



FIVE CASES OF ACUTE ARTHRITIS: BRUCELLOSIS AND LITERATURE REVIEW

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Abstract

Brucellosis is a zoonotic disease frequently observed in regions where animal husbandry is intensive in Eastern and Southeast Anatolia. The most common transmission route is raw milk and unpasteurized dairy products. The condition can affect many organs and systems in the body, and clinical findings can vary depending on the location. This condition should be considered in the differential diagnosis of acute joint pain due to unknown causes. Early diagnosis of *Brucella* septic arthritis in endemic regions is important to prevent serious complications. Here, clinical, laboratory, and imaging data of five healthy patients with acute joint involvement who visited the outpatient clinic were presented with the support of visuals and literature.

Keywords: Brucellosis, endemic, arthritis, joint involvement

INTRODUCTION

Brucellosis is a zoonotic disease that is frequently observed in regions where animal husbandry is concentrated in Eastern and Southeast Anatolia. The most common route of transmission is through consumption of raw milk and unpasteurized dairy products obtained from animals infected with this gram-negative bacillus of the genus *Brucella* (1). After contamination, it first enters the reticuloendothelial system and spreads through the blood, causing various symptoms. The condition can affect many organs and systems, and clinical findings may vary depending on the location. It often presents as fever, fatigue, and non-specific widespread joint pain (2).

Osteoarticular involvement is a common finding in brucellosis. The most important clinical forms of osteoarticular arthritis are osteomyelitis, spondylitis, sacroiliitis, and peripheral arthritis.

Soft tissue involvement around the joint may also cause tenosynovitis and bursitis. In addition, it can cause serious damage, such as the destruction of vertebrae and abscess formation in paravertebral muscle tissue (3).

Although the first symptoms are usually complaints such as fatigue, sweating, and fever, in the presence of low back pain, the pain character resembles inflammatory pain and can be confused with rheumatic diseases. This is still an increasing problem in differential diagnosis, especially in developing countries. It should be considered in patients with acute joint pain of unknown cause. This section presents five cases of brucellosis treated in an outpatient clinic with acute joint involvement.

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DETAILS OF CASE REPORTS

Case 1

46-year-old male patient with a history of continuous low back pain and weakness for two weeks. His back pain was worse at night and could not be relieved with simple painkillers. He also stated that he had been in pain throughout the day for the last month and had difficulty walking due to the pain. Since the onset of pain, he had lost about 3 kg of weight, along with a decrease in his appetite. He mentioned no fever or night sweats. He had no known disease, no history of drug use, and no family history. In the locomotor system examination, we observed pain and joint movement limitation in both hips. The Fabere test was positive on the left side. Laboratory findings included: white blood cell (WBC) count of $8.700/\text{mm}^3$ (normal range: $3.500\text{--}11.000/\text{mm}^3$), hemoglobin of 14.6 g/dL (normal range: $12.8\text{--}16.8\text{ g/dL}$), C-reactive protein (CRP) of 29.9 mg/L (normal range: $0.1\text{--}5\text{ mg/L}$), and erythrocyte sedimentation rate (ESR) of 55 mm/hour (normal range: $0\text{--}20\text{ mm/hour}$). Rheumatic factor (RF), viral hepatitis B serology and anti-hepatitis C virus (anti-HCV) antibodies were negative. HLA-B27 was positive. Plain chest and pelvic X-ray results were normal. Magnetic resonance imaging (MRI) of the sacroiliac joint revealed similar changes; signal changes that may be compatible with bone marrow edema and inflammation were observed in the T2A series on the iliac and sacral bone faces overlooking the left sacroiliac joint. The findings were in favor of active sacroiliitis on the left and spondylodiscitis on the Thoracolumbar MRI (Figure 1). After a detailed analysis, he mentioned that he probably had eaten unpasteurized products. The Rose Bengal screening test (RBT) was positive, so a *Brucella* tube agglutination test was performed. The serum standard tube agglutination titer was $1/320$ (normal range: $<1/160$). He was referred to the infectious disease department, and the diagnosis of brucellosis was confirmed. The patient was treated with oral doxycycline and rifampicin for 8 weeks. Upon follow-up, the patient showed a significant decrease in low back pain, CRP levels returned to normal, and the *Brucella* agglutination test was positive at a $1/80$ titer. A non-steroidal anti-inflammatory drug (NSAID) was administered on demand.

