Case Report

Tubercular longitudinally extensive transverse myelitis (LETM): An enigma for primary care physicians

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Abstract

Albeit, all forms of tuberculosis (TB) are endemic in India, spinal intramedullary TB and tubercular longitudinally extensive transverse myelitis (LETM) is deemed extremely rare. With recent advances in the field of neurology, autoimmune astrocytopathy (neuromyelitis optica spectrum disorders, NMOSD), myelin-oligodendrocyte glycoprotein associated encephalomyelitis (MOG-EM), metabolic myelopathy, connective tissue diseases and viral infections have gained considerable focus in the list of differentials of LETM whereas tubercular association is often forgotten. This report presents a rare case of acute transverse myelopathy which unveiled previously undiagnosed pulmonary tuberculosis in an adult rural Indian male. The patient responded well to anti-tubercular therapy and corticosteroids. Exact pathogenesis of LETM in TB remains elusive. Association of TB with MOG-EM has been one of the recent hot-cakes. However, an ill-defined immune-inflammatory response to the infectious agent is the likely cause of tubercular LETM. Hence, the primary care physicians who are the first medical contacts of acute LETM cases and in most cases due to diagnostic dilemma there is an unavoidable delay in accurate diagnosis and initiation of therapy. Primary care doctors should nurture a high index of suspicion to diagnose this potentially lifetime-debilitating yet absolutely treatable clinical condition i.e. tubercular LETM.

Keywords: Longitudinally extensive transverse myelitis, myelopathy, tuberculosis

Introduction

Tuberculosis (TB), both pulmonary and extrapulmonary, is endemic in India.[1] Tubercular infection of central nervous system (CNS) is still a major cause of morbidity and mortality in low-to-middle-income countries.[2] Spectrum of CNS-TB include most frequently tubercular meningitis followed by tuberculoma, tubercular abscess, cerebral miliary TB, TB encephalitis and encephalopathy, tubercular arteritis[3] and spinal tuberculosis.[4]

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Spinal intramedullary tuberculosis (SIMT) is rarest form of CNS-TB[4,5] and manifests in the form of myelo-radiculitis, intramedullary tuberculomas, anterior spinal artery thrombosis and transverse myelitis[6] which is rarely fulfills criteria of a longitudinally extensive transverse myelitis (LETM).[7] Extensive inflammation, hyperintense lesions on T2-weighted images on magnetic resonance imaging (MRI) of spinal cord spanning over three or more contiguous vertebral segments and significant neurodeficits are hallmarks of LETM.[8] Several etiologies of LETM have been reported in recent times including infections, autoimmune diseases, connective tissue diseases, malignancy, metabolic myelopathies, etc., and neuromyelitis optica spectrum disorders (NMOSD) remains the classical causative association.[8] LETM usually involves the cervico-dorsal portion of spinal cord; however holocord involvement has been described previously.[9]

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Exact pathogenesis of LETM in TB is yet to be elucidated, however, an immune-inflammatory response to the infectious agent or the infection itself has been postulated as a cause in previous literatures.[7,10]

The authors, hereby, present a rare case of acute transverse myelopathy which unveiled previously undiagnosed pulmonary tuberculosis. The patient responded well to anti-tubercular therapy and corticosteroids. This case will emphasize upon the fact that in endemic zones SIMT, especially tubercular LETM, should always be kept in the differential diagnoses of acute transverse myelopathy because delay in diagnosis will lead to long term morbidity and debility. Hence, the primary care physicians who get the cases earliest should cultivate a high index of suspicion to diagnose a potentially lifetime-debilitating yet absolutely treatable clinical condition i.e. tubercular LETM.

Case History

A 32-year-old man from rural India presented to emergency with complaints of weakness in both lower limbs and associated urinary retention for last 14 days. Two weeks ago, he was working in his agricultural field in the morning when he suddenly experienced dull aching localized pain in his mid-back area. The pain subsided within few hours and was followed by inability to pass urine along with pain and fullness in lower abdomen. In the evening hours on the same day, he felt weakness of his both lower extremities involving both proximal and distal group of muscles simultaneously. The weakness progressed rapidly and within a day he became bed ridden. There was no history of any weakness of upper limbs, neck or bulbar muscles but he complained of difficulty in sitting up from supine posture. There was no history of thinning, twitching or sudden involuntary painful flexion of lower limbs. He also complained of decreased sensation to touch and pain below upper abdomen and a girdle like sensation in the upper mid back area. He was catheterized on the very first day of his illness and till now it has to be kept in-situ. He had constipation for last 13 days. There was no history of headache, nausea-vomiting, double vision, diminished visual acuity, painful eye movements, and color desaturation, difficulty in swallowing and intractable hiccoughs. He gives a history of recent onset low-grade evening rise of temperature and cough with phlegm production from las5t three weeks. There was no history of joint pain, oro-genital ulcers, and hair loss or photosensitivity. His appetite is normal but there is history of loosening of clothes suggestive of involuntary weight loss. No history of associated shortness of breath, night sweats, sense of heaviness or discomfort/pain over chest, hemoptysis, past history of any significant personal illness and family history of any significant and similar diseases.

