Image-guided percutaneous biopsy and pathological diagnosis in atypical tuberculous spondylitis: a case series and clinical outcomes

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Background: Tuberculous spondylitis can be difficult to distinguish from alternative spinal pathologies such as malignancy, particularly if the imaging features are not typical. Biopsy and histopathological analysis are facilitative to the early and accurate diagnosis of atypical tuberculous spondylitis and the clinical management. The purpose of this study is to describe some of the atypical imaging features of tuberculous spondylitis diagnosed by image-guided percutaneous biopsy, as well as associated treatment outcomes.

Methods: We performed a retrospective analysis of all patients diagnosed with tuberculous spondylitis after image-guided percutaneous biopsy at The Third Affiliated Hospital of Southern Medical University between 2013 and 2020. Of the patients identified, those with atypical imaging features were selected for case review. All patients were given anti-tuberculous medication treatment with or without surgery. The imaging features, histological and microbiological results, and clinical presentations and outcomes were evaluated. Neurological function was evaluated according to the Frankel grading system. The clinical outcomes were evaluated by Visual Analogic Scale (VAS) scores for pain, imaging [X-ray, computed tomography (CT), and magnetic resonance imaging (MRI)] results, and laboratory examinations. Comparison of VAS scores was made by Student t-test.

Results: Of the 102 patients identified with tuberculous spondylitis between 2013 and 2020, eight patients (two females and six males) with a mean age of 41.6 years (range, 18–61 years) demonstrated atypical imaging findings, including central vertebral body lesion, multiple skip vertebral lesions, extradural mass lesion and anterior subperiosteal lesion. All eight patients received anti-tuberculous medication treatment, and six underwent surgery. One patient developed a pleural effusion after debridement of the thoracic lesion. The mean follow-up period was 16.2 months (6–37 months). The VAS scores before treatment and at the final follow-up showed significant differences (7.25±1.49 and 0.0±0.0, respectively, P<0.01). Improved neurological function were observed in all patients. Solid fusion and osteogenic osteosclerosis were observed at the final follow-up, and no recurrence was observed in any cases.

Conclusions: All eight patients had a good prognosis. Image-guided biopsy and histopathological analysis are helpful for the early diagnosis of tuberculous spondylitis, especially when imaging features are not typical for this condition.
Introduction

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and is more common in older people and immune-compromised populations like HIV positive patients (1). The spine is the most common site of musculoskeletal TB. Tuberculous spondylitis was originally known as Pott's Disease and represents the most common form of extrapulmonary TB (2-4).

The typical imaging manifestation of spinal TB is vertebral destruction caused by the spread of infection originating from the intervertebral space to the opposing end plates and two adjacent vertebral bodies, with or without a paravertebral abscess (5). Spinal TB without the typical features mentioned above is harder to recognize and diagnose (6), and degenerative disc disease, pyogenic and fungal infections, or inflammatory and neoplastic lesions are common differential diagnoses under these circumstances. The atypical imaging manifestations and the wide range of clinical presentations for patients with spinal TB may result in difficulties and delays in diagnosis, with possible associated unnecessary morbidity (1-3). The treatment of atypical tuberculous spondylitis reported in the literature is mostly in the form of case report and literature review. The definition of atypical imaging features in spinal TB were as follows: anterior subperiosteal lesion, central vertebral bony lesion with disc preservation, multivertebral lesions (skip lesions), isolated involvement of the posterior elements of the vertebral body, extradural mass lesion, and intramedullary lesion (tuberculoma) (3,6-9). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Third Affiliated Hospital of Southern Medical University (No. 2022-008). Informed consent was taken from all the patients.

For each patient identified, clinical presentations, physical examinations, routine laboratory tests [including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tuberculin skin testing with purified protein derivative (PPD), serum tuberculosis antibody (TA) IgG], imaging and histopathology studies, management, and clinical and imaging outcomes were reviewed. Biopsy was performed under image-guided CT or C-arm fluoroscopy. The route of the needle puncture was based on the location and extent of the lesion. In the presence of multiple lesions, puncture was performed on the most viable and safest part of the lesion. Guided by imaging, a standard 12-gauge core needle biopsy set (Guanlong, Shandong, China) was used to perform the biopsy. After confirming the needle
tip had reached the lesion, a specimen was obtained, and the needle was withdrawn. The samples obtained from the biopsy were submitted for cytologic, histologic, and bacteriologic examination. The diagnosis of TB spondylitis was confirmed when the tissue culture positive for *M. tuberculosis*, or the histological and cytological examination of specimens revealed granulomas, multinucleated giant cells, Langhans’ giant cells, or Ziehl-Neelsen staining demonstrating acid-fast bacilli (AFB).

