Atypical HIV-Vacuolar Myelopathy. Case Report and Literature Review.

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Case report

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Abstract

**Background:** Here, we report an atypical presentation of HIV-vacuolar myelopathy and search the available medical literature about atypical presentations of human immunodeficiency virus associate vacuolar myelopathy (HIVVM) and immunoglobulin therapy response.

**Case:** A 26-year-old lady who was four weeks postpartum presented to us with acute flaccid quadriparesis, with no sensory level. Extensive workup ruled out other causes of myelopathy.

She developed a stage 3 acute kidney injury, and MRI showed diffuse cord atrophy involving the lower cervical and thoracic cord. The patient received IV-immunoglobulin, ARV’s, and supportive therapy with inadequate response. Unfortunately, she developed nosocomial pneumonia and died.

**Discussion:** In HIV-VM, there is spinal cord atrophy, which mainly involves the thoracic cord. In our case, this pathological process also affected the spinal cord’s cervical region, leading to flaccid tetraplegia, no responding to the treatment, including intravenous immunoglobulin.

**Keynotes**

Vacuolar myelopathy, HIV, Immunoglobulin therapy, flaccid tetraplegia, hypokalaemia. Renal failure.

**Background**

HIV-associated vacuolar myelopathy (HIV-VM) is the most common and primary etiology of myelopathy in HIV/AIDS patients worldwide, leading to progressive spastic paralysis of the limbs, sensory ataxia, and autonomic dysfunction [1]. It derives its name from its pathological nature: formation of vacuoles in the lateral and posterior columns, mainly on the spinal cord [2]. Some authors first reported in 1985 [3]. Initially considered to present when HIV was in its advanced stages, many authors said it earlier, even when the immunity was right [3]. The prevalence ranges from 22–55% [4], it does bear a poor prognosis [7], and due to its high pathological prevalence, it could be underreported in the literature [5]. Up to date, the pathogenesis is not fully understood; it is essential to note that this is a diagnosis of exclusion requiring evaluation and eliminating other aetiologies [1–4]. Differential diagnosis includes HIV-associated transverse myelitis during seroconversion, Infections, e.g., Viral -Herpes simplex (HSV), Varicella Zoster (VZV), Cytomegalovirus (CMV), Human T-cell Lymphotropic Virus type 1 (HTLV-1/2); Bacterial – mycobacterium tuberculosis, neurosyphilis, Multiple sclerosis, Vitamin B-12 deficiency, and compressive myelopathy among others. MRI scans are useful in diagnosis; T2-weighted images often show symmetric non-enhancing high signal areas present on multiple contiguous slices, which result from extensive vacuolation (hence the name). Lesions may be confined to the posterior column, especially the gracile tracts, or be diffuse [3, 7]. Currently, there is no definitive treatment; however, most modalities focus on symptomatic therapies, combined Anti-retroviral treatment (cART) [9], and some authors have found some good outcomes prescribing IV-immunoglobulins [3, 10].
Here we report a young female case in her postpartum stage who had an atypical HIV-VM presentation. She was a known HIV patient on cART, morbidly obese, confused, and quadriplegic with a history of renal failure and hypokalaemia that was corrected. Her condition suppressed the viral load, and CD4+ count was high. Unfortunately, she did not respond to IV-immunoglobulin therapy, being a relevant information for the medical community.

Our research questions were: How often IVIg is used to treat HIV-VM? How many positive results including atypical presentations have been published?

**Material And Method**

We search for publications about HIV-vacuolar myelopathy and intravenous immunoglobulin therapy answer the two previous research questions using the procedure mentioned below and present our patient.

**Literature search strategy**

Our literature review utilized the PRISMA (Preferred Reporting Items for Systemic review and Meta-Analysis) statement and the PRISMA checklist. We suggest searching from 1st, January 2010 up to 30th September 2020. We included all studies (case reports, case series, and observational cohort studies) reported HIV-VM and IVIG treatment during the initial search. We also reviewed the following databases for published studies: Medline EMBASE, Scopus online databases, Google Scholar, Science Direct, Scielo, LILACS, BIREME, and Cochrane library to identify articles evaluating HIV-VM and IVIG therapy*. All items about “AIDS-myelopathy* OR primary infectious myelopathy* OR HIV-VM* OR neurological manifestations of HIV/AIDS* OR Nosocomial myelopathy* OR Spinal cord syndrome/HIV/AIDS* OR Neuro-AIDS* OR Unknow cause myelopathy*OR infectious spinal cord disease* where * is the PubMed wildcard for every possible word beginning or ending. We did not consider other neurological manifestations beyond the scope of the current work.

