



Retrospective Evaluation of 14 Patients with Bone and Joint Tuberculosis in Mersin, Turkey

Kemik-Eklem Tüberkülozlu 14 Olgunun Retrospektif Olarak Değerlendirilmesi, Mersin, Türkiye

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ABSTRACT

Introduction: Tuberculosis (TB), caused by *Mycobacterium tuberculosis* complex (MTC), is a granulomatous infection and can be localized in pulmonary and extrapulmonary sites. Of all TB cases, 1-3% and of the extrapulmonary TB cases, 10-11% is bone and joint TB. In this study we aimed to retrospectively analyze the demographical, microbiological, radiological and histopathological characteristics of the patients with suspected bone and joint TB.

Materials and Methods: Between January 2005-July 2019, 285 patients with suspected bone and joint TB were examined retrospectively. Mycobacterial culture and/or Ehrlich-Ziehl-Neelsen (EZN) positive patients were included into the study. The demographic characteristics, pathological, radiological and microbiological findings of the patients were evaluated.

Results: MTC positivity was detected in 14 of 285 cases by EZN and/or culture. Mean age of the cases was 34.85 years (min-max: 2-64 years). No physical examination findings compatible with TB were detected in the patients. Moreover, it was found that all of the cases had pain and/or movement limitation, trauma in two cases, contact story with TB in one case. Chronic granulomatous inflammations characterized with caseification necrosis were detected in 5 cases. Radiological findings of 11 cases were consistent with TB.

Conclusion: Bone-joint TB might be an important reason of chronic bone-joint pains and movement limitations. Therefore, we suggest that clinical, radiological, histopathological and microbiological findings should be evaluated together in the diagnosis of bone joint TB.

Key Words: Bone and joint tuberculosis; Mycobacterial bone infections; Diagnosis; Treatment

ÖZ

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Giriş: Tüberküloz (TB), *Mycobacterium tuberculosis complex* (MTC)'in neden olduğu akciğer ve akciğer dışı bölgelerde lokalize olabilen granülomatöz bir enfeksiyondur. Tüm TB olgularının %1-3'ü, akciğer dışı TB olgularının %10'u kemik-eklem TB'sidir. Bu çalışmada kemik-eklem TB şüpheli hastaların demografik, mikrobiyolojik, radyolojik ve histopatolojik özelliklerinin retrospektif olarak değerlendirilmesi amaçlanmıştır.

Materyal ve Metod: Ocak 2005-Temmuz 2019 tarihleri arasında kemik-eklem TB şüphesi olan 285 hasta retrospektif olarak incelendi. Mikobakteriyel kültür ve/veya Ehrlich-Ziehl-Neelsen (EZN) pozitifliği olan hastalar çalışmaya dahil edildi. Hastaların demografik özellikleri, patolojik, radyolojik ve mikrobiyolojik bulguları değerlendirildi.

Bulgular: EZN ve/veya kültür ile 285 olgunun 14'ünde MTC pozitifliği tespit edilmiştir. Olguların yaş ortalaması 34.85 (min-max: 2-64) yıl idi. Olgularda TB ile uyumlu fizik muayene bulguları saptanmamıştır. Tüm olgularda ağrı ve/veya hareket kısıtlılığı, iki olguda travma, bir olguda TB ile temas öyküsü tespit edilmiştir. Kazeifikasyon nekrozu ile karakterize kronik granülomatöz inflamasyon beş olguda tespit edilmiştir. On bir olgunun radyolojik bulgusu TB ile uyumlu bulunmuştur.

Sonuç: Kemik-eklem TB'si, kronik kemik-eklem ağrılarının ve hareket kısıtlılığının önemli bir nedeni olabilir. Bu neden ile kemik eklem TB tanısında klinik, radyolojik, histopatolojik ve mikrobiyolojik bulguların birlikte değerlendirilmesi gerektiği düşünülmektedir.

