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Spinal tuberculous disease is common in tuberculous meningitis

[1]Mei-Ling Sharon TAI, [2]Hazman Mohd NOR, [3]Shanthi VISWANATHAN, [2]Kartini RAHMAT, [4]Norzaini Rose MOHD ZAIN, [1]Zhen Yuan POW, [1]Lay Sim ONG, [3]Mohd Hanip RAFIA, [1]Chong Tin TAN

[1]Division of Neurology, Department of Medicine and [2]Department of Biomedical Imaging, Faculty of Medicine, University Malaya, Kuala Lumpur; [3]Department of Neurology and [4]Department of Radiology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Abstract

Background: Tuberculous disease of spine (spinal TB) is under-recognized in tuberculous (TB) meningitis. The objective of the study was to evaluate the frequency, clinical and neuroimaging changes, and outcome in the patients with spinal TB. *Methods:* All the patients with spinal TB admitted in the two largest tertiary hospitals in Kuala Lumpur from 2009 to 2017 were recruited, the clinical features were documented, the magnetic resonance imaging (MRI) of the spine was performed. Clinical outcome was assessed with Modified Rankin scale (MRS). *Results:* Twenty two patients were recruited. This was out of 70 TB meningitis patients (31.4%) seen over the same period. Eighteen (81.8%) patients had concomitant TB meningitis. The clinical features consisted of systemic symptoms with fever (63.6%), meningitis symptoms with altered sensorium (45.5%), myelopathy with paraparesis (36.4%). The findings on spinal MRI were discitis (36.4%), spinal meningeal enhancement (31.8%), spinal cord compression (31.8%), psoas abscess (27.3%), osteomyelitis (22.7%), and cord oedema (22.7%). All except two patients (90.9%) had involvement in psoas muscle, bone or leptomeningeal enhancement, features that can be used to differentiate from myelopathy that affect the parenchyma only, such as demyelination. Unusual manifestations were syringomyelia and paradoxical manifestations seen in 3 patients each. The outcome were overall poor, with 68% having MRS 3 or more.
Conclusion: Spinal TB is common in TB meningitis. The outcome is overall poor. A heightened awareness is crucial to enable early diagnosis and treatment.

Keywords: Spinal tuberculosis, tuberculous meningitis, syringomyelia, enhancement, abscess

INTRODUCTION

Tuberculous disease of the central nervous system (CNS) is uncommon and involves only 0.5–2% of all the tuberculous cases.[1] The majority of the cases are found in the developing countries.[2] Tuberculous disease of the spine involves the vertebrae (such as Pott's disease of the spine) and non-osseous structures of the spine.[3,4] Nonosseous spinal cord involvement is a very rare manifestation of tuberculosis.[2-4] Spinal TB is known to be associated especially with pulmonary disease.[1]

Despite effective therapy for tuberculous (TB) meningitis, late complications in the spine which include syringomyelia, myelopathy and vascular diseases may occur.[5] There should be increased awareness of spinal tuberculous (spinal TB) disease to achieve an early diagnosis and proper treatment.[1] Late treatment can lead to irreversible neurological sequelae.[1] The spinal cord and spinal nerve root involvement contribute significantly to the disability of the patients, and this is often overlooked.[6]

The primary objective of this study was to evaluate the frequency, clinical and neuroimaging changes of the spinal cord, arachnoiditis and vertebral involvement in the patients with tuberculous disease of spine in Malaysia, which is facing re-emergence of TB and TB meningitis in the recent years. The secondary objective was to assess the clinical outcome in these patients.

METHODS

This was a cohort study of patients with

Address correspondence to: Dr Mei-Ling Sharon Tai, Division of Neurology, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. Email: sharont1990@gmail.com

tuberculous disease of spine with prospective follow-up and prospective inclusion of new cases. This study was conducted in University Malaya Medical Centre (UMMC) and Kuala Lumpur General Hospital, two large referral hospitals in Kuala Lumpur, Malaysia.

Patient selection

In this study, 22 consecutive patients with tuberculous disease of spine were recruited. The patients of Pott's spine and prolapsed intervertebral disc were excluded from the study. The study period was from January 2009 to April 2017. Seventy patients with TB meningitis was seen during the same period. The study was approved by the Institutional Ethics Committee of UMMC and Ministry of Health. All patients or their legally acceptable representatives provided informed consent for the study.

Clinical assessment

We collected the data on the demographic characteristics, onset of the disease and clinical features on admission. The data of the patients included limb weakness, pain in lower limbs, numbness or paresthesia in lower limbs, bowel symptoms (constipation) and bladder problems (hesitancy, intermittency, straining, retention, frequency, urgency, urge incontinence). The findings of the signs such as, weakness, tone, reflex, and sensory changes, were recorded. History of concomitant TB meningitis was recorded. The medical illnesses such as HIV, Hepatitis B, Hepatitis C and others were recorded. Clinical conditions were assessed serially. The patients were followed up for at six months.

