ELSEVIER

CrossMark

The Spine Journal 15 (2015) 2509–2517

THE SPINE JOURNAL

Clinical Study

Comparison of brucellar and tuberculous spondylodiscitis patients: results of the multicenter "Backbone-1 Study"

Hakan Erdem, MD[1,*], Nazif Elaldi, MD[2], Ayse Batirel, MD[3], Sani Aliyu, MD[4], Gonul Sengoz, MD[5], Filiz Pehlivanoglu, MD[5], Ergys Ramosaco, MD[6], Serda Gulsun, MD[7], Recep Tekin, MD[8], Birgul Mete, MD[9], Ilker Inanc Balkan, MD[9], Dilek Yildiz Sevgi, MD[10], Efthymia Giannitsioti, MD[11], Archontoula Fragou, MD[11], Selcuk Kaya, MD[12], Birsen Cetin, MD[13], Tunc Oktenoglu, MD[14], Aygul DoganCelik, MD[15], Banu Karaca, MD[16], Elif Sahin Horasan, MD[17], Mehmet Ulug, MD[18], Asuman Inan, MD[19], Safak Kaya, MD[7], Esra Arslanalp, MD[20], Selma Ates-Guler, MD[21], Ayse Willke, MD[20], Sebnem Senol, MD[22], Dilara Inan, MD[23], Ertugrul Guclu, MD[24], Gunay Tuncer-Ertem, MD[25], Meliha Meric-Koc, MD[20], Meltem Tasbakan, MD[26], Seniha Senbayrak, MD[19], Gonul Cicek-Senturk, MD[27], Fatma Sırmatel, MD[28], Gulfem Ocal, MD[3], Sesin Kocagoz, MD[29], Hulya Kusoglu, MD[29], Tumer Guven, MD[30], Ali Irfan Baran, MD[31], Behiye Dede, MD[32], Fatma Yilmaz-Karadag, MD[33], Sukran Kose, MD[34], Hava Yilmaz, MD[35], Gonul Aslan, MD[27], D. Ashraf ALGallad, MD[36], Salih Cesur, MD[25], Rehab El-Sokkary, MD[36], Nural Bekiroğlu, PhD[37], Haluk Vahaboglu, MD[33]

[1]*Department of Infectious Diseases and Clinical Microbiology, Gulhane Medical Academy, Ankara, Turkey*
[2]*Department of Infectious Diseases and Clinical Microbiology, Cumhuriyet University School of Medicine, Sivas, Turkey*
[3]*Department of Infectious Diseases and Clinical Microbiology, Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey*
[4]*Clinical Microbiology and Public Health Laboratory, Cambridge University Hospitals Foundation Trust, Addenbrooke's Hospital, Cambridge, UK*
[5]*Department of Infectious Diseases and Clinical Microbiology, Haseki Training and Research Hospital, Istanbul, Turkey*
[6]*University Hospital Center "Mother Teresa", Infectious Diseases Hospital, Tirana, Albania*
[7]*Department of Infectious Diseases and Clinical Microbiology, Diyarbakir Training and Research Hospital, Diyarbakir, Turkey*
[8]*Department of Infectious Diseases and Clinical Microbiology, Dicle University School of Medicine, Diyarbakir, Turkey*
[9]*Department of Infectious Diseases and Clinical Microbiology, Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey*
[10]*Department of Infectious Diseases and Clinical Microbiology, Sisli Etfal Training and Research Hospital, Istanbul, Turkey*
[11]*Department of Internal Medicine, Athens University Medical School, Attikon University General Hospital, Athens, Greece*
[12]*Department of Infectious Diseases and Clinical Microbiology, Karadeniz Technical University School of Medicine, Trabzon, Turkey*
[13]*Department of Infectious Diseases and Clinical Microbiology, Koc University School of Medicine, Istanbul, Turkey*
[14]*Department of Neurosurgery, Koc University School of Medicine, Istanbul, Turkey*
[15]*Department of Infectious Diseases and Clinical Microbiology, Trakya University School of Medicine, Edirne, Turkey*
[16]*Department of Infectious Diseases and Clinical Microbiology, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey*
[17]*Department of Infectious Diseases and Clinical Microbiology, Mersin University School of Medicine, Mersin, Turkey*
[18]*Department of Infectious Diseases and Clinical Microbiology, Private Umit Hospital, Eskisehir, Turkey*
[19]*Department of Infectious Diseases and Clinical Microbiology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey*
[20]*Department of Infectious Diseases and Clinical Microbiology, Kocaeli University School of Medicine, Kocaeli, Turkey*
[21]*Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Sutcu Imam University, Kahramanmaras, Turkey*
[22]*Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Celal Bayar University, Manisa, Turkey*
[23]*Department of Infectious Diseases and Clinical Microbiology, Akdeniz University School of Medicine, Antalya, Turkey*
[24]*Department of Infectious Diseases and Clinical Microbiology, Sakarya University School of Medicine, Sakarya, Turkey*
[25]*Department of Infectious Diseases and Clinical Microbiology, Ankara Training and Research Hospital, Ankara, Turkey*
[26]*Department of Infectious Diseases and Clinical Microbiology, Ege University School of Medicine, Izmir, Turkey*
[27]*Department of Infectious Diseases and Clinical Microbiology, Diskapi Yildirim Beyazit Training & Research Hospital, Ankara, Turkey*
[28]*Department of Infectious Diseases and Clinical Microbiology, Izzet Baysal University School of Medicine, Bolu, Turkey*
[29]*Department of Infectious Diseases and Clinical Microbiology, Acibadem University School of Medicine, Istanbul, Turkey*
[30]*Department of Infectious Diseases and Clinical Microbiology, Ankara Atatürk Training & Research Hospital, Ankara, Turkey*
[31]*Department of Infectious Diseases and Clinical Microbiology, Yuzuncuyil University School of Medicine, Van, Turkey*
[32]*Department of Infectious Diseases and Clinical Microbiology, Umraniye Training and Research Hospital, Istanbul, Turkey*
[33]*Department of Infectious Diseases and Clinical Microbiology, Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey*

