Successful Treatment of Human Immunodeficiency Virus-Associated Highly Active Antiretroviral Therapy-Resistant Vacuolar Myelopathy with Intravenous Immunoglobulin

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Abstract

For the first time, human immunodeficiency virus (HIV)-associated vacuolar myelopathy (VM) was detailed in an autopsy-based study of 89 cases in 1985. This condition is the most common cause for spinal cord lesions in HIV patients. VM’s pathogenic mechanism remains unclear; however, it is assumed that the disease can be related to both, the direct neurotoxic impact of the HIV and HIV-induced activation of immunopathological processes in the central nervous system (CNS). Reviewed in this paper is a case where the VM presentation deteriorated drastically when treated with highly active antiretroviral therapy, and almost completely regressed after the patient received the intravenous immunoglobulin (IVIg) treatment. The considered case demonstrates the viability of IVIg treatment in patients with HIV-associated CNS pathology, particularly when autoimmune reactions are suspected. The results of placebo-controlled studies of IVIg in patients with HIV-associated myelopathy may give a reliable evaluation of IVIg use in this context.

Keywords: Human immunodeficiency virus-associated lesions of the nervous system, human immunodeficiency virus-associated myelopathy, intravenous immunoglobulin administration

INTRODUCTION

For the first time, human immunodeficiency virus (HIV)-associated vacuolar myelopathy (VM) was detailed in the course of an autopsy-based study of 89 cases in 1985. This condition is the most common cause for spinal cord lesions in HIV patients. The pathogenic mechanism of VM remains unclear; however, it is assumed that the disease can be related to both, the direct neurotoxic impact of the HIV and HIV-induced activation of immunopathological processes in the central nervous system (CNS). VM is encountered more often against the backdrop of low CD4+ count and high viral load.

VM’s clinical presentation is marked with progressive spastic paraparesis of the lower extremities compounded with deep sensory, and bowel and bladder disturbances. Use of highly active antiretroviral therapy (HAART) results in partial regression of the neurological deficit in some patients. At the same time, a VM-specific therapy as well as methods to repair the lost functions have not yet been developed.

Reviewed in this paper is a case where the VM presentation deteriorated drastically when treated with HAART and almost completely regressed after the patient received intravenous immunoglobulin (IVIg) treatment. Cases of health improvement due to IVIg therapy have been reviewed in the literature. The unique character of our case is in total recovery from the neurological disturbances and the duration of observation. In addition, we review a diagnostic approach to VM and possible therapeutic mechanisms of IVIg.

CASE REPORT

In September 2015, a 35-year-old male patient presented with a 1-year history of progressive difficulty in walking. He also complained of severe asthenia, urine retention, and bowel incontinence. During that time, he had episodes of intermittent leg weakness that spanned up to 12 h a day. In June 2015, he had a sudden falling accident due to the muscle weakness and numbness in his legs. These symptoms could persist for about 30 min and then spontaneously regressed by themselves.

After being admitted to the hospital, the patient was diagnosed with HIV infection, with magnetic resonance imaging (MRI) of the brain and spinal cord showing no abnormality. The HIV test was positive. Neurological examination revealed diminished strength in the right lower limb (grade 4/5).

Laboratory report: CD4+ T lymphocyte count-90 c/µl, HIV ribonucleic acid (RNA) level-90,000 copies/ml, severe
thrombocytopenia (22 × 10^9/L). Vitamin B12 level was within normal limits. Cerebrospinal fluid (CSF) examination revealed as follows: Cytosis – 11 × 10^6/L, protein – 0.37 g/L, and glucose – 2.9 mmol/L. Infectious agents (Epstein–Barr virus [EBV]), herpes 1, 2, 6, human cytomegalovirus (HCMV), toxoplasma, candida, and syphilis were not detected. Active tuberculosis (TB) was ruled out by a chest X-ray examination and a skin test. Due to severe immunodeficiency, the patient was started on isoniazid (300 mg/day) and Vitamin B6 (30 mg/day) as primary TB prevention measures and co-trimoxazole (960 mg/day) to prevent pneumocystis pneumonia. On June 20, 2015, the HAART was started (abacavir 300 mg × 2/day, lamivudine 150 mg × 2/day, darunavir 800 mg/day, and ritonavir 100 mg/day). Over the two following weeks after initiating the HAART, his clinical condition deteriorated with increasing lower limb weakness, myalgia in the lower extremities caused by minimal efforts, pronounced shakiness of walk, and the use of a crutch. Neurological problems were attributed to HIV-induced polyneuropathy. After his discharge from the hospital, the lower limb weakness started to gradually increase, accompanied by progressive urine retention and bowel incontinence which resulted in his admission to an AIDS center in August 2015. Repeated CSF analysis revealed the following: protein – 0.7 g/L, glucose – 3.43 mmol/L, cytosis – 9.7 × 10^6/L, lymphocytes – 24, neutrophils – 5, chloride – 112.5 mmol/L, deoxy RNA of EBV, HCMV, herpes 1, 2, 6, John Cunningham virus-not presented. HIV RNA level in the CSF was 904 copies/ml. The tests revealed oligoclonal immunoglobulin G (IgG) in the CSF and polyclonal IgG in the serum (2nd type of synthesis). Electroneuromyography failed to reveal the signs of polyneuropathy. The blood tests exhibited an increase in the CD4+ T lymphocyte count (441 cells/µL), a reduction in HIV RNA down to 548 copies/ml which led us to suspect immune reconstitution inflammatory syndrome. Therapy with pentoxifylline, ipidacrine, and Vitamin B was not effective. MRI of the spinal cord showed T2 hyperintensity extending from the level of T7 to the level of T9.