Case 2

A 22-year-old male patient presented with a history of left hip pain for 2 weeks. He was referred to the orthopedic clinic because of inflammation. The joint was tender with a restricted range of motion. He had no history of trauma or drug use. He also complained of fatigue and low-grade fever. He stated that he lived in a village, that there were livestock nearby, and that animal husbandry was performed. During the examination, his

body temperature was elevated ($37.8\text{ }^{\circ}\text{C}$), and mild tenderness was noted over the right sacroiliac joint. The peripheral WBC count was 12.500 cells/mm^3 , CRP level was 45.1 mg/L (normal range: $0.1\text{--}5\text{ mg/L}$), and ESR was 76 mm/h (normal range: $0\text{--}20\text{ mm/hour}$). RF, viral hepatitis serology (HBsAg and anti-HCV), and HLA-B27 were negative. MRI of the left hip showed effusion and

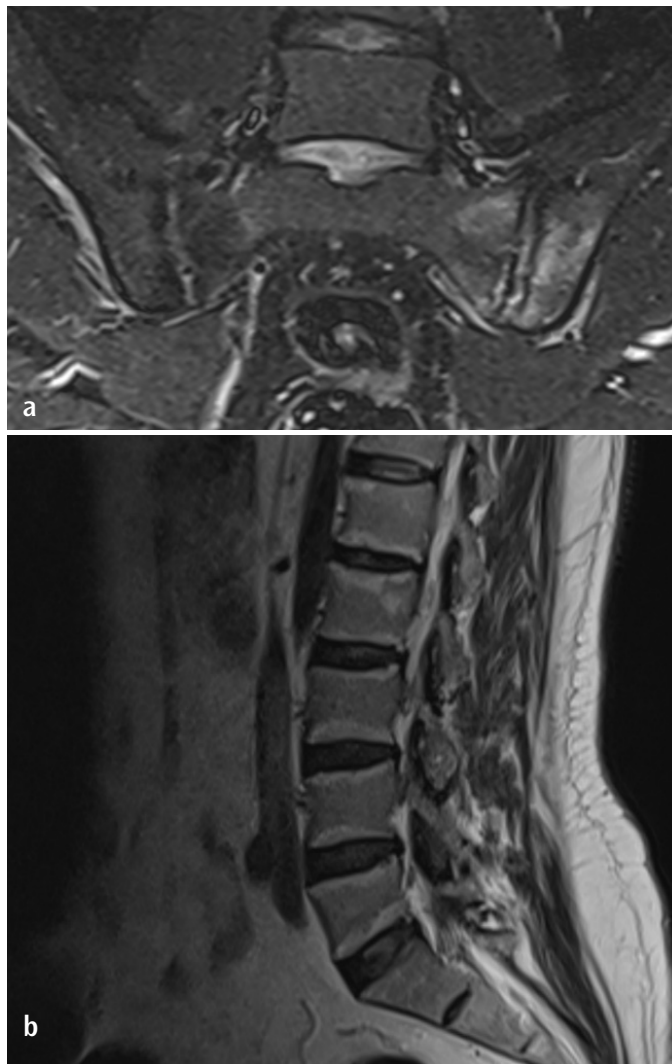


Figure 1. a) Sacroiliac MRI: Areas with millimetric cystic signal characteristics and slight irregularities were observed on the bone surfaces forming the sacroiliac joint on the right. On the left side, in addition to similar changes, signal changes that may be compatible with bone marrow edema and inflammation were observed in a T2A series of the iliac and sacral bone faces overlooking the sacroiliac joint. The findings were in favor of active sacroiliitis on the left. b) Thoracolumbar MRI: T1 and T2 are compatible with fatty degeneration in the lower thoracic vertebra and lumbar vertebra, and edema in the lumbar vertebra corpus appears suspicious for spondylodiscitis
MRI: Magnetic resonance imaging

