**Genitourinary Involvement in Human Brucellosis: A Retrospective Analysis of Thirty Two Cases**

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**ABSTRACT**

**Introduction**: Brucellosis is zoonotic infection caused by Brucella bacteria. It is endemic in Turkey. Brucellosis can be followed by genitourinary complications in 2-20% of cases. The most common genitourinary complication in males is unilateral brucellar epididymo-orchitis (BEO). However, it can also rarely cause acute interstitial nephritis, pyelonephritis, prostatitis, focal and diffuse glomerulonephritis and renal abscess. The purpose of this study was to evaluate patients with genitourinary involvement brucellosis.

**Materials and Methods**: Thirty-two patients diagnosed with brucellosis and with a history of pain or swelling in the testes, scrotal redness, and sensitivity during urination or renal complaints were evaluated retrospectively.

**Results**: Mean age of patients was 41.71±14.56 years. The most common symptoms were lethargy, high fever, sweating, lack of appetite, scrotal swelling and scrotal redness. Left testicular swelling was present in 13 cases, right testicular swelling in nine and bilateral involvement in three. The most common laboratory findings were leukocytosis, and C-reactive protein (CRP), sedimentation (ESR), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation. All cases were successfully resolved with medical treatment.

**Conclusion**: Brucellosis must not be forgotten in genitourinary involvements, especially in endemic regions. Occupation, contact with animals and consumption of unpasteurized milk or milk products should be investigated at anamnesis. Antibiotic combinations are generally sufficient in treatment. Orchietomy and other surgical procedures are rarely required.

**Key words**: Brucellosis, epididymo-orchitis, genitourinary, nephritis, treatment

**INTRODUCTION**

Brucellosis is a zoonosis caused by Brucella bacteria (Calmenero et al., 2007; Young et al., 2003). The most commonly isolated subtype in patients is Brucella melitensis (Dağlı et al., 2011). Brucellosis is transmitted through animal body fluids, pregnancy material, infected milk and dairy products (Young et al., 2003; Afsar et al., 1993; Stamatiou et al., 2009). It can also be transmitted through the skin and mucosa and inhalation (Young et al., 2003; Stamatiou et al., 2009; Memish et al., 2001). Brucellosis is endemic in Turkey, and is particularly common in Eastern, Central and Southeast Anatolia (Çelen et al., 2010). Symptoms and findings may involve all organs and systems (Franco et al., 2007). It can mimic numerous diseases by assuming different clinical forms (Dağlı et al., 2011; Hatipoğlu et al., 2004; Erdem et al., 2014). Genitourinary involvement is the second most common form after musculoskeletal involvement (Calmenero et al., 2007; Young et al., 2003; Savascı et al.,...
Genitourinary involvement takes the form of epididymitis, orchitis, epididymo-orchitis, prostatitis, cystitis, pyelonephritis, interstitial nephritis, exudative glomerulonephritis, seminal vesiculitis and renal and testicular abscess (Çelen et al., 2010; Stamatiou et al., 2009). The most important complication of genitourinary brucellosis is epididymo-orchitis (Akıncı et al., 2006; Navarro-Martínez et al., 2001). This manifests with findings such as fever, sweating, lack of appetite, lethargy, weight loss, joint pain, headache and testicular pain and swelling (Young et al., 2003; Hatzopoulou et al., 2004; Erdem et al., 2014). The purpose of this study was to evaluate the clinical symptoms, laboratory findings, treatments and outcomes in patients with genitourinary brucellosis.

MATERIALS-METHODS

Thirty-two patients with genitourinary brucellosis treated at the Atatürk University Faculty of Medicine Department of Clinical Microbiology and Infectious Diseases and Şifa Hospital Department of Infectious Diseases were included in the study. Patient records between January 2012 and December 2014 were retrospectively evaluated in terms of demographic data, clinical and laboratory findings, time of onset of symptoms, response to treatment and relapse levels. Rose Bengal, Wright standard tube agglutination and Coombs tests were studied. These tests were performed in line with standard procedures (Erdem et al., 2014; Uncu et al., 2006).

Rose Bengal test positivity and tube agglutination test (≥1/160) positivity, presence of ultrasound findings or growth of Brucella spp. in culture were used as diagnostic criteria in cases with clinical findings. Complete blood count, biochemical examinations, CRP, ESR and urogram were performed in all cases. Cases with symptoms lasting less than 2 months were regarded as acute brucellosis, those with symptoms lasting 2-12 months as subacute and those with symptoms lasting more than 12 months as chronic brucellosis. Scrotal and abdominal ultrasonographies were performed in appropriate cases. Oral doxycycline 100 mg twice a day, oral rifampicin 600 mg/day, oral trimetoprima-sulfametaxazol 160/800 mg twice a day and intramuscular streptomycin 1 g once a day were used in treatment. Combinations of two or three drugs containing antibiotics were applied for at least 6 weeks. Relapse was defined as re-emergence of symptoms and blood culture positivity after treatment. Renal biopsy revealed mesangiocapillary glomerulonephritis in one patient.