Anahtar Kelimeler: Kemik ve eklem tüberkülozu; Mikobakteriyel kemik enfeksiyonları; Tanı; Tedavi

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis complex* (MTC), is a granulomatous infection and an important public health problem in many parts of the world in spite of improvements in diagnosis and treatment^[1]. Pulmonary TB is the most common infection form, but extrapulmonary tuberculosis (EPTB) has significant morbidity and mortality rates. In the world, 1-3% of all TB cases and 10% of EPTB cases are located in bone and joint tissues. Skeletal involvement is present in approximately 10% of patients with EPTB. The spine is the most commonly affected skeleton area. Spinal TB accounts for about 50% of skeletal TB cases^[1,2]. In our country, the incidence of bone/joint TB in EPTB cases is approximately 7%, and TB ranks third after TB lymphadenitis and pleural TB^[3].

Early diagnosis of TB and anti-TB treatment on time is very important to prevent bone dest-

truction and disability. The diagnosis of bone/joint TB can be difficult due to the painless/indolent nature of the disease and therefore requires a high degree of suspicion^[4]. Clinical and radiologic findings of musculoskeletal TB may mimic those of many other infections and malignancy. There are no pathognomonic imaging signs^[5]. The definitive diagnosis of spinal TB is made by microbiological and histological examination of fine needle biopsy specimens taken with computed tomography (CT). In cases with highly suggestive clinical suspicion, caseous granulomatous lesions are observed and diagnosed when acid-fast bacilli are found (sensitivity around 70%)^[6]. In some regions around the world, microbiological diagnosis is an important problem. Bone and joint TB (BJTB) is a paucibacillary disease, so microbiological diagnosis is possible in only 10%-30% of cases^[7].

In this study, we aimed to retrospectively analyze the demographical, microbiological, radiological and histopathological characteristics of patients with BJTB.

MATERIALS and METHODS

Between January 2005 and July 2019, samples of 285 patients with suspected BJTB were examined retrospectively. Patients with Ehrlich-Ziehl-Neelsen (EZN) and/or culture positivity were included into the study group. Additionally, the patients' demographic characteristics, pathological and radiological findings, microbiologic and drug sensitivity tests results were evaluated.

A total of 285 clinical samples with suspected BJTB [bone tissue (n= 128, 45%), synovial fluid (n= 99, 34.7%), abscess (n= 48, 16.8%) and bone marrow aspirates (n= 10, 3.5%)], which were referred to the Mycobacteriology Laboratory in the Department of Medical Microbiology, Faculty of Medicine, Mersin University, were routinely tested. Only one sample from each patient was included into the study. Repeated samples were excluded from the study. The clinical samples were obtained by debridement in seven cases, fine needle aspiration in five cases and knee arthrodesis in one case. Samples were homogenized and decontaminated with N-acetyl-L-cysteine (NALC-NaOH) method, which is suggested by the Centers for Disease Control and Prevention (CDC)^[8]. Following homogenization and decontamination, the samples were cultured [Löwenstein-Jensen (LJ) and liquid system (BACTEC MGIT 960)] and smears were prepared. The smears were stained with EZN to reveal the presence of acid fast bacilli (ARB)^[9]. In culture-positive isolates, MTC was identified as microscopic and macroscopic colony morphology, and biochemical methods [niacin accumulation, nitrate reduction, catalase activity, growth on para-nitrobenzoic acid (PNB) medium]^[9]. The susceptibility of the isolates to first-line anti-TB drugs [streptomycin (SM), isoniazid (INH), rifampicin (RIF), ethambutol (EMB)] was determined by using liquid automation systems^[10]. All cases were negative for human immunodeficiency virus (HIV) co-infection.

A 64-slice CT scanner (Toshiba Aquillion 64, Toshiba Medical Systems, Tokyo, Japan) was

used to perform CT examination of lumbar spine without contrast medium. With the DICOM imaging program (Vitrea; Vital Images), multiplanar reconstruction sections (MPR) were created. MRI (Optima 360, GE Healthcare, Milwaukee, USA) examination of spine, knee and hip were performed with intravenous gadolinium DTPA. In each case, the images were evaluated by one radiologist on axial, coronal and sagittal images on magnetic resonance image (MRI) or CT.

