluated throughout the study were male and BEO was determined in 21 (16.4%) patients. A total of 18 (85.7%) patients had a titer of $\geq 1:160$ in standard agglutination test (STA). Three patients with STA < 160 were diagnosed by blood culture. When all the male patients were evaluated in terms of demographic, clinical, and laboratory findings, animal contact, rural living, and subacute clinical type were statistically significantly higher in the group that developed epididymo-orchitis. None of the patients underwent surgery after medical treatment, but due to a delay in diagnosis of brucellosis, orchiectomy was performed in 1 patient with the suspicion of tumor.

Conclusion: In endemic countries like Turkey, BEO should be considered in the differential diagnosis of epididymo-orchitis. In uncomplicated patients, medical treatment is adequate for BEO.

Key words: Brucellosis, epididymo-orchitis, medical treatment, ciprofloxacin

1. Introduction

Brucellosis is a frequently encountered zoonosis in various regions of the world, including the Mediterranean region (1). The number of reported cases each year is about 500,000, but this number is lower than the real incidence (2). It is endemic in some regions of Turkey, especially in the Central Anatolian region (3). Although the mortality from brucellosis is low, the disease continues to be a major public health problem because of the high morbidity (4).

The disease usually presents as fever with no apparent focus, although focal forms are present in 20% to 40% of cases (5). The reproductive system is the second most common site of focal brucellosis. Brucellosis can present as epididymo-orchitis (EO) in men and it is often difficult to differentiate brucellosis from other local diseases (6).

In our study, we aimed to describe the clinical and laboratory characteristics, treatment, and final outcomes of 21 patients with *Brucella* epididymo-orchitis (BEO) from our hospital in Turkey.

2. Materials and methods

A total of 21 patients with EO due to brucellosis, who were diagnosed between June 2001 and June 2013 and treated at Eskişehir Yunus Emre State Hospital, located in the city of Eskişehir in the Central Anatolia region of Turkey, were evaluated retrospectively. The history, physical examination, routine laboratory, and microbiology and radiology test results were evaluated.

Diagnosis was made by clinical symptoms together with the following laboratory test results: titer of $\geq 1:160$ in the standard tube agglutination test (STA), and/or isolation of *Brucella* species from blood and other bodily fluids or tissues. Patients with a titer of $\geq 1:160$ in the STA, and those with lower titers but showing a 4-fold increase in 2 weeks' time, were considered to be positive. *Brucella abortus* antigens were used in the STA test. Rose-Bengal test (RBT) positivity was checked twice with the STA test.

For the cultures, a standard blood culture system consisting of biphasic brain-heart infusion medium was

* This study was presented in part at the 3rd Eurasia Congress of Infectious Diseases, Baku, Azerbaijan, 1-4 October, Abstract No. 199.

** Correspondence: hasannaz73@mytel.com

used until 2006. The BACTEC 9050 and BacT/Alert 3D Mériex automated blood culture systems were used until 2008 and 2009, respectively.

Among the patients with brucellosis, the diagnosis of EO was based on clinical findings (scrotal swelling, pain, or tenderness) and/or ultrasonographic examination.

Therapeutic failure was considered to be the persistence or worsening of the symptoms or signs of the disease after 1 month of treatment. Relapse was defined as reappearance of symptoms or signs of the disease (as assessed by the patient's physician), or a new positive blood culture result obtained after the end of therapy.

Cases with symptom duration of less than 8 weeks were considered to be acute, the ones between 8 and 52 weeks to be subacute, and the ones that lasted more than 1 year to be chronic (7).

Dual or triple combinations of doxycycline, rifampicin, streptomycin, ciprofloxacin, and gentamicin were used in the treatment. Streptomycin was administered for 3 weeks, gentamicin for 10 days, and doxycycline, rifampicin, and ciprofloxacin for 6 or 12 weeks based on clinical response and development of complications.

The chi-square test was used to compare the qualitative variables. Student's t-test or the Mann-Whitney U test were used to compare the quantitative variables. Statistical analysis was performed using SPSS 13.0.