http://dx.doi.org/10.1016/j.spinee.2015.09.024

[34]Department of Infectious Diseases and Clinical Microbiology, Tepecik Training and Research Hospital, Izmir, Turkey
[35]Department of Infectious Diseases and Clinical Microbiology, Ondokuz Mayis University School of Medicine, Samsun, Turkey
[36]Infection Control Unit, Zagazig University Hospitals, Az Zagazig, Egypt
[37]Department of Biostatistics, School of Medicine, Marmara University, Istanbul, Turkey

Received 1 July 2015; revised 24 August 2015; accepted 3 September 2015

Abstract

BACKGROUND CONTEXT: No direct comparison between brucellar spondylodiscitis (BSD) and tuberculous spondylodiscitis (TSD) exists in the literature.
PURPOSE: This study aimed to compare directly the clinical features, laboratory and radiological aspects, treatment, and outcome data of patients diagnosed as BSD and TSD.
STUDY DESIGN: A retrospective, multinational, and multicenter study was used.
PATIENT SAMPLE: A total of 641 (TSD, 314 and BSD, 327) spondylodiscitis patients from 35 different centers in four countries (Turkey, Egypt, Albania, and Greece) were included.
OUTCOME MEASURES: The pre- and peri- or post-treatment spinal deformity and neurologic deficit parameters, and mortality were carried out.
METHODS: Brucellar spondylodiscitis and TSD groups were compared for demographics, clinical, laboratory, radiological, surgical interventions, treatment, and outcome data. The Student *t* test and Mann-Whitney *U* test were used for group comparisons. Significance was analyzed as two sided and inferred at 0.05 levels.
RESULTS: The median baseline laboratory parameters including white blood cell count, C-reactive protein, and erythrocyte sedimentation rate were higher in TSD than BSD (p<.0001). Prevertebral, paravertebral, epidural, and psoas abscess formations along with loss of vertebral corpus height and calcification were significantly more frequent in TSD compared with BSD (p<.01). Surgical interventions and percutaneous sampling or abscess drainage were applied more frequently in TSD (p<.0001). Spinal complications including gibbus deformity, kyphosis, and scoliosis, and the number of spinal neurologic deficits, including loss of sensation, motor weakness, and paralysis were significantly higher in the TSD group (p<.05). Mortality rate was 2.22% (7 patients) in TSD, and it was 0.61% (2 patients) in the BSD group (p=.1).
CONCLUSIONS: The results of this study show that TSD is a more suppurative disease with abscess formation requiring surgical intervention and characterized with spinal complications. We propose that using a constellation of constitutional symptoms (fever, back pain, and weight loss), pulmonary involvement, high inflammatory markers, and radiological findings will help to differentiate between TSD and BSD at an early stage before microbiological results are available.

Keywords: Brucellosis; Complication; Outcome; Sequelae; Spondylodiscitis; Tuberculosis

FDA device/drug status: Not applicable.

Author disclosures: ***HE:*** Nothing to disclose. ***NE:*** Nothing to disclose. ***AB:*** Nothing to disclose. ***SA:*** Nothing to disclose. ***GS:*** Nothing to disclose. ***FP:*** Nothing to disclose. ***ER:*** Nothing to disclose. ***SG:*** Nothing to disclose. ***RT:*** Nothing to disclose. ***BM:*** Nothing to disclose. ***IIB:*** Nothing to disclose. ***DYS:*** Nothing to disclose. ***EfG:*** Nothing to disclose. ***AF:*** Nothing to disclose. ***SelK:*** Nothing to disclose. ***BC:*** Nothing to disclose. ***TO:*** Nothing to disclose. ***ADC:*** Nothing to disclose. ***BK:*** Nothing to disclose. ***ESH:*** Nothing to disclose. ***MU:*** Nothing to disclose. ***AI:*** Nothing to disclose. ***SaK:*** Nothing to disclose. ***EA:*** Nothing to disclose. ***SAG:*** Nothing to disclose. ***AW:*** Nothing to disclose. ***SebS:*** Nothing to disclose. ***DI:*** Nothing to disclose. ***ErG:*** Nothing to disclose. ***GTE:*** Nothing to disclose. ***MMK:*** Nothing to disclose. ***MT:*** Nothing to disclose. ***SenS:*** Nothing to disclose. ***GCS:*** Nothing to disclose. ***FS:*** Nothing to disclose. ***GO:*** Nothing to disclose. ***SesK:*** Nothing to disclose. ***HK:*** Nothing to disclose. ***TG:*** Nothing to disclose. ***AIB:*** Nothing to disclose. ***BD:*** Nothing to disclose. ***FYK:*** Nothing to disclose. ***SuK:*** Nothing to disclose. ***HY:*** Nothing to disclose. ***GA:*** Nothing to disclose. ***DAA:*** Nothing to disclose. ***SC:*** Nothing to disclose. ***RE:*** Nothing to disclose. ***NB:*** Nothing to disclose. ***HV:*** Nothing to disclose.

We have no competing interests to declare.

