

INTRODUCTION

Central nervous system tuberculosis (CNS TB) is a rare disease, which occurs with an incidence rate of 0.5 - 2.0% in individuals with systemic disease.¹⁻⁴ CNS tuberculosis often manifests in one of three distinct forms including tuberculous meningitis, tuberculoma, or spinal tuberculous arachnoiditis. Of those aforementioned, intramedullary tuberculoma (IMT) is the rarest form of disease involvement. Although overall tuberculosis case incidence has declined steadily in the United States over the past two decades, it is unknown if the incidence of IMT has changed because it is not reported separately.

Current knowledge regarding the clinical course of IMT is limited. Prior case reports have suggested that IMT has a gender and age predilection, occurring more frequently in younger, male patients.^{1,5,6} Other potential risk factors for disease development include malnutrition, alcoholism, concomitant malignancy, human immunodeficiency virus (HIV) infection, and the use of immunosuppressive medications.^{1,7} The clinical presentation of IMT remains largely nonspecific and the most common symptoms observed are those suggesting subacute spinal cord compression, such as headache, fever, lethargy, confusion, and focal motor and sensory deficits corresponding to the level of the lesion.^{1,6} Although radiographic findings of IMT also are frequently nonspecific, the dorsal thoracic spine is implicated in the majority of cases.⁵⁻⁶

IMT remains challenging to diagnose because there lack clear guidelines for spinal TB diagnosis and treatment. As a result, it is possible for individuals with this disease process to have a protracted clinical course and even be misdiagnosed. We present the case of an elderly male with an intramedullary dorsal spinal cord lesion at the T10-T11 level with associated right lower back pain and clinical signs of L4 radiculopathy who was diagnosed with an intramedullary tuberculoma.

CASE REPORT

A 71-year-old male with a past medical history of cervical spinal fusion surgery, C5 nerve palsy, lumbar spinal decompression surgery, and non-Hodgkin lymphoma status post chemotherapy with R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) presented to his primary care physician with concerns of chronic recurrent right hip and lower back pain which acutely worsened. The patient also acknowledged new-onset progressive numbness of his right thigh with associated intermittent, sharp muscle spasms. However, the patient denied recent urinary or bowel incontinence and speech or vision changes.

The patient's physical exam was unremarkable aside from poor coordination, hyperalgesia of the bilateral lower extremities, moderate tenderness to palpation of the lumbar spine at L1-L2 level, a positive bilateral straight leg test, and an unsteady tandem gait. Skin examination also revealed a violaceous plaque noted on the patient's anterior right thigh just above the knee. An initial lumbar magnetic

resonance imaging (MRI) with contrast was completed and revealed moderate multilevel lumbar spondylotic changes with facet joint degeneration without evidence of destructive osseous lesions or intradural masses. Given these relatively benign physical exam and radiographic findings, the patient was diagnosed with lumbar radiculopathy and treated with analgesics and a fluoroscopy-guided lumbar transforaminal epidural (LTFE).

Despite initial treatment, the patient's pain progressively worsened, therefore, he was scheduled for a repeat lumbar MRI to elucidate the etiology of his pain and worsening motor weakness. Repeat lumbar MRI with and without contrast was completed two months after he initially became symptomatic. It showed an abnormal focal increased T2 signal and a rounded area of enhancement within the right posterior aspect of the distal thoracic cord at the T11 level. The etiology of this new lesion was unclear and a thoracic MRI with and without contrast was completed and showed a pathologic cord signal with expansion and abnormal enhancement involving T7-T12 (Figures 1 and 2). The differential diagnoses at this time included transverse myelitis, recurrent lymphoma, cord infarction, or neoplasm.