Laboratory findings

The data on cerebrospinal fluid (CSF) opening pressure, CSF glucose, CSF protein, CSF white cell count (differential lymphocyte and neutrophil), CSF TB PCR, CSF acid-fast bacilli (AFB) smear, as well as CSF AFB culture with sensitivity was documented. The other data collected included pus AFB direct smear, pus AFB culture with sensitivity, sputum AFB culture with sensitivity, and sputum AFB direct smear.

Neuroimaging

The Magnetic Resonance Imaging (MRI) of the spine (1.5-Tesla Signa HDx MR system, GE healthcare), was performed. Mid-sagittal T2-weighted sequence, precontrast and postcontrast T1-weighted imaging of the whole spine were done. The radiological findings of the Magnetic Resonance Imaging (MRI) of the spine, such as discitis, spinal meningeal enhancement, psoas abscess, intraspinal abscess, osteomyelitis, spinal cord oedema, lumbosacral arachnoiditis, spondylitis, syringomyelia, transverse myelitis, spinal cord tuberculoma, compression fracture and burst fracture, were recorded. The findings of the chest radiograph (CXR) and Computed Tomography (CT) thorax were also collected.

The presence of low signal intensity on T1-weighted imaging and high signal intensity on the corresponding region of T2-weighted imaging with a well-defined margin was taken as an evidence of syringomyelia.[6,7] Myelitis was identified by hyperintense signal on T2-weighted image associated with cord oedema, enlargement, and marginal enhancement on contrast.[6,7]

Lumbosacral arachnoiditis was identified by irregularity of thecal sac, nodularity and thickening of nerve roots, and their clumping.[6,8] It was classified into one of the three patterns of involvement according to Delamarter classification: central conglomerations of cauda equina nerve roots; peripheral clumping of nerve roots giving empty thecal sac appearance; and soft tissue mass replacing subarachnoid space giving rise to a central opacity.[9] Discitis was defined as hyperintense signal in T2WI in the disc with loss of intranuclear cleft and/or reduction in disc height and enhancement of the disc margins on post contrast T1WI.[10]

In the patients with TB meningitis, Magnetic Resonance Imaging (MRI) of the brain was performed using 3.0-Tesla Signa HDx MR system (GE healthcare). The findings of the chest radiograph (CXR) and Computed Tomography (CT) thorax were also collected.

Case definitions

Radiculopathy was defined by nerve root pain, weakness and wasting of muscles consistent with radicular distribution, sensory loss in dermatomal pattern, and asymmetrically absent tendon reflexes.[6,11,12] Myelopathy was defined by paraplegia or quadriplegia, presence of a sensory level below the level of the lesion, as well as bladder involvement. [6,11,12]

TB meningitis was defined as "definite" if cerebrospinal fluid (CSF) acid-fast bacilli (AFB) direct smear/mycobacterial culture/ polymerase chain reaction (PCR) for mycobacteria tuberculosis or histopathological were positive.

TB meningtis was defined as "probable" in TB meningitis patients with one or more of the following: suspected active pulmonary tuberculosis (PTB) on chest radiography, acid-fast bacilli in any specimen other than the CSF, and clinical evidence of other extrapulmonary tuberculosis.[13]

TB meningitis was termed as "possible" in patients with at least four of the following: a history of tuberculosis, CSF pleocytosis, lymphocyte predominance in the CSF, duration of illness of more than five days, a ratio of CSF glucose to plasma glucose of less than 0.5, absence of Cryptococcus in CSF, altered consciousness, turbid/yellow CSF, focal neurological signs or response to antituberculous therapy.[13,14] The diagnosis is based on modification of Thwaites criteria.[13]

The severity of TB meningitis was categorised at the time of admission according to British Medical Research Council criteria.[13] The patients in stage 1 were fully conscious and rational (Glasgow Coma Scale; GCS 15), with meningeal signs but no focal neurological deficit.[13] The patients in stage 2 had GCS score 11-14 or 15 with focal neurological signs.[13] The patients in stage 3 had a GCS score of 10 and less.[13]

Treatment

The information of treatment and clinical progress (including neurosurgical intervention) were documented. All the patients were treated with the first line antituberculous therapy comprising of intensive phase (ethambutol, isoniazid, rifampicin and pyrazinamide) for 2 months followed by maintenance phase (isoniazid, rifampicin). The total duration of antituberculous treatment was 12-18 months. The treatment regimen was based on the British Infection Society guidelines. [15] All the patients with severe spinal TB received dexamethasone.

Evaluation of clinical outcome

Modified Rankin scale (MRS) was used to assess the clinical outcome on admission and at six months after the admission. The range of MRS score is 0-6.[13,16]

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 – Death.