Biopsy specimens consisting of abscess and bone tissue were examined grossly and processed by using routine histopathologic method (fixation and paraffin embedding) and then stained with Hematoxylin-Eosin. After staining, the characteristic microscopic features such as necrosis, granulomas and giant cells were examined.

RESULTS

ARB positivity was detected by EZN and/or culture in 14 of 285 (4.91%) clinic specimens. Only one sample of each patient was included into the study and repetitive samples were excluded. Of the 14 cases, 8 (57.14%) were females [the average age was 43.75 years (min-max: 26-64 years)], 6 (42.86%) were males [the average age was 23 years (min-max: 2-63 years)] and mean age of the cases was 34.85 years (min-max: 2-64 years). In one case, only EZN positivity was detected, and MTC was isolated by culture (LJ and/or liquid systems) in 13 cases. Of the culture positive 13 cases, EZN positivity was detected in five clinic specimens (three abscess and two bone tissue). Additionally, two MTC isolate was resistant to INH. Four major drugs [INH, RIF, EMB, and pyrazinamide (PZA)] were administered in the first two months. Treatment with INH and RIF was continued for a further 10 months. Anti-TB drug therapy of 8 cases that had clinical and laboratory improvement was discontinued after one year. No drug side effects were observed in 11 cases during 12 months of anti-TB treatment and clinical information of four cases could not be reached after treatment.

There were ten cases of low back pain, two cases of knee pain, one case of ankle pain and one case of pain in the hips. Clinical symptoms and signs consistent with TB were not present

Table 1. Clinical, microbiological, histopathological and radiological findings of 14 cases

Variables	Patients (n= 14)	
Sex		
Male	6	
Female	8	
Average age	34.85 years (min-max: 2-64 years)	
Affected site location		
Thoracic		1/14 (7.1%)
Lumbar		6/14 (42.8%)
Knee		2 /14(14.3%)
Hip		3/14 (21.4%)
Metatarsal bones		1/14 (7.1%)
Sacral		1/14 (7.1%)
Microbiological findings		
EZN positivity		6/14 (42.8%)
LJ/Liquid systems		13/14 (92.8%)
Drug susceptibility testing		
INH resistance		2/14 (14.3%)
Histopathology findings	Chronic granulomatous inflammations characterized with caseification necrosis	5 /14(35.7%)
Radiological MRI and CT findings		
Disk space involvement		7/14 (50%)
Paraspinal and soft tissue abscess		9/14 (64.3%)
Epidural abscess		4/14 (28.6%)
Tenosynovitis		2 /14(14.3%)
Osteomyelitis, spondylodiscitis, spondylitis		8/14 (57.1%)
Bone erosion		7/14 (50%)
Intraosseous abscess		3/14 (21.4%)
Myositis		1/14 (7.1%)
Joint space narrowing		3 /14(21.4%)
Fistula		1 /14(7.1%)

in the cases. Pulmonary TB coexistence was not detected in any of the cases according to chest radiographs. Moreover, it was found that all of the cases had pain and/or movement limitation, trauma in two cases, contact story with TB in one case (Table 1, 2). Clinical symptoms and duration of these symptoms, follow-up time of anti-TB treatments are given in Table 2.

It is evaluated that the radiological findings of the cases were in accordance with TB. Clinical, microbiological, histopathological and radiological findings are presented in detail in Table 1. Eight of the twelve patients had MRI (Figure 1, 2) images and three patients had CT (Figure 3) images.

Chronic granulomatous inflammations characterized with caseification necrosis were detected in five cases (Figure 4-6).

DISCUSSION

The symptoms of BJTB infections are non-specific and their clinically course is slowly progressive, which leads to a delayed diagnosis and severe damage to bones or joints. As TB is a multi-dimensional disease, the diagnosis of BJTB requires high clinical suspicion^[7]. Early diagnosis is important to prevent from destruction and disability in BJTB. It may be associated with morbidity and mortality despite appropriate medical and surgical treatment^[1].