**Study and cohort selection**

We select all publications (case reports, case series, and observational cohort studies) reporting HIV-VM, IVIg Therapy during the initial search. Later we progressively s excluded all duplicate studies, those publications not meeting inclusion criteria because reported only HIV/AIDS, Primary myelopathy separately and HIV-VM not related with IVIg therapy, and those without an English translation.

**Results**

Between 1st January 2010, and 30th September 2020, our literature search yielded 621 publications. After removing duplicate articles, we retained 457 unique records. Considering the title and abstracts, we discarded 21 journals, keeping 38 items, screening the full text we selected 32 publications regarding COVID-19/Neurological complications. Finally, we found a total of 2 publications referring to HIV-VM and
IVlg. From all groups, we did not find any published study about no improvement of HIV-VM after IVlg treatment. See Appendix A: The PRISMA flow diagram of included studies for this review.

**Case Presentation**

Ms. N is a 26-years-old African lady admitted at Nelson Mandela Academic Central Hospital (NMACH) in Mthatha, South Africa. She presented in May 2020 with a history of inability to walk and confusion. We could not establish the duration of symptoms, signs, and the mode of onset in the admission chart, and she gave no further history due to her confusional state.

Of note, this patient was still in her puerperal phase. She was admitted in the maternity ward at NMAH two months ago with severe preeclampsia and HELLP syndrome. This entity is a severe form of preeclampsia characterized by hemolysis (H), elevated liver enzymes (EL), and low platelets (LP) in a pregnant or puerperal patient (usually within seven days of delivery). Her clinical picture worsened by stage 3 acute kidney injury (creatinine was > 3 times the baseline), she had received intermittent hemodialysis, and renal function wholly recovered before discharge.

Her medical history was remarkable for HIV, with a CD4:1051 cell/µL and a suppressed viral load (< 20 copies/ml) on a modified first-line regimen (ABC/3TC/EFV). She is a known hypertensive patient hydrochlorothiazide and Amlodipine, and there is no previous history of target organ damage. However, according to her old chart that she had defaulted on her antihypertensive for about a month. Her family history was non-significant, and she was a non-smoker, never used illicit drugs, and occasionally used alcohol. She did not have any travel history outside Eastern Cape Province in South Africa.

On examination, we found her to be obese (BMI 36 kg/m²), with pink mucosal membranes, anicteric, and afebrile. Her vital signs demonstrated a tachycardia (heart rate: 130) and elevated BP: 147/109 mmHg. The patient was confused. No cranial nerve abnormalities or meningeal signs; she had bilateral mild horizontal vestibular nystagmus. Her motor examination revealed the power of 0/5 in all limbs (proximally and distally), with hypotonia in all limbs and absent deep tendons reflexes. The sensory test was exceedingly difficult to perform due to her confusional state, but she seemed to respond to light touch and pain. On her respiratory examination, we confirmed fine crepitation in the right lower zones of the chest.

Given her acute presentation of flaccid quadriplegia, our differentials included Landry-Guillain-Barre syndrome and its variants, HIV-related neuropathies, metabolic derangements (hypokalaemia), vitamin B12 deficiency, CMV peripheral neuropathy, inflammatory myopathies, and neuromuscular junction disorders.