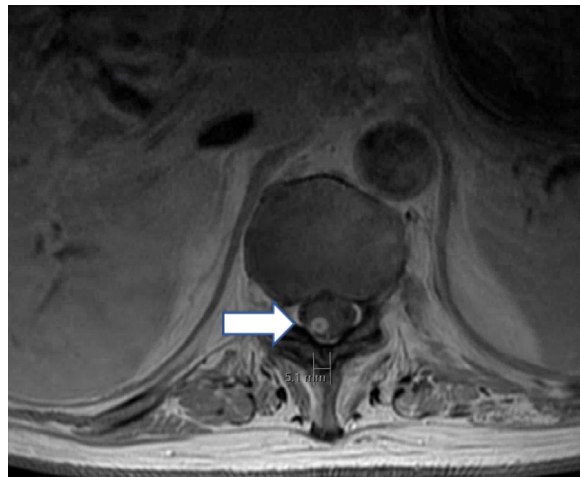


Figure 1. Axial T1 MRI at the level of T10-T11, revealing a pathologic cord signal with a hypointense center and peripheral ring enhancement, suggestive of development of the "target sign."

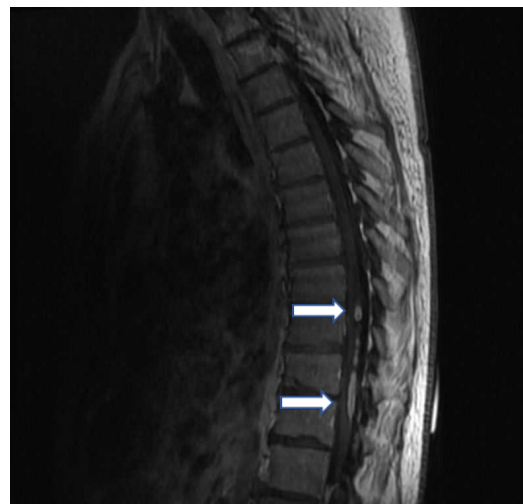


Figure 2. Sagittal T1 Flair MRI demonstrating pathologic cord enhancement from T7-T12.

The patient was admitted to the hospital for further evaluation and management. Upon hospital admission, the patient was afebrile with normal vital signs. Initial lab work revealed a white blood count of $6.3 \times 10^3/\text{mm}^3$, hemoglobin of 9.6 g/dL, platelets of $277 \times 10^3/\text{mm}^3$, neutrophils at 53%, and lymphocytes at 33%. Inflammatory markers revealed an erythrocyte sedimentation rate of 104 mm/hr and c-reactive protein of 4.0 mg/L. The patient's HIV test was negative. Cerebrospinal fluid analysis was completed to rule out the possibility of lymphomatous meningitis. CSF analysis revealed a clear, colorless sample with lymphocytic pleocytosis and elevated protein. Atypical lymphocytes were noted, but no evidence of lymphoma was observed on flow cytometry. Microscopic testing of the cerebrospinal fluid for acid fast bacteria, fungi, mycobacterium, and cryptococcus neoformans were negative. The patient's TB spot test also was negative.

F-18 fluorodeoxyglucose (FDG) PET/CT imaging divulged a linear focus of mildly accentuated FDG activity from the middle of the T10 to the middle of the T11 vertebral body, correlating with the signal abnormality noted in prior imaging studies. Biopsy of the lesion was subsequently performed to establish a histopathological diagnosis. The biopsy disclosed an area of necrosis surrounded by pale histiocytes consistent with necrotizing granulomatous inflammation. Given the imaging and histopathological findings, the suspicion was that the lesion represented spinal tuberculosis. However, initial special stains of the biopsy specimen for microorganisms, including Ziehl-Neelsen and Grocott methenamine silver stains, were negative. Additional stains of the biopsy specimen for microorganisms, including the Fite stain for acid fast bacilli and periodic Acid-Schiff for fungi, were completed and revealed rare acid-fast bacilli identified on Fite stain, thus confirming the suspected diagnosis of intramedullary spinal tuberculoma.