Statistical Analyses

Statistical analyses were performed with IBM SPSS version 20 (Chicago, IL, USA). Descriptive statistics were used. Percentages and frequencies were given in categoric variables and mean plus standard deviation in continuous variables.

RESULTS

Thirty (93.8%) patients were male and 2 (6.2%) female. Mean age was 41.71±14.56 years (min 16 - max 63).

Length of hospitalization ranged from 5 to 19 days, with a mean of 8.5 days. Time to hospitalization after onset of symptoms was 27.53±13.18 days. Treatment was commenced in a mean 26.34 days after onset of symptoms. Treatment was initiated 3.71±2.26 days after hospitalization. Acute brucellosis was present in all patients apart from 2 (6.2%). Animal husbandry in 13 (40.6%) cases and consumption of unpasteurized milk and milk products in 15 (46.9%) were determined as the most significant risk factors. Two (6.2%) patients worked in veterinary medicine or animal care, 1 (3.1%) in an abattoir and 1 (3.1%) in refuse collection. Weakness was present in 31 (96.9%) patients, fever in 29 (90.6%), sweating in 29 (90.6%), arthralgia in 26 (81.3%), lack of appetite in 26 (81.3%), lumbar pain in 20 (62.5%) and loss of weight in 18 (56.3%). Dysuria was determined in 12 (37.5%) patients and hematuria in 4 (12.5%).

There was no history of immunosuppression or infertility. The most common physical examination findings were hepatomegaly in 30 patients (93.5%), splenomegaly in 24 (75%), scrotal swelling in 25 (78.1%) and scrotal redness in 24 (75%). Testicular swelling was unilateral in 21 (90.6%) patients and bilateral in 3 (9.4%). Left testis swelling was present in 13 (40.6%) patients and right testis swelling in 9 (28.1%). The signs and symptoms reported at presentation are shown in table 1. Genitourinary ultrasonography was performed in 20 cases. Inflammation was determined in all patients, edema in 16 (50%), mass in 5 (15.6%) and abscess in 2 (6.2%). Brucella bacteria grew in blood culture in 6 (18.8%) cases. No growth occurred in urine or genital fluid culture. Accompanying sacroiliitis was present in 7 (21.8%) patients.

The results of laboratory analyses with genitourinary brucellosis patients are presented in Table 2. Antibodies were investigated using ELISA in 14 patients. IgG was positive and IgM negative in 5 patients and both were negative in 4. IgM was positive and IgG negative in 3 patients and both were positive in 2 patients. Epididymo-orchitis was diagnosed in 26 (81.3%) patients, pyelonephritis in 4 (12.5%), urethritis in 1 (3.1%) and glomerulonephritis in 1 (3.1%). Brucellosis-related glomerulonephritis was determined in a 58-year-old male patient. The pathology was reported as postinfectious glomerulonephritis. Proteinuria and edemas improved with treatment. Rose Bengal was positive in 28 (87.5%) patients. Growth occurred in blood culture in one patient with BEO with negative Rose Bengal and Wright test. Wright test values were positive at 1/160 or over in 30 (93.5%) patients (Figure 1).

Doxycycline and rifampicin therapy was administered to 13 (40.6%) patients, doxycycline and streptomycin to 9 (28.1%), doxycycline, rifampicin and streptomycin to 8 (25%) and doxycycline, streptomycin and trimetoprima-sulfametaxazol to 2 (6.2%). No failures occurred in medical treatment. No testicular abscess developed. No recurrence was observed, and no orchietomy was performed in any case.

DISCUSSION
Brucellosis is responsible for 2-20% of all cases of epididymo-orchitis in endemic countries (Stamatiou et al., 2009; Akinçi et al., 2006; Navarro-Martinez et al., 2001; Al-Tawfiq et al., 2006). The most widespread symptoms are scrotal pain and swelling, high fever and sweating (Çelen et al., 2010; Navarro-Martinez et al., 2001). Buzgan et al. (2010) examined 1028 cases of brucellosis and reported genitourinary involvement in 3.7%. These cases predominantly consisted of brucellar epididymo-orchitis (BEO) (3.4%). Another study of 912 patients with brucellosis reported an incidence of BEO of 7.6% (Calmenero et al., 2007). Unilateral epididymo-orchitis is the most common genitourinary complication in males (Memish et al., 2001; Akinçi et al., 2006; Navarro-Martinez et al., 2001).

