

Characteristics and Management of Brucellosis-Related Spondylodiscitis: A Prospective Study

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Abstract

Introduction: Brucellosis-Related Spondylodiscitis (BSD) presents diagnostic and therapeutic challenges due to nonspecific clinical signs, delayed appearance of radiological findings, and the lack of precise therapeutic consensus.

Objective: This study aimed to determine the epidemiological, clinical, biological, radiological, therapeutic, and outcome characteristics of BSD.

Patients and methods: A prospective study was conducted, including all patients hospitalized in the infectious diseases department between 2011 and 2020 with a confirmed diagnosis of BSD. Diagnosis was established based on a combination of clinical, biological, and radiological evidence.

Results: The study comprised 41 cases. The mean age of patients was 52.2±15.7 years, with a male predominance (71%). Consumption of contaminated dairy products (90.2%) was the primary mode of transmission. The average time to consultation was 101.5±68 days. Febrile spinal pain was reported in all cases. Wright serology was positive in all cases. *Brucella melitensis* was isolated in 5 blood cultures (12.8%). The lumbar spine was the most commonly affected site (65.8%). Reported complications included paravertebral abscesses (61%), psoas abscesses (29.3%), epiduritis (61%), and spinal cord compression (14.6%). The most commonly used antibiotic combination was doxycycline-rifampicin-trimethoprim-sulfamethoxazole (39%). The mean treatment duration was 7.3±3.1 months. Favorable outcomes were observed in 63.1% of cases.

Conclusion: Brucellosis-related spondylodiscitis remains a public health concern in endemic countries, warranting the implementation of strategies for eradicating animal brucellosis and establishing safety and hygiene measures for human prevention.

Keywords: Spondylodiscitis; Brucella; Wright's agglutination; Rifampicin; Tetracyclines; Prophylaxis.

Introduction

Brucellosis, also known as Malta fever, melitococcosis, sud-oralgic fever, and Mediterranean undulant fever [1], is an anthropozoonosis endemic in Mediterranean regions, the Middle East, Asia, Central and South America, and Africa [2,3]. Classic reservoirs of the bacteria are livestock animals, and transmission occurs through direct contact with infected animals or

their biological products, as well as through the ingestion of raw milk and derivatives [4,5]. In developed countries, brucellosis is considered an occupational disease with low prevalence due to widespread infection control in animals and milk pasteurization. However, in developing countries, it remains a significant public health concern due to its high prevalence, impact on both animal productivity and human health, leading to work absenteeism, high expenses for diagnosis, treatment, and erad-

ication programs [6,7].

Brucellosis is a systemic infection characterized by a wide clinical polymorphism. Osteoarticular involvement accounts for 10 to 80% of all focal forms of brucellosis [8]. Among these, Brucellosis-Related Spondylodiscitis (BSD) is the most frequent osteoarticular localization, comprising 2 to 65% of cases [9]. BSD poses diagnostic and therapeutic challenges due to its non-specific symptoms, delayed appearance of radiological anomalies compared to clinical symptoms, and the absence of a well-defined therapeutic consensus.

The objectives of our study were to:

- Describe the epidemiological, clinical, biological, and radiological aspects of BSD.
- Discuss the circumstances and diagnostic difficulties associated with BSD.
- Detail the therapeutic modalities and outcomes of BSD.

Patients and methods

We conducted a prospective study including all patients hospitalized in the infectious diseases department between 2011 and 2020 with a confirmed diagnosis of BSD. The diagnosis of BSD was established based on a combination of clinical, biological, and radiological evidence [7,10,11]:

- Clinical data consistent with the diagnosis.
- Spinal involvement confirmed through imaging.
- Detection of specific antibodies using Wright's agglutination test (WAT) with a titer greater than 1/160 and/or isolation of *Brucella* from blood or other specimens.

Results

Epidemiology

During the study period, a total of 157 patients were admitted to the infectious diseases department with a diagnosis of brucellosis, of which osteoarticular brucellosis was identified in 49 patients. BSD was confirmed in 41 patients, representing a frequency of 26.1% of all brucellosis cases and 83.7% of osteoarticular involvements. Within the same timeframe, 142 patients were hospitalized for infectious spondylodiscitis, with a brucella origin identified in 41 patients, resulting in a frequency of 28.9%. The peak of hospitalizations was observed in October (7 cases). Contamination predominantly occurred in the summer for 14 patients (34.1%).