* Corresponding author. Department of Infectious Diseases and Clinical Microbiology, GATA School of Medicine, Gulhane Askeri Tıp Akademisi, Enfeksiyon Hastalıklar A.D., Etlik, Ankara 06018, Turkey.
E-mail address: hakanerdem1969@yahoo.com (H. Erdem)

Introduction

Spinal infection involving the intervertebral discs and the adjacent vertebrae, interchangeably termed as spondylodiscitis, disc space infection, or vertebral osteomyelitis, is an infectious complication that is difficult to treat. Although nowadays mortality from spondylodiscitis is rare because of the availability of antimicrobial treatment compared with the pre-antibiotic era [1], patients still experience therapeutic failure, frequent relapses, and sequelae [2]. The etiologic agents can be broadly divided into conventional bacterial pathogens causing pyogenic infection (such as staphylococci, streptococci, and Gram negatives) and atypical pathogens such as *Brucella* sp. and *Mycobacterium tuberculosis*. Brucellar spondylodiscitis (BSD) and tuberculous spondylodiscitis (TSD) are endemic in many parts of the world [3–5]. For instance, a local study from the Mediterranean Region, where brucellosis is endemic, showed that one-third of all spondylodiscitis cases were due to brucellosis whereas TSD accounted for only 5% of the cases [6].

There are studies comparing pyogenic spondylodiscitis (PSD) and TSD patients in the literature [7]. There are also studies comparing the clinical features of all three types of spondylodiscitis (PSD, TSD, and BSD) [8]. However, despite the complicated nature of BSD with frequent osteoarticular involvements, it is generally underestimated and, to the best of our knowledge, no direct comparison between BSD and TSD alone exists in the literature. Thus, in Backbone-1 study, we aim to directly compare the clinical features and the laboratory aspects of BSD and TSD. A separate study (Backbone-2) will provide outcome analysis for TSD and is therefore not included here.

Materials and methods

Study design, setting, and patients

This retrospective multicenter survey included TSD and BSD patients from 35 different centers in four countries (Turkey, Egypt, Albania, and Greece). This study was approved ethically by the institutional review board of Dr Lutfi Kirdar Education and Research Hospital in Istanbul.

Inclusion criteria

Patients who presented with clinical and radiological evidence of inflammation of one or more vertebrae or discitis plus microbiological evidence or histopathologic evidence on bone or paravertebral soft tissue specimens or clinical and radiological response to antimicrobial therapy were included in the study.

Microbiological evidence includes one or more of the following for TSD:

(a) Isolation of *M. tuberculosis* in culture of blood, bone, bone marrow, deep soft tissues, or (paravertebral, epidural, or psoas) abscess
(b) Positive microscopy using Ziehl-Neelsen staining for acid-fast bacilli from bone, bone marrow, deep soft tissue, or (paravertebral, epidural, or psoas) abscess or any sterile body tissue
(c) Positive tuberculin skin test
(d) Positive microbiological culture using fully automated or semi-automated rapid culture systems (BACTEC 460TB)
(e) Positive polymerase chain reaction for *M. tuberculosis* complex.

Microbiological evidence includes one or more of the following for BSD:

(a) A positive Wright standard agglutination test with a titer of ≥1/160
(b) A positive Brucella Coombs test with a titer of ≥1/160
(c) A positive enzyme-linked immunosorbent assay test for Brucellae
(d) Isolation of *Brucellae* spp. from blood, bone, bone marrow, deep soft tissue, or abscess (paravertebral, epidural or psoas) culture.

Radiologic clues of spondylodiscitis were detected according to basic concepts [9,10].

Exclusion criteria

Patients who were <18 years of age and with growth of pyogenic bacteria or fungi in the culture of the materials obtained from blood, bone, bone marrow, deep soft tissue or abscess material were excluded from the study.

BSD patients were treated with the various combinations of doxycycline, rifampicin, streptomycin, trimethoprim-sulfamethoxazole, ciprofloxacin, and ceftriaxone according to general therapeutic concepts [11] for a mean of 13.61±6.22 weeks. Accordingly, TSD patients were treated with standard anti-tuberculous medications [12] for a mean of 11.6±2.5 months.

EVIDENCE & METHODS

Context
The authors present results of a retrospective multicenter study examining differences in the clinical presentation and outcome of patients with Brucellar spondylodiscitis as compared with tuberculous spondylodiscitis.

Contribution
The authors report on the cases of 641 patients from 35 different countries with a relatively even distribution of tubercular versus Brucellar spondylodiscitides. The clinical course of tuberculous spondylodiscitis appears to be more aggressive with a higher rate of abscess formation and need for surgical intervention. The authors propose a number of factors that could be used to differentiate tuberculous from Brucellar spinal infection.

Implications
Clearly, the true utility of this study rests on the need to differentiate Brucellar from tuberculous spondylodiscitis in a clinical setting. While presenting a large series of patients with useful data from the standpoint of epidemiology and medical informatics, the evidence presented is Level IV in nature due to the study's design and limitations. While the metrics proposed as being indicative of tuberculous spinal infection may be of some use, their true validity should be tested in additional independent cohorts.

—The Editors

Definitions

Vertebral osteomyelitis (=spondylodiscitis) is defined as infection of the intervertebral disc and the adjacent vertebrae.

Clinical cure is defined as resolution of all signs and symptoms without any sequelae.

Therapeutic failure is defined as inability to achieve therapeutic goals, which include pain relief, maintenance of mechanical stability of the spine, preservation or restoration of sensory or motor neurologic functions. This is assessed by clinical and laboratory evaluation of patients regarding the parameters of persistence or deterioration of symptoms and the absence of a decline in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels.