Surgery was considered for those patients who had vertebral compression with progressive neurological symptoms or unstable vertebral column deformity. Vertebral surgery was performed under general anesthesia in a prone position. After exposing the lamina, facet joints, and transverse processes from the posterior midline approach, transpedicular screws were installed in the thoracolumbar vertebral body at least one level above and below the diseased vertebra(e). A temporary rod was fixed to stabilize the spine and avoid spinal cord injury during decompression and debridement. A unilateral facetectomy and semi-laminectomy decompression were then performed on the affected side. After pediculectomy of the affected vertebra(e), curettage of the lesion in the vertebral body was performed using the transpedicular approach. The cavity formed after debridement of the lesion inside the vertebral body was filled with autogenous bone from the healthy lamina or an autogenous iliac bone graft, and correction of the deformity was accomplished by installing permanent rods with moderate compression maneuvers. Debridement and decompression without fixation were performed in patients with severe neurological defects or progressive neurological symptoms, with slight bone destruction and good spinal stability.

A combination of anti-tuberculous medications was given to all the patients for a total of 1 year once confirmed as TB spondylitis, including rifampicin (RMP) 450 mg/day, ethambutol (EMB) 750 mg/day, pyrazinamide (PZA) 750 mg/day, and isoniazid (INH) 300 mg/day. Streptomycin [(SM) 750 mg/day] was only given in the first month to avoid the possible cumulative dose ototoxicity. A decreased ESR and CRP was considered a useful measure of valid response to the treatment. Renal and liver functioning were monitored dynamically to detect hepatorenal toxicity when the patient was taking an anti-tuberculous medication.

Radiographs, CT scans and MR imaging were taken of each patient before hospital discharge and during follow-up, monitoring the sites for bone healing or bone graft fusion, hardware failure, as well as signs of recurrence.

The incidence of complications (intra- and postoperative), changes in neurological status at the final follow-up, and clinical outcomes were evaluated. Neurological function was evaluated according to the Frankel grading system. The patients’ clinical outcomes were evaluated by Visual Analogic Scale (VAS) scores for pain, imaging [X-ray, computed tomography (CT), and magnetic resonance imaging (MRI)] results, and laboratory examination.

### Statistical analysis

Comparison of VAS scores was made by Student *t*-test. All statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). A *P*<0.05 was considered statistically significant.

