Clinical Reasoning: Rapidly Progressive Dementia in a Man With HIV Infection and Undetectable Plasma Viral Load

Lorraine Chishimba Chishimba, MMED, Mashina Chomba, MBChB MMed, Stanley Zimba, MMED, STP, Melody Tunsubilege Asukile, MBChB, MMed, FC Neurol(SA), Obrie Makai, MMED, and Deanna R. Saylor, MD, MHS

Correspondence
Dr. Saylor
deanna@jhmi.edu

Neurology® 2023;100:344-348. doi:10.1212/WNL.0000000000201576

Abstract

Neurocognitive decline associated with HIV infection remains prevalent even in the antiretroviral therapy (ART) era, albeit usually in less severe forms. The differential diagnosis of cognitive impairment in this population is quite broad, including infectious causes such as CNS opportunistic infections, causes directly related to HIV such as HIV-associated neurocognitive disorders, and causes entirely unrelated to HIV infection such as primary dementia syndromes. In this case report, a 47-year-old man with HIV on ART with an undetectable plasma viral load presented with rapidly progressive dementia to a clinic in Zambia. He had been functioning independently and fully employed before symptom onset but had to stop working within 2 months of symptom onset because of the severity and rapidity of his cognitive decline. Initial workup led to an empiric diagnosis and initiation of an empiric treatment regimen, which was ultimately ineffective. This prompted re-evaluation, additional workup, and, ultimately, discovering the correct diagnosis. This case highlights the stepwise approach to developing a diagnosis in a resource-limited setting where there exists a high burden of HIV infection, including the necessity of empiric diagnoses of treatment plans when investigations are limited and the importance of reconsidering these diagnoses in the face of additional clinical information. In addition, it highlights both infectious and noninfectious causes of cognitive decline in people with HIV.

From the Department of Internal Medicine (L.C.C., M.C., S.Z., M.T.A., D.R.S.), University Teaching Hospital, Lusaka, Zambia; Department of Internal Medicine (S.Z., D.R.S.), University of Zambia School of Medicine, Lusaka; Department of Internal Medicine (O.M.), Infectious Diseases Unit, University of Zambia, Lusaka; and Department of Neurology (D.R.S.), Johns Hopkins University School of Medicine, Baltimore, MD.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Section 1

A 47-year-old man with HIV on antiretroviral therapy (ART) for 18 years presented to a neurology clinic in Zambia with progressive cognitive decline over 2 months characterized by memory impairment, inability to recognize friends, tangential speech, wandering, and inability to continue working. He denied other neurologic symptoms. Medical history was notable for a bulbar urethral stricture. His ART regimen comprised tenofovir, emtricitabine, and ritonavir-boosted atazanavir. He had a period of ART noncompliance a year earlier, but had been compliant for 6 months. He did not use tobacco, alcohol, or other substances.

Physical examination revealed orientation to person and place only, poor memory in all domains, poor naming and comprehension, psychomotor slowing, and failure to follow complex or simple commands. He had a positive glabellar sign and hyperreflexia in both legs. The remainder of his neurologic examination was normal.

Questions for Considerations:

1. What is the localization for his presentation?
2. What is the differential diagnosis?
3. What investigations can help narrow the diagnosis?

GO TO SECTION 2

Section 2

The patient had rapidly progressive dementia (RPD) given cognitive decline with marked functional impairment within 2 months.[1] Cognitive symptoms and signs without focal deficits suggest a diffuse cerebral process with psychomotor slowing and frontal release signs suggesting frontal lobe involvement.

The differential diagnosis for his presentation is broad. Given his HIV status, HIV-associated neurocognitive disorder (HAND) was considered because it remains common in the ART era, albeit usually mild. Low CD4 nadir is a risk factor of HAND, but our patient's CD4 nadir was unknown.[2] However, acute progression is unusual for HAND. HIV infection may directly cause RPD through mechanisms such as HIV encephalitis, $CD8^+$ T-cell encephalitis, and CSF escape and indirectly through CNS opportunistic infections.[1,3] Other causes of RPD, regardless of HIV status, include infectious processes (e.g. viral encephalitis, Creutzfeld-Jacob disease, neurosyphilis), toxic-metabolic processes (e.g. vitamin B12 and B1 deficiencies, metal toxicity, endocrinopathies), autoimmune etiologies (e.g. CNS lupus, autoimmune encephalitis), malignancy (e.g. carcinomatous meningitis, paraneoplastic encephalitis), illicit drug use, and iatrogenic causes (e.g. chemotherapy).[1] The patient had no history of drug use, toxin exposure, endocrinopathies, or metabolic disturbances. Neurodegenerative conditions (e.g. Alzheimer disease) were less likely given the acute course.[1]

