Testicular infection in brucellosis: Report of 34 cases

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Abstract Background/Purpose: To present clinical and laboratory features, treatment options, and outcome in patients with brucellar testicular infection and to compare them with analogous in brucellar patients without testicular involvement.

Methods: Thirty four brucellar patients with testicular infection treated in two general hospitals in the Republic of Macedonia, during the period 1998–2009, were retrospectively analyzed. Their clinical and laboratory characteristics were compared with analogous in 364 male brucellar patients without testicular infection, who were treated at the same hospitals during the same time period.

Results: Brucellar testicular infection was evident in 34 (8.5%) out of 398 male patients with brucellosis. The median age of the patients was 46.5 years. In all patients testicular involvement was presented as an acute form with a median duration of 5 days (range, 2–14 days) prior to diagnosis. Twenty-three of the patients had at least one other simultaneous focal infection. After starting with the treatment testicular infection lasted a median 10 days, range 7–21 days. Brucellar patients with testicular infection when compared with other brucellar patients more frequently manifested fever (97% vs. 61%), concomitant spondylitis (32% vs. 16%), and urinary system involvement (12% vs. 2%). Also, the relapse rate in patients with testicular involvement was significantly higher (24% vs. 9%).

Conclusion: In endemic regions brucellosis should be taken into consideration in any patient with testicular infection. Brucellar testicular involvement is usually characterized with a severe acute clinical presentation and a high percentage of relapses which entails the need of timely recognition and proper treatment duration of at least 60 days.

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Introduction

Human brucellosis is a zoonosis that is characterized by a wide clinical heterogeneity affecting different systems of the human body. Genitourinary involvement is among the commonest focal manifestations of human brucellosis,1–4 presented as epididymo-orchitis, prostatitis, cystitis, interstitial nephritis, pyelonephritis, immunoglobulin A nephropathy, exudative glomerulonephritis, and renal and testicular abscess.5–6 Brucellar epididymo-orchitis (BOE), by far the commonest genitourinary manifestation, was described for the first time by Hardy in 1929 and Wainwright in 1929.6 This focal manifestation is a result of urine Brucella removal or as a blood-borne septic metastasis.9–11 Clinical presentation of BOE is most frequently acute,6,11–14 rarely subacute10,15,16 or chronic.6,15 BOE may cause complications like necrotizing orchitis,5,17–18 testicular abscess,11,15,19 infarction,17,20 atrophy,21 and suppurative necrosis.17,20 Also, cases with aspermia and infertility have been described.11,14,15

Characteristics and prognosis of BOE have been described in many studies and communications, but comprising a small number of patients.13,22–24 This clinical entity is also rarely presented in studies related to the Balkan Peninsula.10,11 a region where brucellosis is considered to be an endemic disease. In this retrospective study we attempted to present the main demographic, clinical, and laboratory features, therapeutic experiences and outcome in patients with brucellar testicular infection in the Republic of Macedonia as an endemic region and to compare them with analogous in brucellar patients without testicular involvement.

Methods

The medical records and follow-up protocols of 34 brucellar patients with testicular infection treated at the Departments for Infectious Diseases in Veles and Bitola, Republic of Macedonia, during the period 1998–2009, were retrospectively analyzed. Their clinical and laboratory features were compared with analogous in 364 male brucellar patients, 18 years or older, without testicular infection that were treated at the same hospitals during the same period. The study was approved by the Ethics Committee of the Medical Faculty in Skopje, Republic of Macedonia.