a widespread focal area of enhanced marrow signal intensity in the femur bone (Figure 2). The RBT was positive, and the Wright agglutination test was positive at a 1/640 titer. After evaluation with an infectious disease physician regarding the differential diagnosis, the patient was treated. He received three months of rifampicin and doxycycline and was fully recovered. The following treatment with short-term NSAIDs for joint pain, his symptoms and complaints improved dramatically. Sulfasalazine was administered at a dose of 2000 mg/day for 6 months.

Case 3

A 42-year-old man was admitted with an 8-week history of left-sided back and buttock pain. His pain was not relieved by NSAID and progressively worsened over 4 weeks. He complained of listlessness, night sweating, and pain-restricting movements in bed and while walking. The morning stiffness lasted more than an hour. His left hip flexion was limited, and he was moderately tender to palpation at the right sacroiliac joint. The patient lived in a rural area and was engaged in animal husbandry. The blood results included an increased CRP level of 45.1 mg/L (normal range: 0.1-5 mg/L) and an increased ESR of 76 mm/hour (normal range: 0-20 mm/hour), and normal liver and renal function tests. RF, HBsAg and anti-HCV, and tuberculin skin tests were negative. HLA-B27 was positive. An X-ray examination of the hip was normal. MRI of the sacroiliac joint was performed in favor of active sacroiliitis, and the left hip showed enhanced marrow signal intensity and effusion (Figure 3a, b). The RBT for brucellosis was positive, and the Wright agglutination test was positive at 1/320 titers. The patient was initially treated with doxycycline and rifampicin for six weeks. The complaints of all patients decreased after treatment. CRP levels returned to normal, and the *Brucella* agglutination test was positive at a 1/40 titer after treatment.

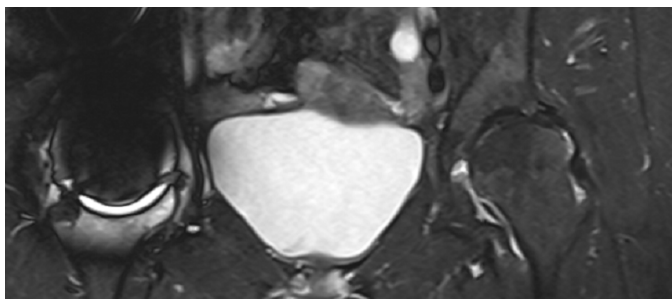


Figure 2. MRI of the left hip showing effusion and a widespread focal area of enhanced marrow signal intensity in the femur bone
MRI: Magnetic resonance imaging

Case 4

A 51-year-old female patient was admitted with a 3-week history of left knee pain. Her knee had worsened over the past 10 days and was swollen; she was unable to walk. The other complaints were listlessness, night sweating, and mild fever over the past 2 weeks. She had no known disease in her medical history. She mentioned that her son was a farmer in the village. The blood results included an increased CRP level of 18.2 mg/L (normal range: 0.1-5 mg/L), an increased ESR of 76 mm/h (normal range: 0-20 mm/hour), a normal WBC count of 13.300/mm³, and renal function tests. RF and viral hepatitis serology (HBsAg and anti-HCV) were negative, HLA-B27 was negative, and the anti-tuberculosis antibody test was negative. She aspirated

