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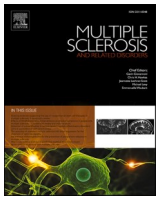

Correspondence

Long-term MRI and clinical stability in an HIV-positive patient with multiple sclerosis on tenofovir: A case report

1. Introduction

The Epstein-Barr virus (EBV) is the likely leading cause of multiple sclerosis (MS). (Bjornevik et al., 2022) Debates continue regarding the potential benefit of antiviral treatment for EBV after the onset of MS. Tenofovir prodrugs, used in highly active antiretroviral therapy (HAART) for HIV treatment, have shown potent inhibition of EBV in B-cells *in vitro*. (Drosu et al., 2020) Intriguingly, several case reports describe people with MS on HAART containing tenofovir with no evidence of MS disease activity, (Chalkley and Berger, 2014; Delgado et al., 2014; Labella et al., 2021; Maulucci et al., 2015; Torkildsen et al., 2020; Skarlis et al., 2018) and epidemiological studies have reported a lower incidence of MS in patients with HIV. (Gold et al., 2015; Nexø et al., 2013) Although these observations could be due to immunosuppression from HIV, patients on HAART often maintain undetectable viral loads and normal CD4 T cell counts. This raises the question of whether HIV treatment may be reducing MS disease activity by inadvertently treating EBV. Here, we present the case of an MS patient with significant brain and spinal cord disease burden at diagnosis who has remained clinically and radiologically stable for more than nine years while on a HAART regimen containing tenofovir and in the extended absence of disease-modifying therapies (DMTs) for MS.

2. Case report and literature review

In January 2011, a 25-year-old woman presented to the Emergency Department at Boston Medical Center for headaches and coordination difficulties, leading to multiple falls. She had visited multiple times since 2009 for recurrent headaches, loss of coordination, and falls, but no MRI imaging was performed during those visits. A CT scan of the head performed in 2010 was unrevealing. During her 2011 visit, an MRI scan was conducted for the first time, revealing extensive demyelinating disease. The MRI showed multiple periventricular T2/FLAIR lesions, several lesions in the posterior fossa and corpus callosum, and the cervical and thoracic spine, particularly at the C2-4, C5-6, and T2 segments. None of the lesions showed gadolinium enhancement (Fig. 1).

She was referred to the MS clinic at Brigham and Women's Hospital in Boston, MA, where she was formally diagnosed and started on fingolimod. However, she was poorly compliant and stopped taking it one year later as she felt it did not help with her MS symptoms and was too expensive. At the time, she was unemployed because of MS fatigue and weakness. In September 2012, she had another clinical relapse characterized by one week of incoordination, which was treated with IV steroids. HIV testing performed one month later was negative, and fingolimod was restarted but was stopped again shortly after. In March 2013, she had another clinical relapse marked by right arm numbness, for which she again received IV steroids. Fingolimod was restarted, but she continued to have fatigue and balance issues with frequent falls and again discontinued treatment. Over that year, she noted worsening cognitive decline, forgetfulness, impaired concentration, and poor sleep without restfulness. She described often being confused during the day. MRI performed in August 2013 was unchanged.

At a follow-up appointment in 2014, she was advised to restart fingolimod. However, routine HIV screening was unexpectedly positive, and her CD4 count was 163. She was immediately started on elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild) with excellent adherence, and her viral load became undetectable with normalization of the CD4 count. For MS, she was switched to glatiramer acetate (GA) but developed injection site reactions and stopped treatment a few months later. Four months after starting HAART, she reported feeling that her balance and incontinence had improved. One year later, the improvements in her balance were sustained, and she noticed that cognitively, she felt sharper and had less tremulousness. She also noticed that she had stopped falling. Due to nausea, her HIV therapy was switched to emtricitabine/tenofovir disoproxil fumarate (Truvada) and dolutegravir. Two years after her HIV diagnosis, she continued to endorse that her MS was more stable than when she was on fingolimod. In 2016, she was switched to emtricitabine/tenofovir alafenamide (Descovy) and dolutegravir. An attempt was made to restart GA, which was again self-discontinued. In 2019, her HAART regimen was switched to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy). In 2021, she reported the persistence of pre-existing throbbing arm and shoulder pain and received a course of IV steroids with attempts again made to restart GA. To date, she has not had any clinical relapses since her HIV diagnosis, no MRI disease activity on eight consecutive MRIs performed since 2014, and no disability progression despite being mostly off DMTs now for over nine years. At her latest clinic visit in 2023, she had chronic back pain secondary to lumbar spinal stenosis and continued to have some urinary hesitancy and numbness but was otherwise doing well. Her latest viral load was undetectable, and CD4 count was 596. She reported no fatigue and was gainfully employed.