Scores of 0-2 and 3-6 were defined as good and poor outcome respectively.[13,16]

Statistical analysis

All descriptive statistics were done using Statistical Package for Social Sciences, SPSS (Version 20.0, SPSS Inc., Chicago, USA). Chi square test (or Fisher's exact test) were used to analyse categorical data. Continuous variables were analyzed with Student's t test. A p value of < 0.05 was taken as statistical significance.

RESULTS

(a) Demography characteristics and clinical manifestations of the patients with tuberculous disease of spine

Twenty two patients with tuberculous disease of the spine admitted to University Malaya Medical Centre (UMMC) and Hospital Kuala Lumpur from 2009 to 2017 were recruited (Table 1). The mean age was 36.0±14.2 years old. Close to half of the patients were males (54.5%). The ethnic composition reflected that of the community, with 50.0% Malays, 22.7% Chinese, and 13.6% Indians. There were 13.6% (3) non-Malaysians consisting of 2 Indonesians (9.1%) and one Myammar (4.5%) national.

The presenting features consisted of systemic symptoms with fever (63.6%), loss of appetite (50%) and loss of weight (36.4%); TB meningitis with altered sensorium (45.5%), headache (31.8%), mean GCS on admission of 13.9±2.0 (range 8-15); myelopathy symptoms with sensory loss/sensory level (36.3%).

Table 1 lists the clinical features, with systemic features, meningitis symptoms, and myelopathy. Paraparesis was present in eight (36.4 %) patients, which was of upper motor neuron type in 4 (18.2%) patients and lower motor neuron type in 4 (18.2%) patients. Quadriparesis was present in 5 (22.7 %) patients.

(b) Spinal neuroimaging results

Table 2 list the MRI spine findings, and Table 3 shows the detailed neuroimaging results for each of the 22 patients. As shown, the most common

Table 1: **Baseline clinical, cerebrospinal (CSF) and neuroimaging characteristics of spinal TB patients**

	Patients, n=22
Age (mean±SD)	36.0±14.2
Gender (n, %)	
Male	12 (54.5%)
Female	10 (45.5%)
Ethnic group (n, %)	
Malay	11 (50.0%)
Chinese	5 (22.7%)
Indian	3 (13.6 %)
Non-Malaysians	3 (13.6%)
Clinical features (n, %)	
Fever	14 (63.6%)
Loss of appetite	11 (50.0%)
Reflex changes	10 (45.5%)
Altered sensorium	10 (45.5%)
Loss of weight	8 (36.4%)
Paraparesis	8 (36.4%)
Sensory loss/sensory level	8 (36.4%)
Headache	7 (31.8%)
Lethargy	7 (31.8%)
Tone changes	7 (31.8%)
Vomiting	6 (27.3%)
Back pain	6 (27.3%)
Cough	5 (22.7%)
Quadriparesis	5 (22.7%)
Extensor plantar response	5 (22.7%)
Bladder involvement	5 (22.7%)
Ptosis	5 (22.7%)
Seizure	4 (18.2 %)
Bowel involvement	4 (18.2%)
Paraesthesia in lower limbs, hemiparesis, neck stiffness, third cranial nerve palsy	3 (13.6%) each
Pain in lower limbs, nausea	2 (9.1) each
Papilloedema, monoparesis	1 (4.5%) each
Stage of illness on admission (n, %)	
Stage 1	3 (13.6%)
Stage 2	17 (77.3%)
Stage 3	2 (9.1%)
Other extrapulmonary TB (n, %)	
PTB	12 (54.5%)
Pleural effusion/Pleural TB	3 (13.6%)
TB lymph nodes	3 (13.6%)
Other medical illnesses (n, %)	
Diabetes mellitus (DM)	3 (13.6%)
Hypertension (HT)	3 (13.6%)
Ischaemic heart disease (IHD)	2 (9.1%)
HIV, Hepatitis B, Hepatitis C	1 (4.5%) each

