

Brucellar reproductive system injury: A retrospective study of 22 cases and review of the literature

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Abstract

Objective: We aimed to describe the clinical characteristics and prognosis of 22 patients with *Brucella*-induced reproductive system injury.

Methods: We assessed 22 patients with reproductive system injury between 2010 and 2018 at The First Affiliated Hospital of Xinjiang Medical University.

Results: The disease is predominant in men. Male patients had orchitis, erectile dysfunction, prostatitis, and urethral stricture, while female patients had vaginitis and cervicitis. Some patients had laboratory abnormalities and liver injury. Patients received combination therapy of rifampicin and doxycycline. Doxycycline combined with levofloxacin or moxifloxacin was administered to patients with rifampicin intolerance. All patients had received antibiotic therapy for at least 6 weeks. One patient was lost to follow-up, one patient relapsed because of osteoarthropathy, and one patient had dysuria resulting from chronic prostatitis. The clinical symptoms resolved in the other patients, and the overall patient prognosis was good.

Conclusion: Clinicians should pay attention to brucellosis-induced reproductive system damage. The two-drug regimen of rifampicin+doxycycline is recommended for these patients. Doxycycline combined with levofloxacin or moxifloxacin should be used in patients with brucellosis-induced reproductive system damage who have rifampicin intolerance. The treatment course should be at least 6 weeks.

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Keywords

Brucellosis, reproductive system, clinical features, rifampicin intolerance, doxycycline, levofloxacin, moxifloxacin

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Introduction

Brucellosis is an infectious disease that is caused directly or indirectly by *Brucella* Gram-negative cocci, and this disease has a different degrees of severity in humans and livestock.¹ It is a systemic infectious disease that can affect any organ or system in the body and show different clinical symptoms. *Brucella* invades the reproductive system mostly in men, mainly including orchitis, epididymitis, hydrocele, and prostatitis, with orchitis and epididymitis being the most common. Reproductive system injury caused by brucellosis is rare, and it has been reported in only a few cases.²⁻⁵ This study aimed to describe 22 cases of reproductive system injury that was caused by *Brucella* and to present a relevant literature review.

Materials and methods

Study population

There were 801 patients with brucellosis who were admitted to the First Affiliated Hospital of Xinjiang Medical University from July 2008 to July 2018. Among them, 22 patients had complications of a reproductive system injury. The diagnosis of brucellosis was based on the Guidelines for Diagnosis and Treatment of brucellosis that was published by the Ministry of Health of the People's Republic of China.⁶ There were 21 patients in the acute stage (course <6 months) and one patient in the chronic stage (course >6 months). Reproductive system complications are mainly diagnosed through clinical signs

and symptoms; in men, these include orchitis that mainly manifests as testicular redness in men, and in women, this includes hypogastrium pain. The diagnosis is confirmed by imaging. A diagnosis of either brucellosis diagnosis or a reproductive system injury could be diagnosed as brucellosis reproductive system injury disease. The exclusion criteria were as follows: (1) Patients with a history of immune system disorders or tumor; (2) patients with an immunity disorder; (3) patients with a history of serious diseases or dysfunction of other systems such as respiratory, cardiovascular, kidney, liver, nervous; and (4) patients who used immunomodulators, immunosuppressive drugs, and corticosteroids for a long time or for nearly 3 months. The review board at our hospital provided an exemption for this study, and all patient data were de-identified. Patients provided verbal consent for the use of their data.

Clinical assessment and definitions

We used a self-designed brucellosis patient case questionnaire to retrospectively analyze the data from 22 patients with reproductive system injury. Data collected from the enrolled patients included demographic characteristics, clinical features, laboratory tests, imaging findings, treatment, and prognosis, and quality control of the investigation was also performed. Descriptive epidemiological methods were used for the retrospective analysis, and summary statistics were presented including the number (%) and the mean \pm standard deviation (SD).

Results

Patient characteristics

Among the 22 patients who were enrolled into this study, 21 patients were male and one was female. The average age (\pm SD) of the patients was 41.91 ± 10.52 years (range, 22–56 years). Most of the patients ($n=19$, 86.4%) were farmers who had cows and sheep and one (4.5%) patient denied a history of contact with cattle or sheep. In two (9.1%) patients, the cause was unknown. Detailed epidemiological characteristics are shown in Table 1.

Presentation of signs and symptoms

Table 2 shows the clinical characteristics in the 22 patients, including common signs and symptoms. The most common symptoms in the patients were fever, sweating, anorexia, and weight loss. In men with orchitis, testicular epididymitis, prostatitis, or urethral orifice stricture, the main

manifestation was testicular swelling and pain and dysuria. One woman had from vaginitis and cervicitis. The main manifestations in women were increased leucorrhea, irregular menstruation, and hypogastrium pain.