Spinal complications were defined as any sensory or motor neurologic deficit, spinal instability, and any spinal deformity (kyphosis, scoliosis, kyphoscoliosis, or Gibbus deformity) and abscess formation.

Spinal instability was defined as abnormal movement of spinal segments to applied loads out of the normal constraints.

Sequelae was defined as persistent pain, abnormal physical findings, or functional limitation for longer than 6 months after treatment.

Neurologic deficit is compromise or loss of sensory or motor neurologic function(s) by compression of the spinal cord or nerve roots.

Gibbus deformity is a type of structural kyphosis resulting from wedge-shaped vertebral bodies.

Scoliosis is a form of deformity caused by curvature of the spine in the coronal plane.

Kyphosis is posterior curvature of the thoracic spine in the sagittal plane.

Data collection and statistical methods

All demographics, clinical, laboratory, radiological, surgical intervention, treatment, and outcome data were retrieved from patient charts by participant centers and were entered into a computer database. The SPSS in the Windows V.17.0 Software (Chicago, IL, USA) program was used for statistical documentation. Categorical variables were presented as frequency and percentage, continuous variables were presented as mean±standard deviation (range) or, where required, median (interquartile range). Numeric data were first tested for normality and then analyzed using Student *t* test for parametric data, the Mann-Whitney *U* test was used for variables for nonparametric data for group comparisons (patients with BSD vs. patients with TSD). Significance was analyzed as two sided and inferred at 0.05 levels.

Results

In this study, 314 tuberculous and 327 BSD patients were included. The mean (standard deviation) age of the patients for BSD and TSD were 52.4±16.6 and 50.6±18.0 years, respectively (p=.20). Males made up 163 (51.9%) of TSD and 172 (52.6%) of BSD patients.

Table 1
Comparison of baseline patient characteristics for tuberculous and brucellar spondylodiscitis groups (N=641)

Variable	Tuberculous (n=314)	Brucellar (n=327)	p-Value
Median age (IQR), y	53 (35–65)	55 (41–65)	.344
Male Gender, n (%)	163 (51.9)	172 (52.6)	.862
History of brucellosis, n (%)	0 (0.0)	6 (1.83)	**.031**
History of familial brucellosis, n (%)	2 (0.64)	2 (0.61)	1.0
History of tuberculosis, n (%)	4 (1.27)	0 (0.0)	.057
History of familial tuberculosis, n (%)	4 (1.27)	1 (0.31)	.208
Comorbidities, n (%)			
Diabetes mellitus	36 (11.46)	49 (14.98)	.189
Chronic renal failure	14 (4.46)	10 (3.06)	.351
Malignancy	7 (2.23)	2 (0.61)	.101
Immunosuppression*	7 (2.23)	2 (0.61)	.101
Others†	60 (19.11)	22 (6.73)	**<.0001**
Other site of concomitant involvement, n (%)	51 (16.24)	11 (3.36)	**<.0001**
Respiratory system	29 (56.86)	0 (0.0)	ND
Meningitis	13 (25.49)	3 (27.27)	ND
Lymphoid system	6 (11.76)	0 (0.0)	ND
Gastrointestinal system	1 (1.96)	0 (0.0)	ND
Peripheral joint	2 (3.92)	2 (18.18)	ND
Urogenital system‡	0 (0.0)	6 (54.54)	ND
Clinical findings/constitutional symptoms, n (%)			
Fever	139 (44.27)	222 (67.89)	**<.0001**
Fatigue	161 (51.27)	196 (59.94)	**.027**
Loss of appetite	154 (49)	119 (36.39)	**.001**
Sweating	152 (48.4)	162 (49.54)	.774
Arthralgia	131 (41.72)	146 (44.65)	.454
Lumbago/local tenderness	261 (83.12)	207 (63.3)	**.002**
Back pain/local tenderness	176 (56.05)	99 (30.28)	**<.0001**
Weight loss	132 (42.04)	46 (14.07)	**<.0001**
Median (IQR) weight loss, kg	6 (5–10)	5 (4–8)	.174
Hepatomegaly	41 (13.06)	80 (24.46)	**.0002**
Splenomegaly	34 (10.83)	68 (20.79)	**.0006**
Median (IQR) time symptoms onset to therapy, d	30 (18–54)	25 (15–45)	**.002**

IQR, interquartile range.

* Treatment with antineoplastic chemotherapy, glucocorticoids, TNF-alpha blockers.

† Hypertension, coronary artery disease, chronic obstructive pulmonary disease, bronchial asthma, nephrolithiasis.

‡ Orchitis or epidydimorchitis.

Significant values are presented as bold (p<0.05).

Patients with TSD had more involvement of concomitant sites (particularly the respiratory system) when compared with BSD (51 [16.24%] vs. 11 [3.36%], p<.0001). BSD patients complained of fever and fatigue more frequently compared with TSD cases, whereas TSD patients suffered loss of appetite, back pain and local tenderness, and weight loss more frequently than BSD patients. Blood parameters such as white blood cell count, CRP, and ESR levels were higher in TSD than BSD (p<.0001 for all comparisons). A comparison of demographic characteristics, clinical, and laboratory features for TSD and BSD patients is presented in Table 1.

