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Case Report Open Access

Loss of HIV Virologic Control Originating in the Cerebrospinal Fluid Due to Inadvertent Protease Inhibitor Monotherapy

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Abstract

There is increasing recognition that the ongoing replication of Human Immunodeficiency Virus (HIV) within the central nervous system can have important prognostic implications, both in terms of HIV control and neurological symptoms. We present a case of loss of HIV virological control in a patient receiving unintended protease inhibitor monotherapy.

Keywords: Human immunodeficiency virus; HIV; cerebrospinal fluid; CSF; viral control; viral escape; protease inhibitor monotherapy

Case Report

A 40 year old man, with well controlled HIV (CD4 533 cells/mm^3 (45%) and undetectable viral load), but a prior history of complicated HIV/AIDS, presented with an eight day history of general malaise, chills, fevers and sweats, a mild dry cough and headache. His past history is significant for HIV diagnosed in 1983 and complicated by cerebral toxoplasmosis and PCP in the 1990s, Hepatitis B surface antigen positive, viral load undetectable, Hepatitis C antibody positive, RNA undetectable, hemophilia A and a remote seizure secondary to a subdural hematoma in 1995. From an antiretroviral drug perspective, he is treatment experienced, having received zidovudine (AZT) and zalcitabine (DDC) in 1993, which was subsequently switched to didanosine (DDI) and lamuvidine (3TC) which was then stopped. In 1995 he was initiated on saquinavir, lamivudine and DDC due to a CD4 of zero. Six months later, he continued to have detectable virus and was switched to stavudine (d4T), indinavir, 3TC and nevirapine without the benefit of genotype testing; viral suppression was achieved on this regimen. In 2005 his medications were changed to tenofovir, emtricitabine (FTC), nevirapine and indinavir. A year later atazanavir/ritonavir was substituted for indinavir. In 2007, nevirapine was discontinued. Viral load remained undetectable since 1996 throughout these changes in therapy.

On presentation with the acute febrile illness, initial work-up including a complete blood count with differential, blood cultures, chest radiograph and nasopharyngeal culture for bacteria and viruses was negative. Ten days after presentation, his symptoms had not resolved, with ongoing fevers to 38.5°C, myalgias and new lightheadedness. He was admitted, and an extensive work -up for possible etiology of his symptoms was unrevealing. CT of the sinuses, chest and abdomen was unremarkable. An investigation of potential infectious, inflammatory and neoplastic causes of fever, influenza, respiratory syncytial virus, tuberculosis, Epstein Barr virus, Cryptococcus, cytomegalovirus, Bartonella, Lyme, autoimmune disease, thyroxicosis, pulmonary embolism, and lymphoma, was negative. He was discharged with a working diagnosis of bupropion hypersensitivity.

Despite some improvement in his fever curve after bupropion discontinuation, he continued to complain of dizziness, lightheadedness, and fatigue. One month after his initial presentation he represented with vertigo and diplopia. Magnetic Resonance (MR) imaging of brain and MR angiogram demonstrated no acute abnormalities. Lumbar puncture revealed a lymphocytic pleocytosis and elevated protein. Cerebrospinal fluid (CSF) cultures were negative as was a CSF PCR for herpes simplex, EBV and a CSF VDRL. Ten days later he had a generalized tonic clonic seizure and was readmitted to the hospital. During this hospital admission, a repeat plasma HIV viral load was 316 copies/ml, having previously been undetectable. HIV genotype testing of both plasma and CNS isolates was performed; findings are reported in Table 1.

Quest Diagnostics, Inc., San Juan Capistrano, CA, USA and the original sequence in FASTA format was obtained for additional analysis, performed plasma genotype testing. CNS genotype testing was performed at Tufts Medical Center, Boston, USA using a previously described population based sequencing assay and primer sets optimized for HIV-1 subtype B [1]. HIV drug resistance (HIVDR) mutations were defined using the Stanford HIVdb and quality assurance scoring was performed using the Stanford HIV CPR tool [2].Subtype analysis was performed using the REGA subtyping tool [3,4]. Sequence analysis demonstrated three amino acid differences, two involving mixtures (Table 1) No differences in drug resistance positions were noted (Table 1). The patient's virus was subtype B. Subsequent switch to mariviroc, tenofovir, FTC, darunavir/ritonavir and raltegravir resulted in viral suppression and the patient has had no further neurological symptoms for 2 years.