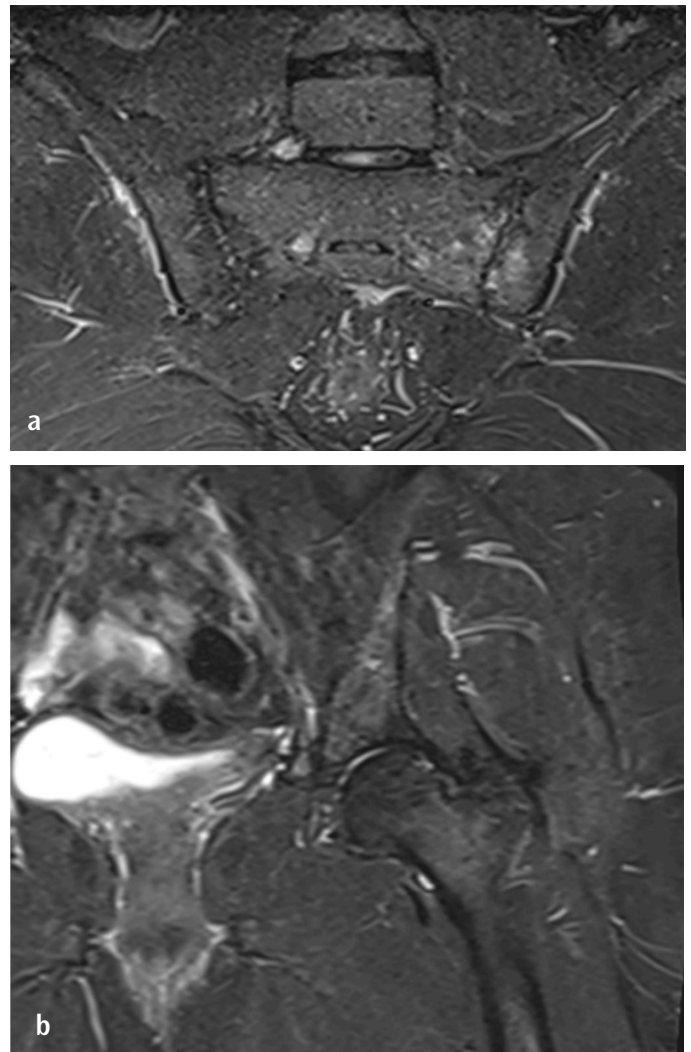


Figure 3. a) Active sacroiliitis is seen in the left iliac bone on T2WI, b) Magnetic resonance images of the left hip showing enhanced marrow signal intensity and effusion on T2WI
WI: Weighted imaging

the synovial fluid and sent a sample for culture. There was no bacterial growth in blood cultures, but *Brucella melitensis* was isolated in bursal aspiration fluid cultures on the fourth day of incubation. MRI of the left knee showed enhanced marrow signal intensity and effusion on T2WI (Figure 4). The RBT for brucellosis was positive, and the Wright agglutination test was positive at a 1/640 titer. The following treatment with NSAIDs, doxycycline, and rifampicin, her symptoms and complaints improved. Sulfasalazine was administered at 2000 mg/day for 6 months. *Brucella's* agglutination test was positive at a 1/80 titer.

Case 5

A 52-year-old man was admitted with a 4-week history of right shoulder pain and night sweating. The patient reported occasional tactile fevers over the past 2 weeks. He mentioned that his son was a farmer, and he had kept a few animals. He was moderately tender, with right shoulder palpation. He could not move his shoulder in any direction. The morning stiffness lasted more than 2 hours. Laboratory studies revealed a mildly elevated ESR of 43 mm/hour, CRP of 36.8 mg/L, and WBC count of 11.800/

mm³. Normal liver and renal function tests. RF and viral hepatitis serology (HBsAg and anti-HCV) were negative. HLA-B27 was positive, but the anti-tuberculosis antibody test was negative. Imaging methods were also used for differential diagnosis. The patient's right shoulder MRI revealed findings consistent with effusion and tendinitis (Figure 5a, b). The RBT for brucellosis was positive, and the Wright agglutination test revealed positivity for 1/320. He was referred to the infectious disease department, and the diagnosis of brucellosis was confirmed. The patient was treated with oral doxycycline (200 mg) daily and rifampicin (300 mg) three times a day, combined with absolute bed rest for six weeks. Upon follow-up, the patient showed a significant decrease in lower back pain, CRP levels returned to normal, and the *Brucella* agglutination test was positive at a 1/40 titer. NSAIDs were administered on demand.