According to our results, the rate of EZN positivity was 2.1% (6/285) while the culture positivity rate was 4.56% (13/285). Sirzai et al. have reported that EZN positivity was detected in a vertebral biopsy specimen^[11]. In the case reported by Ural et al., EZN examination in synovial fluid was evaluated as negative and the diagnosis

Table 2. Demographic, clinical, laboratory characteristics and clinical condition after treatment of 14 cases

Case/ inquiries	Age/sex	Clinic and duration of the disease		Sample	EZN	LJ/Liquid systems	Radiological evaluations		Pathology	TB story/ contact	Surgical treatment	After anti-TB treatment and follow-up time
							-Typical finding					
Case 1	26/F	Knee pain, flix, limitation of movement/10 years	Bone tissue	Negative	Positive	Positive	Not available	Not available	Negative	Knee ar- throdesis	Lack of movement at the knee due to arthrodesis; pain free, independently mobile/9 years	
Case 2	40/F	Back pain/Not available	Abscess	Negative	Positive	Not available	Not available	Not available	Positive	Not avail- able	Not available	
Case 3	28/M	Knee pain, back pain/8 months	Bone tissue	Positive	Positive	Not available	Positive	Debride- ment	Negative	Debride- ment	Not available	
Case 4	10/M	Pain in the left hip, Impaired walk- ing/5 years	Bone tissue	Negative	Positive	Positive	Negative	Debride- ment	Negative	Debride- ment	Not available	
Case 5	26/F	Pain in left ankle, swelling/1 year	Abscess	Negative	Positive	Not available	Positive	Debride- ment	Negative	Debride- ment	Fully normal, pain free, in- dependently mobile/1 year	
Case 6	23/M	Back pain, leg pain/7 months	Abscess	Positive	Positive	Positive	Negative	Fine needle aspiration	Negative	Fine needle aspiration	Good overall health, pain free, independently mobile/3 years	
Case 7	32/F	Back pain/2 years	Abscess	Positive	Positive	Positive	Negative	Fine needle aspiration	Negative	Fine needle aspiration	Not available	
Case 8	64/F	Back pain/10 years	Abscess	Negative	Positive	Positive	Negative	Fine needle aspiration	Negative	Fine needle aspiration	Pain free, independently mobile/5 years	
Case 9	55/F	Back pain, inability to walk/7 months	Abscess	Positive	Positive	Positive	Negative	Fine needle aspiration	Negative	Fine needle aspiration	Operated in an external medical center 2 years ago, paraplegic and bed bound/4 years	
Case 10	2/M	Back pain Swell- ing, Limitation of movement/6 months	Abscess	Positive	Negative	Positive	Positive	Debride- ment	Negative	Debride- ment	Normal values in clinical and radiological treatment, pain free, mobile/7 years	
Case 11	12/M	Back pain/1 year	Bone tissue	Positive	Positive	Positive	Negative	Debride- ment	Negative	Debride- ment	Operated in an external medical center 2 years ago, pain free, independently mobile/4 years	
Case 12	63/M	Back pain/5 months	Abscess	Negative	Positive	Positive	Positive	Fine needle aspiration	Negative	Fine needle aspiration	Pain free, mobile/1 year	
Case 13	49/F	Back pain/3 months	Abscess	Negative	Positive	Positive	Negative	Debride- ment	Negative	Debride- ment	Still receiving anti-TB treatment (in 5 th months)	
Case 14	58/F	Back pain/17months	Abscess	Negative	Positive	Positive	Positive	Debride- ment	Negative	Debride- ment	Still receiving anti-TB treatment (in 4 th months)	

