

# HIV-associated vacuolar myelopathy: A rare initial presentation of HIV

SAGE Open Medical Case Reports  
Volume 8: 1–4  
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DOI: 10.1177/2050313X20945562  
journals.sagepub.com/home/sco



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## Abstract

HIV-associated vacuolar myelopathy, or AIDS-associated myelopathy, is a rare initial presentation of HIV. One of the common HIV-associated neurocognitive disorders, HIV-associated vacuolar myelopathy presents with advanced immunosuppression in patients and is frequently associated with dementia. However, most cases are subclinical with characteristic findings identified through physical examination and/or imaging modalities. HIV-associated vacuolar myelopathy is characterized by progressive spastic paraparesis, gait disturbance and lower extremity sensory abnormalities including vibratory sensation. Magnetic resonance imaging findings in the spinal cord are abnormal in some patients with HIV-associated myelopathy, characteristically showing spinal cord atrophy at the level of the thoracic spine, but they may also be normal. Unfamiliarity with this as initial presentation of HIV infection may lead to failure to diagnose and intervene appropriately. We present a case of newly diagnosed HIV with myelopathy and dementia with minimal spinal cord involvement on magnetic resonance imaging.

## Keywords

Infectious diseases, radiology, neurology, HIV-associated vacuolar myelopathy, magnetic resonance imaging spinal cord, AIDS-related myelopathy, highly active antiretroviral therapy, human immunodeficiency virus, weakness of lower extremities

Date received: 27 August 2019; accepted: 5 July 2020

## Introduction

HIV-associated vacuolar myelopathy (HIVM), or AIDS-associated myelopathy, is a rare initial presentation of HIV, but one of the relatively common primary HIV-associated neurocognitive disorders (HAND).<sup>1</sup> Since highly active antiretroviral therapy (HAART) has been available, it is thought that less than 10% of patients with AIDS develop HIVM.<sup>2</sup> However, despite HAART, about 70% of HIV patients develop some form of neurological manifestations of the disease. In HIV-endemic areas, there is a reported prevalence ranging from 2% to 16.9% of HIV myelopathy in various forms; however, in low-resource countries, it is thought to be secondary to human T-cell lymphocytic virus-1, tuberculosis, herpes zoster or syphilis.<sup>3</sup>

It typically presents in advanced immunosuppression with progressive spastic paraparesis with gait disorders and lower extremity sensory abnormalities. Because HIVM is a late manifestation of HIV disease, most patients will have concomitant HIV encephalopathy and dementia. Impotence and urinary problems can also occur.<sup>1,2,4–9</sup> Magnetic resonance imaging

(MRI) findings in the spinal cord are abnormal in some patients with HIV-associated myelopathy, characteristically showing spinal cord atrophy with the posterior and lateral columns affected throughout, and changes most severe at the thoracic level of the spinal cord. Pathologic evaluation of the spinal cord demonstrates vacuolation of white matter.<sup>10</sup> This is a diagnosis of exclusion mandating at least a lumbar puncture to rule out cytomegalovirus (CMV) polyradiculopathy and an MRI or computed tomography (CT) with contrast to exclude an epidural lymphoma. While the aetiology of HIVM is unclear, it is thought to be related to impaired myelin metabolism in the setting of neurotoxic cytokines. HAART therapy has variable

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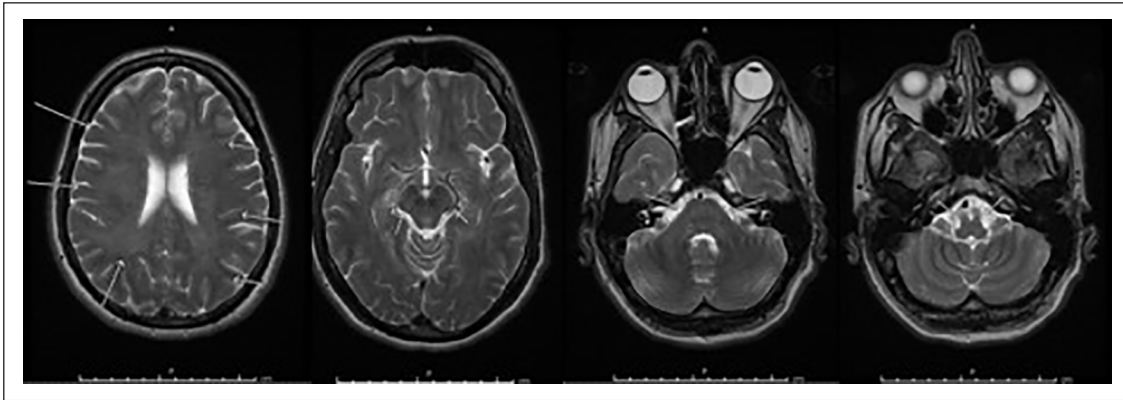
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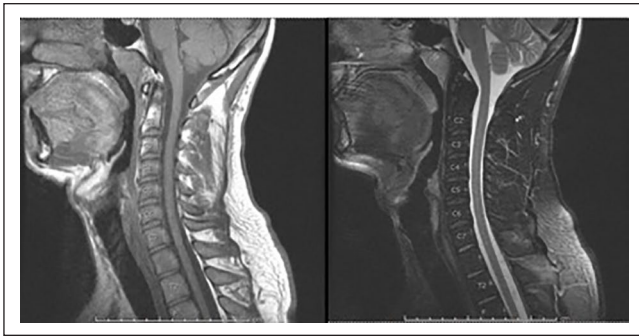
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**Figure 1.** MRI brain shows subtle but extensive areas of confluent increased T2 signal intensity throughout the periventricular and juxtacortical white matter. These changes extend along the corticospinal tracts through the midbrain, pons and ventral medulla.