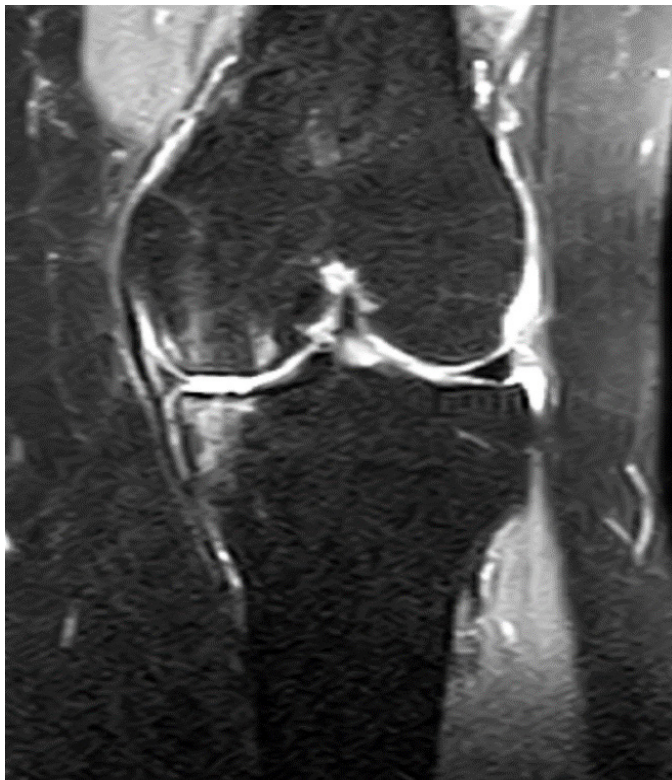


Figure 4. Magnetic resonance images of the left knee show increased joint fluid extending into the suprapatellar pouch. A millimetric Baker cyst is observed in the popliteal fossa