The patient was directed to our clinic on September 01, 2015 where upon examination the following was revealed: neurological examination revealed spastic paraparesis (Grade 2/5) of the lower limbs with brisk reflexes, positive Babinski’s sign on both sides, increased tone. No sensory abnormalities were noticed. Walking required the use of two crutches. The MRI revealed lesions in both the brain and the spinal cord: Axial T2-weighted image (T2-WI) shows diffuse, symmetric, periventricular leukopathy sparing the subcortical fibers, without mass effect, and contrast enhancement; T2-WI of the spine demonstrates bilateral dorsolateral column high T2 signal at the level of T6–T9 vertebral segments, where tracts corticospinalis (pyramidalis) lateralis is located [Figure 1]. Considering the clinical condition supported by the laboratory and MRI data, the patient was diagnosed with HIV myelopathy, HIV associated encephalopathy. Due to the lack of positive response to the HAART therapy, it was decided to resort to IVIg 5% IV 400 mg/kg/day for 5 days. Significant improvement was observed within 3 days: lower limb palsy subsided dramatically, complete resolution of bowel/bladder dysfunction and of asthenia were noticed.

Neurological examination in December 2015 revealed spastic paraparesis (grade 4/5) of the lower limbs with positive Babinski’s sign bilaterally, normal muscle tone, moderate gait disorder, and intention tremor in the lower extremities when performing coordination tests. No sensory abnormalities were noticed.

Neurological examination in January 2016 revealed no palsy or sensory processing disorders, or ataxic gait; however, bilateral positive Babinski’s sign is retained. MRI results showed no negative dynamics [Figure 2]. A follow-up examination in 6, 12, and 24 months revealed the following: absence of palsy, pathological muscle fatigue in the lower extremities, pathological signs on both sides, hyperaesthesia in both feet, no ataxia.

**Discussion**

VM needs to be differentiated from a wide spectrum of opportunistic infections, tumor and metabolic lesions, compression, and ischemic myelopathy. The typical MRI signs of HIV myelopathy include: moderate spinal cord atrophy and bilateral symmetrical lateral and dorsal column involvement.[9] Postcontrast enhancement is not characteristic of VM, and its presence suggests the neoplastic or inflammatory nature of the spinal cord lesion. Due to similar MRI presentation, the most difficult differential diagnosis is that between the HIV-associated myelopathy, subacute combined degeneration and myelitis.

In the present case, MRI findings were typical of VM with a longitudinal dorsolateral lesion of the lower regions of

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**Figure 1:** Axial T2-weighted image shows diffuse, symmetric, periventricular leukopathy sparing the subcortical fibers (a), without mass effect and contrast enhancement (b). T2-weighted image of the spine demonstrate bilateral dorsolateral column high T2 signal at the level of Th6-Th9 vertebral segments (c and d). No associated cord enlargement. Note focal protrusions at the Th7-8 and Th8-9 levels with mild cord compression (c). There was no evidence of abnormal enhancement in the postcontrast study (e).
the spinal cord. We also observed spinal cord protrusions at the level of the lesion which prompted the inclusion of a compression-ischemic injury to the list of possible diagnoses. The tumor was ruled out due to normal volume of the spinal cord at the lesion level. Bacterial or fungal infection was deemed unlikely due to CSF laboratory results and the absence of contrast enhancement. Viral myelitis, subacute combined degeneration, and neurosyphilis were not confirmed in the laboratory tests.

The treatment of VM remains an unresolved issue. In contrast to a host of pathological processes associated with HIV which regress on application of the HAART, a positive clinical response in patients with VM is not observed very often,[5,6] which might be due to insufficient eradication of the virus that possesses direct neurotoxic activity or due to a cascade of autoimmune mechanisms in the CNS launched by the production of proinflammatory cytokines initiated by HIV.[9]

The IVIg therapy in the reviewed case was selected based on a hypothesis that the drug can affect both these processes. Indeed, the persistent viraemia is most likely to continue due to long-lasting memory cell infection prior to the onset of therapy.[10] Lindkvist et al., when treating nine HIV-infected patients with Guillain–Barré syndrome that received the HAART, demonstrated that administration of IVIg in high doses (30 g/day for 5 days) reduced the latent pool of HIV in the dormant memory CD4+ T-cells.[11] Cikurel et al. in a study to evaluate the efficacy of IVIg in patients with VM demonstrated that all patients reported reduced palsy in the lower limbs which might be attributed to the anti-inflammatory effect of IVIg leading to suppression of the complement cascade, inhibition of production of proinflammatory cytokines by monocytes, enhancement of anti-idiotypic reactions, neutralization of growth factors for B-cell, inhibition of the T-cell proliferative responses with clonal expansion and activation of T-reg cells and downregulation of the Th1.7 Binding of anti-idiotypic antibodies with epitopes and IgGs and M on the B-lymphocytes and thus inhibiting production of autoimmune antibodies appears to be the most significant mechanism of IVIg due to the intrathecal production of oligoclonal Ig which is a marker for the chronic autoimmune inflammatory process in the CNS.

The reported case demonstrates the viability of IVIg treatment in patients with HIV-associated CNS pathology, particularly when autoimmune reactions are suspected. The results of the placebo-controlled studies of IVIg in patients with HIV-associated myelopathy can give a reliable evaluation of using IVIg in the context of this pathology.

**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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