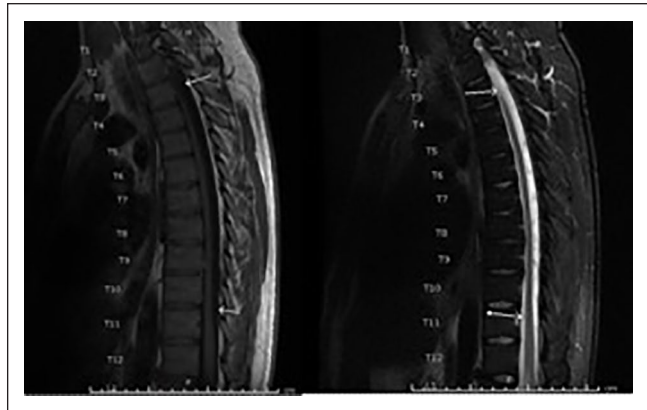


**Figure 2.** Consecutive T1 and T2 sagittal sections of cervical spine show normal findings with no cord atrophy or signal changes.

effect on HIVM, but recommended in all cases to prevent opportunistic infections and death.

### Case presentation

A 34-year-old man presented with weight loss, progressively worsening gait, confusion, back pain and urinary incontinence. Initial examination of both lower extremities showed Muscle Power Assessment (MRC) 3 out of 5 in both extremities, spastic paraparesis with brisk knee reflexes, absent ankle jerk and diffuse sensory deficits. Skin examination was notable for seborrheic dermatitis and oral thrush. Initial laboratory workup showed lymphopenia with absolute lymphocyte count of 0.90 K/ $\mu$ L (normal 1–4.8 K/ $\mu$ L). MRI brain showed increased T2 signal intensity throughout the periventricular and juxtacortical white matter extending along the corticospinal tracts in the brain stem (Figure 1). MRI of the cervical spine was normal, while imaging of the thoracic spine showed mild diffuse cord atrophy most apparent from T3 to T10 (Figures 2 and 3). MRI lumbar spine showed a small right paracentral disc extrusion at the level of L5-S1 (Figure 4). Lumbar puncture was negative for syphilis, toxoplasmosis, Cryptococcus, Cytomegalovirus and Epstein–Barr Virus. Cerebrospinal fluid (CSF) counts were notable for elevated



**Figure 3.** MRI thoracic spine T1 and T2 sagittal sections show mild diffuse cord atrophy most prominent from T3 to T10.



**Figure 4.** Consecutive T2 sagittal sections of MRI lumbar spine show a small right paracentral disc protrusion at L5-S1.

protein to 163 mg/dL and total white blood cell (WBC) count of 36 cells/ $\mu$ L with 95% lymphocytes. A fourth-generation HIV Ag/Ab assay was found to be positive. Initial HIV viral load was 300,000 copies/mL and CD4<sup>+</sup> count was 89 cells/ $\mu$ L. He was started on emtricitabine/tenofovir disoproxil

fumarate and Raltegravir. Later, his Raltegravir was switched to dolutegravir.

## Discussion

HIVM is an uncommon initial presentation of HIV, but a common neurological manifestation in patients with or without HAART. It is more frequently reported in advanced immunosuppression with associated HIV dementia.<sup>9</sup> HIVM typically presents as a slow, progressive spastic paraparesis with associated gait disturbance often with sensory abnormalities in the lower extremities. Impotence and urinary frequency, urgency or incontinence can also occur.<sup>2,4</sup>

While the aetiology is unclear, there are two mechanisms that have been implicated – impaired B12 utilization and the neurotoxic environment caused by HIV. Impaired utilization of B12 causes abnormal production of S-adenosyl methionine (SAM), the major methyl group donor in the nervous system. This may explain the clinical and pathological similarity of HIVM to B12 deficiency myelopathy – subacute combined degeneration of spinal cord. Second, neurotoxic cytokines produced by HIV-induced macrophages lead to further depletion of methyl groups required for metabolism of metabolites.<sup>1,2,4-7</sup>

