MAJOR ARTICLE

Epididymoorchitis Due to *Brucella mellitensis:* A Retrospective Study of 59 Patients

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Epididymoorchitis is a focal form of human brucellosis described in 2%–20% of patients with brucellosis. We assessed 59 cases of *Brucella* epididymoorchitis (BEO) between 1991 and 1999. The median age of patients was 34 years (range, 15–75 years). The onset of symptoms was acute in 46 patients (78%). Scrotal pain and swelling (100% of patients), fever (88%), and sweating (73%) were the most common symptoms. *Brucella* species was isolated from blood cultures in 41 patients (69%) and from epididymal aspiration in 4 patients. Treatment consisted of a combination of a doxycycline and an aminoglycoside ($n = 39$) or rifampin ($n = 10$); trimethoprim-sulfamethoxazole with rifampin ($n = 3$); or trimethoprim-sulfamethoxazole as monotherapy ($n = 7$). The median duration of therapy was 45 days (range, 21–90 days). The infections of 9 patients (15%) failed to respond to therapy, and 15 patients relapsed (25%). Three patients with necrotizing orchitis whose infections were unresponsive to antibiotics required an orchiectomy. In general, classical brucellosis therapy is adequate for BEO.

Brucellosis is an endemic enzootic disease [1] that can involve many organs and tissues [2]. *Brucella* epididymoorchitis (BEO) is a focal complication of the human brucellosis and has been described in 2%–20% of patients with brucellosis [3–9] (6% in our preliminary study) [4]. BEO can cause serious complications such as necrotizing orchitis, and therefore it must be considered in the differential diagnosis of acute scrotum in endemic areas [3, 4, 10–17]. However, genitourinary complications of brucellosis have rarely been documented in the medical literature; the number of published articles describing cases of BEO is scarce [3, 4, 10–13] (MEDLINE 1966–2000, Indice Médico Español 1971–1999).

In the present study, we describe the clinical characteristics, treatment, and final outcomes of 59 patients with BEO from 3 Spanish hospitals. To provide a comprehensive description of this entity, we discuss our results in light of the results of other series of cases that have been reported in medical literature [3, 4, 10–13]. To our knowledge, this is the largest series of BEO described to date.

PATIENTS AND METHODS

Study population. Between 1991 and 1999, a total of 59 cases of epididymoorchitis due to *Brucella mellitensis* were diagnosed and followed up prospectively at hospitals in Albacete, Hellin, and Bellvitge, located in Spain. In this country, the incidence of brucellosis was 27.73–18.24 cases per 100,000 inhabitants during the period 1991–1997 [1].

The diagnosis of brucellosis was made by isolating *Brucella* species from blood culture or epididymal aspiration or by standard tube agglutination testing, re-

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Table 1. Other focal diseases present in 59 patients with brucellar epididymoorchitis.

Focal disease	Patients, no. (%)
Osteoarticular involvement	25 (42)
Sacroiliitis	8 (14)
Tenosynovitis	8 (14)
Spondylitis	6 (10)
Peripheral arthritis	5 (8)
Coxitis	2 (3)
Bursitis	1 (2)
Prostatitis	3 (5)
Granulomatous hepatitis	3 (5)

NOTE. Some patients had >1 focal disease.

vealing a titer of antibodies to *Brucella* of ⩾1:160 in addition to compatible clinical findings (e.g., orchitis and fever, sweating, arthralgia, hepatomegaly, splenomegaly, signs of focal disease). The diagnosis of epididymoorchitis was based on clinical symptoms, and orchitis was defined as the finding of scrotal pain and swelling [18].

Clinical assessment and definitions. All patients were assessed prospectively according to the protocol described in our reports elsewhere [19–22]. This protocol included demographic, clinical, and laboratory data. Ultrasonography and other diagnostic imaging studies were performed according to the symptoms of the patients. The patients were assessed initially, on days 7 and 45, and at the end of therapy. At the end of therapy, patients were reassessed (as outpatients) at months 1, 2, 3, 6, 9, and 12 and annually thereafter, as well as whenever clinical symptoms reappeared.