The patient was initiated on an anti-tuberculous pharmacotherapy regimen of rifampin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 1500 mg/day, and ethambutol 1200 mg/day (RIPE therapy), supplemented with adjuvant pyridoxine 50 mg/day.⁸ He was continued on RIPE treatment for two months followed by 10 months of continuation therapy with rifampin and isoniazid alone. Pharmacotherapy was supplemented with analgesics, physical therapy, and occupational therapy. The patient was followed on a monthly basis in the outpatient setting throughout treatment. After completing 12 months of pharmacotherapy, a repeat thoracic MRI with and without contrast was done, which revealed slight improvement in the T2 hyperintense signal within the thoracic spinal cord adjacent to the focal areas of enhancement at T8 - T9 and T10 - T11. These focal areas of enhancement did not appear to have changed significantly and no new areas of enhancement or abnormal signal were observed to suggest disease progression. Over the next two years he had persistent radicular pain, but his disability significantly improved from initial presentation. He is alive without recurrence of disease and has had significant improvement in his gait and mobility, now ambulating with a cane.

DISCUSSION

Tuberculosis of the central nervous system is a rare disease which often manifests in three distinct forms: tuberculous meningitis, intracranial tuberculoma, or spinal tuberculosis.¹ Specifically, spinal tuberculosis may present as one of a variety of lesions, including tuberculous spondylitis (Pott's disease), arachnoiditis, meningitis, or as an intramedullary lesion.⁴ Of these aforementioned lesions, intramedullary tuberculosis (tuberculoma) is the rarest form of disease involvement, accounting for approximately 8% of all cases of spinal TB.

Though spinal intramedullary tuberculomas (IMTs) are quite rare even in countries where TB is endemic, they carry an extremely high risk of morbidity and mortality and can have catastrophic clinical effects on a patient if diagnosis is delayed.^{3,5} IMTs are difficult to diagnose due to factors including the infrequency with which this type of lesion is seen and lack of strong understanding of disease pathogenesis and progression. Although this disease process is treatable, to date, specific guidelines on diagnosis of spinal IMT and treatment for disease eradication are poorly delineated.

The case above presented the epitome of diagnostic dilemmas because there lacked a clear definition of a diagnostic gold standard for spinal IMT. The current diagnostic recommendations for spinal TB based on prior case reports, include MRI of the spine in combination with spinal lesion biopsy for histopathologic confirmation, culture, and staining for *M. tuberculosis*.^{3,5,9,10} Although an important component of diagnosis, the sensitivity and specificity of MRI for IMT are limited. The MRI findings will vary greatly depending on the stage of tuberculoma formation and disease progression. In the early phase of disease progression, IMT often presents with a poorly formed collagenous capsule with surrounding edema and the lesion will appear iso- to hypointense on T1 and T2-weighted MRI. In later stages of disease, capsule thickening and granulation in addition to the central caseating necrosis leads to the appearance of a ring-enhancing lesion with a hypointense center on MRI; as caseating necrosis further progresses, part of the center of the lesion can become hyperintense leading to a radiographic finding sometimes referred to as the "target sign" (Figures 1 and 2).^{3,10} While this "target sign" can be useful in suggesting IMT, it is not unique to the diagnosis of spinal IMT.

In the case presented above, our patient's diagnosis and initiation of treatment, including the five drug anti-tuberculosis regimen, was based upon physical exam findings of focal neurologic deficits and an integumentary finding consistent with lupus vulgaris, a cutaneous manifestation of TB. This diagnosis was supported further by the suggestive MRI findings revealing a characteristic "target sign" lesion and histopathologic findings of necrotizing granulomatous inflammation in conjunction with the rare positive acid-fast bacilli noted on the Fite stain. This begged the questions: "What should be the role of the Fite stain versus the Ziehl-Neelsen stain in the diagnosis of spinal IMT?" and "How could the Fite stain be utilized in future cases of suspected IMT, to clarify and solidify a diagnosis?"