Table 2
Results of laboratory tests for tuberculous and brucellar spondylodiscitis patient groups (N=641)

Variable	Tuberculous (n=314)	Brucellar (n=327)	p-value
Baseline laboratory analyses, Median (IQR)			
White blood cell count, ($\times 10^9$/L)	8.0 (6.3–10.6)	6.65 (5.2–8.3)	**<.0001**
C-reactive protein, (mg/L)	30 (8.0–78.2)	17 (3.4–50.0)	**<.0001**
Erythrocyte sedimentation rate, (mm/h)	70 (43–95)	42 (25–62.3)	**<.0001**
Positive tuberculin skin test, n/N (%)	158/211 (74.9)	5/96 (5.21)	**<.0001**
No. of patients with positive culture, n/N (%)	110/271 (40.59)	81/301 (26.91)	**.0005**
Positive culture specimens, n (%)			
Blood	2 (0.74)	73 (24.25)	NA
Bone biopsy	12 (4.43)	1 (0.33)	NA
Bone marrow	1 (0.37)	7 (2.33)	NA
Deep soft tissue	16 (5.9)	–	NA
Abscess material	78 (28.78)	–	NA
Paravertebral abscess	54 (19.93)	–	NA
Epidural abscess	5 (1.85)	–	NA
Psoas abscess	21 (7.75)	–	NA
Lymph node	1 (0.37)	–	NA
Microorganisms, identified, n (%)			
Mycobacterium tuberculosis complex	59 (53.63)	–	NA
Mycobacterium tuberculosis	49 (44.54)	–	NA
Non-tuberculous mycobacteria	1 (0.91)	–	NA
Brucella melitensis	–	38 (46.91)	NA
Untyped	–	43 (53.09)	NA
Serological analyses, n (%)			
Positive STA test (≥1:160), n/N	–	301/320 (94.06)	NA
ELISA test for brucellosis	–	19 (5.81)	NA
Positive immunoglobulin M	–	3 (15.79)	NA
Positive immunoglobulin G	–	6 (31.58)	NA
Antimicrobial susceptibility test, n (%)	3 (0.96)	–	NA
Histopathological examination, n/N (%)	200	28	NA
Compatible with disease	147 (73.5)	16 (57.14)	
Non-specific findings	38 (19.0)	10 (35.71)	
Insufficient material	15 (7.5)	2 (7.14)	
Site of histopathological examination, n (%)	200	28	NA
Bone	52 (26.0)	6 (23.8)	
Paravertebral soft tissue	94 (47.0)	19 (73.8)	
Bone+paravertebral soft tissue	15 (7.5)	3 (10.7)	
Other foci	36 (18.0)	–	
Level of histopathological examination, n (%)	166	28	NA
Cervical	7 (4.21)	2 (7.14)	
Thoracic	82 (49.39)	6 (23.8)	
Lumbar	76 (45.78)	20 (71.43)	
Sacral	1 (0.6)	–	

STA, standard tube agglutination; NA, not applicable; ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range.
Significant values are presented as bold (p<0.05).

Baseline laboratory tests, microbiological, radiological, and histopathologic data related to TSD and BSD patients are presented in Table 2.

Patients with TSD had imaging data that were more compatible with spondylodiscitis than those with BSD (n=298 [94.9%] vs. 293 [89.6%], p=.012). The presence of prevertebral, paravertebral, epidural, and psoas abscess formations was more frequently observed in TSD; anterior involvement, loss of vertebral corpus height and calcification was also significantly more common in TSD when compared with BSD (p<.01 for all comparisons). Whereas thoracic and thoracolumbar involvement was in favor of TSD, lumbar involvement was more frequent in BSD (p<.0001 for all comparisons). Accordingly, both multiple (>2 vertebrae) level and non-adjacent multiple-level involvements were higher in TSD (p<.05 for all comparisons). All the comparisons between the groups are presented in Table 3.

Surgical interventions in general and percutaneous sampling or abscess drainage were more frequently applied in TSD (p<.0001 for all comparisons). Therapeutic response was evaluated basically with clinical parameters and CRP or ESR normalization. The mean normalization periods of ESR were 56.4±54.55 and 36.17±34.71 days for TSD and BSD, respectively. Despite the median days between the groups being the same, the difference was statistically different (p<.0001). Accordingly, the mean normalization periods of CRP were 37.86±46.53 and 26.63±34.4 days for TSD and BSD,

Table 3
Imaging findings for tuberculous and brucellar spondylodiscitis patient groups (N=641)

	Tuberculous (n=314)	Brucellar (n=327)	p-Value
Imaging method, n (%)			
Magnetic resonance imaging	289 (92.04)	301 (92.05)	.996
Computerized tomography	118 (37.58)	71 (21.71)	**<.0001**
Bone/soft tissue scintigraphy	26 (8.28)	15 (4.59)	.1
Imaging findings, n (%)			
Compatible with spondylodiscitis	298 (94.9)	293 (89.6)	**.012**
Increased activity consistent with spondylodiscitis	213 (67.83)	226 (69.11)	.728
Increased activity consistent with spondylitis	81 (25.79)	99 (30.28)	.207
Prevertebral abscess	37 (11.78)	17 (5.19)	**.003**
Paravertebral abscess	188 (59.87)	70 (21.41)	**<.0001**
Epidural abscess	54 (17.19)	27 (8.26)	**<.0001**
Psoas abscess	75 (23.88)	15 (4.59)	**<.0001**
Radiculitis	16 (5.09)	14 (4.28)	.626
Neo-ossification	19 (6.05)	14 (4.28)	.311
Anterior involvement	114 (36.31)	72 (22.02)	**<.0001**
Multiple (>2 vertebrae) involvement	159 (50.63)	174 (53.21)	.514
Loss of vertebral corpus height	151 (48.09)	78 (23.85)	**<.0001**
Calcification	36 (11.46)	15 (4.59)	**0.001**
Involved vertebrae			
Cervical, n (%)	15 (4.78)	10 (3.06)	.261
Cervicothoracic, n (%)	3 (0.96)	1 (0.31)	.364
Thoracic, n (%)	153 (48.73)	58 (17.74)	**<.0001**
Thoracolumbar, n (%)	40 (12.74)	14 (4.28)	**<.0001**
Lumbar, n (%)	175 (55.73)	247 (75.54)	**<.0001**
Lumbosacral, n (%)	24 (7.64)	29 (8.87)	.573
Sacral, n (%)	27 (8.59)	49 (14.98)	**.012**
Mean±SD number of involved vertebrae	2.5±1.0	2.3±1.0	**.013**
Median (range) number of involved vertebrae	2 (1-8)	2 (1–8)	**.023**
Multiple (>2 vertebrae) level involved, n (%)	106 (33.76)	70 (21.41)	**.0005**
Non-adjacent multiple level involvement, n (%)	26 (8.28)	13 (3.98)	**.023**

