Case Report

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HIV infection and multiple sclerosis: a case with unexpected "no evidence of disease activity" status

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Abstract

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system whose etiology remains unclear. It has been suggested that MS can be triggered by certain viruses; however, human immunodeficiency virus (HIV) infection is associated with reduced incidence of MS. We present the case of a young patient diagnosed with active relapsing-remitting MS whose clinical course substantially improved following HIV infection and treatment. The patient achieved no evidence of disease activity status without any disease-modifying drugs. Both HIV-induced immunosuppression and antiretroviral therapy may have attenuated the clinical course in this patient.

Keywords

Multiple sclerosis, human immunodeficiency virus, human endogenous retrovirus, highly active antiretroviral therapy, immunosuppression, no evidence of disease activity, Epstein–Barr virus

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Introduction

Patients infected with human immunodeficiency virus (HIV) have lower risks of developing multiple sclerosis (MS) than healthy controls.[1,2] In addition to decreased MS incidence, HIV infection may attenuate the clinical course of MS.[3] At least two hypotheses might explain this observation.

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First, HIV-induced immunosuppression might attenuate the development of immune responses associated with MS.[4] Second, highly active antiretroviral therapy (HAART) inhibits Epstein–Barr virus (EBV) replication and human endogenous retrovirus (HERV) expression, both of which have been linked to MS pathogenesis.[5–7] Infections by viruses such as EBV may induce increased HERV expression, triggering inflammatory responses through Toll-like receptor 4 engagement. This has been postulated as a potential trigger for MS.[5]

Here we present the case of a patient with active MS who achieved no evidence of disease activity (NEDA) status following HIV diagnosis and treatment, in the absence of other disease-modifying drugs. Written informed consent for publication of patient information was obtained. Because all information was anonymized, institutional ethical approval was not required.

Case report

A 23-year-old man with no medical history apart from plaque psoriasis had a 1-week self-limited episode of blurry vision in his right eye in April 2003. His family medical history revealed a first cousin with psoriasis and a paternal uncle with relapsing-remitting MS (RRMS).

Approximately 1 month later, he was admitted to hospital because of gait instability, diplopia, and hemifacial numbness. Physical examination showed 20/25 visual acuity in his right eye, abduction right eye limitation, and right hemifacial hypoesthesia. Cranial magnetic resonance imaging (MRI) without contrast showed a left frontal juxtacortical lesion and several periventricular and subcortical lesions. Lumbar puncture revealed normal cerebrospinal fluid (white blood cells 2/mm^3, glucose 57 mg/dL, and protein 34 mg/dL). Oligoclonal bands, IgG index and albumin level were not tested. Blood tests and indicators of autoimmunity were all negative, including tests for HIV. He was diagnosed with RRMS and then lost to follow-up prior to administration of disease modifying drugs. Over the next 2 years, he had two additional relapses (ataxia and lower-limb paresis), both of which resolved spontaneously.

In July 2006, the patient developed an exanthema. He was diagnosed with syphilis and HIV based on the following blood test results: Rapid Plasma Reagin titer 1/32, positive *Treponema pallidum* hemagglutination assay, positive ELISA and western blot detection of HIV, HIV viral load 6420 copies/mL, and CD4+ lymphocytes 586 cells/mm^3). He received penicillin G without initiating HAART. During the following 3 years, he was free from relapses in the absence of antiretroviral therapy. In 2009, HAART was initiated after he presented with pharyngeal mycosis. At that time, decreased CD4+ lymphocytes (250 cells/mm^3) were detected. HAART with emtricitabine, tenofovir and efavirenz was initiated and the patient has maintained normal CD4+ lymphocyte levels and undetectable viral loads since then.

He resumed follow-up in our Neurology Department in 2014. He had not experienced any additional relapses since he was diagnosed with HIV in 2006. He was asymptomatic with an Expanding Disability Status Scale (EDSS) score of 0. Brain MRI identified several new periventricular lesions compared with the prior results (May 2003); neither sets of imaging data showed contrast enhancement (Figure 1). No new lesions, relapses, or increased disability appeared on annual follow-ups including brain MRI since 2014. His last outpatient visit was in February 2020, and showed no new radiological lesions and no clinical changes. At this time, he had achieved NEDA status.

