

Longitudinally Extensive Transverse Myelitis and Optic Neuropathy Associated with Syphilitic Meningomyelitis and Human Immunodeficiency Virus Infection: A Case Report and Review of the Literature

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Abstract

The incidence of co-infection with *Treponema pallidum* and human immunodeficiency virus (HIV) is increasing in developing and developed countries. The neurological complications of both infections occasionally occur simultaneously during a clinical course. We herein report the case of an HIV carrier with syphilitic meningomyelitis and subclinical optic neuropathy. The patient presumably had latent syphilis and slowly developed longitudinally extensive transverse myelitis (LETM). A cerebrospinal fluid examination confirmed the diagnosis of active neurosyphilis based on an elevated *T. pallidum* hemagglutination assay index. A change in the patient's immune status, possibly due to HIV, might have converted the syphilis from latent to active, leading to LETM of the spinal cord.

Key words: syphilitic meningomyelitis, TPHA index, optic neuropathy, human immunodeficiency virus, longitudinally extensive transverse myelitis

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Introduction

Syphilis is a sexually-transmitted disease caused by *Treponema pallidum* infection. Its clinical symptoms include fever, focal or generalized skin lesions, lymph node enlargement, and various neurological disorders, which occur over a period of several years (1). Although tabes dorsalis and progressive paralysis are crucial neurological features of tertiary syphilis, other complications, including meningitis, meningomyelitis, meningovascular syphilis causing stroke and seizure, optic neuritis and/or perineuritis, uveitis, and cranial neuritis, in the earlier stage are also crucial (1-4). Recent reports have shown that the number of patients co-infected with *T. pallidum* and human immunodeficiency virus (HIV) has been increasing. In the United States, 16% of all syphilis patients, and 28% of male syphilis patients were co-infected with HIV (1). Notably, carrier-stage patients who are co-infected with *T. pallidum* and HIV are prone to a clinical exacerbation of syphilis and/or acquired immunode-

ficiency syndrome (1). Syphilitic meningomyelitis is a rare spinal cord syphilis that is pathologically characterized by meningeal inflammation and spinal cord ischemia and edema due to syphilitic vasculopathy (3-13). The clinical symptoms of syphilitic meningomyelitis usually develop at between 1 and 30 years after the initial infection (average: 6 years) (14). These inflammatory and ischemic changes are partially reversible, because treatment with penicillin and corticosteroids can diminish the affected lesions to a certain extent (5, 9, 13).

We herein report a case of a patient with syphilitic meningomyelitis and asymptomatic optic neuropathy accompanied by HIV infection. On magnetic resonance imaging (MRI), the patient was found to exhibit atypical longitudinally extensive transverse myelitis (LETM) at the cervical and thoracic levels that radiologically mimicked neuromyelitis optica (NMO). The patient also had subclinical right optic neuropathy with prolonged P100 latency that was detected using a flash visual evoked potential (VEP) study. Although both *T. pallidum* and HIV infection can cause myelopathy, it