### Results

Eight patients (two females and six males) with a mean age of 41.6 years (range, 18–61 years) met these criteria (*Table 1*). All the eight patients presented with atypical imaging features of spinal TB: three had central vertebral body lesion with preserved discs, three had multiple skip vertebral lesions, one had extradural mass lesion, and one had anterior subperiosteal lesion. All patients presented with back pain and tenderness. Two patients had unexplained recurrent fever, one had mild kyphosis deformity in the thoracolumbar junction, and six had neurologic deficits on physical and neurological examinations. HIV and PPD tests were negative in all eight patients. TB antibody tests were positive in two cases. Bacteriologic culture results were negative in all cases except one case was not submitted for examination. Serum T cell spot test of TB infection (T-SPOT) and TB PCR (GeneXpertMTB/RIF) tests were only performed at our hospital after 2016, and when these results were available, they were included in the review. The T-SPOT test was performed in two cases, both with negative results. GeneXpertMTB was performed in one case with negative result. All eight patients received a confirmed diagnosis of TB following histological and cytological examination of the specimens obtained by image-guided biopsy, which revealed granulomas, multinucleated giant cells, Langhans’ giant cells, or Ziehl-Neelsen staining demonstrating AFB. All patients received anti-TB medication for one year. Two patients who had no neurological deficit symptoms received anti-TB medication alone. Five patients underwent surgery that included decompression by laminectomy, transpedicular...
| No./age/sex | Clinical features | Imaging features | Laboratory examination | Vertebral level | Extraspinal involvement | Bacteriologic examination | Histopathology | Surgery | Anti-TB medication | Complications | Follow-up (months) | Frankel Score* | Quality of life (VAS)* | Imaging* |
|-------------|------------------|-----------------|-----------------------|----------------|------------------------|---------------------------|---------------|---------|------------------|---------------|-------------------|-----------------|------------------------|---------|
| 1/41/F      | Pain, radiculopathy vertebral lesion | Central vertebral lesion | PPD(−); TA(−); HIV(−) | L3 | − | − | Epithelioid granulomata, AFB (+) | DEB + AUTO + STAB | RMP, EMB, PZA, INH, SM | No | 12 | D→E | 9→0 | Solid fusion |
| 2/58/M      | Pain, fever | Central vertebral lesion | PPD(−); TA(−); HIV(−) | T8 | + | − | Numerous neutrophils, AFB (+) | − | RMP, EMB, PZA, INH, SM | No | 6 | E→E | 8→0 | Osteogenic osteosclerosis |
| 3/18/M      | Pain, fever, kyphosis deformity, radiculopathy | Multivertebral lesions | PPD(−); TA(−); HIV(−) | L1, L3, L5 | − | N/A | Multinucleated giant cells, AFB (+) | DEB + AUTO + STAB | RMP, EMB, PZA, INH, SM | No | 20 | D→E | 9→0 | Solid fusion |
| 4/60/M      | Pain, radiculopathy | Central vertebral lesion | PPD(−); TA(+) | L2, L3 | − | − | Caseous necrosis granulomas | DEB + AUTO + STAB | RMP, EMB, INH, SM | No | 24 | D→E | 6→0 | Solid fusion |
| 5/61/F      | Pain | Multivertebral lesions | PPD(−); TA(−); HIV(−) | C5, T6, L3 | − | − | Langhans’ giant cells, AFB (+) | − | RMP, PZA, INH, SM | No | 6 | E→E | 7→0 | Osteogenic osteosclerosis |
| 6/35/M      | Pain, radiculopathy | Anterior subperiosteal lesion | PPD(−); TA(−) | L5, S1 | − | − | Multinucleated giant cells, AFB (+) | DEB + AUTO + STAB | PMP, PZA, INH, SM | No | 37 | D→E | 8→0 | Solid fusion |
| 7/22/M      | Pain, myelopathy | Extradural mass lesion | PPD(−); TA(−); HIV(−); T-spot(−) | T11, T12 | + | − | Multinucleated giant cells | DEB + AUTO + STAB | RMP, PZA, EMB, INH, SM | No | 17 | C→E | 5→0 | Solid fusion |
| 8/38/M      | Pain, myelopathy | Multivertebral lesions | PPD(−); TA(−); HIV(−); T-spot(−); GeneXpertMTB(−) | T3–T5, L2, L5 | − | − | Granulomatous inflammation | DEB | RMP, PZA, EMB, INH | Pleural effusion | 6 | C→E | 6→0 | Osteogenic osteosclerosis |

*pretreatment→last follow-up; †at last follow-up. VAS scores, Visual Analogue Scale scores; F, female; M, male; PPD, purified protein derivative test; TA, tuberculosis antibody; HIV, human immunodeficiency virus; AFB, acid-fast bacilli; DEB, debridement; AUTO, autograft; STAB, stability; RMP, rifampicin; EMB, ethambutol; PZA, pyrazinamide; INH, isoniazid; SM, streptomycin; N/A, not applicable.
curettage of the lesions, and stabilization of the spine using a posterior approach. One patient received debridement and decompression of the thoracic spine without fixation due to progressive neurological symptoms. This patient suffered pleural effusion after debridement of the thoracic lesion, which resolved after thoracic drainage. All patients were followed up for at least 6 months after treatment completion (median, 16.2 months; range, 6–37 months). Decreased VAS scores and improved neurological function were observed in all patients. At the final follow-up, back pain and neurological deficits had completely resolved in all cases. Solid fusion and osteogenic osteosclerosis were observed at the last follow-up, and no recurrence was observed in any patients. No complications were observed during the follow-up period.