Cerebrospinal fluid	
Opening Pressure, cm H2O (mean±SD)	19.0±12.3 (range 4-75)
White blood cells, cells/ml (mean±SD)	220.8±323.4 (range 0-1152)
Lymphocyte differential in percentage (mean±SD)	36.3±37.9 (range 0-98)
Neutrophil differential in percentage (mean±SD)	66.9±38.2 (range 2-100)
Glucose, mmol/L (mean±SD)	1.8±0.9 (range 0.7-4.2)
Protein, mg/dl (mean±SD)	7.5±7.8 (range 0.4-24.7)
AFB direct smear (n, %)	4 (18.2%)
AFB culture positive (n, %)	6 (35.3%)
-resistance to one or more of antituberculous therapy	0
TB PCR (n, %)	
-positive (out of 12 samples)	3 (25%)
Sputum (n, %)	
AFB culture positive	7 (31.8%)
-resistance to one or more of antituberculous therapy	0
AFB direct smear	2 (9.1%)
Positive AFB culture and AFB direct smear from spinal abscess (n, %)	
Positive AFB culture (out of 14 samples)	3 (35.7%)
Positive AFB direct smear (out of 14 samples)	2 (11.1%)
Spinal granuloma on HPE (n, %)	3 (13.6%)
Tuberculous meningitis and subtypes (n, %)	
Definite	7 (77.8%)
Probable	1 (11.1%)
Possible	1 (11.1%)
Clinical Outcome (Modified Rankin Scale) at 6 months (n, %)	
0	2 (9.1%)
1	3 (13.6%)
2	2 (9.1%)
3	1 (4.5%)
4	5 (22.7%)
5	4 (18.2%)
6	5 (22.7%)

Table 2: MRI of spine imaging findings

	n, (%)
Discitis	8 (36.4%)
Spinal meningeal enhancement	7 (31.8%)
Cord compression	7 (31.8%)
Psoas abscess	6 (27.3%)
Osteomyelitis	5 (22.7%)
Cord oedema	5 (22.7%)
Arachnoiditis	4 (18.2%)
Intraspinal abscess	4 (18.2%)
Spondylitis	3 (13.6%)
Syringomyelia	3 (13.6%)
Myelitis	2 (9.1%)
Cord tuberculoma	2 (9.1%)
Compression fracture	2 (9.1%)
Burst fracture	1 (4.5%)

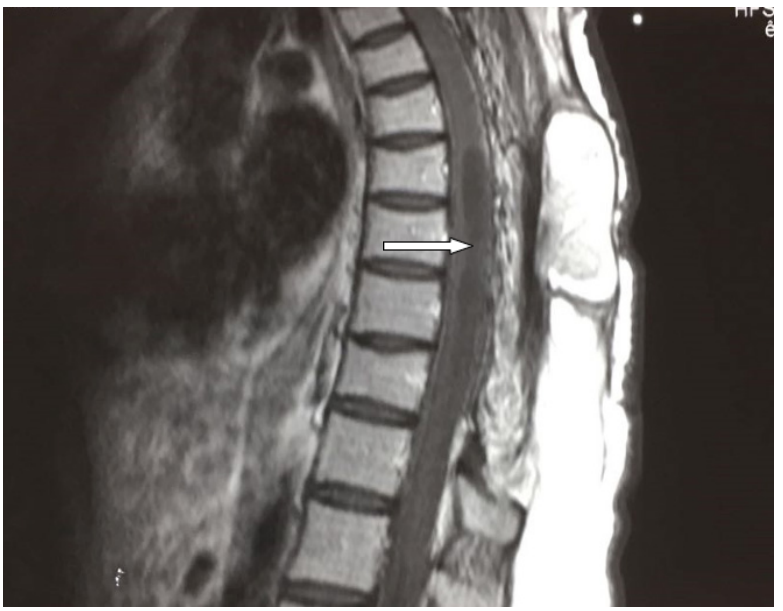

Figure 1. Sagittal T1W image of MRI of spine shows syringomyelia at the thoracic area (arrow)

findings were discitis (36.4%), spinal meningeal enhancement (31.8%), spinal cord compression (31.8%), psoas abscess (27.3%), osteomyelitis (22.7%), and cord oedema (22.7%)

The common locations of tuberculous disease of spine were thoracic (12 patients, 54.5%), followed by lumbar region (8 patients, 36.3%), cervical (4 patients, 18.2%) and sacral area (1 patient, 4.5%).

Discitis was found in the thoracolumbar area in 3 (14.3%) patients, lumbar in 3 (14.3%) patients, thoracic in 1 (4.5%) patient and lumbosacral in 1 (4.5%) patient. Spinal meningeal enhancement was present in cervical region in 3 (14.3%) patients, thoracic region in 3 (14.3%) patients and lumbosacral in 1 (4.5%) patient. Cord compression was found in thoracic in 3 (14.3%) patients, cervical in 2 (9.1%) patients, cervicothoracic in 1 (4.5%) patient and thoracolumbar in 1 (4.5%) patient.

Psoas abscesses were seen bilaterally in 3 (14.3%) patients and unilaterally (only right side) in 3 (14.3%) patients. Osteomyelitis was found in thoracolumbar in 2 (9.1%) patients, thoracic region in 1 (4.5%) patient, lumbar in 1 (4.5%) patient and lumbosacral in 1 (4.5%) patient.

Syringomyelia was observed in the thoracic region in 2 (9.1%) patients, and cervical region in 1 (4.5%) patient. All the 3 patients had history of TB meningitis. The period between the initial inflammatory process and the development of syringomyelia was 6 months for the first patient and 3 years for the second patient. One patient had both syringomyelia and arachnoiditis. The MRI of the spine (T1W) showing syringomyelia is illustrated in Figure 1.

