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*Case report*

# Varicella-zoster virus vasculopathy and central nervous system immune reconstitution inflammatory syndrome with human immunodeficiency virus infection treated with steroids

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**Immune reconstitution inflammatory syndrome (IRIS) is widely recognized and rarely involves the central nervous system (CNS). Patients with acquired immunodeficiency syndrome (AIDS) are at an increased risk for developing CNS-IRIS upon initiation of highly active antiretroviral therapy (HAART). This syndrome can be fatal and requires extreme vigilance in determining if a treatable underlying opportunistic infection exists. We report here a case of varicella-zoster virus (VZV) vasculopathy and CNS-IRIS in a human immunodeficiency virus (HIV)-infected patient who required prolonged steroid treatment for clinical stabilization. There are no established treatment regimens for IRIS and the use of corticosteroids in this syndrome remains controversial. Similar to our patient, severe cases of CNS-IRIS may benefit from high-dose intravenous corticosteroid treatment followed by an oral prednisone taper.** *Journal of NeuroVirology* (2009) **15,** 288–291.

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## Introduction

Central nervous system immune reconstitution inflammatory syndrome (CNS-IRIS) in patients with human immunodeficiency virus (HIV) infection is often a fatal illness (Venkataramana *et al*, 2006). There are limited reports of CNS-IRIS, which makes the diagnosis and management of this syndrome challenging. The exact pathogenesis of IRIS is not entirely understood (Murdoch *et al*, 2007), although there are common risk factors associated with IRIS development, including presence of HIV, preexisting opportunistic infections, highly active antiretroviral therapy (HAART) naïve, low nadir CD4 count prior to HAART, and significant decline in HIV viral load after HAART institution (Dhasmana *et al*, 2008; Manabe *et al*, 2007; Shelburne *et al*, 2004). The concomitant use of steroids for CNS-IRIS treatment remains controversial. We report here a case of varicella-zoster virus (VZV) vasculopathy with HIV infection in the setting of IRIS that was responsive to a combination of antiviral and corticosteroid therapy. Our case report is unique given the rare association of VZV vasculopathy in the setting of IRIS and that our patient required prolonged steroid treatment until adequate immune reconstitution was obtained. This highlights that severe cases of CNS-IRIS may require a longer duration of treatment with corticosteroids.

## Case report

A 42-year-old woman with a history of acquired immunodeficiency syndrome (AIDS) and noncompliance with antiretroviral therapy was admitted to our hospital in March 2008 with a herpes zoster rash involving all three divisions of the left trigeminal nerve, left facial weakness, left-sided incoordination,

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normal lower extremity strength, and gait ataxia. Two weeks prior to presentation, the patient started herself on ritonavir and atazanavir for unclear reasons. Brain magnetic resonance imaging (MRI) demonstrated focal nonenhancing lesions in the brainstem and greater periventricular than subcortical T2 and FLAIR hyperintensities that spared the U-fibers (Figure 1A). The diagnosis of VZV vasculopathy was established after real-time polymerase chain reaction (PCR) analysis of the cerebrospinal fluid (CSF) revealed VZV DNA. She was treated with intravenous (IV) acyclovir (10 mg/kg every 8 h) for 2 weeks and started on an appropriate HAART regimen (Truvada and Kaletra) for a CD4 count of 3 cells/$mm^3$ and plasma HIV-1 viral load of 53,085 RNA copies/ml. Prior to discharge, the patient clinically improved and repeat CSF evaluation was negative for VZV DNA by PCR testing. Virological testing was repeated approximately 4 weeks after HAART institution, which demonstrated a CD4 count of 7 cells/$mm^3$ and plasma HIV-1 viral load of 8948 RNA copies/ml.

Four months after her initial hospitalization, the patient was readmitted for mild cognitive impairment with poor recall, partial left third nerve palsy, nonsustained horizontal nystagmus, nonsustained upbeat nystagmus, left upper extremity weakness, hyperreflexia, and spastic paraparesis. Initial head computed tomography (CT) revealed an interval right thalamic infarct and CSF analysis was only remarkable for an HIV viral load of 8347 RNA copies/ml. The patient's repeat CD4 count was now 11 cells/$mm^3$ and plasma HIV-1 viral load was 286 RNA copies/ml. Empiric IV acyclovir (10 mg/kg every 8 h) was started and HAART therapy was changed to include agents (Trizivir and Kaletra) that penetrated the CSF more readily (Antinori *et al*, 2005; Letendre *et al*, 2008). MRI demonstrated extension of her T2 lesions at the cervicomedullary junction, anterior proximal spinal cord and medulla oblongata bilaterally (Figure 1B and C). Despite reintroducing antiviral therapy, the patient's condition continued to worsen. Due to her deteriorating neurological status with concurrent improvement in HIV viral load (Figure 2), IRIS was considered and the patient was treated with IV methylprednisolone (1 g/day). Minimal improvement was seen after 5 days of steroid treatment. Less than 48 h after steroids were stopped, the patient became somulent, dysarthric, weaker, had sustained upbeat nystagmus, and a right sixth nerve palsy. Repeat MRI demonstrated an acute left subcortical infarct and CSF analysis now revealed the presence of VZV DNA. All other CSF viral testing was negative, including JC virus (confirmed by two different