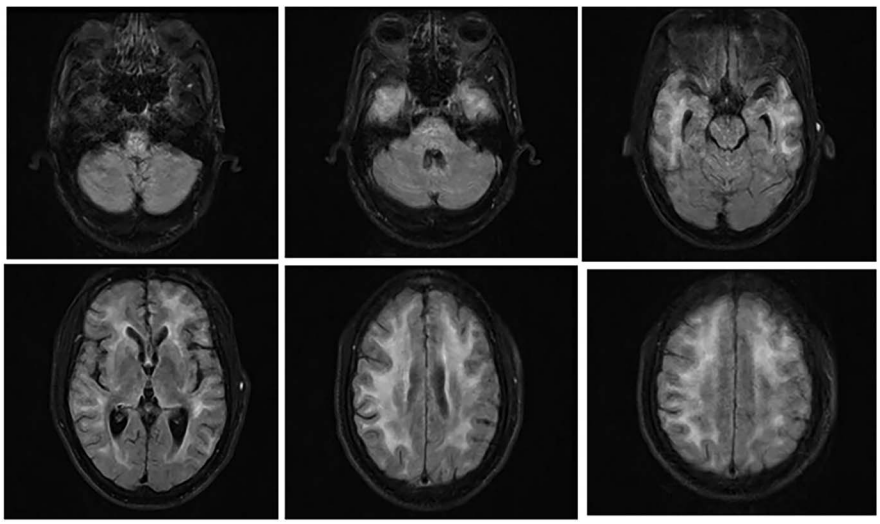
We took a targeted stepwise approach to investigations because of resource limitations and prioritized the most likely diagnoses, starting with infections. Full blood count and metabolic panel were normal. $CD4^+$ T-cell count and plasma HIV viral load (VL) were 522 cells/uL and 54 copies/mL, respectively. Brain MRI showed diffuse T2 white matter hyperintensities with corresponding T1 hypointensities, extending from the brainstem to the hemispheres with no mass effect or diffusion restriction (Figure). CSF studies revealed white cell count 8 cells/mm^3 (reference: 0–5); protein 0.92 g/L (reference: 0.2–0.4); glucose 2.83 mmol/L (reference: 2.2–4.2); and negative Gram stain, cryptococcal antigen, and JC virus (JCV) PCR. While JCV was not detected, the sensitivity of CSF JCV-PCR is typically 60%–80%.[4] Given the possibility of false-negative results and imaging suggestive of progressive multifocal leukoencephalopathy (PML), a 4-week trial of prednisolone was given for a presumptive diagnosis of PML immune reconstitution inflammatory syndrome (IRIS). He improved on steroids, returned to work, and interacted normally with family.

Three months later, he returned to the clinic with recurrence of and worsening cognitive decline characterized by failure to remember family members, tangential speech, auditory and visual hallucinations, wandering, and intermittent falls. He again required assistance in nearly all activities of daily living. Examination was unchanged, except the additional finding of prominent perseveration. The CD4 T-cell count and plasma HIV VL were now 288 cells/uL and 212 copies/mL, respectively. The decline in CD4 and corresponding rise in viral load were attributed to intercurrent urinary tract infection. Rapid plasma reagin for syphilis was nonreactive. CSF analysis showed 7 white blood cells; normal glucose (2.48 mmol/L); and negative cryptococcal antigen, India ink, and Gram stain. Owing to resource constraints, CSF protein and panels for viral and autoimmune encephalitides were unavailable. However, CSF HIV VL was 27,268 copies/mL.

Questions for Considerations:

1. What is the most likely diagnosis?
2. How would you manage this patient?

Figure MRI Brain



MRI FLAIR images demonstrate extensive T2/FLAIR white matter changes without mass effect. There was no diffusion restriction or gadolinium enhancement. FLAIR = fluid-attenuated inversion recovery.

GO TO SECTION 3

Section 3

Given the significantly elevated CSF HIV VL compared with plasma HIV VL, he was diagnosed with symptomatic CSF discordance syndrome. His ART regimen was changed to dolutegravir, ritonavir-boosted dorunavir, and lamivudine. Three months later, his cognitive symptoms had resolved such that he had returned to work and was at his preillness cognitive baseline. Neurologic examination was normal. Repeat CSF revealed normal white cell count, protein, and glucose and an undetectable CSF HIV VL.