Laboratory tests

In 21 patients, the Rose Bengal Plate Test (RBPT) results were positive, and the standard tube agglutination test results were positive ($\geq 1:100$), among which the highest

Table 2. Clinical signs and symptoms of patients with brucellosis.

Symptoms	Number of patients	Percent
Orchitis		
Left	2	9.1
Right	7	31.8
Bilateral	0	0
Epididymo-orchitis		
Left	3	13.6
Right	3	13.6
Bilateral	2	9.1
Orchitis with hydrocele		
Left	2	9.1
Right	3	13.6
Bilateral	0	0
Erectile dysfunction	15	68.2
Prostatitis	2	9.1
Urethral stricture	2	9.1
Vaginitis and chronic cervicitis	1	4.5
Fever	18	81.8
Sweating	8	36.4
Anorexia	9	40.9
Muscle ache	4	18.2
Osteoarticular involvement	9	40.9
Knee joint involvement	5	22.7
Lumbar vertebra involvement	6	27.3
Sacroiliac and hip joint involvement	6	27.3
Fatigue	11	50
Headache	6	27.3
Cough	4	18.2
Weight loss	9	40.9

Table 1. Baseline demographic and epidemiological characteristics of patients with brucellosis.

	Number	Percent
Gender		
Male	21	95.5
Female	1	4.5
Age (average, years)		
20–29 years	4	18.2
30–39 years	3	13.6
40–49 years	8	36.4
≥ 50 years	7	31.8
Area		
City	3	13.6
Agricultural and Pastoral areas	19	86.4
Time range		
2010–2013	8	36.4
2014–2016	6	27.2
2017–2018	8	36.4
Month		
January–April	2	9.1
May–August	13	59.1
September–December	7	31.8

antibody titer was 1:800. Nineteen patients underwent blood culture examination. Among them, *Brucella* Malta was cultured in four patients. There were 18 (81.8%) patients with an elevated erythrocyte sedimentation rate (ESR) and 16 (72.7%) patients with increased C-reactive protein (CRP), CRP, ESR, and γ -glutamyl transpeptidase levels, which were significant abnormalities. Table 3 shows the results of laboratory examinations.

Imaging examination

All patients underwent abdominal ultrasonography, and among them, five (22.7%) patients had hepatomegaly, while the remaining patients had a normal sized liver. Six patients underwent lymph node ultrasonography, and four (66.7%) patients showed lymph node enlargement, mainly in the neck, groin, and axillary nodes.

Table 3. Laboratory results from 22 patients with *Brucella*-induced reproductive system injury.

Laboratory tests	Number of patients	Percent
Leukopenia (white blood cells <4,000/mm ³)	2	9.1
Anemia (Hb, male; <14 mg/dL; female, <12 mg/dL)	4	18.2
Thrombocytopenia (platelets <100,000/mm ³)	2	9.1
Increased ESR (>20 mm/hour)	18	81.8
Increased CRP (>8 mg/L)	16	72.7
Increased ALT (>50 U/L)	7	31.8
Increased AST (>50 U/L)	5	22.7
Increased γ -GT (>50 U/L)	18	81.8
Positive standard tube agglutination test ($\geq 1:100$)	21	100
Blood culture	16	72.7
Positive	4	18.2
Negative	12	54.5

Hb, hemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ -GT, γ -glutamyl transpeptidase.

Treatment and prognosis

The average length of patient stay in the hospital was 9.68 ± 4.20 days (range, 2–22 days). Patients received rifampicin and doxycycline or doxycycline combined with levofloxacin or moxifloxacin in patients with rifampicin intolerance. One patient underwent spermatic cord block, and one patient underwent right testicular mass resection. All patients had received antibiotic therapy for at least 6 weeks. One patient was lost follow-up, two patients had a poor prognosis, one had recurrence because of osteoarthropathy, and one had urinary dysfunction resulting from chronic prostatitis. The clinical symptoms in other patients resolved and the overall prognosis was good.

Discussion

Brucellosis is a zoonotic allergic disease caused by *Brucella*, which is a natural focus of an infectious disease.⁷ Human brucellosis can cause multiple types of organ damage after infection. Reproductive system involvement is one of the most common local manifestations of human brucellosis.⁸ The most common reproductive complication of brucellosis is testicular epididymitis, which accounts for 2% to 20% of brucellosis patients.⁹ Through this retrospective analysis, we found that the incidence of reproductive complications in brucellosis was 2.7% (22/801), which is consistent with the data in the literature (1.4% to 25%).^{10,11} However, the incidence rate is lower than that reported in the Chinese literature,^{4,5} which may be related to the characteristics of the population that was investigated, the diagnostic criteria that were used, the diagnostic procedures that were used, and the types of research that were performed (such as prospective or retrospective analysis).