In her investigations, the MRI brain was completely normal. The MRI spine showed diffuse cord atrophy with dorsal signal abnormality involving the lower cervical and thoracic spine, as shown in Figs. 1 and 2 (Appendix B). These findings made us think of HIV-VM and subacute combined degeneration of the spinal cord.
We did an extensive serological and CSF workup to exclude both infectious and non-infectious causes of myelopathy. Blood levels for Vitamin B12 and folate were normal (491 pmol/l and 32.7 nmol/L, respectively), her CD4 was 1051 cells/μL with a viral load of <20 copies/ml. Full blood count showed leucocytosis of 17 × 10⁹ /L with mild anemia (Hb 11.6 g/dl) and reactive thrombocytosis (platelet: 506 × 10⁹/L) high C reactive protein of 241 mg/L with negative blood cultures. Her U/E revealed hypokalaemia of 2.1 mmol/L, and calcium, magnesium, and phosphate were normal. Creatine kinase was normal (20 U/L), and her thyroid function tests: TSH: 5.9 mIU/L, FT4 12.8 pmol/L.

Her CSF demonstrated high protein: 0.69 g/L, glucose 3.5 mmol/L, polymorphs: 0 cells/μL, lymphocytes: 4 cells/μL, erythrocytes: 240 cells/μL.

Repeat CSF showed an adverse polymerase chain reaction for viral studies, including herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and JC virus. Serum and CSF cryptococcal antigen testing and Bartonella serology were negative. We did not detect CSF antibodies to aquaporin-4 and oligoclonal immunoglobulin bands. CSF VDRL was non-reactive.

We exclude metabolic alkalosis and hypokalaemia, a state of mineralocorticoid excess because of hypertension, and we did a renin/aldosterone ratio. Then, the aldosterone renin ratio was 1.28 (< 40), CT scan of adrenal glands was normal.

Considering that there is no clear obstructive, vascular, or neoplastic lesion noted on imaging, the likelihood of the pathology being secondary to direct infection by HIV remains high.

This patient was complicated by nosocomial pneumonia with type 1 respiratory failure. A gram-negative bacillus was cultured in her repeat blood and CSF.

Her treatment included Polygam 40 g daily intravenously for 5 days, anti-retroviral: abacavir/lamivudine/efavirenz 1 tablet daily orally, Piptaz 4.5 g intravenously six-hourly, Aldactone 100 mg orally bd, slow k 2 tablets po twice daily, Thiamine 100 mg po daily, Pyridoxine 25 mg po daily, and oxygen by facemask. In the management of the patient, the physiotherapists and occupational therapists worked hard. Her situation was discussed with the intensive care unit considering her respiratory failure, but she was declared poor prognosis and not accepted.

Her potassium improved to normal, but she remained with power 0/5 in all limbs. Despite IV Immunoglobulin therapy at the higher dosages, the patient did not improve and demise on June 8, 2020.

**Discussion And Conclusion**

In HIV-VM, there is spinal cord atrophy, which mainly involves the thoracic cord. Sometimes the cervical cord is involved as well [11], in which case patients will present with quadriplegiasis like our patient. HIV-VM has been documented in the past to be associated with HIV-Neurocognitive disorders (HIV-NCD) [12], and sometimes we can see the same damage of the spinal cord, in the cerebral hemispheres. In our case, the MRI of the brain was completely normal.
The spinal cord atrophy results from vacuoles' formation mainly in the posterolateral columns (thereby mostly involving the corticospinal tract and the fasciculus Gracilis and Cuneatus (like vitamin B12 deficiency) leading to subacute combined degeneration of the spinal cord. In which situation, B12 level in serum is low, and those patients respond very well to parenteral B12. The exact pathophysiology resulting in the formation of vacuoles (still unclear), but proposed mechanisms include:

1) Activation of macrophages in the CNS, which can cause the release of myelotoxic substances or impair the metabolism of Vit B12.

2) Oligodendrocyte/myelin injury from the presence of TNF alpha and other cytokines. These will also augment macrophage activity, which can damage myelin.

3) Direct infection of astrocytes [13].

Investigations made by Petito et al. confirmed that 26.8% of patients who had autopsy proven VM had signs and symptoms of VM [14].

The usual HIV-VM presentation is progressive spastic paraparesis, ataxic gait, sphincter disturbance, and erectile dysfunction with no sensory level. Usually occurring in the setting of advanced HIV, and sometimes associated with HIV-NCD.