Discussion

We present a case of RPD in an ART-treated man with HIV and peripheral viral suppression. Cognition improved with steroid treatment of empirically diagnosed PML-IRIS. However, recurrent symptoms prompted further workup, which led to the diagnosis of CSF discordance.

CSF HIV VL is a proxy for independent replication of HIV in brain parenchyma where HIV directly infects neurons, astrocytes, and oligodendrocytes but preferentially infects microglia and perivascular macrophages. HIV persists in these cells because they are not susceptible to the cytotoxic mechanisms of T-lymphocytes and, hence, can become reservoirs for persistent HIV replication.[5] Although HIV enters the brain within 2 weeks of primary infection, plasma HIV suppression is generally accompanied by CNS viral suppression in ART-treated individuals.[6]

CSF discordance is defined as CSF HIV VL greater than 0.5 or 1Log_{10} of plasma HIV VL. CSF escape is defined as any detectable CSF HIV VL when plasma HIV VL is undetectable.[7] The exact incidence of CSF escape/discordance is unknown, especially outside high-income countries, and challenging to determine because it is often asymptomatic, transient, and of unclear significance. However, a pooled estimate from high-income countries estimated its prevalence at 7.1% of ART-treated individuals.[8] Risk factors of CSF escape/discordance include low-level plasma viremia, maintenance of the same ART regimen for many years, and, in particular, taking a ritonavir-boosted protease inhibitor (PI) for many years.[8] For example, atazanavir, a PI, and tenofovir, a nucleoside reverse transcriptase inhibitor, have been associated with CSF escape/discordance likely because of their low concentrations in CSF.[9-11] All of these factors were present in our patient.

Clinical manifestations of CSF escape/discordance vary from asymptomatic to death and its course from acute to subacute. Symptomatic manifestations include meningoencephalitis, psychosis, and personality changes, but progressive cognitive decline is most common. CSF escape/discordance should be suspected when new neurologic symptoms arise in ART-treated patients with well-controlled HIV infection. CSF may have high protein, lymphocytic pleocytosis, or abnormal glucose in the absence of an identified infection while brain MRI may reveal diffuse white matter hyperintensities on T2 and T2-FLAIR sequences.[12,13] Of note, CSF discordance/escape can co-occur with $CD8^+$ encephalitis, an inflammatory brain disease characterized by marked infiltration of the cerebrum by $CD8^+$ T cells that presents with acute or subacute deterioration of cerebral function characterized by headache, confusion, and progressive cognitive decline, among other features.[9,14]

Treatment of CSF escape/discordance includes optimization of the ART regimen with special attention to the possibility of CNS compartmentalization. CNS compartmentalization occurs when CNS viral reservoirs develop mutations unique from circulating plasma HIV strains.[5] If these mutations are ART-resistant, then CNS viral reservoirs become resistant to ART that may still be effectively suppressing plasma virus. In these situations, ART regimens should be optimized based on both CSF and plasma ART resistance profiles to ensure adequate peripheral and CNS viral suppression. Optimization can also be achieved by using ART agents with effective CNS penetration.[7] However, no randomized controlled trials exist to support these practices, and treatment does not always result in immediate symptom resolution as demonstrated in this case.

Our patient improved transiently after steroids, although steroids are not a standard treatment of CSF discordance.[7,15] Although our patient did not have neuropathologic confirmation of $CD8^+$ encephalitis (diagnostic gold standard) because of resource limitations, his MRI showed T2 white matter hyperintensities as are reported in $CD8^+$ encephalitis.[9] Steroids often improve CD8 encephalitis, so it is possible that our patient had an overlap of CSF discordance and CD8 encephalitis that improved with both steroids and optimization of his ART regimen. Repeat neuroimaging was not performed because the patient improved such that repeat imaging was unlikely to change management and would incur significant costs for the patient.

It is important to note that this case report highlights challenges of evaluating RPD in settings where resource limitations often preclude a comprehensive initial evaluation. Instead, a stepwise approach based on prevailing local epidemiology is undertaken and empiric treatment often initiated. However, close clinical follow-up and re-evaluation of empiric diagnoses is essential. For example, in retrospect, our patient likely never had PML-IRIS. Close follow-up and critical evaluation of prior presumptive diagnoses, however, enabled correct diagnosis and initiation of appropriate treatment.