In the third patient, she had intradural extramedullary cord tuberculoma (IDEM) after TB meningitis, and she had laminectomy and excision of the tuberculoma. This was followed by syringomyelia after 5 years from the onset of TBM, which was managed conservatively. The syringomyelia was progressive. Due to worsening neurological deficits, she had syringotomy.

Spondylitis was present in lumbar in 2 (9.1%) patients, and thoracolumbar in 1 (4.5%) patient. Transverse myelitis was in the cervical region in 1 (4.5%) patient and thoracic area in another (4.5%) patient.

Compression fracture was present in the thoracic region in 1 (4.5%) patient and lumbar area in another (4.5%) patient. In the 2 (9.1%) patients with cord tuberculoma, it was located at the intradural extramedullary in 1 (4.5%) patient in the thoracic area, and in another patient (4.5%), it was located intramedullary in the thoracic region. One (4.5%) patient had burst fracture in the thoracic region.

Three patients (13.6%) developed paradoxical manifestations of the tuberculous disease of the spine. The paradoxical manifestations were worsening psoas abscess bilaterally and spondylodiscitis in 1 (4.5%) patient, worsening bone destruction in 1 (4.5%) patient, and

increasing size of cervical paravertebral lesion with further cord compression in another (4.5%) patient.

(c) Clinical outcome and CSF parameters

As shown in Table 1, 15 (68.2%) patients had poor outcome (MRS 3-6), while 7 (31.8%) had good outcome (MRS 0-2). Out of these 15 patients with poor outcome, five (33.3%) patients had psoas abscess and five (33.3%) patients also had leptomeningeal enhancement (Table 2). The types of spinal TB were not associated with clinical outcome. The clinical outcome was also not associated with paraparesis, quadriparesis, pain in the lower limbs, paraesthesia in the lower limbs, tone abnormality, reflex abnormality, extensor plantar response and sensory abnormality. We also could not identify any CSF factor that was associated with the outcome. (Table 4) The symptomatic myeloradiculopathy was not associated with CSF protein, CSF glucose, CSF white blood cells, stages of illness on admission (Table 4). Arachnoiditis was also not associated with raised CSF protein.

(d) Management

Thirteen (59.1%) patients were given dexamethasone, in which 9 (40.9%) improved on dexamethasone. Five (22.7%) patients had psoas abscess drainage. Five (22.7%) patients had surgery performed. Two (9.1%) had transpedicular biopsy of vertebrae, whereas 2 (9.1%) had laminectomy and excision. One of the patients who had laminectomy and excision of IDEM tuberculoma, had syringotomy for the syringomyelia. Syringe-subarachnoid shunt insertion was attempted, but was unsuccessful. One (4.5%) patient had decompression, C6 & C7 lateral mass screw, T1/T2/T3 pedicle screw fixation and cross linking.

DISCUSSION

We identified 22 TB spine in the study period. Over the same period, there were 70 patients with TB meningitis.[17] Thus, spinal TB was seen in 31.4% of TB meningitis patients. This suggests that spinal TB is common among patients with TB meningitis, thus requiring more attention to the spinal involvement in TB meningitis.

The clinical outcome of the patients with spinal TB was poor. 68% of the patients had MRS of three or more. Interestingly, in some of these patients, the spinal TB was not symptomatic (9/22, 41%), the clinical feature was dominated by cerebral and other symptoms. Therefore, a high index of suspicion for spinal TB is important. Although it was not statistically significant, psoas abscess and leptomeningeal enhancement were seen in one-third of the patients with spinal TB who had poor clinical outcome. Early diagnosis of psoas abscess with adequate medical therapy and surgical drainage are essential to prevent these patients from developing sepsis and septic shock, thus improving the disease outcome.[17]

More than four-fifth of our patients with spinal TB had concomitant TB meningitis, consistent with a previous study.[6] Therefore all the TB meningitis patients should be screened early for spinal TB. The presence of systemic symptoms and clinical features of TB meningitis are important clues to the diagnosis of spinal TB.

In this study, only two patients (cases 3 and 18) had the imaging features which were confined to the spinal cord (cord tuberculoma, cord oedema and syringomyelia). The rest of the patients had concomitant involvement of lesions in the muscle (psoas abscess), bone (discitis, osteomyelitis, compression / burst fracture), subarachnoid (arachnoiditis) or leptomeningeal (leptomeningeal enhancement). These features can thus be used to differentiate TB myelopathy from other intrinsic causes of myelopathy such as demyelination.