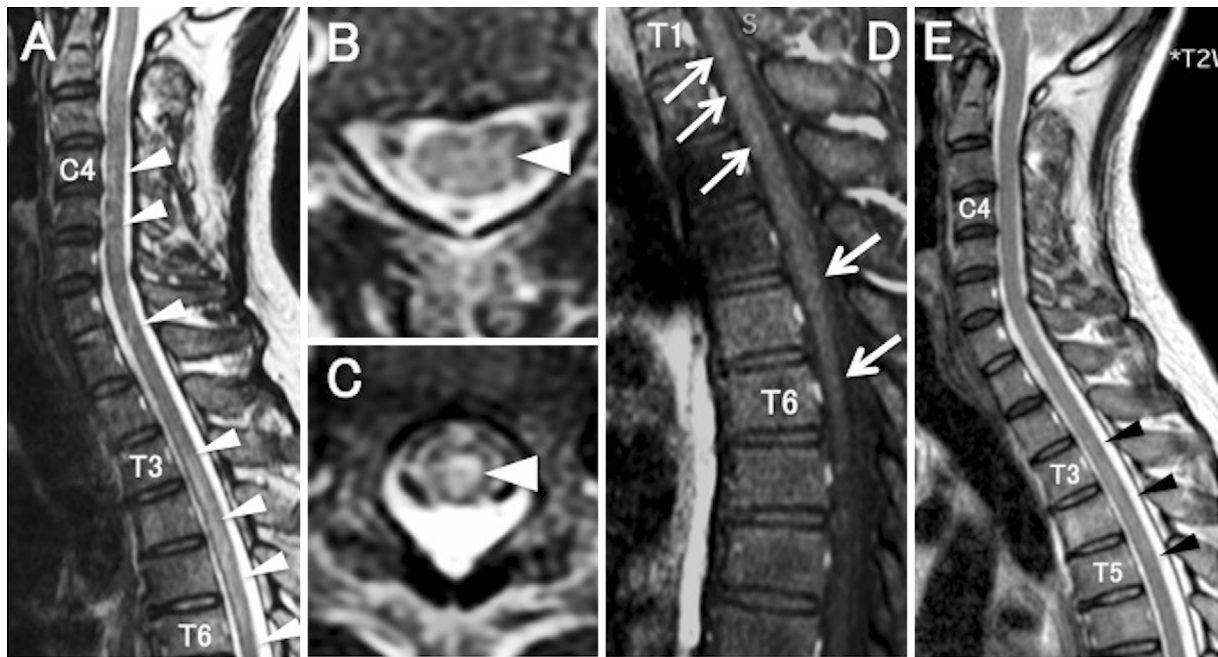


Figure 1. T2-weighted MRI of the spinal cord on admission showing patchy and partially continuous high-intensity lesions around the central canal extending from the level C4 to T6 in the sagittal view (white arrowheads) (A) with a subtle uptake of gadolinium in the superficial portion from T2 to T6 (white arrows) (D). An axial view of the cervical (B) and thoracic levels (C) revealing high-intensity lesions in the central portion of the spinal cord (white arrowheads). MRI at 2 weeks after antituberculous and steroid pulse therapies, revealing a reduction in the size of the cervical and thoracic cord lesions (black arrowheads) (E). MRI: magnetic resonance imaging

is considered that the elevated treponema pallidum hemagglutination assay (TPHA) index reflected the active syphilitic meningomyelitis under an HIV carrier state in our patient.

Case Report

A 49-year-old bisexual man had experienced a feeling of residual urine at micturition 5 months before admission. He had also suffered from progressive gait disturbance with spasticity, paresthesia, a loss of pain and temperature sensations in the bilateral lower limbs, and urinary retention for 2 weeks. A previous serological examination when he was in his 20s had revealed an elevated *T. pallidum* hemagglutination assay (TPHA) titer; however, he had no apparent symptoms of syphilitic infection. In addition, he had no allergic diseases (such as bronchial asthma or atopic dermatitis).

On admission, his cognitive function was normal. A neurological examination, which included examinations of the patient's visual acuity, visual fields, optic fundus, and pupillary light reflex, was normal. He did not exhibit muscle weakness, but the deep tendon reflexes in the arms and legs were brisk, and the patient was bilaterally positive for the Babinski sign. He noticed glove and stocking-type paresthesia in the bilateral extremities. The sensation of vibration was mildly decreased in both legs, but the sense of position was intact. Sensory ataxia was suspected because the patient was positive for the Romberg sign. He experienced gait dis-

turbance with spasticity, but his coordination was intact.