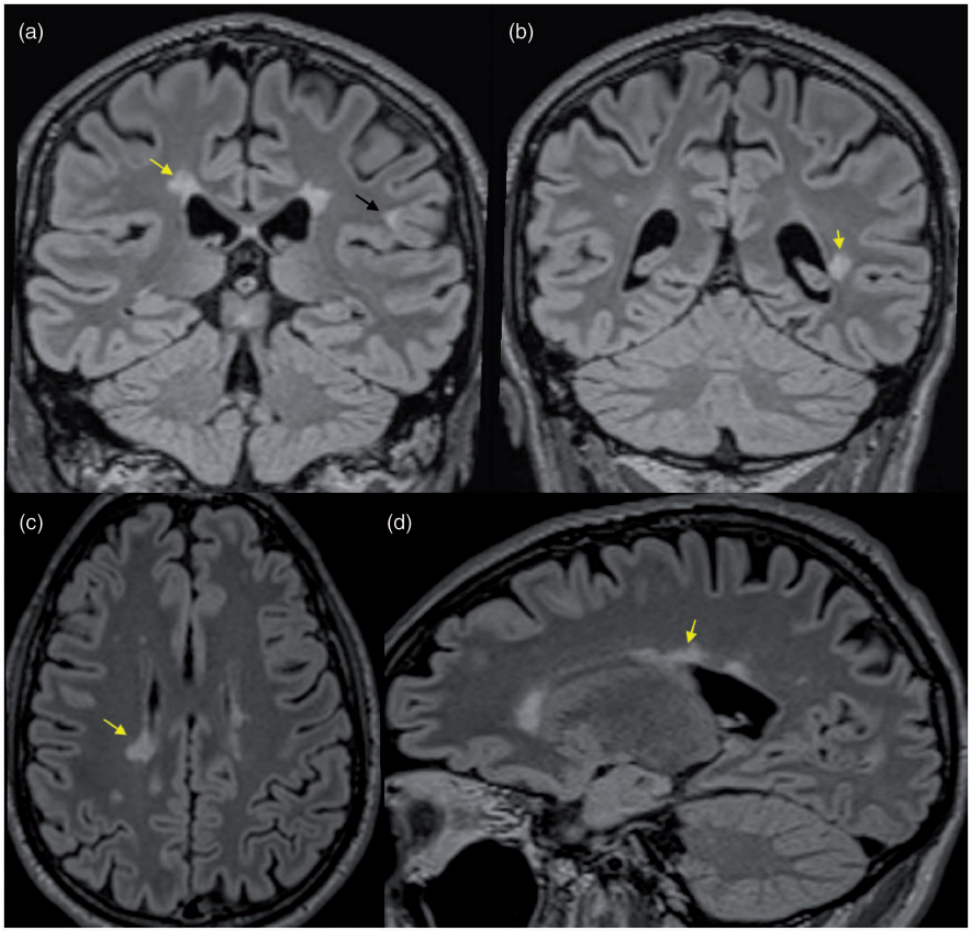

Figure 1. Brain MRI performed in 2014 showing typical multiple sclerosis lesions: a) coronal fluid-attenuated inversion recovery (FLAIR) weighted bilateral periventricular lesions (yellow arrow); b) coronal FLAIR weighted left periventricular lesion (yellow arrow) and juxtacortical lesion (black arrow); c) axial FLAIR weighted, periventricular lesions (yellow arrow); and d) sagittal FLAIR weighted corpus callosum lesions (yellow arrow).

In 2016, he stopped taking efavirenz because of intolerance. Elvitegravir and cobicistat were added to his regimen. In 2017, he was diagnosed with ulcerative colitis following recurrent episodes of rectorrhagia. Rectal mesalazine was started and improved his symptoms.

From 2009 to 2020 his CD4+ lymphocyte counts remained around 700 cells/mm^3.

Discussion

The lower incidence of MS in HIV patients was first observed by Gold et al.[2] They found a rate ratio of 0.38 for MS incidence among HIV patients compared with HIV-negative individuals. However, they did not investigate HAART or CD4+ cell counts, which could have been useful in understanding the underlying mechanism.

HIV infection may induce aberrant immune responses that simulate a MS-like syndrome.[8] It is possible that primary HIV infection, in the window period, was the cause of the initial manifestations in our patient. However, further relapses, characteristic MRI lesions, and a family history of MS makes this possibility unlikely.

The patient studied here had active RRMS and four relapses over 4 years in the absence of any disease-modifying drugs. He had several risk factors for aggressive MS: male sex, short intervals between relapses (two within 2 months), and characteristic brainstem symptoms during one relapse. However, he has not developed any new relapses since he was diagnosed with HIV and corresponding CD4+ cell lymphopenia. HAART was initiated 3 years after his diagnosis and he did not experience any relapses during this period either. This implies that factors apart from HAART may have influenced the clinical course of MS in this patient. CD4+ lymphocyte counts were lowest at the time of HIV diagnosis prior to HAART (around 250 cells/mm^3). Thus, the absence of relapses throughout this period might be related with the patient's progressive immunosuppression. Koudriavtseva et al. studied CD4+ lymphocyte counts in treated and untreated HIV and MS patients. They concluded that immunosuppression, with low CD4+ cell counts, was the determinant of the benign course of MS in HIV patients.[4] This conclusion agrees with the results of other case reports of patients in whom MS diagnosis was made concurrently with HIV diagnosis or in the first year after HIV diagnosis, when CD4+ cell counts were within the normal range.[3,9,10]