Significant values are presented as bold (p<0.05).

respectively (p<.0001). Although mortality did not differ between the two groups, post-treatment sequelae were more frequent in TSD patients (p<.0001). Comparisons of surgical interventions, follow-up findings, and outcomes for TSD and BSD patients are presented in Table 4.

The predominant neurologic deficits detected in TSD and BSD patients included loss of sensation, motor weakness, and paralysis. Both the number of patients with spinal complications and the number of spinal neurologic deficits were significantly higher in the TSD group (p<.0001 for all comparisons). The TSD group also had a significantly higher frequency of spinal instabilities and spinal deformities, including gibbus, kyphosis, scoliosis, and kyphoscoliosis (p<.001 for all comparisons). Spinal complications of TSD and BSD patients are presented in Table 5.

Discussion

The majority of our spondylodiscitis patients were over 50 years of age, as expected from the literature [5,13]. Although comorbidities such as diabetes mellitus are known to facilitate the development of spondylodiscitis [14], our study did not show any significant difference in the frequency of diabetes mellitus, chronic renal failure, malignancy, and immunosuppression between the two groups. It is not unexpected that one-sixth of TSD cases had concomitant involvement particularly at the respiratory tract. A Spanish study reported a 30% incidence of active or healed pulmonary tuberculosis among 37 TSD cases [15]. In our study, BSD patients tended to be more febrile and experienced fatigue more frequently compared with TSD cases, highlighting the systemic affects of brucellosis [11]. The more destructive nature of TSD is demonstrated by the more common features of back pain, local tenderness, and spinal complications including neurologic deficits. We found inflammatory parameters such as white blood cell count, CRP, and ESR to be significantly higher in TSD cases. The median values of CRP and ESR for BSD patients were about half that of TSD cases (30 mg/L and 70 mm/h for TSD patients compared with 17 mg/L and 42 mm/h for BSD cases, respectively).

The infectious agent was recovered in 40% of TSD and one-fourth of BSD cases, with culture processes more likely to yield a pathogen in TSD than BSD. However, the pathogens were more likely to be recovered from blood cultures in BSD whereas local aspiration specimens were the source of recovery in TSD patients. This is not unexpected as *Brucella* species do not grow well on solid media [16–19]. In our study, serologic tests were particularly useful in BSD, accounting for the majority of BSD diagnoses and reducing the need for invasive sampling. We used histopathologic examination to aid diagnosis, particularly in patients with thoracic or lumbar paravertebral soft tissue involvement. Although most of the histopathology was done on TSD cases (64% compared with less than 10% of BSD cases), a histologic diagnosis was made in about three-fourth and half of TSD and BSD cases, respectively.

Magnetic resonance imaging (MRI) was the most sensitive method in the radiological diagnosis of spondylodiscitis [5,20]. According to our data, MRI followed by computerized tomography were the most frequently used imaging method, with TSD more frequently compatible with spondylodiscitis in 95% of the cases compared with BSD patients in 90% of the cases. Based on MRI, TSD was mostly localized to thoracic and thoracolumbar regions whereas BSD predominantly involved the lumbar area. In addition to this, either adjacent or non-adjacent multiple-level involvements were more frequent in TSD patients. Consequently, abscess formation in and around the infected area including prevertebral, paravertebral, psoas, and epidural sites were

Table 4
Comparison of surgical interventions, follow-up findings, and outcomes for tuberculous and brucellar spondylodiscitis patient groups (N=641)