Figures 1-3 illustrate the process of diagnosis and treatment in 3 of our patients.

Discussion

Spinal TB is one of the oldest diseases known to mankind and has a common occurrence with high morbidity and mortality, particularly in those with low immunity or poor nutritional status (5). Early diagnosis and treatment are considered the most important strategies to preserve neurological function and prevent spinal deformity (5). However, there are insufficient discussions on the diagnostic and treatment criteria for spinal TB with atypical imaging findings.

Biopsy is indicated when a lesion requires tissue sampling to establish aetiology, or to understand important treatment or prognostic information (5). In cases of possible spinal TB, tissue biopsy is important, not only because the diagnosis can often be adequately made on the basis of supporting histological features or the presence of AFB, but because a positive culture for M. tuberculosis remains the gold-standard for diagnosis and allows for drug susceptibility testing which is critical in guiding treatment. Tissue biopsy is essential in those cases where imaging features are not typical, as a combination of histological assessment, microscopy to detect the presence of AFB and tissue culture can differentiate TB spondylitis from alternative diagnoses such as vertebral neoplasm or pyogenic spondylitis (5). Compared to incisional biopsy, image-guided percutaneous needle biopsy is safer. The latter approach offers precise spatial localization and is relatively safe procedure with lower risk of complications (10). Reported percutaneous risk rates are 0–10% compared to 16% for open biopsy (11,12). Hemorrhage, nerve injury, and infection are the main complications in percutaneous biopsy (11).

Currently, CT-guided bone biopsy is considered to be the best modality (13). It provides an accurate three-dimensional image of the lesion location, allowing better navigation of the puncture route to safely avoid injury to neurovascular structures (13,14). Puncture needle biopsy guided by C-arm fluoroscopy is also commonly used to perform bone biopsies. Compared to CT, fluoroscopy has less ionizing radiation, a lower cost, and a shorter procedure time. However, its accuracy in targeting lesions is less precise, especially with soft tissue lesions. Therefore, C-arm fluoroscopy is reserved for biopsies of large bone lesions without vital neurovascular structure involvement.

Most percutaneous vertebral biopsies are performed using a posterior approach. An approach through bone structures (transpedicular) is safer than traversing through soft tissue and has greater yield for lytic than blastic lesions (5). The transpedicular procedure is the safest way to biopsy lesions from a vertebral body without violating the epidural space. Care must be taken to avoid breakage of the pedicle with consequent epidural space contamination (15). When multiple lesions are present, the selection of the biopsy site and puncture approach should be carefully considered, including safety issues, ease of accessibility, and the most representative lesion found on imaging.

Etiological confirmation can be made either by demonstration of AFB on the pathological specimens and/or histopathological evidence of necrotizing (or non-necrotizing) granulomatous inflammation in the appropriate clinical context (16). Ziehl-Neelsen staining for AFB has low sensitivity and specificity, particularly for pauci-bacillary TB as is commonly the case in TB spondylitis (17). Indeed, only a 52% smear positivity rate for AFB has been reported for spinal TB (18). Cytologic examination of the sample can help confirm the inflammatory process, including direct visualization of pathogen with proper staining. In our case series, AFB were observed microscopically in five cases, suggesting a diagnosis of TB. Ultimately, clinical and radiological resolution with TB treatment provides further reassurance as to the underlying diagnosis of TB spondylitis in each of these eight cases. The culture positivity rate of M. tuberculosis has been reported to be 83% in spinal TB (18); in contrast, negative positive culture results were demonstrated in seven of our cases who received bacteriologic culture. Our results of failed positive culture may be due to the fact that most patients were receiving anti-TB medication at the time of the biopsy. Therefore, histological evidence for a
diagnosis of TB is critical for timely treatment. The literature shows that approximately 60% of spinal TB diagnoses are confirmed by histology (5). Epithelioid cell granulomas, granulomatous necrotic background, and lymphocytic infiltration are the three most common histopathologic findings (19,20), whereas typical scattered multinucleated
and Langhans' giant cells were observed in only 56% of the patients (19). False-negative biopsy results in TB are not uncommon. When bacteriology proves negative, an empiric treatment with anti-TB medication can be considered if the clinical symptoms and imaging are consistent with spinal TB (5).