3. Results

One hundred and twenty-eight out of 192 patients evaluated throughout the study were males (66.7%) and EO was detected in 21 (16.4%) cases. The mean age of the patients with BEO was 44.6 ± 16.2 years (range: 18–81 years). While 15 of these patients (71.4%) lived in a rural region, 6 of them lived in a urban region (28.6%). Fourteen had (66.7%) had occupational exposure history, 16 (76.2%) had history of consumption of unpasteurized milk and dairy products, and 3 (14.3%) had brucellosis history in their families. Thirteen (61.9%), 7 (33.3%), and 1 (4.8%) of the patients had acute, subacute, and chronic brucellosis, respectively (Table 1).

The most frequent complaints were scrotal pain in 21 patients (100%), malaise in 13 patients (61.9%), arthralgia in 10 patients (47.6%), lumbar pain in 8 patients (38%), sweating in 7 patients (33.3%), myalgia in 6 patients

Table 1. Characteristics and laboratory findings of 128 male patients with brucellosis with or without EO.

	EO n = 21 (%)	Without EO n = 107 (%)	P
Age, years (mean \pm SD)	44.6 \pm 16.2	46.4 \pm 16.7	0.643
Unpasteurized milk and products	16 (76.2)	59 (55.1)	0.122
Rural area	15 (71.4)	43 (40.2)	0.017*
Occupational exposure	14 (66.7)	40 (37.4)	0.025*
Positive family history	3 (14.3)	17 (15.9)	1.000
Clinical type			
Acute	13 (61.9)	89 (83.2)	0.023*
Subacute	7 (33.3)	11 (10.3)	
Chronic	1 (4.8)	7 (6.5)	0.431
Hepatomegaly	7 (33.3)	24 (22.4)	1.000
Splenomegaly	1 (4.8)	9 (8.4)	0.428
ESR (>20 mm/h)	11 (52.4)	43 (40.2)	0.201
Anemia	6 (28.6)	16 (14.9)	1.000
Leukocytosis	3 (14.3)	17 (15.9)	1.000
Leukopenia	1 (4.8)	9 (8.4)	0.082
Thrombocytosis	4 (19)	7 (6.5)	1.000
Thrombocytopenia	3 (14.3)	16 (14.9)	0.409
STA (median, range)	160 (0–1280)	160 (160–1280)	0.737
Relapse	2 (9.5)	17 (15.8)	0.255
Therapeutic failure	2 (9.5)	4 (3.7)	

*Significant.

(28.6%), nausea in 2 patients (9.5%), anorexia in 2 patients (9.5%), and weight loss in 2 patients (9.5%). The most frequent physical signs were fever in 14 patients (66.7%), scrotal swelling in 13 patients (61.9%), hepatomegaly in 7 patients (33.3%), and splenomegaly in 1 patient (4.8%). C-reactive protein (CRP) level was studied in 18 patients. The most frequent laboratory findings were CRP elevation in 17/18 cases (94.4%), elevated erythrocyte sedimentation rate (ESR) in 11 cases (52.4%), anemia in 6 cases (28.6%), thrombocytosis in 4 cases (19%), thrombocytopenia in 3 cases (14.3%), leukocytosis in 3 cases (14.3%), and leukopenia 1 case (4.8%). Seven out of 21 patients with EO (33.3%) had other complications including peripheral arthritis, discitis, pyelonephritis, hepatitis, and rash (Table 1).

When the male patients with or without EO were examined in terms of demographic, clinical, and laboratory findings, rural living, occupational exposure, and subacute clinical type were statistically significantly higher in the group that developed EO. Characteristics and laboratory

findings of 128 male patients with brucellosis with or without EO are given in Table 1.

The RBT was positive in all cases. Reproduction was determined in 8 of 15 patients from whom blood samples for culture were collected. Three patients with STA of <160 were diagnosed by blood culture. BEO was diagnosed by clinical and physical examination in 3 patients (14.3%) and by scrotal ultrasonography (USG) and/or color Doppler ultrasonography in 18 patients (85.7%). In USG, focal hypoechoic testicular area(s) were detected in 16 patients, testicular heterogeneity in 13 patients, increased testicular vascularization in 11 patients, enlargement of epididymis and/or testis in 10 patients, and hydrocele in 2 patients.