The diagnosis of brucellosis was based on clinical findings compatible with brucellosis, supported by detection of specific antibodies at significant titers and/or demonstration of at least a fourfold rise in antibody titer in serum samples obtained 3–4 weeks apart. Antibody titers were determined by the standard tube agglutination, Brucella Coombs, and/or Brucella Lact assays as previously described.25,26

All of the patients underwent standard diagnostic protocol including detailed history, physical examination, and laboratory analysis—erythrocyte sedimentation rate, C-reactive protein, hemoglobin, white blood cells, lymphocytes, platelets, urine analysis, alanine aminotransferase, and serological tests for brucellosis. Patients were treated with various antimicrobial combinations that contained two or three of the following antimicrobials: oral doxycycline 100–200 mg/d; oral rifampin, 900 mg/d; oral trimethoprim/sulfamethoxazole (co-trimoxazole) 960 mg twice daily; and intramuscular gentamicin, 5 mg/kg/d. Gentamicin was administered 7–14 days, and the other drugs were given 45 days or longer if spondylitis, brucellosis of the central nervous system or therapeutic failure was evident. After finishing the treatment all patients were followed-up clinically and serologically every other month during the first 3 months, and every 3–4 months afterwards.

The investigated patients were divided into two groups: with (n = 34) and without (n = 364) testicular infection. The comparisons were performed in terms of the demographic and epidemiological data, clinical manifestations, laboratory characteristics, and outcome. Orchitis and epididymitis were diagnosed by the presence of acute scrotal pain, swelling and tender scrotal, and/or epidymal enlargement which were associated with the first episode of the actual disease and could not be attributed to other causes. Duration of testicular infection was defined as the number of days that elapsed from the start of treatment until the disappearance of all inflammatory signs. Relapse was accepted as the reappearance of symptoms and signs after the antibrucellar treatment was completed and therapeutic failure as persistence of symptoms and signs of the disease for more than 45 days of antibiotic therapy initiation.

The Chi-square test or Fisher’s exact test (when Chi-square could not be applied) were used for comparison of qualitative variables between the groups. For quantitative variables Mann–Whitney U test was performed. A p-value of < 0.05 was considered significant.

Results

Among 398 male patients with brucellosis that were treated during the analyzed period at the Departments for Infectious Diseases in Veles and Bitola, 34 (8.5%) had testicular involvement. Besides orchitis and/or epididymitis, 23 of the patients had other coexisting focal forms of brucellosis: 13 peripheral arthritis; 11 spondylitis; three sacroiliitis; three radiculitis; three cystitis; two respiratory; two gastrointestinal; and one each of bursitis, tendinitis, and pyelonephritis (some of the patients had more than 1 simultaneous focal form). Out of the patients with brucellar testicular infection 21 manifested orchitis, 12 epididymo-orchitis, and one patient had epididymitis. Their distribution is presented in Table 1.

Testicular infection was the only manifestation of the disease in four patients, and in 30 other patients besides testicular, other symptoms and signs attributable to brucellosis e.g., fever, sweating, arthralgia, headache, loss of appetite, backache, malaise, hepatomegaly, splenomegaly, and osteoartricular involvement were also present. In three patients testicular manifestations appeared parallel with the general signs and symptoms; in one patient they were preceding them, whereas in the remaining 26 patients testicular infection appeared after initiation of brucellosis. In all cases the clinical presentation was acute and the brucellar etiology of testicular symptoms and signs

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was achieved in a median of 5 days (range, 2–14 days) since the beginning. The affected testicle was two to six times enlarged in comparison to the unaffected one.

As presented in Tables 2 and 3 significant differences between the two groups were found concerning the presence of fever, concomitant spondylitis, and urinary tract involvement, as well as higher values of white blood cells and C-reactive protein in favor of patients with testicular involvement.

Patients were treated with various therapeutic combinations and different time duration (Table 4). Combination with rifampin/doxycycline/co-trimoxazole was performed in 24 (70%) patients and 197 (54%) patients with and without testicular infection, respectively. The combination rifampin/doxycycline/gentamicin was used in 8 (24%) patients and 133 (37%) patients of the designated groups respectively, whereas with the combination rifampin/doxycycline were treated 2 (6%) of the patients and 34 (9%) of the patients, respectively (p = 0.181).