It is said that spinal TB originate by three possible mechanisms of pathogenesis, haematogenous spread with osteoarticular TB and TB discitis with secondary spinal extension, TB meningitis with spread via the subarachnoid space, and Rich focus with tuberculoma involving the spinal cord.[1,18] The imaging features of our patients with large proportion having concomitant involvement of muscle, bone, subarachnoid or leptomeninges suggests that hematogenous and subarachnoid spread may be the more important pathogenesis, rather than Rich focus with tuberculoma affecting the cord.

In the present study, there were unusual manifestations of spinal TB such as syringomyelia with intradural extramedullary (IDEM) tuberculoma as well as syringomyelia with arachnoiditis.

Syringomyelia as a complication of spinal TB and TB meningitis has rarely been reported.[3,19-21] Till date, there were only 29 cases of syringomyelia due to TB reported in the literature.[23-29] There were 3 (13.6%) patients with syringomyelia among our series of spinal TB. In our patients with syringomyelia, the latency between the initial TB spine to development of syringomyelia was

Table 3: **Clinical, radiological and clinical outcome of the patients**

No.	Age	Limb Weak-ness a/w TB spine	Bowel/ Bladder inv	Initial (I)/ Paradox (P)	Spinal level	Baseline GCS	MRI spine findings	MRS at 6 months
1	32	P	N	I	L	14	Psoas abscess, discitis, osteomyelitis	4
2	33	N	N	I	TL	15	Discitis, osteomyelitis	1
3	36	P	Bl	I	CT	14	Cord compression, cord oedema	1
4	34	N	N	I	LS	8	Discitis, osteomyelitis, spinal meningeal enhancement	6
5	23	N	N	I	T	15	Discitis, cord tuberculoma, cord oedema	0
6	23	N	N	I	T	14	Psoas abscess, osteomyelitis, cord compression, intraspinal abscess	5
7	20	P	N	I	C	15	Spinal meningeal enhancement	6
8	34	N	Bo	I	C	14	Cord compression, spinal meningeal enhancement	2
9	23	N	N	I	C	11	Spinal meningeal enhancement, transverse myelitis, cord oedema	6
10	28	N	N	P	L	14	Psoas abscess, discitis, spondylitis, intraspinal abscess	5
11	60	P	N	I	L	14	Discitis	5
12	34	P	N	P	TL	15	Psoas abscess, osteomyelitis, intraspinal abscess	0
13	59	Q	N	P	C	15	Cord compression, cord oedema compression fracture	1
14	75	Q	Bl, Bo	I	TL	15	Discitis, cord compression, cord oedema, spondylitis, burst fracture	5

15	26	Q	Bl, Bo	I	T	15	Cord compression, arachnoiditis	4
16	29	N	N	I	NA	15	Psoas abscess	4
17	33	N	N	I	C,L	15	Spondylitis, arachnoiditis, syringomyelia	3
18	37	Q	N	I	T	15	Cord tuberculoma, syringomyelia	4
19	28	P	Bl	I	T	14	Spinal meningeal enhancement, arachnoiditis	2
20	34	Q	N	I	T	9	Spinal meningeal enhancement, transverse myelitis, syringomyelia	4
21	33	P	Bl, Bo	I	T	15	Spinal meningeal enhancement, arachnoiditis	6
22	59	P	N	I	TL	15	Psoas abscess, discitis, compression fracture, intraspinal abscess	6

Y, Yes; N, No; NA, Not applicable; a/w, associated with; L, lumbar; TL, thoracolumbar; T, thoracic; CT, cervicothoracic; C, cervical; LS, lumbosacral; P, paraparesis; Q, quadriparesis; Bl, Bladder; Bo, Bowel

Table 4: Association of symptomatic myeloradiculopathy with CSF parameters, stage of illness on admission and clinical outcome at 6 months

	Symptomatic myeloradiculopathy (n=13)	**Asymptomatic myeloradiculopathy (n=9)**	**p value**
CSF protein, mg/dl (mean±SD)	9.25±8.53	5.80±6.98	0.36
CSF glucose, mmol/L (mean±SD)	1.94±1.01	1.66±0.77	0.53
CSF white blood cells, cells/ml (mean±SD)	184.25±396.69	253.22±262.57	0.68
Clinical outcome at 6 months (n, %)			
Poor outcome	9 (69.2%)	6 (66.7%)	1.00
Good outcome	4 (30.8%)	3 (33.3%)	
Stages of illness (n, %)			
Stage 1 (early stage)	1 (7.7%)	2 (22.2%)	0.54
Stage 2 and 3 (advanced stages)	12 (92.3%)	7 (77.8%)	

6 months, 3 years and five years. This duration of time is relatively short as compared to what was described in the previous reports. In the literature, the latent period between the initial inflammatory process and the development of symptoms related to syringomyelia is generally longer, varying from 6 - 30 years.[5,28-30] However, the shortest interval between TB meningitis and syringomyelia formation in the literature is as early as seven days to 10 -11 days.[28,30-32] There were only three published case reports of syringomyelia in acute stage of TB meningitis.[28,30,32] The reason for the long latency to the development of syringomyelia is unclear.