Orchiectomy was performed for suspected malignancy after USG in patient number 16 (Table 2), who presented to the urology clinic with a complaint of scrotal swelling. This patient was diagnosed with granulomatous orchitis after pathological examination. Tumor markers were negative. After 1 month, the patient presented with a complaint of scrotal swelling in the other testicle. RBT was found to be

Table 2. Characteristics of patients with BEO.

	Clinical type	Localization	Other complications	Blood culture	STA	Therapy	Outcome
1 (57)	Acute	Bilateral EO	Pyelonephritis		1/160	DR	Cure
2 (27)	Chronic	Left EO	Polyarthritis		1/320	DSC	Cure
3 (20)	Acute	Left EO	Rash		1/160	DR	Cure
4 (52)	Subacute	Right orchitis	Monoarthritis	-	1/160	DR	Relapse
5 (81)	Subacute	Right EO	-	-	1/1280	DR	TF
6 (65)	Acute	Left EO	-	-	1/160	CR	Cure
7 (40)	Acute	Right orchitis	-	-	1/160	DR	Cure
8 (30)	Acute	Left EO	-	-	1/320	DG	Cure
9 (46)	Subacute	Right EO	-	+	1/320	CR	Cure
10 (56)	Acute	Right orchitis	-	+	1/160	DG	Cure
11 (34)	Acute	Right EO	Hepatitis	+	1/640	CR	Cure
12 (47)	Subacute	Left EO	-	+	1/320	DC	TF
13 (27)	Subacute	Left orchitis	Discitis	-	1/320	DR	Relapse
14 (36)	Acute	Left orchitis	Monoarthritis	+	1/320	CR	Cure
15 (46)	Subacute	Left EO	-	-	1/160	DR	Cure
16 (38)	Subacute	Right EO	-	+	1/80	CR	Cure
17 (57)	Acute	Right EO	-	+	Negative	DR	Cure
18 (39)	Acute	Left orchitis	-	+	1/80	DR	Cure
19 (58)	Acute	Right orchitis	-	-	1/320	DR	Cure
20 (55)	Acute	Right orchitis	-	-	1/640	DG	Cure
21 (18)	Acute	Left EO	-	-	1/160	DS	Cure

TF: Therapeutic failure.

D: Doxycycline, R: rifampicin, S: streptomycin, C: ciprofloxacin, G: gentamicin.

positive and the STA test was positive with a titer of 1/80. *Brucella* spp. developed in the blood culture of the patient, who was suspected for malignancy in the other testicle in USG. A 90-day rifampicin + ciprofloxacin therapy was completed with full recovery. Patients numbers 17 and 18 (Table 2) were followed for nonspecific epididymo-orchitis (NEO) and were diagnosed with *Brucella* spp. reproduction in blood culture, while STA values were negative (titer <1/80). Characteristics of patients with BEO are given in Table 2.

The most frequently used antibiotic combinations were: doxycycline + rifampicin (10 patients), rifampicin + ciprofloxacin (5 patients), doxycycline + gentamicin (3 patients), doxycycline + streptomycin (1 patient), doxycycline + ciprofloxacin (1 patient), and doxycycline + streptomycin + ciprofloxacin (1 patient). While 2 patients (9.5%) suffered a relapse after medical treatment, 2 (9.5%) suffered therapeutic failure. Full recovery was achieved with altered treatment. None of the patients underwent surgery after medical treatment. In one patient, due to the delay in the diagnosis of brucellosis, orchiectomy was performed with the suspicion of tumor. There was no mortality.

4. Discussion

Brucellosis is a multisystemic infectious disease, which can involve many organs and tissues (8). EO is the most frequent genitourinary complication, affecting 2% to 20% of males with brucellosis (9). A rate of EO as high as 16.4% was detected in our study.