Variable	Tuberculous (n=314)	Brucellar (n=327)	p-Value
No. of patients having surgical intervention, n (%)	211 (67.19)	35 (10.7)	**<.0001**
Percutaneous biopsy and abscess drainage	134 (42.68)	23 (7.03)	**<.0001**
Transpedicular stabilization and fusion	23 (7.32)	2 (0.61)	**<.0001**
Multiple surgical interventions	22 (7.0)	1 (0.31)	**<.0001**
Laminectomy	13 (4.14)	8 (2.45)	.229
Drainage and intermittent irrigation	7 (2.23)	4 (1.22)	.375
Corpectomy and stabilization	1 (0.32)	0 (0.0)	.489
Pseudofusion after a year	0 (0.0)	2 (0.61)	.499
Discectomy	1 (0.32)	3 (0.92)	.624
Reason for surgical intervention, n (%)			
Diagnostic	49 (23.22)	3 (8.57)	.071
Diagnostic+therapeutic	68 (32.23)	3 (8.57)	**.0041**
Therapeutic	78 (36.97)	29 (82.86)	**<.0001**
Surgical complication occurred, n (%)	2 (0.95)	0 (0.0)	1.0
Reasons of surgical intervention, n (%)			
Pain	57 (27.01)	13 (37.14)	.162
Neurologic deficit	24 (11.37)	8 (22.86)	.061
Not specified	130 (61.61)	14 (40.0)	**.0162**
Response to treatment			
Clinical (fever, pain relief, etc.) cure, n (%)	230 (73.25)	308 (94.19)	**<.0001**
CRP normalization, n (%)	246 (78.34)	242 (74.0)	.198
Median time (IQR) to CRP normalization, d	25 (15, 42.5)	19 (12, 30)	**<.0001**
ESR normalization, n (%)	198 (63.06)	235 (71.87)	**.017**
Median time (IQR) to ESR normalization, d	28 (42,60)	28 (20, 40.5)	**<.0001**
Follow-up imaging results, n (%)	198	190	
Cure	48 (15.29)	40 (12.23)	.261
Radiological improvement	137 (43.63)	143 (43.73)	.979
Worsening of radiological findings	13 (4.14)	7 (2.14)	.146
Outcomes, n (%)			
Mortality	7 (2.22)	2 (0.61)	.1
Post-treatment sequelae	77 (24.52)	12 (3.67)	**<.0001**
Kyphosis	35 (11.15)	0 (0.0)	ND
Gibbus deformity	18 (5.73)	0 (0.0)	ND
Motor weakness	17 (5.41)	2 (0.61)	ND
Paraplegia	17 (5.41)	0 (0.0)	ND
Scoliosis	15 (4.78)	3 (0.92)	ND
Loss of sensation	12 (3.82)	1 (0.31)	ND
Kyphoscoliosis	3 (0.95)	1 (0.31)	ND
Vertebral compression fracture	2 (0.64)	0 (0.0)	ND
Persistent pain	2 (0.64)	5 (1.53)	ND
Urinary retention	1 (0.32)	0 (0.0)	ND
Polyneuropathy	1 (0.32)	0 (0.0)	ND

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ND, not determined; IQR, interquartile range.
Significant values are presented as bold (p<0.05).

more common in TSD cases. Paravertebral abscesses were the most frequent, affecting approximately 60% of TSD and 20% of BSD cases. Linked to the expanding area of pyogenic infection, loss of vertebral corpus height was seen in half of TSD patients and about one-fourth of BSD cases, with TSD cases more likely to have anterior involvement or calcification. We observed more suppurative disease among patients with TSD, with two-thirds of TSD patients requiring surgical or percutaneous interventions such as abscess drainage, transpedicular stabilization, and fusion and laminectomy compared with only 10% of BSD cases. Although we did not observe any difference in radiological regression or progression based on serial imaging between the two groups, the excessive bone and soft tissue involvement seen in TSD cases would partly explain the delayed therapeutic responses manifested by late ESR and CRP normalizations in TSD cases compared with BSD patients. Median normalization times for ESR and CRP were seen within a month of therapy in both groups although a significant heterogeinity existed among the patients.

The presence of neurologic complications is always of grave concern in patients with spondylodiscitis. We observed a high frequency of neurologic complications among our patients on admission; four-fifths of hospitalized TSD patients had spinal complications and neurologic deficits, including loss of sensation and motor weakness. This compares to a 53% incidence of weakness in one Korean series of TSD cases [21]. On the other hand, BSD remains a relatively less

Table 5
Spinal complications for tuberculous and brucellar spondylodiscitis patient groups (N=641)*

	Pre-treatment			Peri- or post-treatment		
	Tuberculous (n=314)	Brucellar (n=327)	p-Value	Tuberculous (n=314)	Brucellar (n=327)	p-Value
Patients with spinal complication	256 (81.5)	109 (33.3)	**<.0001**	33 (10.51)	19 (5.81)	**.029**
No. of spinal neurologic deficit	124 (39.49)	45 (13.76)	**<.0001**	20 (6.37)	6 (1.83)	**.004**
Loss of sensation	74 (23.57)	19 (5.81)	ND	8 (2.55)	1 (0.03)	ND
Motor weakness	97 (30.89)	28 (8.56)	ND	11 (3.5)	5 (1.53)	ND
Paralysis	14 (4.46)	2 (0.06)	ND	1 (0.03)	0 (0.0)	ND
Patients with spinal instability	66 (21.02)	20 (6.12)	**<.0001**	5 (1.59)	5 (1.53)	1.0
Patients with spinal deformity	51 (16.24)	22 (6.73)	**.0002**	13 (4.14)	9 (2.75)	.335
Gibbus deformity	18 (5.73)	4 (0.12)	ND	0 (0.0)	3 (0.92)	ND
Kyphosis	21 (6.69)	11 (3.36)	ND	9 (2.87)	2 (0.06)	ND
Scoliosis	9 (2.87)	6 (1.83)	ND	4 (1.27)	4 (0.12)	ND
Kyphoscoliosis	3 (0.96)	1 (0.03)	ND	0 (0.0)	0 (0.0)	ND

ND, not determined.
* Data presented as n (%).
Significant values are presented as bold (p<0.05).

destructive process. We detected spinal complications in a third of patients admitted with BSD and either instability or deformity in 6% of the cases. This is similar to the findings from one of the largest comparative series of PSD, TSD, and BSD in the literature, where about a fifth of 105 BSD cases had a neurologic deficit on presentation [8]. It is quite clear that TSD is a much more destructive process, and therefore, the goals of disease eradication, pain relief, and restoration of neurologic function and spinal stability [3] would be much more difficult to achieve in TSD cases than with BSD.