Patients were classified into 3 groups according to the clinical outcome of brucellar orchitis: (1) patients who recovered and who at the end of the follow-up did not have any symptoms or signs of infection; (2) those whose infections failed to respond to therapy who continuously had symptoms or signs that suggested persistent infection after 45 days of treatment; and (3) patients who had initially recovered after treatment but experienced clinical relapse. Histologic findings are described in 2 patients who required orchiectomy

Microbiologic studies. Standard tube agglutination testing, the rose bengal test, and the Coombs test for antibodies to *Brucella* species were performed according to standard methods [23] with commercial reagents (Knickerbocker). Blood cultures were performed, as reported elsewhere [23], and incubated for 30 days; BACTEC NR 730 or BACTEC 950 (Becton Dickinson) was used. All isolates were identified as recommended by Hausler et al. [24]. The isolated strains were sent to a reference center (Laboratorio Regional de Brucelosis, Valladolid, Spain) for confirmation and biotyping. All *Brucella* isolates were identified as *Brucella melitensis.*

Statistical analysis. The χ^2 test, Fisher's exact test, *t* test, and Wilcoxon–Mann-Whitney rank-sum test were used as necessary [25]. Two-tailed *P* values were calculated; $P < .05$ was considered statistically significant. Calculations were performed with the statistical package Epi Info, version 6 [26].

RESULTS

Demographic characteristics. The median age of patients was 34 years (range, 15–75 years). A total of 24 patients (41%) lived in rural areas; 49 (83%) had consumed unpasteurized dairy products, which is a risk factor for brucellosis, and 24 (41%) presented occupational exposure.

Presentation of symptoms and signs. The onset of symptoms was acute (⩽30 days) in 46 patients (78%) and subacute or chronic (>30 days) in 13 patients (22%). The time from onset of symptoms to diagnosis of epididymoorchitis was 3–365 days (median, 30 days). For 25 patients (42%), the diagnosis of brucellosis and orchitis were made almost simultaneously (within 2 weeks of each other). In these 25 patients, the disease process was more acute (the time from onset of symptoms to diagnosis was 3–120 days; median, 21 days). Twelve patients (20%) were diagnosed with brucellosis and at least 2 weeks later were also diagnosed with orchitis. Twenty-two patients (37%) were diagnosed with orchitis 0.5–12 months before they were diagnosed with brucellar orchitis.

We found different focal diseases other than the epididymoorchitis in 25 patients (42%; table 1). The symptoms reported at presentation are shown in table 2. None of the patients was asymptomatic. Scrotal pain and swelling, fever, and sweat-

Table 2. Specific signs and symptoms of 59 patients with brucellar epididymoorchitis.

Finding	Patients, no. (%)
Scrotal pain and swelling	59 (100)
Fever (temperature, ⩾38°C)	52 (88)
Sweating	43 (73)
Shivers	37 (63)
Arthralgias	33 (56)
Asthenia	31 (53)
Hepatosplenomegaly	18 (31)
Weight loss	15 (25)
Cough and respiratory symptoms	15 (25)
Arthritis	7 (12)
General lymphadenopathy[a]	5 (8)
Rash	4 (7)
Lower urinary tract symptoms	4 (7)

[a] Not inguinal lymphadenopathy.

ing were the most common symptoms. In 24 patients (41%), the fever was continuous. Nineteen patients (32%) presented with undulant fever.

Laboratory data. Erythrocyte sedimentation rates (ESRs) were measured in 48 patients; ESR ranged 1–94 mm/h (median, 25 mm/h). Thirty patients (63%) had ESRs >20 mm/h, and 17 (35%) had ESRs >40 mm/h. C-reactive protein levels were measured in 7 patients (median, 70 mg/L; range, 2–78 mg/L). Anemia (hemoglobin concentration <13.5 g/dL) was found in 21 patients (36%). Leukocytosis ($\geqslant$10,500 WBCs/mm^3) was found in 14 patients (24%) and leukopenia (<4500 WBCs/mm^3) in 6 patients (10%). Thrombocytopenia (<150,000 platelets/mm^3) was discovered in 9 patients (15%). A slight to moderate increase in serum hepatic transaminase level was observed in 29 patients (49%). Elevated serum γ-glutamyl transpeptidase and alkaline phosphatase concentrations with normal bilirubin level (dissociated cholestasis) were found in 15 patients (25%). Renal function tests were consistently normal. Urinalysis was normal in 51 patients (86%). Seven patients had hematuria, proteinuria, pyuria, or some combination of these (12%).