Brain MRI was unremarkable. T2-weighted MRI of the spinal cord revealed partially discontinuous LETM with high-intensity lesions extending from the C4 level to the T6 level (Fig. 1A); in the axial section, the pericentral area was mainly affected (Fig. 1B, C). On T1-weighted images with gadolinium enhancement, spotty contrasted lesions were visible at the surface of the thoracic cord (T2-6, Fig. 1D). On orbital MRI, short T1 inversion recovery images of the coronal section revealed a ring-shaped, high-intense perineural lesion of the right optic nerve (Fig. 2A). Axial T2-weighted MRI revealed a "tram-track sign" on the right optic nerve (Fig. 2B). Flash VEP revealed two bottoms (P1 and P2) and a prolonged P100 latency (P2, 130.6 ms) on right eye stimulation (Fig. 3A) in comparison to the P100 latency (P1, 120.9 ms) on left eye stimulation (Fig. 3B). A blood examination revealed an elevated TPHA titer ($\times 2,560$; normal $< \times 80$) and a strongly reactive rapid plasma reagin titer (117-fold). The patient's serum was positive for HIV antibodies (HIV-RNA: 3,480 cp/mL). The plasma CD4⁺ lymphocyte count was 837/ μ L. Serum antibodies against herpes simplex virus, varicella zoster virus, human T-lymphotropic virus type 1, Epstein-Barr virus, and cytomegalovirus were not detected. The serum IgE level was elevated (1,022 IU/mL; normal, < 170 IU/mL), and a specific IgE against mites was detected without eosinophilia. Autoantibodies against aquaporin-4 (AQP4), nuclear, SS-A, SS-B, ribonucleoprotein (RNP), and Sm were not detected. The patient was sero-

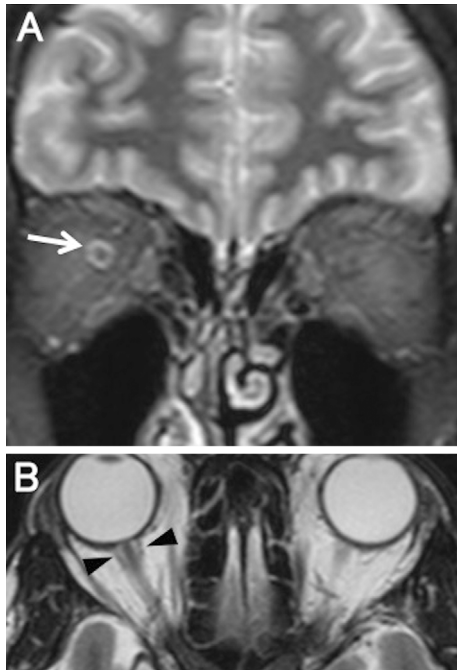


Figure 2. Orbital MRI, coronal view, showing a ring-shaped, high-intensity lesion along the perineural portion of the right optic nerve on short T1-inversion recovery images (white arrow) (A). Orbital MRI, axial view, showing a “tram-track sign” on the right optic nerve on T2-weighted images (black arrowheads) (B). MRI: magnetic resonance imaging

negative for both myeloperoxidase-antineutrophil cytoplasmic antibodies (ANCA) and proteinase 3-ANCA. The levels of angiotensin-converting enzyme, lysozyme, and soluble interleukin-2 receptor were within the normal ranges. A cerebrospinal fluid (CSF) study revealed pleocytosis (202 white blood cells/mm³; 95% lymphocytes) and an elevated total protein level (79 mg/mL). No malignant cells were detected, and oligoclonal bands were not detected in the CSF. The TPHA-albumin index value was elevated (73.3; positive reference value, ≥ 70). The finding that the CSF-TPHA titer was correlated with the albumin quotient (15), strongly supported the diagnosis of active neurosyphilis. The formulas of these indexes were as follows:

The TPHA-albumin index: CSF-TPHA titer/albumin quotient

The albumin quotient: CSF albumin (mg/dL) $\times 10^3$ / serum albumin (mg/dL)

After the intravenous administration of penicillin G potassium (24-million IU/day for 14 days) and methylprednisolone (1,000 mg, daily, for the first 3 days), the symptoms of gait ataxia and sensory disturbance in the lower extremities improved, but the urinary dysfunction remained. Antiretroviral therapy (ART) was not administered because of the patient's high CD4⁺ T-cell count.