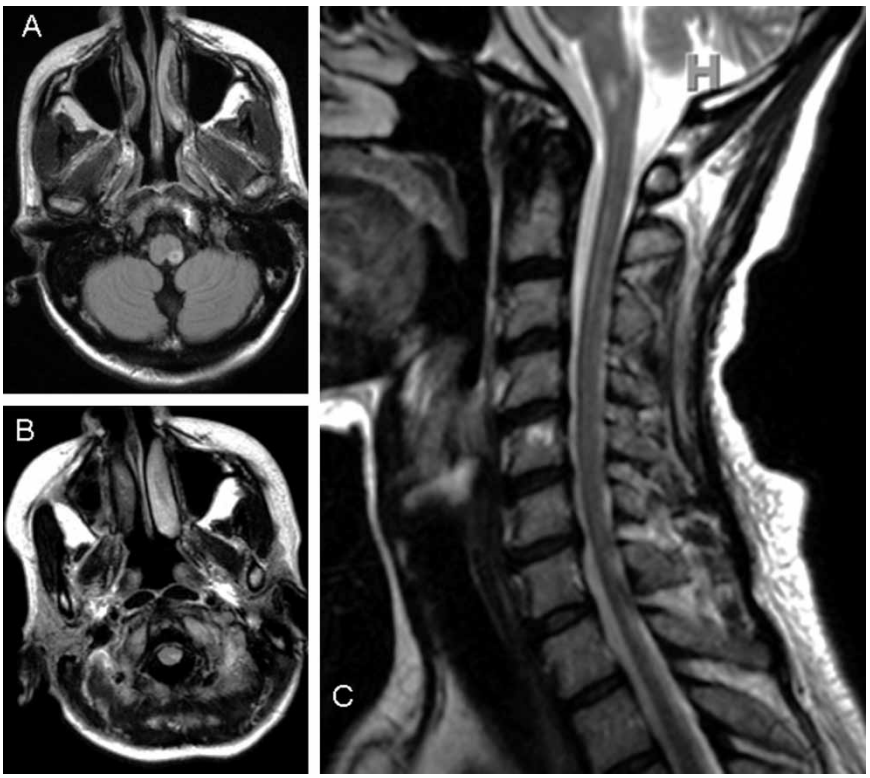


**Figure 1** Brain and cervical spine MRI. (**A**) Initial axial fluid attenuated inversion recovery (FLAIR) sequence showing high signal intensity in the left dorsolateral medulla with minimal central cystic gliosis. (**B**) Axial FLAIR sequence showing high-intensity lesion on the left aspect of the upper cervical spinal cord. (**C**) Sagittal T2-weighted sequence showing high-signal-intensity lesions in anterior proximal spinal cord and medulla oblongata.

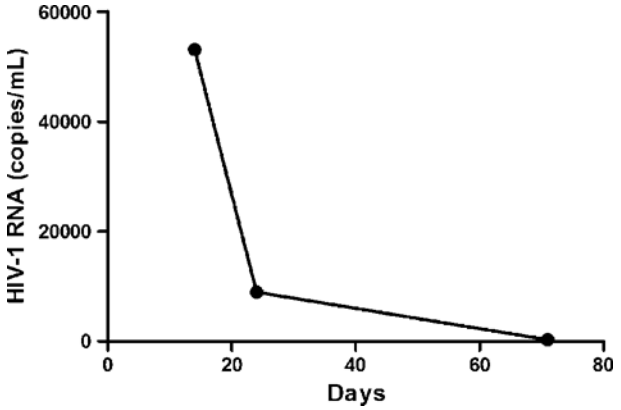


**Figure 2** Quantitative plasma HIV-1 RNA. Day 0 represents start of highly active antiretroviral therapy.

laboratories), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV).

Considering superimposed IRIS, the patient was restarted on IV methylprednisolone, 1 g/day, for 3 days and transitioned to maintenance prednisone (1 mg/kg/day). Robust clinical response was seen after this reinstitution. The patient was awake, attentive, had less nystagmus, improved paraparesis, and regained almost full motor strength in her left upper extremity. She was subsequently transferred to a rehabilitation center. Recently, the patient was seen for follow up in our outpatient center. Her paraparesis is slowly improving even after completing a 2-month prednisone taper and her CD4 count (8 cells/mm$^3$) remains low with improving plasma HIV-1 viral load (70 RNA copies/ml).