After initiation of therapy testicular infection lasted for median of 10 days (range, 7–21 days). As shown in Table 5, a significantly higher number of patients from the group with testicular infection was followed for at least 6 months, and the frequency of relapses was also higher than in the other group. Remarkably, all eight relapses in the group with testicular involvement were in patients that were treated for 45 days. No differences in demographic and clinical parameter between patients with testicular infection that relapsed and those without relapses were noted (data not shown). All four cases with therapeutic failure in the group with testicular involvement had a concomitant spondylitis which was the cause for failure. However, we had no cases with necrotizing orchitis, atrophy, infarction, testicular abscess, supplicative necrosis, or cases requiring surgery.

**Discussion**

In our study testicular infection was found in 8.5% of male patients with brucellosis, which is in agreement with data in the literature (1.4–25%).3,5,12,13,27–30 The reasons for the wide range of presented frequency in the literature are to be explored in the characteristics of the examined population, the used criteria for defining the entity, the used diagnostic procedures as well as whether the study is a prospective or retrospective one. Testicular microtraumas or nonspecific infections in the past, as well as genetic predisposition might be a speculative explanation why some of the patients with brucellosis are prone to testicular infection. Still, until now we do not have a satisfactory answer.

Brucellar testicular infection is usually unilateral,10,13,15,20,22 which was the case in most of our patients. However, unlike other studies where simultaneous involvement of the testicle and epididymis predominated,15,21,23,27 or there was an equal presentation of orchitis and epididymo-orchitis17 in two-thirds of our series...
of patients orchitis has been a predominating inflammation, which might be due to using only clinical criteria in establishing the diagnosis. BEO may occur as an isolated brucellar manifestation5 or it might be within a systemic generalized disease. In the latter case BEO precedes the diseases,13 starts at the same time,14,18 or follows after the general manifestations of brucellosis, which was the case with the largest number of our patients. Even in endemic regions brucellosis recognition is especially difficult when testicular infection is either the first or only manifestation of the disease.

In this study 68% of the patients with testicular infection at the same time had another concomitant focal involvement, osteoarticular in the first order. Simultaneous infection of genital and other organ system in brucellosis is the previously known phenomenon,13,14,17,21,31 usually with much lower percentages than the percentage reported by us. Simultaneous osteoarticular and testicular infection in brucellosis was already described32 as well as spondylitis and orchitis33,34 but much less frequently compared to our investigations. There is only one study comprising seven patients with BEO where frequency of coexisting focal diseases, including those with osteoarticular involvement, is similar to ours.13 We have no adequate sustainable arguments about the frequent presence of spondylitis in our patients with testicular infection, except for the fact that the majority of our patients were treated in hospitals and underwent careful clinical examinations and follow-up. By contrast, in another study BEO was more frequently found in patients without osteoarticular manifestations.35

### Table 3 Laboratory characteristics in patients with and without testicular involvement.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with BEO (n = 34)</th>
<th>Patients without BEO (n = 364)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>29 (2–90)</td>
<td>28 (2–103)</td>
<td>0.938</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>135.5 (105–169)</td>
<td>137 (73–177)</td>
<td>0.277</td>
</tr>
<tr>
<td>White blood cells (× 10⁹/L)</td>
<td>7.4 (4.1–15.1)</td>
<td>6.4 (2.8–16.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>32 (8–54)</td>
<td>34 (11–74)</td>
<td>0.200</td>
</tr>
<tr>
<td>Platelets (× 10¹²/L)</td>
<td>246 (115–622)</td>
<td>222 (93–491)</td>
<td>0.061</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>42 (12–164)</td>
<td>18 (2–290)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alanine aminotransferase (&gt;45 U/L)</td>
<td>12 (35)</td>
<td>123 (34)</td>
<td>0.859</td>
</tr>
</tbody>
</table>

Data are presented as median (range) or n (%).

BEO = brucellar epididymitis/orchitis.