Among our patients with syringomyelia, one had syringomyelia presenting as a delayed complication of intradural extramedullary (IDEM) tuberculoma which occurred after three years. To our knowledge, there was only one previous case reported on a patient with delayed syringomyelia six months after IDEM tuberculoma.[3] The presence of dense cord tuberculoma could have contributed to the development of syringomyelia.[3] Concurrent IDEM tuberculoma and syringomyelia arising as a complication of TB meningitis is extremely rare and only four cases have been reported to date.[2-4,22]

As mentioned above, spinal cord tuberculoma is uncommon, seen only in two (9.1%) of our patients. This is consistent with the report in the literature.[33,34] In the literature, intramedullary tuberculoma is known to be more common than intradural extramedullary (IDEM) tuberculoma.[2] Intradural extramedullary (IDEM) tuberculomas account for only 1% of all spinal tuberculomas.[2,3,35] There were approximately 30 cases of IDEM tuberculomas reported in the literature.[2-4,22,23,36]

The manifestations which are associated with the spinal cord and spinal nerve root involvement, such as tuberculous radiculomyelitis, spinal tuberculoma, myelitis, syringomyelia and spinal abscess may appear paradoxically, following antituberculosis treatment.[6,37-38] In our study cohort, the paradoxical manifestations were worsening psoas abscess bilaterally and spondylodiscitis in one patient, worsening bone destruction in one patient, and increasing size of cervical paravertebral lesion with further cord compression in another patient, all involving extra-neural tissues. We have previously reported that paradoxical manifestation is common in HIV negative TB meningitis.[38]

Our study had several limitations. Firstly, the sample size was small. In addition, this was a study conducted in two tertiary hospitals. Thus, the extrapolation of results to a larger population was limited, with its referral bias.

In conclusion, spinal TB is common in TB meningitis, generally with poor clinical outcome. Therefore, high index of suspicion is crucial to enable rapid diagnosis and treatment.

DISCLOSURE

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Conflict of interest: None

REFERENCES

1. Tanriverdi T, Kizilkiliç O, Hanci M, Kaynar MY, Unalan H, Oz B. Atypical intradural spinal tuberculosis: report of three cases. *Spinal Cord* 2003; 41(7):403-9.
2. Sharma B, Nagpal K, Handa R, Gupta P. Intradural extramedullary and intracranial tuberculomas with concurrent communicating syringomyelia. *BMJ Case Rep* 2014 Feb 4; 2014.
3. Gul S, Celebı G, Kalayci M, Acikgoz B. Syringomyelia and intradural extramedullary tuberculoma of the spinal cord as a late complication of tuberculous meningitis. *Turk Neurosurg* 2010; 20(4):561-5.
4. Muthukumar N, Sureshkumar V. Concurrent syringomyelia and intradural extramedullary tuberculoma as late complications of tuberculous meningitis. *J Clin Neurosci* 2007; 14:1225-1230.
5. Nagashima T. Yamamoto K, Tamura S, *et al*. Pathophysiology and treatment of syringomyelia associated with tuberculous meningitis. In: Tamaki N, Batzdorf U, Nagashima T. eds: Syringomyelia. Springer, Tokyo. 2001:253-8.
6. Gupta R, Garg RK, Jain A, Malhotra HS, Verma R, Sharma PK. Spinal cord and spinal nerve root involvement (myeloradiculopathy) in tuberculous meningitis. *Medicine (Baltimore)* 2015; 94(3):e404.
7. Murphy KJ, Brunberg JA, Quint DJ, et al. Spinal cord infection: myelitis and abscess formation. *AJNR Am J Neuroradiol* 1998; 19:341-8.
8. Chang KH, Han MH, Choi YW, *et al*. Tuberculous arachnoiditis of the spine: findings on myelography CT, and MR imaging. *AJNR Am J Neuroradiol* 1989; 10:1255-62.
9. Delamarter RB, Ross JS, Masaryk TJ, *et al*. Diagnosis of lumbar arachnoiditis by magnetic resonance imaging. *Spine* (Phila Pa 1976). 1990; 15:304-10.
10. Jain AK, Sreenivasan R, Saini NS, Kumar S, Jain S, Dhammi IK. Magnetic resonance evaluation of tubercular lesion in spine. *Int Orthop* 2012; 36(2):261-9.
11. Gupta RK, Gupta S, Kumar S, *et al*. MRI in intraspinal tuberculosis. *Neuroradiology* 1994; 36:39-43.
12. Sharma A, Goyal M, Mishra NK, *et al*. MR imaging of tubercular spinal arachnoiditis. *AJR Am J Roentgenol* 1997; 168:807-12.