It can also, albeit rarely, lead to interstitial nephritis, pyelonephritis, prostatitis, renal abscess, cystitis and focal or diffuse glomerulonephritis (Stamatiou et al., 2009; Al-Tawfiq et al., 2006; Üstün et al., 2005). Erdem et al. (2014) reported that 90% of patients were male with a level of scrotal area involvement of 93%. Salpingitis, cervicitis and pelvic abscess may be seen in women (Uncu et al., 2006). The incidence of pyelonephritis in women (86.8%) is significantly higher than that in men (3.1%) (Erdem et al., 2014). Males represented 93.8% of our patients, and BEO was present in 81.3%. Pyelonephritis was diagnosed in one woman only.

There is no reliable and effective vaccination for humans. Brucellosis is an occupational disease for veterinarians, farmers and laboratory and abattoir personnel (Stamatiou et al., 2009). Navarro-Martinez et al.’s study (2001) reported a high level of occupational exposure of 41%. That same study reported a consumption of unpasteurized milk and milk products level of 83%. Memish et al. (2001) investigated 26 cases of BEO and identified consumption of raw milk and milk products (38%) and occupational laboratory exposure (4%). Akinçi et al. (2006) reported a consumption of unpasteurized milk level of 88.2% and occupational exposure of 11.8%. A history of consumption of raw milk and milk products was present in 46.9% of our cases, animal husbandry in 40.6% and working as a veterinarian in 6.3%. The majority of patients lived in rural areas.

BEO is generally seen in the acute period (the first 8 weeks). Seventy-eight percent of patients in Navarro-Martinez et al.’s study (2001) presented in the acute period. All patients were reported to be in the acute period in another study (Stamatiou et al., 2009). All our patients were also diagnosed in the acute period, with the exception of 2 presenting in the subacute period. Unilateral epididymo-orchitis is most common in males (Savascı et al., 2014; Akinçi et al., 2006; Navarro-Martinez et al., 2001). Cases of bilateral involvement have also been reported, however (Memish et al., 2001). In one study of BEO involving 35 patients, bilateral involvement occurred in only 3 subjects (Buzgan et al., 2010). The most common symptoms are generally unilateral scrotal pain and swelling and fever (Savascı et al., 2014; Navarro-Martinez et al., 2001). Left testicular involvement was reported in 16 patients in one study and right testicular involvement in 11 (Savascı et al., 2014). Right testicular involvement was determined in 15 cases in another study, and left testicular involvement in 10 (Roushan et al., 2009). Involvement was unilateral in 90.6% of our cases and bilateral in 9.4%. The left testis was involved in 40.6% of patients and the right in 28.1%.

Urinary tract symptoms have been reported in very few patients (7%) in the literature (Afsar et al., 1993). Khan et al. (1998) and Akinçi et al. (2006), however, reported high levels of urinary tract symptoms of 69% and 47%, respectively. One typical characteristic in cases of BEO is very little change at urine analyses. Calmenero et al. (2007) reported urinary symptoms in 4.2% of patients and that urine analysis was normal in 69%. Another study reported normal urine analysis in 86% of cases (Navarro-Martinez et al., 2001). Dysuria has been reported in 28.5% of cases (Savascı et al., 2014). The study with the widest series reported dysuria in 55.3% of women, hematuria in 26.3% and genital discharge in 10.5%. Dysuria was reported in 20.2% of males, urethral discharge in 5.7% and hematuria in 4.5% (Erdem et al., 2014). Calmenero et al. (2007) observed proteinuria, hematuria, pyuria and combinations thereof in 31% (Navarro-Martinez et al., 2001; Papatsorius et al., 2002; Ibrahim et al., 1988). Dysuria was determined in 37.5% of our patients and hematuria in 12.5%.

BEO can be differentiated from other forms of acute epididymo-orchitis through symptoms specific to itself including gradual onset, prolonged length of disease, epidemiological history, undulant fever and normal urographic findings (Memish et al., 2001; Navarro-Martinez et al., 2001; Yurdakul et al., 1995). Fever, scrotal swelling and testicular pain are more pronounced in BEO. Fever is present days or even weeks prior to scrotal symptoms (Calmenero et al., 2007; Memish et al., 2001; Papatsorius et al., 2002). Other characteristics include absence of lower urinary symptoms, normal urogram, absence of inflammation findings in the scrotal skin and leukocyte numbers being normal or close to normal (Memish et al., 2001; Navarro-Martinez et al., 2001; Papatsorius et al., 2002). Growth levels in urine cultures are low in brucellosis with genitourinary involvement. Nonetheless, urine culture is recommended in order to exclude other agents (Calmenero et al., 2007; Papatsorius et al., 2002; Ibrahim et al., 1988). Growth in urine culture has been identified in very few studies (Dağlı et al., 2011; Uncu et al., 2006). No growth occurred in urine cultures from any of our patients.