We included 29 males (71%) and 12 females (29%). The male-to-female ratio was 2.42. The mean age of patients was 52.2±15.7 years, with the highest frequency observed in the age group between 50 and 60 years (31.7%). Contact with domestic animals was reported in 35 patients (85.4%). Sixteen patients (39%) were farmers. The consumption of raw milk and/or unpasteurized dairy products was reported in 37 patients (90.2%). Family history of brucellosis was described by 8 patients (19.5%).

Clinical study

The average time from onset of symptoms to consultation was 101.5±68 days, with a range of 21 to 330 days. The primary reason for consultation was spinal pain associated with fever in

all patients. Fever was reported by all patients during the course of their illness. Sweating was described by 31 patients (75.6%), mainly occurring at night and with an unpleasant odor.

The main osteoarticular symptom was spinal pain, which was present in all patients. Other symptoms included arthralgia (43.9%), myalgia (24.4%), and sacroiliac pain (12.2%). A temperature above 38°C was recorded in 22 patients (53.7%). Tenderness at the spinous processes and spinal stiffness were common (83% and 58.5% respectively). Paravertebral muscle spasm was present in 20 patients (48.8%), and pain in the sacroiliac joints was noted in 8 patients (19.5%). Neurological deficits were observed in 16 patients (39%), including motor deficits in 10 patients (24.4%), with 2 of them having cervical involvement. Sensory deficits were noted in 14 patients (34.1%). Two patients (4.8%) experienced urinary problems in the form of dysuria, and 1 patient had abolished osteotendinous reflexes (2.4%). Among patients with motor deficits, epiduritis and spinal cord compression were noted in 6 and 2 cases respectively.

Hepatomegaly and splenomegaly were found upon admission in 2 and 4 patients respectively. Axillary lymphadenopathy was reported in 1 patient (2.4%). Additionally, orchitis and sacroiliitis were associated with 2 patients (4.8%) and 4 patients (9.7%) respectively.

Biological study

Anemia was found in 9 patients (21.9%). Leukopenia was present in 4 patients (9.7%). Erythrocyte Sedimentation Rate (ESR) was measured in 39 patients, with an average of 50.4 ± 31.5 mm at the first hour. C-Reactive Protein (CRP) was measured in 33 patients, and it was positive in 27 patients (81.8%), with an average value of 49.6±61.3 mg/L. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) levels were measured in 39 patients (95.1%). Elevated ALT and AST levels above 40 IU/L were observed in 8 patients (20.5%) and 9 patients (23.1%) respectively. Gamma-Glutamyl Transferase (GGT) levels were measured in 27 patients (65.8%). Hepatic cholestasis was noted in 3 patients (11.1%).

Blood Cultures (BC) were performed in 39 patients (95.1%), and they were positive in 5 patients (12.8%). The isolated microorganism was *Brucella melitensis* in all cases. Among the 12 patients who presented with psoas abscess, *Brucella* testing in the aspirated abscess fluid was conducted in 7 patients, and it was negative in all cases. Wright's Agglutination Test (WAT) was performed for all patients and was positive in all cases, with titers ranging from 1/160 to 1/10240. Rose Bengal test was conducted in 40 patients (98%), and it was positive in 100% of cases.

Spinal Disc-Vertebral Biopsy (DVBD) was performed in 11 patients (26.8%). Histopathological examination revealed inflammatory changes in 7 patients (63.6%) and paravertebral abscess without specificity or signs of malignancy in 2 patients (18.2%). In our study, *Brucella* identification was not performed using the PCR technique. Moreover, DVBD showed caseous necrosis in 2 patients (18.2%).