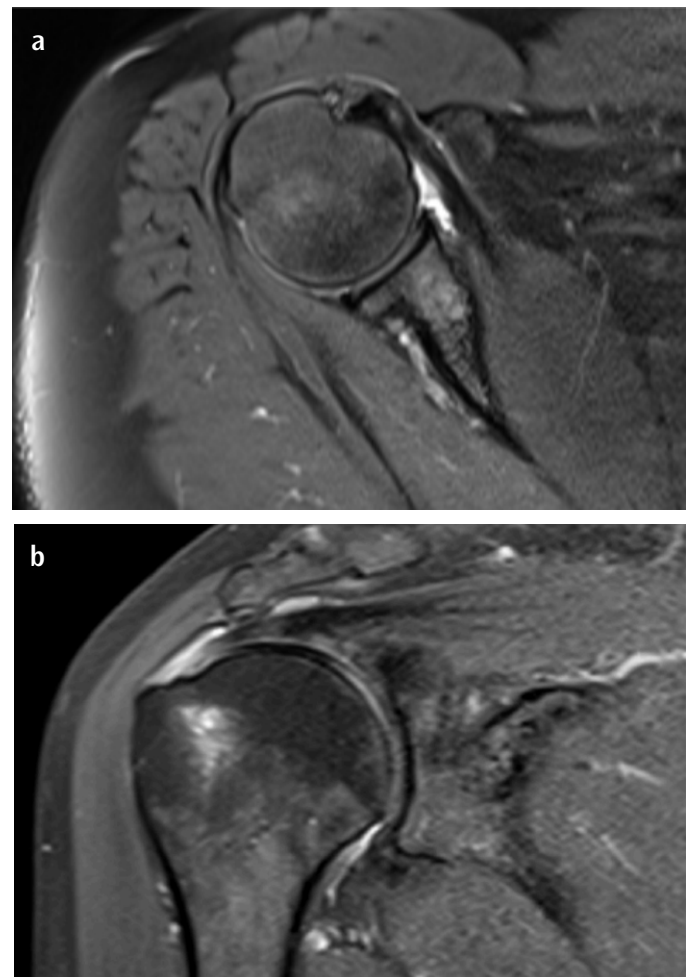


Figure 5. T2-weighted (a) sagittal and (b) coronal magnetic resonance images of right shoulder showing an increase in the subacromial subcoracoid bursa and intra-articular fluid in the bicipital groove (biceps tendinitis) and fluid around the subscapularis tendon (tendonitis)

DISCUSSION

In this study, five cases of acute joint involvement secondary to *Brucella abortus* infection were included. *Brucella* species (spp.) are highly virulent and cause acute and common infections in humans and animals. The most frequently isolated species of brucellosis worldwide is *B. melitensis*. The most common reservoirs are sheep and goats. *Abortus* is found especially in cattle. These gram-negative bacteria can persist in raw milk and other dairy products for a long time. They are inactivated by boiling and pasteurization (3,4).

This bacterium is known to cause neurological, cardiovascular, respiratory, and genitourinary infections and frequently causes musculoskeletal involvement (5).

Brucellosis is an important public health problem in Turkey, and various studies have shown that its prevalence varies between 1% and 7% in regions where it is endemic in Turkey. This study examined the situation in the Middle-Eastern Anatolia region. In different studies conducted in this region, cases were frequently (21.7%) reported in the Eastern Anatolia Region (6). In a prevalence study in Erzincan province, as seen in a study in the literature in 2007, RBT and *Brucella* antibodies were investigated with serological methods in 1715 people aged 15 and over in a non-probability sample in the province and its surroundings. Seropositivity was detected in 83 (4.83%) samples. RBT positivity was found to be 3.89% in the center and 8.55% in rural areas (7). Serology and culture are required to definitively diagnose brucellosis. Although isolation of *Brucella* spp. from blood or

other tissues is the gold standard for diagnosis, this approach makes diagnosis difficult due to the low rate of culture reproduction. In cases of joint involvement, isolating *Brucella* spp. in the relevant joint bursal aspiration fluid culture can be used for diagnosis. The most commonly used serological test is the serum agglutination test. Titers of 1:160 and above are considered significant in endemic areas. Routine blood markers, such as ESR and CRP, used to monitor infections are often high, but being normal does not rule out infection (3,8). In all cases, the serological values were high and returned to normal after optimal treatments as indicated in Table 1.

According to previous studies, osteoarticular involvement varies between 20% and 60%, and spondylitis due to spinal involvement is observed in 8-13% of cases. The most common musculoskeletal symptom of brucellosis is sacroiliitis, followed by peripheral arthritis (arthralgia), spondylitis, osteomyelitis, and bursitis (4,9). Sacroiliitis is usually unilateral, does not cause destruction, and responds to antibiotic treatment. Arthritis often presents as monoarthritis or asymmetric peripheral oligoarthritis. Peripheral *Brucella* arthritis usually affects large and weight-bearing hip, knee, and ankle joints. Generally, the onset of arthritis is acute and very painful, with redness, increased temperature, effusion, and limitations of movement in the affected joint. Arthritis is either infectious or reactive, and the frequency of arthritic development increases with increasing duration of infection. Peripheral arthritis responds to antibiotic therapy, but spontaneous recurrence may occur (10).