3. Discussion

Although speculative, it is intriguing to consider the possibility that the improvement in this patient's MS condition after her HIV diagnosis was a direct effect of HAART on MS. Interestingly, she was maintained on a regimen containing tenofovir prodrugs for the entirety of her HIV treatment course. While the possibility that the HIV infection itself affected her MS disease course by modulating immune responses cannot be ruled out, she experienced amelioration of incoordination, cognition, and fatigue that coincided with starting HIV therapy. Given her

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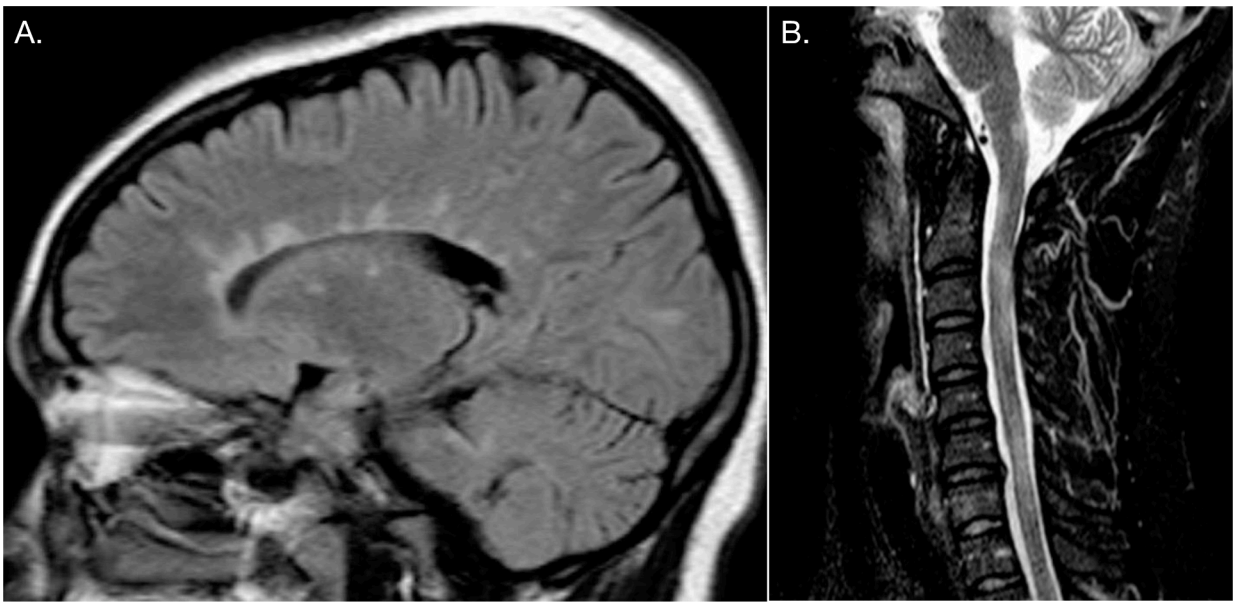

Fig. 1. (A) MRI of the brain, T2 weighted imaging performed in 2011 showing numerous periventricular demyelinating plaques. (B) Spinal MRI performed at diagnosis, demonstrating multiple cervical cord lesions.

extensive disease burden at presentation, two clinical relapses in the years following diagnosis, and worsening symptoms on fingolimod, stability in her disease course for almost a decade is unexpected. Parenthetically, it is interesting that despite repeated non-compliance with her MS medications over the years, she has been more compliant with her HIV treatments due to fewer side effects.

4. Conclusion

Further research into tenofovir-based therapies for MS is warranted. In the future, it is crucial that trial designs incorporate a rational selection of primary endpoints, drawing from cases such as this one which suggest early treatment with evaluation of MRI disease activity and clinical relapses as suitable endpoints. Rigorous, placebo-controlled trials of antivirals used as monotherapy are essential to answer critical questions concerning the role of EBV in MS.

CRediT authorship contribution statement

Natalia Drosu: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **Kjetil Bjornevik:** Conceptualization, Investigation, Writing – review & editing. **Philippe Bilodeau:** Conceptualization, Investigation, Writing – review & editing. **Michael Levy:** Conceptualization, Investigation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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