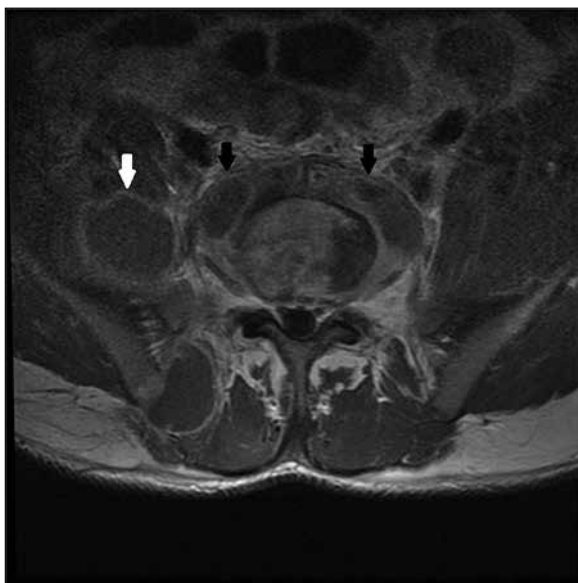


Figure 1. On enhanced T1W lumbar axial MRI, paraspinal (black arrows) and psoas muscle (white arrow) abscess (case 6).

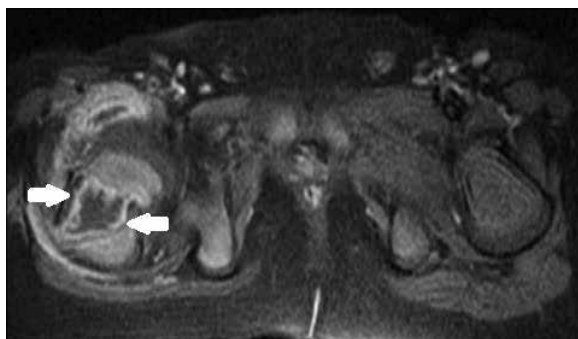


Figure 2. On enhanced hip axial MRI, intraosseous abscess in right femur head and neck (case 10).

was confirmed by culture^[12]. In our TB cases, radiological findings consistent with TB were detected; on the other hand, the histopathological examination showed caseification necrosis characterized by chronic granulomatous inflammation only in four cases (Table 1, 2).

Studies demonstrate that the incidence of BJTB varies depending on sex^[1]. The study by Yoon et al. has reported that the incidence of miliary TB was 77.8% in women^[13]. However, the study by Jutte and et al. has pointed to a higher incidence of BJTB, which was 51% in men^[14]. The studies by Sharma et al. and by Gogia et al. have indicated a higher incidence in men, respectively as 55.4% and 63.3%^[15,16].



Figure 3. On lumbar CT axial imaging, soft tissue abscess (white arrow) and bone erosion (case 9).

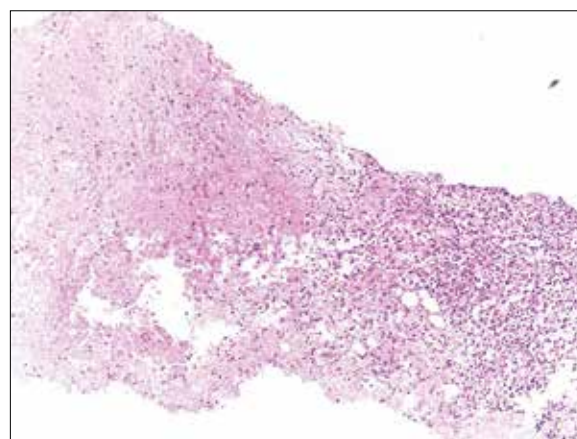


Figure 4. Necrotizing granulomatous inflammation (HE, x100).

Contrary to other studies, we reported higher incidence in women in our study (57.1%) (Table 2).

All age groups can suffer from BJTB^[17]. The study by Shi et al. has reported a higher incidence of spinal TB among the 21-30 age groups^[2]. Enache et al. have pointed to a higher incidence of BJTB among those over 40 years of age^[18]. Our study revealed that the cases ranged from 2-64 years of age, with the most affected age group being 23-28 years of age (n= 4, 33.3%) (Table 2).