Brucellosis is more frequently encountered in the rural areas (10–13). In studies in which BEO cases were examined, living in rural areas, the use of nonpasteurized milk and dairy products, and occupational exposure were reported as 31.3%–76.5%, 22.9%–88.2%, and 38.3%–94.1% respectively (9,14–16). In our study, living in rural areas and occupational exposure were found to be statistically significantly higher in the cases of EO. Bosilkovski et al. reported that urogenital manifestations were frequently observed in the occupational exposure group, similarly to our study (17).

In larger studies that involve both EO and all focal manifestations, acute brucellosis was observed most frequently (9,13–16,18). While the acute form was most frequently observed in our patients, the subacute form was statistically higher in the patients with EO. This may be contingent on the insidious progress of the disease and late diagnosis.

In patients with BEO, leukocytosis is reported in 10%–84.6% of cases, and elevated ESR is reported in 31%–98% of cases (9,14–16,19–22). In our study, leukocytosis and elevation of ESR were seen to be higher in patients with EO, similar to the findings of Akinci et al. (16). Ibrahim

et al. found leukocytosis and elevation of the ESR to be much higher in patients with NEO than in patients with BEO (19).

No reproduction was detected by standard urine culture in larger studies examining BEO cases (9,14–16,19,20). Standard urine culture was generally used to exclude the existence of other microorganisms (14). In BEO cases, blood culture reproduction was reported at a rate of 14%–69% (9,14–16,20–23). A high rate of reproduction, as much as 53.3%, was determined in our patients. Although serological test results can be negative, reproduction can be detected in blood cultures of patients (8,14,15). While 3 patients could not be diagnosed through serological methods, they could be diagnosed by blood culture.

USG is a valuable method for ruling out noninfectious causes and diagnosing BEO (14,24,25). In a comparison study performed by Öztürk et al. on 28 patients with BEO and 28 patients with NEO using gray-scale and color Doppler USG, internal echo, scrotal skin thickness, testicular heterogeneity, and focal hypoechoic testicular area(s) findings were statistically significantly higher in patients with BEO (24). Similarly, focal hypoechoic testicular area(s) and testicular heterogeneity were the most frequent findings in our cases.

Either the combination of doxycycline and rifampicin for 6 weeks or the combination of doxycycline (for 6 weeks) and streptomycin (for 2 or 3 weeks) is recommended for the treatment of brucellosis (26). We determined that the use of combinations including doxycycline, rifampicin, and ciprofloxacin was higher in our cases. We thought that this would be reliant on the desire to avoid side effects like ototoxicity and nephrotoxicity, and to maintain NEO treatment initiated prior to BEO diagnosis.

Ciprofloxacin is not recommended as the first-line option (26) in the treatment of brucellosis. However, considering the fact that it passes into the ejaculate and seminal fluid 7–10 times more than the plasma concentration (27), we consider that it will be a good alternative in BEO cases. In combinations containing ciprofloxacin, apart from one (14.3%) treatment failure, all patients were fully cured, but we think that more comprehensive prospective studies are required.

In BEO treatment, medical treatment alone is generally sufficient (9,19,20,28–30). Orchiectomy may be rarely required in the presence of findings suggesting abscess or necrotizing orchitis (13,15). However, a cure may be achieved with medical treatment and drainage of abscess may be sufficient suggesting abscess in USG (9,28). Some studies reported that some of the BEO patients had undergone orchiectomy for suspected tumors (31–33).

In the study performed by Navarro-Martinez et al., treatment inadequacy and relapse were observed at rates as high as 15% and 25%, respectively, while relapse rates

were reported to be between 0% and 8.8%, similar to our study (9,14–16,20,23,34). Cure was achieved after the second treatment in our patients that experienced treatment inadequacy and relapse.

In endemic countries, BEO should be kept in mind and microbiological tests should be considered in the

differential diagnosis of patients living in rural regions and engaged in stockbreeding who have complaints of scrotal swelling and pain. In uncomplicated BEO cases, medical treatment is sufficient alone. We consider combinations containing ciprofloxacin to be a good alternative in BEO cases.

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