Humans are generally susceptible to the disease, which mainly occurs in occupational exposure groups, such as herdsmen,

veterinarians, laboratory workers, and slaughterhouse workers. In these data, although 19 patients had a clear history of contact with cattle and sheep, this information is often neglected in the process of epidemiological data collection, which may lead to misdiagnosis and missed diagnosis. A published study³ showed that even in endemic areas, it is difficult for doctors to diagnose brucellosis when the patient only shows orchitis. Through this study, we found that most of the patients came from farming and pastoral areas. The number of male patients was higher compared with that of female patients (there was only one female patient). Age was predominantly between 40 and 56 years. Cases of brucellosis are more common from May to August each year, and the peak incidence occurs in July, which is consistent with the peak of non-reproductive system injury.¹²

Clinical manifestations and complications include fever, which is most typical, and sweating, fatigue, joint pain, anorexia, and weight loss, which are also common in reproductive system complications. Headache, cough, and muscle soreness also account for a certain proportion. In this study, the incidence of orchitis was 40.9%, which was higher compared with 31.8% of the results reported by Erdem et al.¹³ The incidence of right orchitis was higher compared with left orchitis. The incidence of unilateral and bilateral testicular and epididymis involvement was 36.4%, which was lower compared with 58.0% that was reported by Erdem et al.¹³ The incidence of orchitis with hydrocele was 22.7%, and the incidence of right orchitis combined with hydrocele was higher compared with left orchitis. This study also found that brucellosis affects the male reproductive system in addition to the presence of orchitis, and erectile dysfunction accounts for 68.2%. Prostatitis and urethral stricture can also be involved, and they are mainly manifested as an enlarged prostate, tenderness, inflammatory or purulent

secretions that can be seen after compression, and urination that is not smooth. Female patients mainly have vaginitis and cervicitis, which manifests as increased leucorrhea, irregular menstruation, and hypogastric pain. These are important clinical features for differentiating between brucellosis and reproductive complications.

CRP and ESR were more commonly increased in the laboratory test results, and some extent of liver injury can be seen, which was mainly increased by glutamyl transpeptidase (81.8%). Among the 22 patients, five patients had splenomegaly, six patients underwent lymph node ultrasonography, and four patients had lymphadenopathy. The main manifestations were enlargement of cervical, inguinal, and axillary lymph nodes. All 22 patients underwent chest X-ray examination, there was one case of bronchitis and one case of slight inflammation in the lower lingual segment of the left upper lobe. In this study, we found that testicular B-mode ultrasonography mainly manifested unilateral or bilateral testicular enlargement, soft tissue edema, and thickening of the hydrocele and spermatic cord. The testicular parenchyma echo was uneven, and some patients had bilateral epididymis enlargement.

All patients had received antibiotic therapy for at least 6 weeks. Antibiotic treatment included doxycycline combined with rifampicin, and rifampicin intolerant patients were treated with doxycycline combined with levofloxacin or moxifloxacin. One patient underwent spermatic cord occlusion, and one patient underwent right testicular mass resection. Among the 22 patients, one patient was lost follow-up. Among the remaining 21 patients, eight patients were followed for >5 years, 12 were followed for >2 to 3 years, and one was followed for 10 months. Two patients had a poor prognosis, one of whom had recurrence because of osteoarthropathy and one of whom had urinary dysfunction resulting from chronic prostatitis. The clinical symptoms in the

other patients resolved and their overall prognosis was good.

Conclusion

The clinical manifestations of brucellosis with reproductive system complications were different, and the incidence was low. Clinicians should take into consideration brucellosis in patients with unknown fever, testicular enlargement, prostatitis, urethral stricture, and cervicitis in endemic areas. Blood biochemistry and other related examinations should assessed a timely diagnosis, early treatment, and rational drug use should be achieved to avoid a misdiagnosis or a missed diagnosis. The aim is to improve the cure rate of brucellosis in reproductive system injury and to reduce the disability rate.

Consent

This study received verbal consent from the patients.


Declaration of conflicting interest

The authors declare that there is no conflict of interest. The review board at our hospital provided an exemption for this study. Data and details used in this study have been de-identified such that the identity of the patients may not be ascertained in any way.

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Supplemental Material

Supplemental material for this article is available online.

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