### Table 4 Therapeutic options in patients with and without testicular involvement.

<table>
<thead>
<tr>
<th>Therapeutic combination</th>
<th>Patients with BEO: treated/followed ≥6 mo/relapsed</th>
<th>Patients without BEO: treated/followed ≥6 mo/relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>R+D+TMP-SMZ⁶</td>
<td>16/16/7</td>
<td>162/131/17</td>
</tr>
<tr>
<td>R+D+G⁶</td>
<td>3/2/0</td>
<td>99/75/3</td>
</tr>
<tr>
<td>R+D⁵</td>
<td>2/2/1</td>
<td>32/16/3</td>
</tr>
<tr>
<td>R+D+TMP-SMZ⁷</td>
<td>8/8/0</td>
<td>35/33/2</td>
</tr>
<tr>
<td>R+D+G⁷</td>
<td>5/5/0</td>
<td>34/29/0</td>
</tr>
<tr>
<td>R+D⁰</td>
<td>0</td>
<td>2/2/1</td>
</tr>
<tr>
<td>Total</td>
<td>34/33/8</td>
<td>364/286/26</td>
</tr>
</tbody>
</table>

⁶ Therapy duration of 45 days.
⁷ Therapy duration of >45 days.

BEO = brucellar epididymitis/orchitis; D = doxycycline; G = gentamicin; R = rifampin; TMP-SMZ = trimethoprim/sulfamethoxazole.

### Table 5 Outcome in patients with and without testicular involvement.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with BEO (n = 34)</th>
<th>Patients without BEO (n = 364)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defervescence (d)</td>
<td>2 (0–45)</td>
<td>1 (0–35)</td>
<td>0.115</td>
</tr>
<tr>
<td>Followed-up ≥ 6 mo</td>
<td>33 (97)</td>
<td>286 (79)</td>
<td>0.010</td>
</tr>
<tr>
<td>Favorable outcome⁸</td>
<td>21 (64)</td>
<td>241 (84)</td>
<td>0.004⁹</td>
</tr>
<tr>
<td>Relapse⁸</td>
<td>8 (24)</td>
<td>26 (9)</td>
<td></td>
</tr>
<tr>
<td>Therapeutic failure⁸</td>
<td>4 (12)</td>
<td>19 (7)</td>
<td>0.003⁹</td>
</tr>
</tbody>
</table>

⁸ Calculated in patients followed for ≥6 months.
⁹ Favorable outcome vs. relapses.

Data are presented as median (range) or n (%).

BEO = brucellar epididymitis/orchitis.
Patients with BEO in our series were older in comparison with other studies. In the literature, patients with BEO were younger than those without testicular infection, which might be a result of the larger number of patients with concomitant spondylitis that we had. We have shown that patients with BEO significantly more often manifested fever compared to those without this focal form. These cases presented acute testicular infection and besides local manifestations a lot of additional signs and symptoms predominated, including fever. The presence of urinary symptoms in BEO has been described with a wide range from 0% to 69%. This was one of the characteristics that distinguished our patients with and without brucellar testicular infection, and with the frequency of 12% was similar to those reported by others. Also, higher CRP levels and higher leukocyte counts were found in our patients with testicular infection than in brucellar patients without BEO, which has been demonstrated in other studies. In our patients, although high, is comparable to the percentages sufficient, long treatment duration are recommended for testicular infection like mumps, tuberculosis, gonorrhea, Chlamydia trachomatis or enterobacterial infection, hydroceles, testicular torsion and tumor. Brucellosis should have priority in the differential diagnostic considerations. Therefore, until results from larger prospective studies are obtained, our study has shown that testicular involvement in brucellosis is a serious condition with acute and severe presentation, simultaneous infection of other organ systems, and a high percentage of relapses. Consequently, its fast and timely recognition and proper and sufficient, long treatment duration are recommended priorities.

Conflict of interest

The authors declare that they have no conflict of interest.

References