In summary, we present one of the largest comparative studies of TSD and BSD in the literature. Our findings are very similar to those of earlier smaller comparative studies which suggest that constitutional symptoms, raised inflammatory markers, pus formation, and posterior spinous element involvement are predictive markers of TSD [22,23]. We propose that using a constellation of constitutional symptoms (fever, back pain, and weight loss), pulmonary involvement, high inflammatory markers, and radiological findings will help to differentiate between TSD and BSD at an early stage before microbiological results are available.

References

[1] Kulowski J. The Orr treatment of pyogenic osteomyelitis. Ann Surg 1936;103:613–24.
[2] Ulu-Kilic A, Karakas A, Erdem H, Turker T, Inal AS, Ak O, et al. Update on treatment options for spinal brucellosis. Clin Microbiol Infect 2014;20:O75–82.
[3] Berbari EF, Steckelberg JM, Osmon DR. Osteomyelitis. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Churchill Livingstone; 2015. p. 1322–3.
[4] McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. Clin Infect Dis 2002;34:1342–50.
[5] Nolla JM, Ariza J, Gomez-Vaquero C, Fiter J, Bermejo J, Valverde J, et al. Spontaneous pyogenic vertebral osteomyelitis in nondrug users. Semin Arthritis Rheum 2002;31:271–8.
[6] Kaya S, Ercan S, Kaya S, Aktas U, Kamasak K, Ozalp H, et al. Spondylodiscitis: evaluation of patients in a tertiary hospital. J Infect Dev Ctries 2014;8:1272–6.
[7] Yoon YK, Jo YM, Kwon HH, Lee FJ, Park SY, Park SY, et al. Differential diagnosis between tuberculous spondylodiscitis and pyogenic spontaneous spondylodiscitis: a multicenter descriptive and comparative study. Spine J 2015;15:1764–71.
[8] Colmenero JD, Jimenez-Mejias ME, Sanchez-Lora FJ, Reguera JM, Palomino-Nicás J, Martos F, et al. Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and comparative study of 219 cases. Ann Rheum Dis 1997;56:709–15.
[9] Wang D. Diagnosis of tuberculous vertebral osteomyelitis (TVO) in a developed country and literature review. Spinal Cord 2005;43:531–42.
[10] Jung NY, Jee WH, Ha KY, Park CK, Byun JY. Discrimination of tuberculous spondylitis from pyogenic spondylitis on MRI. AJR Am J Roentgenol 2004;182:1405–10.
[11] Gul HC, Erdem H. Brucellosis (brucella species). In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglass, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Elsevier Co.; 2015. p. 2584–9.
[12] Fitzgerald DW, Sterling TR, Haas DW. Mycobacterium tuberculosis. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Churchill Livingstone; 2015. p. 2787–818.
[13] Raya Cruz M, Vilchez Rueda HH, Marinescu CI, Sarasibar Ezcurra H, Riera Jaume M, Payeras Cifre A. Infectious spondylitis in the Balearic Islands: an analysis of 51 cases. Rev Clin Esp 2015;215:251–7.
[14] Kapsalaki E, Gatselis N, Stefos A, Makaritsis K, Vassiou A, Fezoulidis I, et al. Spontaneous spondylodiscitis: presentation, risk factors, diagnosis, management, and outcome. Int J Infect Dis 2009;13:564–9.
[15] Rodriguez-Gomez M, Willisch A, Fernandez-Dominguez L, Lopez-Barros G, Garcia-Porrua C, Gonzalez-Gay MA. Luberculous spondylitis: Epidemiologic and clinical study in non-HIV patients from northwest Spain. Clin Exp Rheumatol 2002;20:327–33.
[16] Erdem H, Inan A, Elaldi N, Beeching N, Tekin R, Gulsun S, et al. Respiratory system involvement in brucellosis: the results of the Kardelen study. Chest 2014;145:87–94.
[17] Erdem H, Kilic S, Sener B, Acikel C, Alp E, Karahocagil M, et al. Diagnosis of chronic brucellar meningitis and meningoencephalitis: the results of the Istanbul-2 study. Clin Microbiol Infect 2013;19:E80–6.

[18] Ozturk-Engin D, Erdem H, Gencer S, Kaya S, Baran AI, Batirel A, et al. Liver involvement in patients with brucellosis: results of the Marmara study. Eur J Clin Microbiol Infect Dis 2014;33:1253–62.
[19] Erdem H, Elaldi N, Ak O, Gulsun S, Tekin R, Ulug M, et al. Genitourinary brucellosis: results of a multicentric study. Clin Microbiol Infect 2014;20:O847–53.
[20] Carragee EJ. The clinical use of magnetic resonance imaging in pyogenic vertebral osteomyelitis. Spine (Phila Pa 1976) 1997;22:780–5.
[21] Weng CY, Chi CY, Shih PJ, Ho CM, Lin PC, Chou CH, et al. Spinal tuberculosis in non-HIV-infected patients: 10 year experience of a medical center in central Taiwan. J Microbiol Immunol Infect 2010;43:464–9.
[22] Turunc T, Demiroglu YZ, Uncu H, Colakoglu S, Arslan H. A comparative analysis of tuberculous, brucellar and pyogenic spontaneous spondylodiscitis patients. J Infect 2007;55:158–63.
[23] Celik AK, Aypak A, Aypak C. Comparative analysis of tuberculous and brucellar spondylodiscitis. Trop Doct 2011;41:172–4.