At two weeks after the administration of these therapies, MRI revealed a reduction in the size of the cervical and thoracic cord lesions (Fig. 1E, compared with Fig. 1A) but no remarkable change in the optic nerve lesion. A follow-up

flash VEP examination that was performed 1 year later showed an improvement in the P100 latency on the right optic nerve (right, 120.3 ms; left, 121.8 ms) (Fig. 3C, D).

Discussion

The patient, who was an HIV carrier, was diagnosed with syphilitic meningomyelitis with longitudinal spinal cord lesions and asymptomatic unilateral optic neuropathy. NMO and atopic myelitis were ruled out because he was negative for anti-AQP4 antibodies, with no evidence of atopic disorder due to eosinophils in the CSF. The spinal cord involvement in neurosyphilis is classified into three clinical subtypes: meningomyelitis, meningovascular disease, and tabes dorsalis (3). Twelve patients with syphilitic meningomyelitis showing MRI abnormalities have been reported to date. A clinical summary of 13 cases of syphilitic meningomyelitis, including our case, is shown in Table. The mean age at the onset of disease was 42.6 years, and most of the reported patients were male (85%). The common neurological findings in 11 patients with syphilitic meningomyelitis were an impaired superficial sensation (91%), hyperreflexia (82%), extremity weakness (73%), impaired deep sensation (55%), urinary disturbance (55%), and pain (36%) (Table). The duration of symptoms was variable, from 3 days to 6 months, and some patients had a clinical course of chronic myelitis similar to that in our patient (7, 8, 10, 11). However, our patient was the only HIV carrier. Eleven out of 13 patients (85%) exhibited LETM. Gadolinium enhancement in the superficial and/or central part of the spinal cord parenchyma was observed in eight cases (3-5, 7, 8, 12, 13, Fig. 1D), which might reflect direct treponemal invasion into the spinal cord from its surface (4). Most patients underwent anti-luetic therapy with penicillin G; in some cases steroids (prednisolone or dexamethasone) were co-administered to prevent Jarisch-Herxheimer reactions, which present as general malaise, myalgia, fever, and headache (5, 8, 11-13). This steroid treatment improved the spinal cord edema caused by primary inflammation (3, 4, 6, and this case). Our patient had presumably been in the latent stage of syphilis before myelopathy, as he had never noticed the initial dermatosclerosis or dermosyphilopathy that are usually seen in early-stage syphilis. Thus, despite being seropositive since his 20s, he had never been treated for syphilis. Based on our patient's clinical history, recent HIV co-infection probably converted his latent syphilis into active meningomyelitis (1), causing urinary disturbance, spastic paraplegia, and sensory disturbance of 5 months in duration. The pathogenesis in this case is primarily considered to be meningomyelitis, according to the clinical course, and the CSF pleocytosis with elevated total protein levels. MRI demonstrated LETM in the cervical and thoracic spinal cord, with several spotty enhanced lesions in the meninges surrounding the spinal cord. However, the high-intensity lesions on T2-weighted MRI partially remained, even after anti-luetic therapy, suggesting that the affected cord lesions involved not only reversible