Standard tube agglutination testing of initial samples was carried out in 48 patients. A total of 25 (52%) of the 48 patients were positive for antibodies to *Brucella* (titer, $\geqslant$1:160). The Coombs test revealed titers of antibody to *Brucella* species of $\geqslant$1:320 for 43 patients. Thus, the Coombs test was positive for 93% of the patients. All 59 patients underwent the rose bengal test; the results were positive for all of them.

Cultures of blood specimens from 41 (69%) of the 59 patients with epididymoorchitis were positive for *Brucella* species. Blood cultures were positive for the 11 patients for whom standard tube agglutination tests were not measured and for the 23 patients in whom the titer was <1:160. Eight patients with negative blood cultures had received antibiotic therapy previously. Epididymal aspiration was performed on 5 patients, and in 4, *Brucella* species was isolated. Routine urine cultures were taken from 13 patients in order to rule out other genitourinary infections, and 2 of them were positive for *Escherichia coli.* Specific *Brucella* urine cultures were not taken. Blood cultures were positive for *Brucella* species in the 2 patients in whom the urine culture was positive for *E. coli,* and *Brucella* species was isolated in the epididymal aspiration from one of them.

Ultrasonographic findings. Ultrasonography was performed on 11 patients. Ten patients (91%) had unilateral involvement of the epididymis and testis, and 1 had bilateral involvement. The testis was enlarged in 7 patients (64%), and 6 (54%) presented hydrocele (figure 1). Epididymis was found in 8 patients (73%). Changes in the echotexture of the testis were detected in 9 sonograms (82%).

Among the 11 patients who underwent ultrasonographic examination, 4 were cured, 4 had infections that failed to respond to therapy, and 3 experienced relapse. Those patients who were cured had unilateral involvement: 3 with a diffuse hypoechoic echotexture of the testis and enlargement of the epididymis and 1 with epididymal involvement only. Among the 4 patients whose infections were unresponsive to antibiotic therapy, ultrasonography disclosed diffuse enlargement of the testis with well-defined hypoechoic areas (figure 1) in 3 of them, and an orchiectomy was performed in 2 patients. Among the 3 patients with relapse, 1 had bilateral orchitis, 1 presented a focal hypoechoic lesion in the testis, and 1 had epididymal enlargement with hyperechoic cysts.