The Ziehl-Neelsen staining technique traditionally has been used as a first-line microbiological test to identify acid-fast bacilli, especially *mycobacterium tuberculosis*.¹¹ It is a rapid, cost-effective test that has a high positive predictive value and thus can be extremely useful, especially in underdeveloped countries where TB is endemic and clinical

resources may be more scarce. However, its usefulness in the detection of spinal tuberculosis is limited by its relatively poor sensitivity. The Ziehl-Neelsen staining technique has a detection rate of 0 - 20% in CSF specimens, thus its sensitivity is suboptimal. Moreover, it requires at least 5,000 - 10,000 bacilli per mL of specimen and requires larger volumes of CSF for spinal TB detection to be feasible.^{11,12} For this reason, the Fite staining method may be a more prudent choice for spinal TB diagnosis.

The Fite stain initially was introduced for detection of *Mycobacterium leprae* which has more precarious acid-fast properties compared to *Mycobacterium tuberculosis*.¹³ This staining technique utilizes a xylene/peanut oil deparaffinizing solvent to minimize the exposure of the bacterial cell wall to organic solvents, thus preserving its acid fast nature.^{12,13} This method is useful in identifying more delicate acid-fast organisms. While the Fite stain's sensitivity has been reported to range from 40 - 70% in the detection of *Mycobacterium leprae*, its sensitivity for the detection of *Mycobacterium tuberculosis* has not been studied to date.^{12,14} One can speculate that the Fite stain would have greater sensitivity for the detection of any acid fast bacteria than the Ziehl-Neelsen method, based on its ability to preserve the acid-fast nature of more delicate species.¹² In our patient, both TB spot testing and initial staining of the CSF and biopsy specimens with the Ziehl-Neelsen acid-fast bacilli stain were negative. The Fite stain technique proved useful in diagnosis and it helped to guide clinical management in our case. Perhaps, the Fite staining method should be an adjuvant diagnostic test for the detection of spinal TB.

Another major issue of concern regarding IMT is that clear guidelines regarding treatment modalities for spinal TB are lacking. There are cases of IMT where microsurgical resection can be beneficial and should be considered (such as in patients with profound neurological deficits or in those with large space-occupying lesions); however the mainstay of treatment suggested thus far for IMT is anti-tuberculosis pharmacotherapy.^{6,9,15,16} Anti-tuberculosis therapy traditionally consists of two phases; an intensive phase where multiple drugs (three or more) are utilized and a continuation phase (with two to three drugs).¹⁷ The intensive phase serves to provide coverage for drug-resistant organisms and quickly reduce bacillary load. The continuation drug phase serves to eliminate drug-sensitive "dormant" bacilli that are responsible for disease relapse.

While the World Health Organization provided clear recommendations for treatment of pulmonary TB including a two-month intensive phase and six-month continuation phase of 2RIPE/6RI (where R: rifampin, I: isoniazid, P: pyrazinamide, E: ethambutol), there lacks clear treatment guidelines including what drug regimen is the most beneficial for IMT treatment and how long the intensive versus continuation phases should last for disease eradication or regression.¹⁸ Our patient was treated with two months intensive phase RIPE therapy and 10 months continuation phase with rifampin and isoniazid (RI). Although our patient did not achieve complete disease eradication, his disease progression was halted as evidenced by the repeat imaging studies taken one year after diagnosis. Further studies analyzing what treatment regimens are most effective for IMT would be beneficial for improving patient outcomes.

CONCLUSION

Intramedullary tuberculoma is an incredibly rare diagnosis which poses a unique diagnostic dilemma to the clinician, as there lacks both a gold standard for diagnostic methodology and specific treatment guidelines for disease treatment and/or eradication. Although rare, this diagnosis should be included on the differential for any patient who presents with progressively worsening symptoms of radiculopathy and a new spinal lesion. TB spot test and Ziehl-Neelsen acid-fast bacilli stain have limited utility in the diagnosis of IMT via CSF sampling or lesion biopsy due to the low sensitivity of both of these tests. Thus, a negative TB spot test, an inability to isolate acid-fast bacilli upon staining, and a failure to culture *M. tuberculosis* should not exclude the diagnosis. Further studies are needed to understand the role and sensitivity of the Fite stain in diagnosing this type of lesion, and clarify specific treatment guidelines for IMT.

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