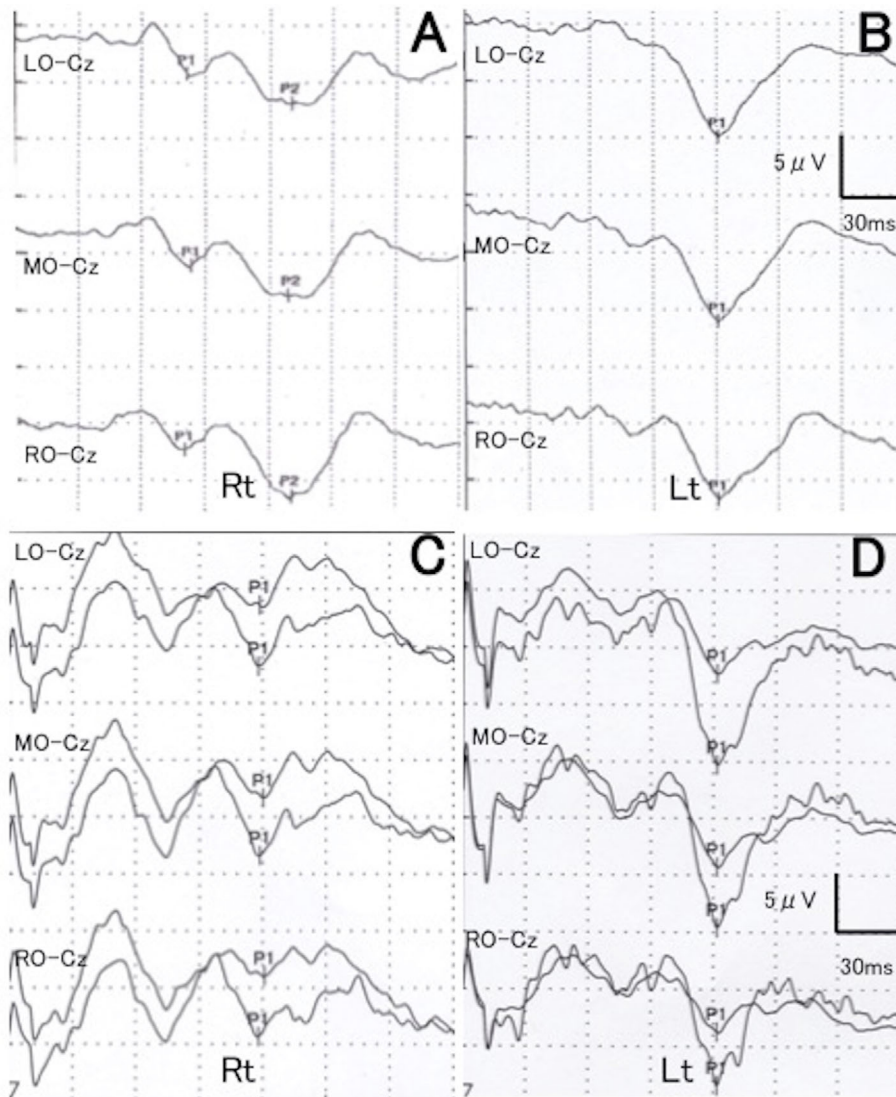


Figure 3. A flash VEP study revealed two bottoms (P1 and P2) and a prolonged P100 latency (P2, 130.6 ms) on right eye stimulation (A) in comparison to the P100 (P1, 120.9 ms) on left eye stimulation (B). A follow-up flash VEP study at 1 year after treatment showed an improvement in the P100 latency (120.3 ms) of the right optic nerve (C) with no bilateral difference (left: P100, 121.8 ms) (D). VEP: visual evoked potential

edema but also spinal cord ischemia from meningovascular syphilis (13). Although LETM can be observed in the NMO, it is crucial to consider syphilitic meningomyelitis as a radiological differential diagnosis. A meningeal enhancement of the spinal cord is more likely to be seen in infectious meningomyelitis than in NMO.

The patient was an HIV carrier. Serum and CSF samples that were taken on admission were positive for HIV-RNA. However, it is unclear when he was co-infected with HIV. The natural course of an HIV patient involves acute viremia, with more than one million copies of HIV-RNA, after viral proliferation in the lymphoid tissue (16). Approximately 50% of HIV patients simultaneously suffer from high fever, rash, and lymph node swelling, and they reach a chronic infectious state after a reduction in HIV by an innate immunological response (16, 17). Our patient did not have acute HIV viremia, but was an HIV carrier; this was evidenced by