His general survey revealed mild anemia. On detailed neurological examination, cognitive functions, cranial nerves' functions cranium and bony spine were intact. Examination of motor system revealed arreflexic, flaccid paraplegia of both lower limbs (MRC grade 0/5 in proximal and distal muscles of both lower limbs) with mute planter response and absent abdominal reflexes. Sensory system examination revealed patchy loss of touch (crude and fine) pain and temperature sensations approximately below D5 segment level. Vibration sense was decreased upto D5 spinous process and joint position senses were absent in lower limbs. Cerebellar functions could not be tested completely due to lower limb weakness. Neurological examination of upper limbs was normal. There were no signs of meningeal irritation and papilloedema or optic neuritis on fundoscopy. On detailed examination of the respiratory system,

Table 1: Clinico-radiological differential diagnoses of the case

Differential diagnoses	Odds
NMOSD including MOG-EM [10-14]	No historical, clinico-radiological and neurophysiological evidence of cerebral and optic nerve involvement Single episode Paired sera for anti-AQP4 and anti-MOG antibodies were negative Diagnostic criteria for NMOSD were not fulfilled [13].
Conglomerated multiple intramedullary tuberculomas with pericentral necrosis edema [5,15,16]	Typical MRI characteristics are hypo or isointense to cord in T1-weighted sequence with only an indirect sign of focal cord expansion and heterogenous intensity on T2-weigted image with central hypointensity and peripheral hyperintensity, which is described as target sign.Peripheral enhancement is characteristic feature of tuberculomaon post contrast images.The central hypointensity on T2- weighted image is suggestive of caseating necrosis. Associated meningeal enhancement, skip lesions, tracking epidular collections, extradural involvement may co-exist. [16]
Tubercular intramedullary spinal cord abscess [12,15,17,18]	Usually subacute in presentation Imaging usually show swollen cord, nodular Leptomeningeal enhancement, with features of central caseous necrosis on DWI and ADC, usually there remain features of residual lesion even after therapy No "precipitation or drop sign'
Anti-MBP antibodies associated myelitis[7,10]	No serological evidence was found
Acute spinal cord ischemia syndromes due to TB associated end-arteritis/thrombosis/ vasculitis [15,19,20]	Usually involves only anterior spinal artery and so spare the posterior column (clearly not in this case) Usually have a background of hypercoagulable state like SLE or APLA or background cardio-vascular malformations etc., (absent in this case) Very poor outcome unlike this case No pencil-like T2 hyperintensity following a vascular territory, no 'owl-eye' lesions, no DWI restriction

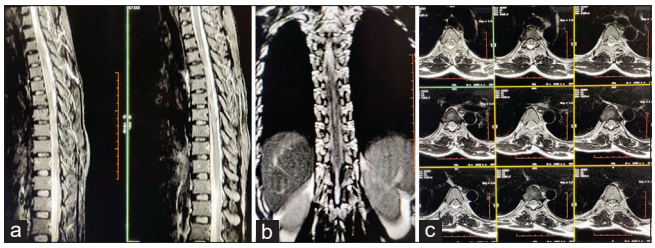

Figure 1: MRI of spine with contrast revealed longitudinally extensive altered intramedullary intensity hyper in T2 (a) mid-sagittal, (b) coronal, C-axial (D3 to D7)) from D3 to distal cord and conus (A), predominantly involving the central portion of cord (c)

there was decreased movement with tubular-bronchial and cavernous breath sounds and increased vocal resonance in the right supraclavicular and upper interscapular regions.

Analyzing the clinical history and examination findings a working diagnosis of acute non-compressive upper dorsal myelopathy in spinal shock stage was considered. Due to its acuteness of presentation and short duration of illness and associated features of infective respiratory illness infective, demyelinating and vascular etiologies were considered first. A) Infective causes: acute infective or para-infectious myelitis or myelo-radiculopathy due to TB, viral or bacterial infection; B) Demyelinating causes: acute transverse myelitis, NMOSD, first episode of multiple sclerosis; C) Vascular causes: acute anterior spinal artery occlusion, vasculitis in connective tissue disorders.

Since a rapidly evolving compressive lesion may often masquerade an acute non-compressive myelopathy, epidural abscess, Caries spine, prolapsed intravertebral disc, acute bleed in a pre-existing intramedullary arterio-venous malformation (AVM) or tumor, acute epidural hematoma were also kept in list of differential diagnoses.