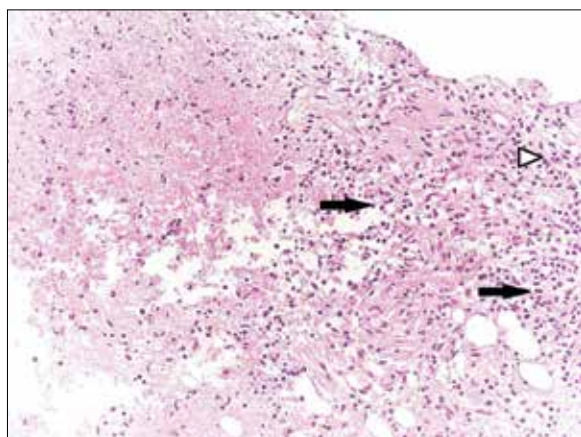


Figure 5. Microgranulomas composed of epithelioid histiocytes in the vicinity of necrosis and lymphoplasmacytic inflammatory cells are seen (HE, x100).

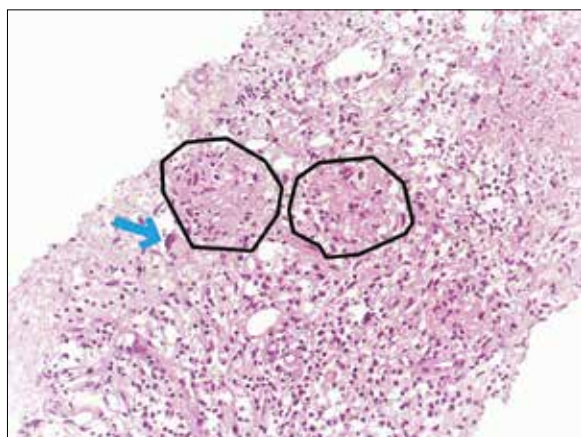


Figure 6. Microgranulomas and histiocytic giant cell (arrow) (HE, x200).

Symptoms are usually insidious in spinal TB. Despite being acute in onset, spinal TB is slowly progressive. The symptoms of diagnosis can appear two weeks to several years. Most patients (83-100%) suffer from back pain, but only one third of them have fever^[6]. The study by Arathi et al. has reported that the most common symptom was swelling and pain^[1]. Shi et al. have indicated that the most common symptom was back pain, and 97.3% of the cases suffered from limitation of movement^[2]. Besides, the study by Weng et al. has found out that all cases (100%) experienced the symptom of back pain^[19]. Schlesinger et al. have reported back and neck pain as the most common symptoms, which were present in 83% of the cases^[20]. The study by

Wang et al. has reported that the most common symptoms were back pain (92.6%, 263 patients), radicular pain (15.1%, 43 patients), numbness (13.7%, 39 patients), weakness (9.9%, 28 patients) respectively^[21]. The most common complaints in case reports reported from our country; Akgun et al.^[22] have reported pain, swelling and limitation of movement, Bagcier et al.^[23] have reported swelling and pain; Ural et al.^[12] have reported pain, redness and swelling. In our study, we demonstrated that the most common symptom was pain, which was present in all cases, and it was followed by back pain by 78.6% (11/14), and swelling by 14.3% (2/14) (Table 2).

There are commonly involved sites associated with TB in spinal region^[24]. Sandhner et al. have reported thoracolumbar region as the most common site of involvement^[17]. The study by Weng et al. has indicated that the lumbar spine and thoracic spine were respectively the most commonly involved sites by 39% and 37%^[19]. In our study, the lumbar spine was the most commonly involved site by 42.8% (6/14) (Table 1).

Microbiological diagnosis of BJTb infections is difficult to make; yet, the exhibition of TB bacillus in the sample taken from the lesion is valuable for the diagnosis. However, the diagnosis performed through bacteriological methods may not be adequate alone^[25,26]. The mycobacterial load in pulmonary lesions is usually 10^7 - 10^9 , while it is $< 10^5$ for BJTb. Various studies have demonstrated that the incidence of positive culture is between 53-88% in BJTb^[27-29]. The samples of bone tissue obtained during operation or obtained by aspiration of the infected synovium may yield a positive result if the samples contain more than 10.000 bacilli/mL. The confirmation of the BJTb infection by the demonstration of tubercle bacilli in lesion should be done, but this is not possible in all cases^[19,30]. In our study, culture positivity was detected in 13 cases and EZN positivity was detected in 6 cases.