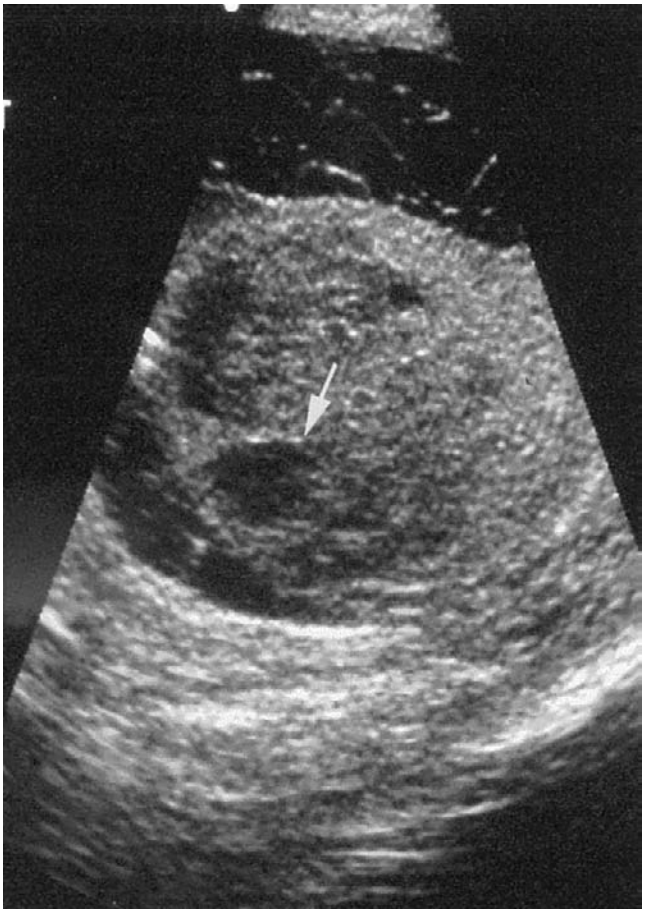

Figure 1. Ultrasonogram of necrotizing orchitis due to *Brucella* species. The testis was enlarged and presented hydrocele. The involved testis contained a focal hypoechoic lesion with distinct margins *(arrow).*

Treatment. All patients received antibiotic therapy. The median duration of antimicrobial therapy was 45 days (range, 21–90 days), and 85% of patients received therapy for $\geqslant$45 days. Duration of therapy varied according to clinical response and the presence of focal disease other than epididymoorchitis or necrotizing orchitis. A total of 39 patients (66%) received a combination of orally administered doxycycline (100 mg q12h) and an im-administered aminoglycoside (1 g of streptomycin per day for the initial 14–21 days, 31 patients; 240 mg of gentamicin per day for the initial 7–15 days, 6 patients; and 300

mg of netilmicin per day for the initial 7–15 days, 2 patients). Ten patients (17%) received a combination of doxycycline (100 mg q12h) and rifampin (900 mg/d administered orally). Seven patients (12%) received trimethoprim-sulfamethoxazole for 21–45 days, and 3 patients (5%) received a combination of rifampin and trimethoprim-sulfamethoxazole.

Response to treatment was variable (table 3). In this series of BEO, no statistically significant differences were observed between the different treatment regimens. Five of the 59 patients with necrotizing orchitis underwent surgical treatment of a testicular abscess. This treatment consisted of drainage of the abscess in 2 patients and orchiectomy in 3. Previously, these 5 patients had received antibiotic treatment for 6 weeks without clinical or ultrasonographic improvement. Four patients received a combination of oral doxycycline and im-administered aminoglycoside; and 1 received a combination of doxycycline and rifampin.

Outcome. All patients were available for follow-up for at least 6 months (median, 19 months). The period of defervescence for 14 patients with fever at the beginning of therapy was 1–45 days (median, 1 day). Patients who recovered experienced rapid regression of symptoms. The infections of 9 patients (15%) failed to respond to therapy, and another 15 patients (25%) relapsed (table 3). All patients whose infections failed to respond to therapy continued to experience moderate or intense pain after 6 weeks of therapy. The patients whose infections failed to respond to therapy received maintenance treatment with doxycycline over a longer period of time, and 5 underwent surgery. The overall long-term clinical response was favorable.

Fifteen (25%) of the 59 patients included in this study experienced a relapse after completion of therapy. Of these 15 patients, all had clinical relapse with characteristic clinical findings, and 4 (27%) had associated brucellar bacteremia. Relapse occurred from 1 to 4 months after completion of therapy.

Histologic samples were taken from 2 patients with a necrotizing orchitis that showed poor response to specific antibiotic therapy and required orchiectomy. These patients are described in further detail below.

Patient 1. A 53-year-old farmer was admitted to the hospital with fever and testicular pain. He had a history of perianal abscesses that required surgical drainage. Acute brucellosis had been diagnosed 6 months earlier, and he received treatment specific to brucellosis. Progressive pain and an increase in testicle size had evolved from the beginning of his illness. Blood cultures and epididymal aspiration were positive for *Brucella* species. In spite of specific therapy, the patient continued to experience inflammation of the scrotum, formation of fistulae, and intratesticular abscesses, which required orchiectomy. Grossly, the testis was symmetrically enlarged. Multiple histologic sections of the testis revealed pronounced granulomatous inflammation marked by the presence of innumerable noncaseating granulomas. The center of the testicle was occupied by multiple foci of tissular necrosis with an abscess. The epididymis showed similar but less severe cellular infiltration.

Table 3. Treatment and outcome for 59 patients with brucellar epididymoorchitis.