Table 1. Brief summary of the clinical and laboratory profiles of the five cases studied

Patient number	Age in years	Gender	Clinical history	Joint involved	CRP	Serology	HLA-B27	Treatments
Case 1	46	Male	Enflammatory back and lower back pain 1 h of morning stiffness, listlessness, and night sweats	Sacroiliac thoracolumbar vertebra	29.9 mg/dL	1/320	Positive	Doxy-rifampin acemetacin (120 mg)
Case 2	22	Male	Hip-groin pain difficulty walking and hip arthritis	L hip	45.1 mg/dL	1/640	-	Doxy/rifampicin naproksen 750 mg/day sle 2x2
Case 3	42	Male	Lower back pain, listlessness, night sweats	Sacroiliac	17 mg/dL	1/320	Positive	Doxy/rifampicin Acemetacin 120 mg
Case 4	51	Female	Knee pain, knee arthritis, listlessness, night sweats	L knee	18.2 mg/dL	1/640	-	Doxy/rifampicin sle 2x2
Case 5	52	Male	Shoulder pain, limited movement arthritis, night sweats	R shoulder	36.8 mg/dL	1/320	Positive	Doxy/rifamicin

L: Left; R: Right; mg: Miligram, slz: Sulfosalazine, Doxy: Doxycycline, MRI: Magnetic resonance imaging, CRP: C-reactive protein

Recent publications have supported the view that there may be a genetic predisposition associated with the *HLA-B27* gene in the development of osteoarticular complications. There are cases of first- and co-occurrence of AS brucellosis that can be confused with non-radiographic Ax-spondyloarthritis (SpA) in the same patient. The frequent occurrence of osteoarticular involvement should be kept in mind in terms of differential diagnosis, and it would be beneficial to evaluate patients with detailed examinations in this regard (11). In these cases, three patients were HLA-B27-positive. In both cases, the patients were given NSAIDs for a while.

Early bone changes are not evident on plain radiography, so MRI is important for early diagnosis. The differential diagnosis of infectious and inflammatory sacroiliitis is extremely important, as their treatments are very different. Early detection of sacroiliitis on MRI is important in the diagnosis of SpA, but the presence of sacroiliitis may cause overdiagnosis. While bilateral sacroiliitis is more common in spondyloarthritis, unilateral involvement involving soft tissue should be considered in septic cases in terms of differential diagnosis (12,13).

Because *Brucella* spondylitis and its associated damage can be confused with spinal tuberculosis (Pott disease), a history of tuberculosis should also be questioned in the differential diagnosis (14). The two cases mentioned here had active sacroiliitis and unilateral asymmetric involvement. Joint pain was completely resolved with a short-term NSAID administered after double antibiotic treatment.

The selection of the appropriate antibiotic combination should be based on the patient. In the triple regimen recommended by the World Health Organization, doxycycline (100 mg twice a day) plus rifampin (600 mg/day) plus streptomycin (1 g/day im 21 days) is recommended to be given for six months. After discontinuing streptomycin treatment at the end of three weeks, patients are switched to doxycycline and rifampin treatment only (3,15). The patients received dual medication (doxycycline and rifampicin treatment) for at least six weeks. In two cases (cases 2 and 4), additional sulfasalazine treatment (2000 mg/day) was administered for 6 months. NSAID treatment was administered in the necessary cases. No side effects were observed, and the patient's complaints about joint involvement and acute phase reactant levels decreased after treatment.

CONCLUSION

Brucellosis is considered an important health problem in Erzincan province. In patients with suspicion of brucellosis, occupational history, living space, and nutritional habits should be examined.

To protect against *Brucella* infection, the blood, milk, or tissue fluids of infected animals should be avoided, animal products should be cooked well, and hygiene rules should be observed. Additionally, appropriate protective measures should be taken for at-risk professional groups (farmers, veterinarians, laboratory workers, etc.).

Because of the different treatments, early recognition of infectious arthritis is important and brucellosis should be considered in these endemic areas. It was prepared with the thought that the facts presented would contribute to the literature and raise awareness in this regard.

Ethics

Informed Consent: Written and oral consent was obtained from all patients included in the study.

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