In patients with BJTb, anti-TB drug therapy is recommended with INH, RIF, EMB and PZA in the initial phase, while INH and RIF are recommended in the maintenance phase of the treatment^[31]. Yasa et al. have reported anti-TB treatment was completed to 12 months^[32]. Ural

et al. have reported that the first line anti-TB drug treatment was initiated for the first 2 months and then continued with INH and RIF only^[12]. In our cases, a four-drug regimen was initiated for the first two months and then continued with INH and RIF for 10 months. Drug resistance in the treatment of TB is an important problem. The report by Weng et al. has revealed that of the 24 *M. tuberculosis* isolates 75% (n= 18) were susceptible to first-line anti-TB drugs (SM, INH, RIF, EMB and pyrazinamide). INH resistance was detected in three patients, SM resistance was detected in one patient another was resistant to both INH and RIF^[19]. Shi et al. have reported that the resistance ratio to INH, RIF and SM was 63.27%, 59.18% and 48.98% respectively^[2]. In our study, two INH resistant isolates were detected.

In addition to bacteriological examination, histopathological examination is essential for bone TB. Sandher et al. have revealed that of the 71 non-caucasian patients, 25 (35%) had positive histology and bacteriology, 15 (21%) had positive bacteriology but non-diagnostic histology, 13 (18%) had positive histology but negative bacteriology, and 18 (25%) were treated on clinical suspicion as both histology and bacteriology were negative^[17]. This present study found out that 33.3% of the cases in the study had both positive histopathology and bacteriology, but only 66.7% had only positive bacteriology. The study by Arathi et al. have indicated that all the cases (n= 16) demonstrated typical epithelioid cell granuloma, which was necrotizing in 11 cases and giant cells were present in 13 cases^[1]. This study demonstrated that necrotizing granulomatous infection and giant cells were present in five cases (Table 2). Only five cases were corrected based on histopathology findings as chronic granulomatous inflammations characterized with caseification necrosis (Figure 3-5).

TB should always be kept in mind when unusual radiographic spinal abnormalities are involved, especially in other organs, and in these cases fine needle aspiration cytology helps diagnosis. Extra-spinal bone TB generally imitation other conditions such as acute bacterial osteom-

yelitis and septic arthritis and lacks typical radiological findings^[7]. For that reason, bacteriological and histological methods must be employed for a fast and correct diagnosis. Typical radiological findings were present in most of the cases in this study. Indeed, radiological findings were not available only for three cases.

In the countries with high incidence of TB, high clinical suspicion is important particularly for BJTB. A delayed diagnosis and treatment can lead to bad complications. Along with high clinical suspicion, radiological, microbiological and pathological findings are significant for the diagnosis and treatment of BJTB.

CONCLUSION

In conclusion, in the light of these findings, BJTB might be an important reason of chronic bone/joint pains and movement limitations. The evaluation of clinical, radiological, histopathological and microbiological findings in bone joint TB is important for accurate diagnosis of the disease in clinical practice. Our 14 cases, who presented with pain and movement limitation, were diagnosed as BJTB with microbiological, histopathological and radiological examinations in bone tissue and abscess samples. The majority of the cases experienced an improvement and/or regression after the anti-TB treatment. We suggest that the isolation of the bacillus and determination of anti-TB drug resistance pattern with clinical findings, radiological and histopathological methods are important for diagnosis.

ETHICS COMMITTEE APPROVAL

Ethics committee approval was not received.

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: GA, NK, MÜ

Analysis/Interpretation: All of authors

Data Acquisition: All of authors

Writing: GA, NK, MÜ

Final Approval: GA

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