Radiological study

All patients underwent standard spine radiography. Disc space narrowing was observed in 40 patients (97.6%). Erosion of the anterosuperior angle was noted in 10 patients (24.4%). Twenty-six patients underwent spinal Computed Tomography (CT) (63.4%) (Figure 1). CT revealed vertebral endplate ero-

sions in all patients. Hypodensity of the intervertebral disc was observed in 22 patients (84.6%). Magnetic Resonance Imaging (MRI) was performed on 32 patients (78%) (Figure 2). The disc showed hypointensity on T1-weighted images in 31 patients (96.9%) and hyperintensity on T2-weighted images in 30 patients (93.7%). Vertebral endplates were hypointense on T1-weighted and hyperintense on T2-weighted images in 29 patients (90.6%), enhancing after gadolinium injection in 27 patients (84.4%).

Overall, the radiological assessment revealed epiduritis in 25 patients (61%), paravertebral abscess in 25 patients (61%), psoas abscess in 12 patients (29.3%), and spinal cord compression in 6 patients (14.6%).

Bone scintigraphy was performed in 12 patients (29.3%). It showed increased uptake at the affected vertebrae in 10 patients (75%), associated with sacroiliac joint uptake in 3 patients (25%).

Single-level involvement was observed in 30 patients (73.1%), of which 4 had multifocal involvement spanning ≥ 3 vertebrae (13.3%). The lumbar spine was the most frequently affected site (65.8%). Contiguous involvement was noted in 3 patients: the thoracolumbar junction was affected in 2 patients with concurrent thoracic or lumbar involvement (1 case each). One patient had involvement of the lumbar and lumbosacral regions. Simultaneous involvement of the cervical, thoracic, and lumbar regions was observed in 1 patient (Table 1).

Treatment

Rifampicin along with a tetracycline (doxycycline and oxytetracycline) were prescribed for all patients. Cotrimoxazole was prescribed for 16 patients (39%), and only 4 patients (9.7%) were treated with ciprofloxacin (Table 2). The average duration of treatment was 7.3 ± 3.1 months, ranging from 3 to 16 months. Corticosteroids were prescribed for 1 patient (2.4%) who presented with bilateral radicular compression.

Among the 12 patients with psoas abscess, radioguided abscess drainage was performed in 7 patients (58.3%). Indications for drainage were based on the significant size of the abscess, with an average size of 10.2 ± 2.9 cm, and lack of regression under medical treatment. No patients underwent surgical abscess drainage. Nine patients received anti-tuberculosis treatment in combination with anti-brucellar treatment for an average duration of 12.2 ± 4.7 months, ranging from 7 to 23 months. Anti-tuberculosis treatment was initiated in 5 patients directly, of whom 4 had motor deficits.

The indication for this treatment was based on:

- The destructive nature of lesions observed in spinal MRI (1 patient).
- Positive tuberculin skin test (Mantoux test) in 3 patients and/or positive detection of Koch’s bacillus in 1 patient.
- Caseous necrosis revealed by DVBD in 2 patients or in a biopsy of a dorsal cutaneous fistula in 1 patient.

We introduced a trial of anti-tuberculosis treatment in 3 patients due to the lack of improvement in clinical symptoms with anti-brucellar treatment alone. One patient was treated with both anti-tuberculosis and anti-brucellar treatments due to therapeutic relapse characterized by bilateral cruralgia and right lower limb weakness.

All patients were advised to use pain relievers and antipyretics, as well as to rest.

Outcome

The mean follow-up duration was 36 ± 5 months. Favorable outcomes were observed in 24 patients (63.1%). All patients achieved afebrile status within an average of 3.7 ± 2.9 days, with disappearance of spinal pain and absence of anatomical or functional sequelae. On the biological level, CRP levels normalized within an average of 59.9 ± 57.5 days, ranging from 4 to 180 days, and follow-up imaging showed significant improvement in spinal lesions.

Sequels were observed in 14 patients (36.8%). These consisted of spinal pain in 12 patients (31.6%) and/or spinal stiffness in 1 patient (2.6%). Sensory deficits in the form of paresthesias were present in 3 patients (7.9%). These paresthesias were bilateral in 2 patients and unilateral in 1 patient. No patients retained residual motor deficits. No cases of death were observed in our study.

Table 1: Levels of spinal involvement in brucellar spondylodiscitis.