Since a pandemic is ongoing, a real-time RT-PCR was done from naso-oro-pharyngeal swabs to rule out SARS-CoV-2 infection. Complete hemogram, plasma sugar, glycated hemoglobin, thyroid, kidney and liver function tests were normal except presence of mild anemia (hemoglobin 11.2 g/dl) and a significant rise in erythrocyte sedimentation rate of 60 mm in first hour. Serologies for HIV, hepatitis B and C and syphilis were negative. A chest X-ray revealed right upper lobe cavitary consolidation. However, sputum for acid fast bacilli (AFB) and Gene-Xpert test were negative and Mantoux test was non-conclusive. A contrast enhanced MRI of spine revealed extensive, non-enhancing, altered intensity that is hyper in T2-weighted images noted at cord from D3 to distal cord and conus region suggestive of LETM [Figure 1]. MRI of orbits and brain were normal. Visual evoked potential (VEP) records were normal in both eyes. Serum vitamin B12, angiotensin converting enzyme (ACE), profiles for autoimmune connective tissue disorders were all non-contributory. Cerebrospinal fluid (CSF) analysis revealed mildly raised protein content with mononuclear pleocytosis (protein 65 mg/dl, cells 12 per microlitre, all lymphocytes). CSF analysis was negative for markers of TB and oligoclonal bands rather an increase in IgG index was noted. Paired sera for anti-aquaporin-4 (AQP4)-antibodies, anti-myelin-oligodendrocyte-glycoprotein (MOG)-antibodies, anti-myelin-basic-protein (MBP)-antibodies were all negative. Viral myelitis was ruled out by testing paired sera for relevant neuroviruses. Since the signs of respiratory infection was not abating even with standard bacterial pneumonia management, radiological signs of pulmonary tuberculosis were evident and a definitive etiology for the isolated LETM was elusive the case was re-tested for sputum for Gene-Xpert and AFB and this time both became positive for rifampicin sensitive Mycobacterium tuberculosis (MTB).

The patient was put on multi-drug anti-tubercular therapy (ATT) under national tuberculosis elimination program (NTEP) and short-course high dose intravenous methylprednisolone (1 g/day for 3 days). Within one week of initiation of therapy the motor powers started improving (MRC grade 2+/5 after one week) and autonomic functions were improving too. He was referred to rehabilitation and was being followed up monthly for the next 6 months. At second month of follow-up, he did not have any demonstrable neurodeficit and was sputum negative and symptom-free. ATT was continued till sixth month and then stopped. He has been asked for periodic follow-up at three months. Follow-up MRI of spinal cord was normal and computed tomography scan of thorax revealed reduction of the lesion with early fibrosis.

Discussion

LETM is an exceedingly rare form of neurological presentation of CNS-TB.[6,7] Clinico-radiological differential diagnoses are summarized [see Table 1].[5,7,10-20] Tubercular LETM is postulated to be a result of an abnormal activation of immune response against cord.[21] Immune-mediated inflammatory secondary demyelination has been the explanation for NMOSD cases associated with pulmonary TB[14] but causative association is doubtful.[11,14] In the presented case, high CSF protein and especially higher CSF IgG index, an indicator for increased intrathecal IgG synthesis, might be a reflection of humoral immune response to tubercular infection or the organism itself. In recent times, anti-AQP-4, anti-MOG and anti-MBP-antibodies have been found in high titers in CSF with tubercular LETM[10] which support the notion of secondary demyelination.[10,22] Besides, MTB infection have been associated with triggering of several autoimmune diseases in human through T-cell mediated molecular mimicry in host[23] and MTB might share few common antigenic epitomes with structural proteins of myelin.[24] Tubercular LETM might also be assumed to be a delayed hypersensitivity reaction.[10] Since NMOSD is nowadays considered an autoimmune astrocytopathy instead of a demyelinating disorder likely mechanism may be a T-cell instigated molecular mimicry that triggered auto-antibody production against AQP-4 water channels,[25] in this case. Further studies are needed to pin-point the exact pathogenesis of tubercular LETM. Many studies have reported ATT has a likely beneficial effect on final outcome of patient with

MTB-associated NMOSD.[10,26,27] Even in this case, ATT with high dose short course steroid provided dramatic therapeutic response but since it remains to be amongst the rarest cases, there are still no consensus guidelines for management.

Early detection of tubercular LETM is mandatory otherwise it may turn into a cavitary syrinx formation and permanent disabilities and proper clinical history, physical examination, high degree of suspicion and early neuroimaging are keys to accurate diagnosis of tubercular LETM. This case highlights the fact that in appropriate background tuberculosis should always be kept in the list of differential diagnoses of acute non-compressive myelopathy with LETM on imaging. Rapid diagnosis not only curtails long-term morbidity but also potentially can cure the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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