13. Thwaites GE, Nguyen DB, Nguyen HD, *et al*. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004; 351:1741-51.
14. Misra UK, Kalita J, Srivastava M, Mandal SK. Prognosis of tuberculous meningitis: a multivariate analysis. *J Neurol Sci* 1996; 137:57-61.
15. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009; 59(3):167-87.
16. Wilson JT, Hareendran A, Grant M, *et al*. Improving the assessment of outcomes in strokes. *Stroke* 2002; 33:2243-6.
17. Navarro López V, Ramos JM, Meseguer V, *et al*. Microbiology and outcome of iliopsoas abscess in 124 patients. *Medicine (Baltimore)* 2009; 88(2):120-30.
18. Donald PR, Schaaf HS, Schoeman JF. Tuberculous meningitis and miliary tuberculosis: the Rich focus revisited. *J Infect* 2005; 50(3):193-5.
19. Garg RK. Tuberculosis of the central nervous system. *Postgrad Med J* 1999; 75: 133-40.
20. Hui ACF, Chan YL, Kay R. Syrinx and tuberculoma formation in tuberculous arachnoiditis. *Can J Neurol Sci* 2001; 28:148-9.
21. Mathuriya SN, Khosla VK, Banerjee AK. Intradural extramedullary tuberculous spinal granulomas. *Clin Neurol Neurosurg* 1988; 90(2):155-8.
22. Jeong DK, Kwon YM. Intradural extramedullary tuberculoma of the spinal cord following tuberculous meningitis. *Korean J Spine* 2015; 12(2):107-10.
23. Sohn S, Jin YJ, Kim KJ, Kim HJ. Long-term sequela of intradural extramedullary tuberculoma in the thoracic dorsal spinal cord: Case report and review of the literature. *Korean J Spine* 2011; 8(4):295-9.
24. Jawad N, Jafri S, Naqvi S, Ahmad SM, Naveed S, Ali Z. A case report on complicated tuberculous meningitis. *Cureus* 2017; 9(5):e1222.
25. Lee JS, Song GS, Son DW. Surgical management of syringomyelia associated with spinal adhesive arachnoiditis, a late complication of tuberculous meningitis: A case report. *Korean J Neurotrauma* 2017; 13(1):34-8.
26. Canova G, Boaro A, Giordan E, Longatti P. Treatment of posttubercular syringomyelia not responsive to antituberculer therapy: Case report and review of literature. *J Neurol Surg Rep* 2017; 78(2):e59-e67.
27. Berri MA, Rouimi A. Syringomyelia as a complication of tuberculous meningoencephalitis. *Pan Afr Med J* 2016; 25:141.
28. Pandey S, Nayak R, Mehndiratta MM. Early Syringomyelia in tubercular meningitis: A rare occurrence. *J Neurol Res* 2013; 3:46-8.
29. Kaynar MY, Kocer N, Gencosmanoglu BE, Hanci M. Syringomyelia as a late complication of tuberculous meningitis. *Acta Neurochirurgica* 2000; 142:935-9.
30. Moghtaderi A, Alavi-Naini R, Rahimi-Movaghar V. Syringomyelia: an early complication of tuberculous meningitis. *Trop Doct* 2006; 36(4):254-5.
31. Fehlings MG, Bernstein M. Syringomyelia as a complication of tuberculous meningitis. *Can J Neurol Sci* 1992; 19:84-7.
32. Daif AK, al Rajeh S, Ogunniyi A, al Boukai A, al Tahan A. Syringomyelia developing as an acute complication of tuberculous meningitis. *Can J Neurol Sci* 1997; 24(1):73-6.
33. Khalid M, Khalid S, Mittal S, Ahmad U. Intramedullary tubercular abscess with syrinx formation. *J Pediatr Neurosci* 2012; 7(1):61-3.
34. Desai KI, Muzumdar DP, Goel A. Holocord intramedullary abscess: An unusual case with review of literature. *Spinal Cord* 1999; 37:866-70.
35. Caplan LR, Norohna AB, Amico LL. Syringomyelia and arachnoiditis. *J Neurol Neurosurg Psychiatry* 1990; 53:106-13.
36. Shim DM, Oh SK, Kim TK, Chae SU. Intradural extramedullary tuberculoma mimicking en plaque meningioma. *Clin Orthop Surg* 2010; 2(4):260-3.
37. Garg RK, Malhotra HS, Kumar N. Paradoxical reaction in HIV negative tuberculous meningitis. *J Neurol Sci* 2014; 340:26–36.
38. Tai MLS, Nor HM, Kadir KAA, et al. Paradoxical Manifestation is Common in HIV-negative Tuberculous Meningitis. *Medicine (Baltimore)* 2016; 95(1):e199795(1):e1997.