To perform laboratory and radiological investigations to exclude other causes of possible spinal cord pathologies is a good recommendation. CSF tests should include cytology, protein level, MCS, CMV, EBV, HSV, TB, JCV, Picornavirus, flavivirus, rhabdovirus, Treponema pallidum, Borellia, and HIV Viral load. Indication of MRI to rule out any other cause of intramedullary/extradural lesions. In the setting of HIV-VM, the MRI may show cord atrophy in the thoracic and cervical regions. The lumbar area can be affected in more rare instances. Also increased T2 weighted signalling of the posterolateral cord usually.

CMV polyradiculomyelitis can present a similar to HIV-VM and is usually distinguishable by the absence of spasticity on exam and MRI findings of diffuse, multisegmented signal abnormalities seen in both grey and white matter, with thickening/enhancement of nerve roots [15].

Somatosensory evoked potential (SSEP) may also be supportive if it shows a functional lesion of the spinal cord, but it does not have any pathognomonic pattern [11].

HIV-VM is a diagnosis of exclusion. Therefore, to rule out other causes of myelopathy, an extensive workup must be done.

A clinical criterion for diagnosing HIV-VM was created by Chong et al. [11], as shown in Table 1 (Appendix B).
Table 1
Criteria for clinical diagnosis of AIDS-associated myelopathy [11]

1. Male or female, over 18 years old, with documented HIV-1 infection.

2. AIDS-associated myelopathy, with or without neuropathy and dementia, defined as:
   a. Presence of at least two of the following symptoms:
      • Paraesthesia and/or numbness in lower extremities or all four limbs
      • Weakness of the limbs
      • Unsteady, stiff, or uncoordinated gait
      • Sensation of electric shock through the back and legs on flexion of the neck (Lhermitte’ sign).
      • Increased urinary frequency, urgency, incontinence, or retention
      • Faecal incontinence or retention
      • Sexual dysfunction with erectile impairment.
   b. Presence of at least two of the following neurologic signs
      • Reduction in vibratory and/or position sensation
      • Brisk deep tendon reflexes
      • Abnormal plantar response
      • Lhermitte’ sign
      • Spastic, ataxic, or ataxo-spastic gait.

3. Signs and symptoms of AIDS-associated myelopathy for at least 6 weeks before consultation.

4. Abnormal somatosensory evoked potential measurement.

5. No other determinable cause for spinal cord disease by serologic and CSF studies

Our patient presentation was atypical because she was virologically suppressed (VL < 20copies/ml), and her CD4 was 1051 cells/uL. It is important to remember that the CSF viral load measurement would have been essential to check for 'CSF viral escape.' We did not check for HIV-VL in the CSF looking to 'viral escape,' We did not have a large enough CSF sample to send for this test. Her confusion could have been due to HIV-NCD, but since she had nosocomial sepsis and hypokalaemia, then it was not the only cause. Also, she had flaccid quadriplegia and absent global reflexes, which is not typical for HIV-VM. Bloods showed hypokalaemia, which can explain an associated peripheral neuropathy worsened by HIV infection and subclinical hypothyroidism, but the weakness persisted in the potassium's correction. Vitamin B12 and folate levels were normal; this ruled out a subacute combined degeneration of the spinal cord. We did an extensive blood and CSF workup for other causes of weakness, which all came back negative. The spinal cord MRI supported the clinical suspicion and showed cord atrophy as well as T2 weighted
hyperintensity of the cervicothoracic spine. We continued her cART and gave her a trial of IVIg, which did not improve the condition. Unfortunately, she developed nosocomial sepsis and died.

Unfortunately, there was no reliable way to confirm vacuolar myelopathy pre-mortem, and the final diagnosis remained a diagnosis of exclusion.

Unfortunately, in our center, we currently do not have access to EMG/NCS.

The treatment of VM remains an unresolved matter. Therefore, there has been no effective treatment of HIV-VM yet other than anti-retroviral medications. Perhaps, prescribing cART such as Zidovudine/Abacavir, which has an excellent CNS penetration, should be implemented earlier on in patients with HIV-VM. Another option if the patient is poorly responsive would be to send for CSF-VL and to test for mutations in the CSF. Treatment with L-methionine and IVIg so far has not yielded any beneficial results [16, 17].