HIVM is a diagnosis of exclusion. Blood workup and lumbar puncture are necessary to evaluate for vitamin B12 deficiency, cytomegalovirus (CMV), Herpes simplex virus (HSV-1 and HSV-2), Human T-cell lymphotropic virus types I and II (HTLV-I and II), enterovirus, toxoplasmosis, JC virus, tuberculosis and syphilis. Tuberculosis is a common diagnosis of myelopathy in endemic areas. Candy et al.<sup>3</sup> presented a study of 84 of their 127 patients with attributable tuberculosis as a cause of the myelopathy in Cape Town where HIV-tuberculosis is coepidemic. There has been no documented correlation between CSF viral load and the presence or progression of HIVM.<sup>8</sup> The CSF of HIVM shows a small number of lymphocytes, slight elevation of protein, with or without giant cells. Imaging of the spinal cord is required to exclude ischaemia, lymphoma and compression.

Imaging will show abnormalities in the lateral and posterior columns of the upper thoracic spine with or without cervical cord involvement. In a study of 21 patients with AIDS or HIV-1 published in the American Journal of Neuroradiology, approximately 86% of patients had abnormal MRI findings in the spinal cord. Spinal cord atrophy was seen in 72% of patients, and intrinsic cord signal abnormalities were seen in 29% of patients.<sup>10</sup> The most common feature was spinal cord atrophy involving the thoracic cord. Somatosensory evoked potentials (SEPs) can support the diagnosis of myelopathy or demonstrate concomitant neuropathy with nerve conduction delays.<sup>11</sup>

The mainstay of treatment remains the initiation of HAART as well as additional supportive measures. While the initiation of HAART generally improves some central nervous system (CNS) disease, its impact on the specific neurological complications of HIVM remains controversial

and may not prevent progression of the disease.<sup>5,6,9,12-14,17</sup> Reports of improvement in myelopathy are few in number, and some cases have reported improvement of spasticity. Highlights from the 2013 Conference on Retroviruses and Opportunistic Infections (CROI) reference several studies that demonstrate that active disease may progressively damage the CNS despite treatment. Hammarlund et al. presented an abstract at the 2017 CROI conference that showed CNS inflammation present after 10 years of effective HAART.<sup>15,18</sup> Pinnetti et al. discussed the role of blood brain barrier dysfunction influencing neuropenetrance and the efficacy of HAART. The persistence of active HIV disease despite treatment is referred to as CSF escape. There are three types of CSF viral escape, and all of which suggest that HIV can be detected in the CSF despite suppression of plasma viruses below clinical limits of measurement. While there are several efforts in determining if HAART medications with higher CNS penetration-effectiveness indices work better, there have been no definitive recommendations for a specific therapy at this time. A few studies have shown that patients with HIVM may benefit from immunoglobulin therapy, but further research is warranted.<sup>16</sup> Supportive measures are aimed towards improving the complications of HIVM including weakness, bowel, bladder and erectile dysfunction, as well as paresthesia and neuropathic pain.

## Conclusion

HIVM is a rare initial presentation of HIV, but a common neurological complication in late stage HIV infection. Most cases are subclinical, and diagnosis relies on high clinical suspicion through physical exam findings and/or imaging modalities. It can present with symmetrical bilateral lower extremity weakness, urinary abnormalities, erectile dysfunction, spasticity, ataxia impaired proprioception over weeks to months and in conjunction with dementia. Pathologic findings most affecting the lateral and posterior spinal column most severely at the level of the middle to lower thoracic level. CT or MRI findings may be normal, or show spinal atrophy or patchy abnormalities on T2-weighted images most prominent in the thoracic spine. While the exact pathogenesis is unclear, it is thought to be secondary to neurotoxic cytokines produced by the HIV virus which damages the spinal cord. This is a diagnosis of exclusion and an extensive infectious workup is mandatory prior to this diagnosis. A negative or non-specific CT or MRI spinal cord imaging does not exclude the possibility of HIVM. SEPs have limited use in diagnosis, but may assist in diagnosing and monitoring improvement of concomitant peripheral nerve abnormalities.

At one-year follow-up, the patient's CD4<sup>+</sup> count was 427 and serum viral load was undetectable. While his behavioural changes had resolved, and some cognitive changes had improved after HAART was initiated, there was no improvement or worsening of his spastic paraparesis and urinary incontinence.

### Author contributions

All authors participated equally in the manuscript preparation and literature review.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

### Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

### Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

### Informed consent

Verbal and written informed consent was obtained from the patient for his anonymized information to be published in this article.

### Guarantor

A Rezaie is the article guarantor.

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