Between 2009 and 2020, our patient's CD4+ lymphocyte counts remained in the normal range without any new relapses or increases in disability (Figure 2). Between 2014 and 2020, MRI showed no new lesions. Thus, NEDA status was achieved and maintained after starting HAART despite recovery of CD4+ cell counts. Immunosuppression can no longer be expected to modify MS course during this phase, leaving HAART itself as a possible explanation. Furthermore, resurgence of autoimmune diseases following HAART initiation, as exemplified by the development of ulcerative colitis in our patient,

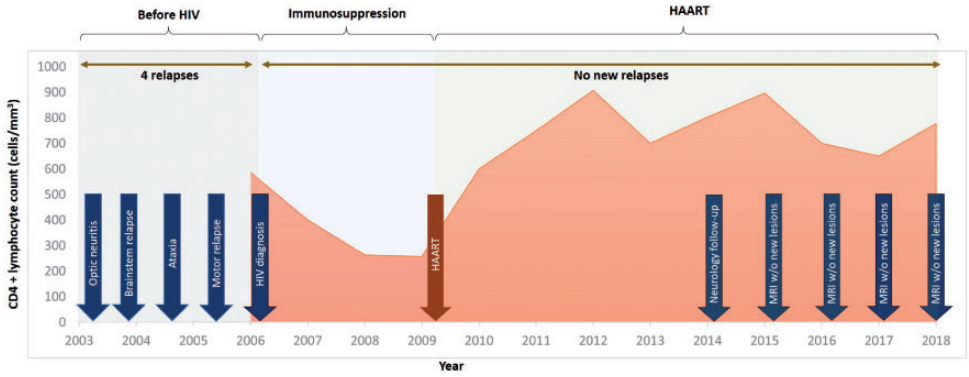

Figure 2. Chronology of the relapses suffered by our patient and CD4+ lymphocyte counts from the time he was diagnosed with HIV. HAART initiation, resumption of neurology follow-up, and timing of brain MRI are shown. The periods encompassed by the two mechanism explaining the absence of relapses (immunosuppression and HAART) are delimited within the timeline.
HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; w/o, without.

also suggests that immunosuppression was an unlikely mechanism at this stage.[11]

Maruszak and Chalkley described the clinical courses of patients with active MS and HIV infection in whom remission from relapse was achieved after HAART initiation.[3,12] In support of the HAART hypothesis, Morandi et al. recently observed that MS patients had higher HERV expression than HIV-infected individuals and healthy controls. Administration of efavirenz alone or an antiretroviral combination diminished HERV expression *in vitro*.[5] Hence, HERV inhibition by HAART may have been one factor involved in the favorable evolution of MS in our patient. Based on this theory, there has been an unsuccessful attempt to treat HIV-negative patients with active MS using raltegravir.[13] However, the short period of treatment (3 months) as well as the use of monotherapy rather than combinations of antiretrovirals might explain the limited efficacy.

MS remission after HAART initiation could also be related to inhibition of EBV replication by some antiretroviral drugs such as lamivudine, zidovudine, and tenofovir.[6,7] EBV seropositivity is strongly associated with MS onset.[14,15] Therefore, because our patient maintained tenofovir use throughout antiretroviral therapy, EBV inhibition itself, irrespective of inhibition of subsequent HERV expression, might be a potential mechanism explaining his benign MS course.

Immunosuppression and HAART have been previously proposed as hypothetical mechanisms through which HIV infection modulates MS. However, ours is the first case report to demonstrate that both mechanisms can apply in the same patient. In contrast with most reports wherein HIV infection usually precedes MS diagnosis,[3,9,10] our case was diagnosed with MS before HIV. This fact, along with the absence of disease-modifying drug administration, allowed us to analyze MS course before and after HIV infection in the absence of other interfering factors.

New research is studying longer treatment of MS patients with combinations of antiretroviral drugs with different mechanisms of action. In these studies, analysis of clinical response according to EBV and HERV status may be enlightening. These analyses may help to identify MS patients who could benefit from these therapies. Eventually, customized treatment strategies could be designed based on EBV and HERV status.

Conclusion

In the patient presented here, HIV infection and HAART modulated MS clinical course. Immunosuppression and HAART may play key roles in modifying MS at different stages. Further studies are needed to understand these relationships.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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