In 2009, Lindkvist et al. studied nine HIV-infected patients with Guillain–Barré syndrome that received the HAART and demonstrated that IVIg administration in high doses (30 g/day for five days) reduce the pool of HIV in the memory of CD4 + T-cells [17]. At the same time, Cikurel et al. studied a series of patients with VM to evaluate IVIg's efficacy. They demonstrated that all patients reported reduced palsy in the lower limbs, due to the anti-inflammatory effect of IVIg, causing suppression of the complement cascade, inhibition of production of pro-inflammatory cytokines mainly by monocytes, and reinforcing the anti-idiotypic response, leading to neutralization of growth factors (B-cell), and inhibition of the T-cell proliferations with clonal expansion and activation of T-reg cells and downregulation of the Th17 [10].

Recently, some authors reported that binding of anti-idiotypic antibodies with epitopes (IgG, and IgM) on the B-lymphocytes and thus inhibiting the production of autoimmune antibodies appears to be the most effective action of IVIg increasing the intrathecal production of oligoclonal Ig, which is a marker for the chronic autoimmune inflammatory process in the CNS [3]. The same author highlighted IVIg treatment's viability in cases presenting HIV-VM, mainly when autoimmune reactions are under suspicion. We like to highlight the study done by Cikurel et al. because it is the only report delivering a number of cases of HIV-VM treated and an important number of improvements (n = 17) after being treated with Ig at the dosage of 2 g/kg for two days of IV infusion but they did not report any improvement of spastic paraparesis and urinary incontinence [10] and they did not report the method to measure the improved symptoms and signs. Other authors also report a complete recovering of symptoms and signs from HIV-VM after being treated with highly active antiretroviral therapy [18, 19] but the procedure to measure the improvements are also questionable.

Reviewed in this manuscript is a case where an atypical HIV-VM presentation did not respond when treated with cART and intravenous immunoglobulin (IVIg), which can doubt therapy's efficacy. Even though our patient did not show any signs of improvement after IVIg therapy, to perform a placebo-controlled clinical trial of IVIg in patients with HIV-VM can be other recommendations to confirm or deny the real benefits of this medication.
Abbreviations

ABC/3TC/EFV - Abacavir/ Lamivudine / Efavirenz

BMI – Basal Metabolic Index

cART- combined Antiretroviral Therapy

CMV – Cytomegalovirus

CSF - Cerebro Spinal Fluid

CSF-VL – Cerebro Spinal Fluid Viral Load

CT – Computed Tomography

EBV – Epstein-Barr Virus

EMG – Electromyography

FT4 – Thyroxine

HAART – Highly Active Anti-Retroviral Therapy

Hb – Haemoglobin

HIV- Human immunodeficiency Virus

HIV-NCD - Human Immunodeficiency Virus-associated Neurocognitive Disorders

HIV-VL – Human Immunodeficiency Virus-associated Viral Load

HIV-VM – Human Immunodeficiency Virus-associated Vacuolar Myelopathy

HTLV – Human T-cell Lymphotropic Virus type 1

HSV – Herpes Simplex Virus

IVIg – Intravenous Immunoglobulins

JCV – John Cunningham Virus

MCS -Microscopy, Culture, Sensitivity

MRI – Magnetic Resonance Imaging

NCS – Nerve Conduction Studies
Declarations

**Ethical issue and consent to publish:** We obtained the written permission from our patient’s family, and they agreed to include all necessary information for publication purposes. All authors certify that we did not reveal names, initials, and other identity issues of this patient in this publication, and complete anonymity is guaranteed.

**Consent for publication:** The necessary consent for publication from the family is received.

**Availability of data:** Data used on this study are available on reasonable request from the corresponding author.

**Competing interest:** All authors: reported no conflicts of interest.

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**Author’s contribution:** All authors contributed equally to the elaboration of this manuscript. MT and SJ collected data and planning this report, JG and LIV wrote the first draft and reviewed bibliographically, TB and HFS wrote the final piece. All authors reviewed the final manuscript, made corrections, and agreed for publications.

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