The treatment principles for spinal TB with atypical imaging findings are similar to cases with typical imaging findings (21). Anti-TB medication treatment is considered essential and should be started as early as the diagnosis is made or highly suspected, preferably after tissue sampling is obtained (5). The precise role of surgery in the management of spinal TB is controversial. Previous study have reported that different levels of neurological recovery can be observed in approximately 40% of spinal TB patients with paraplegia who are treated with anti-TB treatment, rest, and/or traction without spinal surgery (22). Anti-TB treatment alone can be effective in improving neurological symptoms and preventing the progression of spinal deformity (22,23). In some cases, however, surgery may

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**Figure 2** A 58-year-old woman with multiple osteolytic lesions. (A,B) X-rays of the right humerus, right radius, and left fibula demonstrated lytic bone lesions (arrows). (C,D) CT imaging of the chest and thoracic spine showed bilateral pleural effusion, osteolysis, and secondary pathologic fracture of the T8 vertebra. (E) Using a posterolateral approach biopsy is performed of the right humerus lesion. (F) The histopathologic analysis revealed damaged bone tissue with numerous neutrophils without granulomata. Ziehl-Neelsen staining (×400) shows AFB (arrows). CT, computed tomography; AFB, acid-fast bacilli.
be indicated and can provide benefits such as more timely pain relief, effective neurological recovery, less deformity progression, earlier mobility, a higher bone fusion rate, and a shorter hospital stay (5). Some experts have suggested that indications for surgery include tissue sampling for diagnosis when less invasive approaches are not feasible or available, clinical deterioration or lack of clinical improvement, progressive neurological deficit, recurrent neurologic complications, abscess drainage in the cervical spine, large paravertebral abscess drainage, spinal instability, pan-vertebral lesions, severe kyphotic deformity, and refractory disease (24-30).

Oguz et al. (27) proposed a new classification to guide the surgical treatment of spinal TB based on seven clinical and radiological criteria (abscess formation, disc degeneration, vertebral collapse, kyphosis, sagittal index, instability, and neurological problems). This classification system divides spinal TB into three types and recommends specific treatment approaches for each type (drug treatment alone or with abscess drainage and debridement, debridement and fusion with or without decompression, and correction of deformity with internal fixation). Nearly two decades ago, we first reported the one-stage anterior interbody autografting and instrumentation in thoracolumbar spinal TB, resulting in remarkable clinical efficacy (28). In the present study, one-stage posterior debridement using the transpedicular approach was adopted in two cases, followed by anti-TB treatment. Recently, Wang et al. (29) reported that one-stage posterior debridement using titanium mesh cages and posterior instrumentation, achieving excellent clinical results in aged patients with lumbosacral spinal TB. One-stage anterior or posterior surgery in selected cases can significantly improve the efficiency and safety of the operation. These types of surgical approaches for treatment of spinal TB are viable and safe surgical options (27). The appropriate choice of timing, indication, and surgical intervention procedure is vital when treating spinal TB (31-33).

Limitations of this study include: (I) retrospective analysis and thus the possibility of patient selection bias for biopsy; (II) single center experience and referral bias; (III) possibility of both false positive and false negative diagnoses given the lack of sensitivity of the gold standard of tissue culture and TB PCR on pauci-bacillary specimens, which would be inherent in all such studies.
In summary, spinal TB with atypical imaging features has been well documented but is difficult to distinguish from nonspecific infections and malignancies, which can lead to misdiagnosis and inappropriate treatment. However, when diagnosed and adequately treated, long term clinical, microbiological and radiological outcomes are favourable. Unless the clinical and imaging findings are very strongly supportive of a diagnosis of TB spondylitis, pathological analysis should always be conducted to help confirm the diagnosis. Additionally image-guided biopsy to obtain samples for mycobacterial culture (+/− PCR) should always be strongly considered where TB is in the differential diagnosis, in order to not only confirm the diagnosis of spinal TB but to determine the drug susceptibility profile.

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Footnote

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