Biochemical and hematological parameter are not particularly useful in diagnosis (Turunç et al., 2008). Leukocytosis and left shift are not always seen in BEO (Calmenero et al., 2007; Memish et al., 2001). Some studies have reported the opposite, however (Afsar et al., 1993; Savascı et al., 2014; Khan et al., 1989). Even if leukocytosis is seen it cannot be used in differential diagnosis of nonspecific epididymo-orchitis and BEO (Akinçi et al., 2006; Yetkin et al., 2005) 25). Roushan et al. (2009) reported leukocytosis in 35.8% of cases and elevated sedimentation in 62.3%. Navarro-Martinez et al. (2001) determined leukocytosis in 24% of cases, thrombocytopenia in 15% and elevated ESR in 63%. ESR and CRP exhibit mild elevation (Stamatiou et al., 2009). Akinçi et al. (2006) reported that CRP elevation, young age and blood culture positivity were highly significant in
Serology is important in diagnosis. Cases can be diagnosed using the Wright tube agglutination test (≥ 160) and the Coombs test. One of the interesting features in studies is the high positivity in the standard tube agglutination test (Calmenero et al., 2007; Navarro-Martinez et al., 2001; Memish et al., 2001). Roushan et al. (2001) reported positivity ≥ 1/320 in 2 of 26 patients. In agreement with the literature, Wright agglutination titer was ≥ 160 in 93.5% of our patients. Brucellar epididymo-orchitis causes granulomatous type inflammation together with areas of focal necrosis in the testis (Akınçi et al., 2006). Delay in diagnosis or treatment can lead to severe complications, such as testicular abscess, atrophy, suppurative necrosis and necrotizing orchitis (Hapıoğlu et al., 2004; Roushan et al., 2009). Delay in diagnosis or the condition being overlooked by the physician leads to focal complications (Calmenero et al., 2007). Cutaneous fistulization was reported in 2 cases out of one series of 28 patients (Savascı et al., 2014). Complications such as aspermia, oligospermia, infertility and necrotizing orchitis have been reported when brucellar epididymo-orchitis is left untreated (Stamatiou et al., 2009; Akınçi et al., 2006).

Response to medical treatment is generally achieved. Orchietomy levels range from 0.5% to 1% in different series (Navarro-Martinez et al., 2001; Khan et al., 1989). Erdem et al. (2014) performed orchietomy on 6 (1.5%) patients and surgical intervention on 9 (2.3%) patients. Orchietomy was reported in 3 cases due to testicular abscess (Buzgan et al., 2010). Orchietomy was performed in 6 cases with suspected malignity in another study (Savascı et al., 2014). Prolonged infection and delayed or inappropriate antibiotic use are reported as the main causes of testicular loss (Roushan et al., 2009). Response to medical treatment has been achieved without the need for surgery in some studies (Calmenero et al., 2007). Emergency orchietomy need not be performed if focal hypoechoic lesion is determined. Medical treatment must be attempted once cancer has been excluded (Akınçi et al., 2006). Since Navarro-Martinez et al. (2001) worked in a reference hospital they reported a higher requirement for surgery, 8%, compared to previous
Table 1. Clinical signs and symptoms in genitourinary brucellosis

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Patients no. (%)</th>
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<tbody>
<tr>
<td>Weakness</td>
<td>31 (96.9)</td>
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<tr>
<td>Fever</td>
<td>29 (90.6)</td>
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<tr>
<td>Sweating</td>
<td>29 (90.6)</td>
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<tr>
<td>Arthralgias</td>
<td>26 (81.3)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>25 (80.6)</td>
</tr>
<tr>
<td>Scrotal swelling</td>
<td>24 (78.1)</td>
</tr>
<tr>
<td>Scrotal redness</td>
<td>23 (75)</td>
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<tr>
<td>Lumbar pain</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>18 (58.1)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>12 (38.7)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>30 (93.5)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>24 (75)</td>
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Table 2. Laboratory findings in patients with genitourinary brucellosis

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>Mean ±SD</th>
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<tbody>
<tr>
<td>Leukocytes (x10^3)</td>
<td>12131±4475.26</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.61±1.37</td>
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<tr>
<td>Platelets (x10^3)</td>
<td>224968.75 ± 94348.86</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>46.71±24.37</td>
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<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>48.12±18.85</td>
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<tr>
<td>ALP (IU/L)</td>
<td>98.81±36.59</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>203.12±94.81</td>
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<tr>
<td>Sedimentation (mm/h)</td>
<td>42.59±17.31</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>24.50±38.41</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>6 (18.8 %)</td>
</tr>
</tbody>
</table>

ALP alkaline phosphatase; LDH lactate dehydrogenase
Figure 1. Initial titre of Brucella agglutinins in patients with genitourinary brucellosis

REFERENCES