## Discussion

VZV-associated diseases occur with an increased frequency in immunocompromised individuals. Although VZV vasculopathy is a well-described condition, it is difficult to diagnose and often relies on CSF virological confirmation (Nagel *et al*, 2007). Similar to our patient, VZV vasculopathy can lead to ischemic lesions (Nagel *et al*, 2008; Orme *et al*, 2007). These vascular events occur as a consequence of the virus affecting small or large cerebral arteries (Kleinschmidt-DeMasters and Gilden, 2001; Nagel *et al*, 2008). Previous authors have reported that the combination of ischemic lesions on imaging and presence of VZV DNA or anti-VZV immunoglobulin G (IgG) antibody in the CSF, convincingly support the diagnosis of VZV vasculopathy (Nagel *et al*, 2008). Our patient fulfilled these criteria.

With the advent of HAART, many neurological complications from opportunistic infections, such as VZV, have decreased. Occasionally, after introduction of HAART, rapid restoration of the immune system leads to paradoxical neurological deterioration (Gray *et al*, 2005; Riedel *et al*, 2006). This syndrome is now widely recognized and commonly referred to as CNS-IRIS. Most patients with IRIS have an underlying opportunistic infection that has a temporal relationship with the start of HAART. Additionally, plasma HIV viral load decreases and CD4 count increases in a nonlinear fashion (Berkeley *et al*, 2008; Patel *et al*, 2006). Our patient exemplified many of the clinical and serological features for CNS-IRIS. The patient initially developed trigeminal zoster in the setting of advanced AIDS, which eventual involved the CNS. After standard herpes zoster treatment and continuation of HAART, the patient deteriorated neurologically. The patient's HIV viral load had precipitously dropped from 53,085 to 286 RNA copies/ml and her CD4 count increased minimally (Figures 2 and 3). The patient stabilized after introducing IV methylprednisolone and had a precipitous decline in neurological status after stopping the steroids. Upon reinitiating steroids, a robust neurological improvement occurred. Currently, there are no established treatment regimens for IRIS; however, this case along with others suggests that corticosteroids in combination with disease-targeted therapy could treat severe cases effectively.

Our patient is unusual given the rare association of VZV vasculopathy and CNS-IRIS. Most published cases do not report this rare occurrence. Secondly, our patient required prolonged steroid treatment until adequate immune reconstitution was obtained. Similar to our patient, in a recent review article, one patient required further steroid treatment after symptoms recurred (Nagel *et al*, 2008). Steroid responsiveness also occurs in non–HIV-infected patients with VZV vasculitis who may be immune competent (Nagel *et al*, 2008). It remains to be determined if the pathophysiology of the two conditions is similar or different. Prolonged use of steroids in immunocompromised patients carry the risk of development of opportunistic infections, hence should be used with caution and the patients should be carefully monitored. However, severe cases of CNS-IRIS may

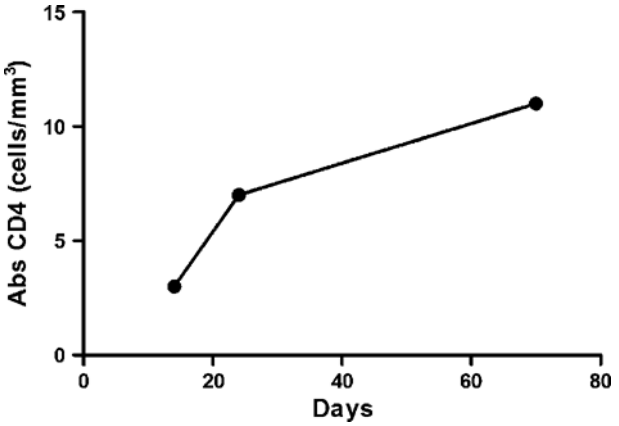


**Figure 3** Quantitative absolute (Abs) CD4 count. Day 0 represents start of highly active antiretroviral therapy.

require a longer duration of treatment with corticosteroids. Histopathological studies show that IRIS is largely mediated via CD8+ T cells (Venkataramana *et al*, 2006), hence it is possible that immunomodulatory drugs that specifically target activated T cells may be better choices for prolonged treatment. Further studies are necessary to evaluate the role of steroids and immunomodulatory drugs for the treatment of CNS-IRIS given the poor clinical outcome related to this syndrome.

***Declaration of interest:*** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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