Treatment	Patients	Failure to respond to therapy	Relapse	Cure
Dox + AG	39 (66)	7 (18)	8 (21)	24 (62)
Dox + Stm	31 (53)	4 (13)	6 (19)	21 (68)
Dox + Gm/Net	8 (13)	3 (37)	2 (25)	3 (37)
Dox + Rif	10 (17)	0	4 (40)	6 (60)
TMP-SMZ	7 (12)	2 (29)	3 (43)	2 (29)
TMP-SMZ + Rif	3 (5)	0	0	3 (100)
Total	59 (100)	9 (15)	15 (25)	35 (59)

NOTE. Data are no. (%) of patients. AG, aminoglycoside; Dox, doxycycline; Gm, gentamicin; Net, netilmicin; Rif; rifampin; Stm; streptomycin; TMP-SMZ, trimethoprim-sulfamethoxazole.

Patient 2. A 27-year-old farmer was admitted to our hospital with fever, sweating, arthritis, and unilateral orchitis. Blood cultures were positive for *Brucella mellitensis,* and the patient received specific antibiotic treatment for 45 days. Relapse occurred 1 month after completion of therapy, and he received antibiotic treatment for another 45 days. Six months after completion of therapy, ultrasonography disclosed a testicular tumor. Because the diagnosis of testicular tumor could not be ruled out, an orchiectomy was performed. The final pathologic diagnosis was granulomatous orchitis with focal necrosis.

DISCUSSION

Infections caused by genus *Brucella* can produce orchitis in susceptible mammals, including humans [27]. According to Reisman et al. [16], Hardy first described *Brucella* species as a cause of granulomatous orchitis in humans in 1928. Since then, many authors have reported sporadic cases of *Brucella* orchitis. Estimates of the incidence of epididymoorchitis in human brucellosis have ranged 2%–20% [3–9].

BEO is rather uncommon in developed countries because brucellosis has practically been eradicated in animals [28]. Nevertheless, cases have been reported in patients from other countries where the disease is endemic or in people who have traveled to these areas and have consumed unpasteurized dairy products [2]. Brucellosis is a relatively common cause of BEO in geographic areas where *B. melitensis* is endemic [3–13]. However, only a few series have been reported in sufficient detail to allow analysis [3, 4, 10–13]. The demographic as well as clinical characteristics of the patients in this study were similar

to those of groups of patients with BEO described elsewhere [3, 4, 10–13], and most patients in this cohort had risk factors for brucellosis.

Diagnosis. The diagnosis of scrotal diseases is usually based on clinical evaluation and laboratory results. BEO can be distinguished from other acute nonspecific types by its gradual onset, longer duration, history of contact with animals, or ingestion of unpasteurized dairy products, typical undulant fever, and normal urographic findings [3, 10, 12]. Although Khan et al. [11] found lower urinary tract symptoms in 69% of patients, other authors have described a characteristic absence of these symptoms [3, 10, 12].

Abnormal blood test results are usually mild and nonspecific. The hemoglobin level may be lower as a result of prolonged infection, and a moderately elevated ESR is found in most cases. Liver function tests disclose a mild to moderate increase in the hepatic transaminase serum levels [22]. The anomalies in liver function tests may be caused by granulomatous *Brucella* hepatitis. However when serious liver malfunction is found, intercurrent disease must always be excluded [11]. In most patients, there are no alterations in urine sediment. In our series, 7 patients (11.9%) had hematuria, proteinuria, pyuria, or some combination of these. On the other hand, 25 patients (42%) with BEO had a focal disease other than epididymoorchitis.

Finding *Brucella* organisms in blood culture constitutes diagnosis, and several specimens should always be taken for culture. Continuous bacteremia and a high frequency of positive blood cultures are typical of infections due to *Brucella* species [19–23]. In addition to blood cultures, culture of epididymal aspiration may reveal the microorganism. Standard urine culture is inadequate for the diagnosis of genitourinary brucellosis; therefore, in our study, it was only performed in order to rule out the presence of other microorganisms. Failure to find the *Brucella* organism in urine culture may result from inadequate microbiologic techniques.