his normal CD4⁺ cell count remained normal and the relatively low number of serum HIV-RNA copies. Neuropathologically, vacuolar myelopathy is known to be a common finding in advanced HIV myelitis. Four patients with HIV myelitis (16-19) at the time of seroconversion or at the early phase of HIV infection have been reported (Table). Andrade et al. reported the case of a patient with acute HIV myelitis presenting with LETM extending from T2 to T11, CSF pleocytosis (302/μL), and a large number of HIV-RNA copies in the blood (743,000 cp/mL) (16). HIV myelitis generally exhibits acute and/or subacute spinal cord lesions with less frequent LETM or the uptake of gadolinium and is frequently accompanied by several non-neurological symptoms that are caused by primary HIV infection (Table). In contrast, syphilitic meningomyelitis more frequently exhibits LETM and the gadolinium enhancement of the intrathecal lesions and on the surface of the spinal cord. Our patient ex-

Table. Clinical Characteristics in Syphilitic Meningomyelitis and Comparison with HIV Myelitis.

	Case 1	2	3	4	5	6	7	8	9	10	11	12	13	This case	Syphilitic meningomyelitis n=13	HIV myelitis n=4
Age	46	63	63	35	30	36	38	46	32	28	31	57	57	49	42.6±6.7 (28-63)	33.5±5.0 (29-40)
Sex	M	M	M	M	F	M	M	M	M	M	M	F	F	M	M: 11, F: 2	M: 4, F: 0
Symptoms duration (d)	7	12	60	14	30	120	120	14	120	180	10	3	3	150	64.6±34.7 (3-180)	23.6±13.5 (7-35)
Serum HIV antibody (+)	-	-	-	-	-	-	-	NA	-	-	NA	-	-	+	1	4
MSM	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	1	4
Frequent period														<6 years after syphilitic infection		Early phase of HIV infection
Neurological symptoms																
Superficial sensory deficit	+	-	+	NA	NA	+	+	+	+	+	+	+	+	+	10/11, 91%	3/4
Hyperreflexia	+	-	-	NA	NA	+	+	+	+	+	+	+	+	+	9/11, 82%	2/4
Weakness in extremities	-	+	+	NA	NA	+	+	-	+	+	+	+	+	-	8/11, 73%	3/4
Impaired deep sense	-	-	-	NA	NA	+	+	+	-	+	-	+	+	+	6/11, 55%	0/4
Urinary disturbance	-	-	+	NA	NA	-	+	+	+	-	+	-	-	+	6/11, 55%	3/4
Pain	+	+	-	NA	NA	+	+	-	-	-	-	-	-	-	4/11, 36%	3/4
Areflexia	-	-	-	NA	NA	-	-	-	-	-	-	-	-	-	0/11	1/4
Physical symptoms																
Rash	-	-	+	NA	NA	-	-	-	-	+	-	-	-	-	2/11, 18%	2/4
Fever	-	-	+	NA	NA	-	-	-	-	-	-	-	-	1/11, 9%	3/4	
Fatigue	-	-	-	NA	NA	-	-	-	-	-	-	-	-	0/11	2/4	
Dry cough	-	-	-	NA	NA	-	-	-	-	-	-	-	-	0/11	2/4	
Sore throat	-	-	-	NA	NA	-	-	-	-	-	-	-	-	0/11	2/4	
Pharyngeal candidiasis	-	-	-	NA	NA	-	-	-	-	-	-	-	-	0/11	2/4	
CSF analysis																
Cell count (μL)	113	303	498	115	170	346	18	↑	40	196	120	↑	202	192.8±83.8 (18-498)	108.8±114.6 (8-302)	
% lymphocytes (%)	100	84	63	85	90	99	72	NA	100	97	100	NA	95			
Protein (mg/dL)	72	92	200	123	57	243	88	↑	40	109	94	Normal	79	108.8±36.0 (40-243)	128.5±141.5 (29-343)	
Immunological reaction for syphilis	iTPA index↑	RPR+ index↑	VDRL+ index↑	VDRL+ index↑	VDRL+ index↑	FTA+ index↑	VDRL+ index↑	VDRL+ index↑	VDRL+ index↑	VDRL+ index↑	TPHA index↑	VDRL+ index↑	VDRL+ index↑	TPHA index↑	iTPA or TPHA index↑	RPR+, VDRDL+, FTA+
Laboratory test																Blood HIV-RNA copy↑ (12,900-2,400,000 cp/mL)
MRI findings (locations)	T6-Con	T6-T11	WS	T4-Con	WS	C-T	T6-T7	T	T5-T12	T6-T8	NA	WS	C4-T6			
LETM	+	+	+	+	+	+	-	+	+	+	-	+	+	+	11/13, 85%	1/4
Gadolinium-enhancement	+	+	+	+	+	+	+	+	+	+	+	+	+	+	9/13, 69%	1/4
No abnormal lesion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/13	1/4
Treatment																
Antiluetic therapy	PCG	CTRX	PCG	PCG	PCG	PCG	PCG	AB	PCG	PCG	PCG	PCG	PCG	PCG	13/13, 100%	NA
Steroids	mPSL	mPSL	DEX	mPSL	-	-	PSL	-	-	DEX	PSL	DEX	mPSL	mPSL	9/13, 69%	2/4
HAART	-	-	-	-	-	-	-	-	-	-	-	-	-	0/13	2/4	
Human immunoglobulin	-	-	-	-	-	-	-	-	-	-	-	-	-	0/13	1/4	
Observation	-	-	-	-	-	-	-	-	-	-	-	-	-	0/13	1/4	