Finally, this case report highlights the need to evaluate for CSF escape/discordance in people with HIV presenting with cognitive decline, especially in those with well-controlled systemic HIV and in whom CNS opportunistic infections have been excluded. This is especially important because CSF

escape/discordance syndromes are treatable but can lead to marked impairment if not promptly diagnosed and treated.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures.Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* May 18, 2022. Accepted in final form October 6, 2022. Submitted and externally peer reviewed. The handling editor was Whitley Aamodt, MD, MPH.

Appendix Authors

Name	Location	Contribution
Lorraine Chishimba Chishimba, MMED	Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mashina Chomba, MBChB MMed	Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia	Drafting/revision of the manuscript for content, including medical writing for content
Stanley Zimba, MMED, STP	Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia; Department of Internal Medicine, University of Zambia School of Medicine, Lusaka Zambia	Drafting/revision of the manuscript for content, including medical writing for content
Melody Tunsubilege Asukile, MBChB, MMed, FC Neurol(SA)	Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia	Drafting/revision of the manuscript for content, including medical writing for content
Obrie Makai, MMED	Department of Internal Medicine, Infectious Diseases Unit, University of Zambia, Lusaka, Zambia	Drafting/revision of the manuscript for content, including medical writing for content
Deanna R. Saylor, MD, MHS	Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia; Department of Internal Medicine, University of Zambia School of Medicine, Lusaka Zambia; Department of Internal Medicine, Infectious Diseases Unit, University of Zambia, Lusaka, Zambia	Drafting/revision of the manuscript for content, including medical writing for content

References

1. Geschwind MD. Rapidly progressive dementia. *Continuum.* 2016;22(2 Dementia): 510-537.
2. Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS.* 2011;25(14):1747-1751.
3. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. *Lancet Infect Dis.* 2013;13(11):976-986.
4. Nakamichi K, Kawamoto M, Ishii J, Saijo M. Improving detection of JC virus by ultrafiltration of cerebrospinal fluid before polymerase chain reaction for the diagnosis of progressive multifocal leukoencephalopathy. *BMC Neurol.* 2019;19(1):252.
5. Harrington PR, Schnell G, Letendre SL, et al. Cross-sectional characterization of HIV-1 env compartmentalization in cerebrospinal fluid over the full disease course. *AIDS.* 2009;23(8):907-915.
6. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol.* 2004;55(3):320-328.
7. Canestri A, Lescure F-X, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. *Clin Infect Dis.* 2010;50(5):773-778.
8. Mukerji SS, Misra V, Lorenz DR, et al. Impact of antiretroviral regimens on cerebrospinal fluid viral escape in a prospective multicohort study of antiretroviral therapy-experienced human immunodeficiency virus-1-infected adults in the United States. *Clin Infect Dis.* 2018;67(8):1182-1190.
9. Manesh A, Barnabas R, Mani S, et al. Symptomatic HIV CNS viral escape among patients on effective cART. *Int J Infect Dis.* 2019;84:39-43.
10. Lahiri CD, Reed-Walker K, Sheth AN, Acosta EP, Vunnava A, Ofotokun I. Cerebrospinal fluid concentrations of tenofovir and emtricitabine in the setting of HIV-1 protease inhibitor-based regimens. *J Clin Pharmacol.* 2016;56(4):492-496.
11. Best BM, Letendre SL, Brigid E, et al. Low atazanavir concentrations in cerebrospinal fluid. *AIDS.* 2009;23(1):83-87.
12. Dravid AN, Natrajan K, Kulkarni MM, et al. Discordant CSF/plasma HIV-1 RNA in individuals on virologically suppressive antiretroviral therapy in Western India. *Medicine.* 2018;97(8):e9969.
13. Peluso MJ, Ferretti F, Peterson J, et al. Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. *AIDS.* 2012;26(14):1765-1774.
14. Mirgh S, Mishra V, Harbada R, Sorabjee J. Knowing the unknown—CD8 encephalitis: a novel form of HIV-associated neurocognitive disorder. *Neurol India.* 2019;67(1):261-264.
15. Dravid AN, Gawali R, Betha TP, et al. Two treatment strategies for management of Neurosymptomatic cerebrospinal fluid HIV escape in Pune, India. Medicine. 2020;99(24).

Clinical Reasoning: Rapidly Progressive Dementia in a Man With HIV Infection and Undetectable Plasma Viral Load

Lorraine Chishimba Chishimba, Mashina Chomba, Stanley Zimba, et al.

Neurology 2023;100;344-348 Published Online before print November 8, 2022
DOI 10.1212/WNL.0000000000201576