Level	Number	Percentage (%)
Cervical	4	9.7
Thoracic	7	17.1
D12-L1	3	7.3
Lumbar	27	65.8
L5-S1	5	12.2

Table 2: Different antibiotic combinations used in the management of brucellar spondylodiscitis.

	Number	Percentage (%)
Rifampin + Doxycycline + Cotrimoxazole	16	39
Rifampin + Doxycycline	14	34.2
Rifampin + Oxytetracycline	7	17.1
Rifampin + Doxycycline + Ciprofloxacin	4	9.7



Figure 1: Lumbar spine contrast-enhanced CT scan: Sagittal reconstructions in bone (b) and soft tissue (a) windows showing disc space narrowing at L3-L4 with irregular vertebral endplates, subchondral geodes, peri-lesional vertebral osteosclerosis, and anterior vertebral osteophytosis. Increased density of prevertebral soft tissues and epidural space is observed, indicative of a 6mm-thick epiduritis extending over the height of 2 vertebrae, compressing the nerve roots of the cauda equina (arrow).

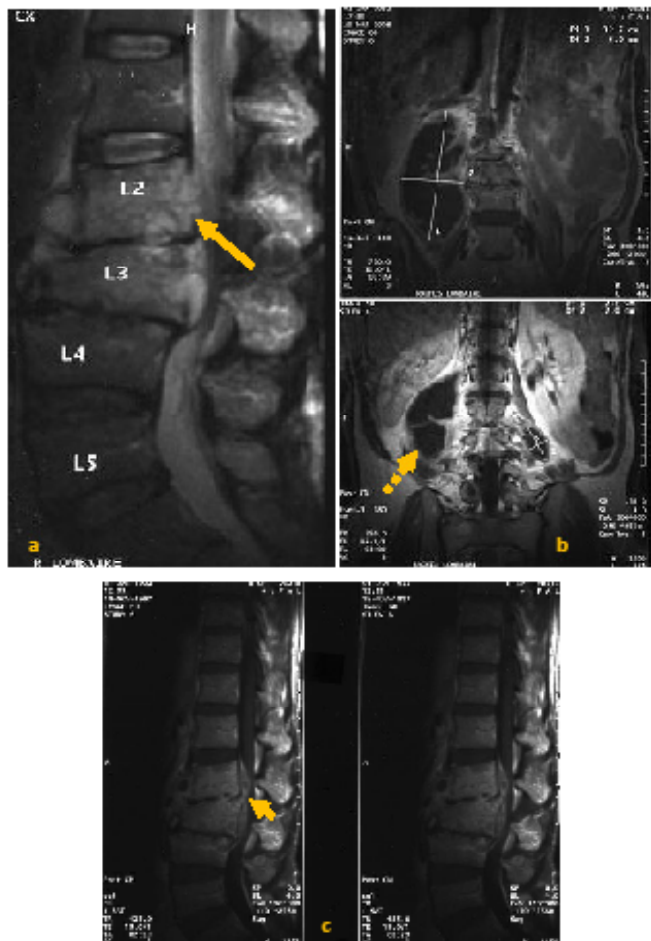


Figure 2: MRI of the lumbar spine in sagittal T2 STIR (a) and T1 with fat saturation and gadolinium contrast-enhanced coronal (b) and sagittal (c) sections demonstrating diffuse T2 hyperintensity involving the disc and vertebral bodies (arrow), heterogeneously enhancing after gadolinium injection, along with an epiduritis (arrowhead) compressing the cauda equina nerve roots and a bilateral psoas abscess (dotted arrow) more clearly visible in the coronal sections, measuring 12.5x6 cm on the right and 2x3.7 cm on the left.

Discussion

Epidemiology Brucellosis is a globally distributed zoonosis, predominantly prevalent in Mediterranean regions, the Middle East, Asia, Central and South America, and Africa [12,13]. According to the World Health Organization (WHO), around 500,000 cases of human brucellosis are reported each year [14,15]. However, its true incidence is often underestimated and varies from country to country. It has significantly declined in developed countries [12,16]. Nevertheless, the incidence of human brucellosis varies in endemic areas, ranging from 0.1 to 200 cases per 100,000 population per year [15,17]. These variations can be attributed to high endemicity of animal brucellosis, increased animal import rates in developing countries [18], and the absence of an effective brucellosis control strategy [7,19].