The presumptive diagnosis of brucellar orchitis can be made via serological testing [3, 4, 10–13, 29]. Positive results (titers of antibodies to *Brucella* species of $\geqslant$1:160 [standard tube agglutination test] or $\geqslant$1:320 [Coombs test]) are common (and are usually high titers), although low titers determined by standard tube agglutination testing have been reported. Rarely do patients with brucellosis have positive blood cultures but negative serological results [22, 28].

Ultrasonography plays an important role in the diagnosis, assessment, and management of patients with BEO [18]. Ultrasonography is more useful in enabling the exclusion of the possibility of abscess or tumor than it is in helping to establish the primary clinical diagnosis. Unilateral epididymoorchitis is the most common genitourinary complication of brucellosis. Infection that is limited to the testis is rare; the epididymis is usually involved in patients who have acute inflammation. Ultrasonographic characteristics are enlargement, a hypoechoic echotexture of the epididymis, the presence of a hydrocele (figure 1), and thickening of scrotal skin. In normal epididymis, very few or no vessels are seen on color Doppler sonograms, but the size and number of vessels increase if the epididymis is inflamed. The changes seen on color Doppler images may precede changes evident on gray-scale sonograms [18].

Granulomatous lesions on the testis result from a group of illnesses that are clinically and pathologically similar. Because granulomatous inflammation can be associated with focal necrotic areas, clinical and ultrasonographic findings resemble those seen in testicular tumors [18]. In patients with a focal hypoechoic lesion in the testis on ultrasonography, orchiectomy is usually performed [4, 14–18].

Treatment. At present, a combination of antibiotics is the most adequate treatment [3, 4, 10–13]. However, managing BEO remains controversial as far as the selection of antibiotics, the duration of treatment, and the role of surgery are concerned [3, 4, 10–13, 14–17]. The most widely used antibiotic combination for therapy is tetracycline (particularly doxycycline) and aminoglycoside. Treatments with trimethoprim-sulfamethoxazole, ciprofloxacin or doxycycline, and rifampin are associated with the worst outcomes, as shown in our studies elsewhere [19–21, 23]. In the present series, no statistically significant differences were observed between the different combinations of antibiotics. It is probably necessary to study a larger number of BEO cases in order to compare the different treatments and find the ideal duration of them.

The duration of antibiotic therapy for BEO varies considerably in the different studies [3, 4, 10–13]. Treatment includes antibiotics administered for a minimum period of 6 weeks. The relapse rates in patients with BEO (25%) appear to be higher than those of patients with brucellosis without epididymoorchitis. Orchiectomy is rarely required [4, 11, 12, 14–17]. In our study, the patients who required testicular drainage, orchiectomy, or both were those who developed necrotizing orchitis, which could not be cured after 6 weeks of therapy. In our series, the rate of surgery (8%) is higher than the rate of other previous series [3, 10, 11]. It is possible that our high rate of surgery is because our hospitals function as reference centers for human brucellosis.

Childhood infection with brucellosis was considered in the past to be rare, but more recent studies have shown it to be common in children in areas endemic for brucellosis. It is possible that epididymoorchitis in infancy may lead to primary infertility in regions where brucellosis is endemic [3]. However, further investigation may be needed on the relation between BEO and male infertility in order to substantiate this hypothesis.

Necrotizing orchitis is a rare form of *Brucella* infection that must be distinguished from necrotizing involvement arising from other pathogens (*Mycobacterium tuberculosis* or *Salmo-*

nella species). Above all, this condition must be distinguished from a tumor [4, 14–18]. Ultrasonography discloses diffuse enlargement of the testis with several well-defined hypoechoic areas (figure 1) [18]. Necrotizing orchitis shows a poor response to specific antibiotic therapy and usually requires orchiectomy [4, 14–17]. In our study, the 5 patients with necrotizing orchitis underwent surgical treatment of a testicular abscess. This treatment consisted of drainage of the abscess in 2 patients and orchiectomy in 3. Histologic analysis of 2 surgical specimens disclosed a lymphohistiocytic infiltrate with noncaseating granulomas in the interstitium and abscess [30].

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