Ref: reference, M: male, F: female, NA: not applicable, MSM: men who have sex with men, iTPA: intrathecal *Treponema pallidum* antibody, VDRL: venereal disease research laboratory, FTA: fluorescent treponemal antibody, TPHA: treponema pallidum hemagglutination assay, T: thoracic, WS: whole spinal cord, Con: conus, C: cervical, LETM: longitudinally extensive transverse myelitis, PCG: penicillin G, AB: antibiotics, CTRX: ceftriaxone, mPSL: methyl-prednisolone, DEX: dexamethasone, PSL: prednisolone, HAART: highly activated anti-retroviral therapy

hibited a slower progression of LETM, without any other physical symptoms of HIV. Thus, it was less likely that the patient's LETM was caused directly by his acute HIV infection. Furthermore, the patient's meningomyelitis was improved by antitubercular and steroid pulse therapies but not by ART.

Several studies have reported the prevalence of ocular syphilis to be as high as 10% in HIV-co-infected patients (1). The most common ocular finding in tertiary syphilis is uveitis (2). Optic perineuritis is a relatively uncommon condition and is generally asymptomatic in syphilis (2). The typical clinical features of optic perineuritis include eye pain, mildly decreased visual acuity, and several visual field defects. However, our patient had no remarkable visual symptoms. Orbital MRI revealed a "tram-track sign" on axial T2-weighted images and a ring-shaped area of high intensity on coronal Short tau inversion recovery (STIR) images without gadolinium enhancement in the optic nerves. As the tram-track sign in the optic nerve is a nonspecific radiological feature, it can also be observed in optic perineuritis (20). Unlike optic neuritis, optic perineuritis generally exhibits no apparent gadolinium enhancement in the optic nerve (2). Our patient demonstrated a remarkable improvement in the pathological latencies of flash VEP after antitubercular and steroid therapy. Thus, the optic nerve involvement observed on MRI might be related to subclinical perineuritis.

Syphilitic meningomyelitis is one of many disorders that can cause LETM. If syphilis is detected in a patient with an elevated CSF TPHA-albumin index, it is crucial to check for serum HIV antibodies, especially in patients with a high risk for HIV (e.g., homosexual and/or bisexual individuals). Determining which of the infections, syphilis or HIV, is associated with the LETM lesions in co-infected patients is crucial for allowing for a prompt diagnosis and the initiation of appropriate treatment.

The authors state that they have no Conflict of Interest (COI).

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