Cerebral spinal fluid		Plasma	
NRTI/NNRTI	**PI**	**NRTI/NNRTI**	**PI**
M41L, D67N, T69D, M184V, L210W, T215Y/V35L, K43Q, E44D, E53D, V118I, K122E, Q174E, D177E, G196E, Q207E, R211K	N37D, R57K, L63T,A71V, I72T, V77I, I93L	M41L, D67N, T69D, M184V, L210W, T215Y/V35L, K43Q, E44D, E53D, V118I, K122E, Q174E, D177E, G196E, Q207E, R211K, **P225LP**	N37D, R57K, L63T,A71V, I72T, **T74AT**, V77I, I93L

Table 1: Results of HIV genotype from plasma and cerebral spinal fluid. Differences between the CSF and plasma sequences in bold.

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Discussion

HIV is a neurotrophic virus, and has been shown to enter the central nervous system early in the course of infection, and to be present at all stages of disease [5]. Prior to the discovery of highly active antiretroviral therapy (HAART), HIV associated central nervous system disorders occurred frequently [6]. Since the introduction of HAART, the incidence of HIV associated neurological disorders has decreased dramatically [6]. Despite this, HIV positive patients continue to be disproportionately affected by central nervous system disorders compared to their HIV negative counterparts [7]. In patients undergoing lumbar puncture for a variety of indications, both HIV related and unrelated, plasma HIV VL was the only predictor of CSF HIV VL in multivariable analysis [8]. In certain circumstances, however, the results of plasma and CSF HIV VL may be discordant; this is often termed 'viral escape'. CSF viral escape has been reported to occur in up to 13% of patients on HAART [8]. In asymptomatic patients, higher CSF HIV VLs are associated with a longer duration of ART and with increasing numbers of viral 'blips' and HAART treatment interruptions [9].

HIV diversity has been described in HIV isolated from the blood and CNS [10,11] in the same individuals, suggesting that compartmental evolution of HIV may differ, with R5 tropic virus more likely to be found in the central nervous system [12]. High genetic diversity between CSF and plasma virus has been shown to be more likely in patients with lower plasma VL, suggesting ongoing replication of HIV occurs in the CSF, despite HAART [12]. When patients are on medications with higher central nervous system penetration measured diversity was lower, implying inhibition of viral replication within the CSF [12]. Moreover, certain HIV medications may not cross the blood brain barrier well, which has led to concern that viral escape may occur in the CSF, promoting ongoing viral replication and the selection of viral resistance. CSF HIV viral loads have been shown to be suppressed on HAART [13,14] however, this may be dependent on the antiretroviral regimen chosen [15,16]. The central nervous system penetration of Atazanavir is variable with levels approximately 100-fold lower in the CSF compared to serum regardless of ritonavir boosting [17].

In this case, our patient had resistant virus, likely due to previous antiretroviral therapy prior to the initiation of HAART and lack of available genotype testing when detectable viral RNA was present. When nevirapine was discontinued in 2007, he was unintentionally maintained on protease inhibitor monotherapy having at some point previously developed tenofovir and FTC resistance (Table 1: RT mutations M184V, M41L, L210W, T215Y). As he had been virally suppressed since 1996, an HIV genotype was not available to guide changes in HAART. Interestingly, there were minimal differences observed between the patient's RT and protease sequence isolated from plasma and CSF. One limitation is that viral quasispecies were not assessed. Both the plasma and CSF sequence were derived by standard population based sequencing, which detects virus present in the majority viral population (~15-20%).Thus, it is possible that had single genome sequencing been performed, greater viral diversity between compartments may have been observed. Despite the minimal differences in virus sequencing between plasma and CSF, we postulate that the patient's loss of virologic control originated in the CSF due to poor penetration of atazanavir/ritonavir into the central nervous system.

Protease monotherapy has been successfully used to maintain HIV viral suppression after initial therapy with HAART [18]. However, cases of viral escape originating in the CSF have been reported in patients receiving darunavir/ritonavir monotherapy [19]. We present a case of viral escape in a patient being treated with unintended atazanavir/ritonavir monotherapy. To our knowledge this is the first such case report. Given that high HIV CSF viral loads have been associated with poor neurocognitive performance and neurologic symptoms [20], the recognition of the potential for ongoing viral replication within the CSF and subsequent loss of virological control has important clinical and prognostic implications. Physicians should be aware that patients receiving boosted protease inhibitors alone may not suppress HIV viral replication within the CSF, facilitating ongoing HIV viral replication, the development of antiretroviral resistance, and ultimately loss of HIV virologic control.

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