Brucellar spondylodiscitis constitutes 3 to 29% of all brucellosis cases [10,13,20,21], and 2 to 68% of brucellosis-related osteoarticular infections [9,22-25]. Moreover, brucellosis accounts for 17 to 48% of all cases of spondylodiscitis in Turkey and Spain [26-28], whereas it represents only 0.4% in France [29,30].

Clinical study

Patients usually consult for spinal pain, which was reported in 92 to 100% of the cases [10,31]. Systemic symptoms were reported among BSD cases, including fever, which has an undu-

lant characteristic [12,32], nocturnal and malodorous sweating, asthenia, weight loss and anorexia [14,33]. In our study, fever was reported among all patients and sweating among 75.6% of the cases. As for the osteoarticular signs, they are generally represented by spinal pain, arthralgia, myalgia [34,35] and sometimes by pain in the sacroiliac joints in the event of associated sacroiliitis.

In fact, during brucellosis there is a succession of different phases. Following the incubation period during which the bacterium multiplies, *Brucella* colonizes the cells of the reticulo-endothelial system, which constitutes the acute phase which is manifested by an undulant suduro-algic fever. Later on, the disease might progress to a subacute phase characterized by the alleviation of fever due to the partial control of the infection by the immune system and by the appearance of secondary sites of the disease. When the evolution is beyond one year, brucellosis evolves towards a chronic phase [36,37]. Therefore, brucellosis is characterized by myriad and non-specific symptoms, whether it's associated by osteoarticular sites or not.

Biological study

The diagnosis of BSD might be confirmed by isolation of *Brucella* by culture or by nucleic acid amplification assays which enable rapid diagnosis of the disease. Otherwise, serological tests remain the primary tools for the diagnosis and post-therapeutic follow-up of brucellosis [38]. In fact, the isolation of *Brucella* can be done from different biological samples such as the intervertebral disc, bone tissue or paravertebral abscess during surgery or by aspiration or by percutaneous discovertebral biopsy [39]. These interventional invasive procedures were required among 0% to 8.5% among series [40]. Therefore, blood cultures and serological tests are of immense help and thus reduce the need for interventional procedures in order to confirm the diagnosis.

Radiological study

As for the radiological evaluation, MRI remain the diagnostic method of choice in spondylodiscitis, epidural abscess and cord or root compression relevant to brucellosis. In MRI, the lesion is found as destructive appearance at antero-superior corner of vertebrae accompanied by prominent osteosclerosis, which is a pathognomonic finding during brucellosis [39].

In default, when MRI is not available, CT scan might help during the diagnostic process. The affected intervertebral disc appears hypodense due to edema and abscess. This is a reliable sign of disc infection [41]. The involvement of the soft tissue results in an obliteration of the fatty planes. An abscess appears as a rounded lesion with a hypodense center and a hyperdense peripheral crown which is strongly enhanced after injection of contrast product [41]. Epidural involvement is also better explored with the injection of contrast products [9].

Treatment

The aims of antimicrobial therapy are to treat acute infection, relieve symptoms and prevent relapse. The agents often used in the treatment of BSD are rifampicin, doxycycline, trimethoprim/sulfamethoxazole, ciprofloxacin, gentamicin and streptomycin [42]. Antibiotic treatment must combine at least two active antibiotics in order to reduce the rate of therapeutic failure and relapse when treatment is stopped [43]. The World Health Organization recommend the use of doxycycline (100 mg twice a day) plus rifampin (600 mg/day) plus streptomycin (1 g per day for 21 days). After 3 weeks, patients continue treat-

ment with doxycycline plus rifampin over six months [44]. In our study, treatment duration were longer, which might lead to the increase of adverse effects and possibly the emergence of antibiotic resistance. Along with medical treatment, surgical procedure might be required for a specific patients with spinal abscess, vertebral collapse, bone destruction and cord compression [42].

To conclude, BSD remain a public health concern in endemic countries warranting the implementation of an urgent strategy for the eradication of animal brucellosis and the implementation of food safety and hygiene measures for human prevention.

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