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Case Report

Progressive tumefactive inflammatory central nervous system demyelinating disease in an acquired immunodeficiency syndrome patient treated with highly active antiretroviral therapy

Eric Lindzen,[1] Valerie Jewells,[2] Thomas Bouldin,[3] Danielle Speer,[1] Walter Royal III,[4] and Silva Markovic-Plese[1,5]

Departments of [1]Neurology, [2]Radiology, [3]Pathology, and [5]Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; and [4]Department of Neurology, University of Maryland, Batlimore, Maryland, USA

We report here a case of progressive tumefactive inflammatory central nervous system (CNS) demyelinating disease in a human immunodeficiency virus (HIV)-seropositive patient treated with highly active antiretroviral therapy (HAART). Biopsy revealed diffuse macrophage and perivascular T-lymphocytic infiltrates with severe demyelination and relative axonal sparing. The disease progressed in a centrifugal fashion, to involve bihemispheric cerebral white matter, with subsequent central necrotic changes and atrophy. Treatment with HAART was discontinued, and inflammatory disease was treated with subcutaneous interferon (IFN)β-1a. Massive brain edema was controlled with courses of intravenous corticosteroids. Following fulminant monophasic disease, the patient stabilized with no evidence of disease progression over long-term follow up. We propose that immune response reconstituted by HAART can unmask an autoimmune response in susceptible individuals, analogous to the enhanced immune response to the preexisting acquired immunodeficiency syndrome (AIDS) opportunistic infections. Therapeutic options are considered. *Journal of NeuroVirology* (2008) **14,** 569–573.

Introduction

As the number of acquired immunodeficiency syndrome (AIDS) patients treated with effective highly active antiretroviral therapy (HAART) increases, evidence is accumulating for the occurrence of immune reconstitution inflammatory syndrome (IRIS), characterized by clinical worsening in the setting of therapeutically induced immune reconstitution (DeSimone *et al,* 2000). The improved immune response leads to an enhanced host response against preexisting opportunistic infections (Gray *et al,* 2003). Paradoxically, in cenral nervous system (CNS) IRIS, the enhanced immune response may lead to a life-threatening worsening of neurological disease (Venkataramana *et al,* 2006). Typically, CNS IRIS occurs within the context of cryptococcal meningitis (Cattelan *et al,* 2004), progressive multifocal leukoencephalopathy (PML; Cinque *et al,* 2001), or human immunodeficiency virus (HIV)-associated AIDS dementia (Langford *et al,* 2002). Although IRIS is still not well defined, there are several predictive factors, including no prior treatment with HAART, a significant drop in the plasma viral load, an increase in the CD4+ count (of >50 cells/μl), and the initiation of HAART within 30 days of diagnosis of an opportunistic infection (Shelburne *et al,* 2005). However, it has been reported that IRIS can occur up to 2 years following the initiation of HAART (Shelburne *et al,* 2005). Recent studies have reported that HAART-treated AIDS patients with CD4+ counts >200 cells/μl more frequently develop extensive focal white

Address correspondence to Silva Markovic-Plese, MD, University of North Carolina at Chapel Hill, 6109 Neurosceince Research Building, 105 Mason Farm Road, Chapel Hill, NC 27599, USA. E-mail: markovics@neurology.unc.edu

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matter lesions in comparison to untreated patients, and a higher incidence of leukoencephalopathy not associated with specific opportunistic infection (Ammassari *et al,* 2000). We report here the first case of progressive tumefactive inflammatory demyelinating CNS disease in a HAART-treated patient with AIDS. We propose that HAART can unmask an autoimmune response in susceptible individuals (Price *et al,* 2002) in response to a significant self-antigen release, analogous to the enhanced immune response to the preexisting opportunistic infections.

Case report

An asymptomatic 36-year-old African American female tested HIV-positive with a CD4+ cell count of 357 cells/μl and a HIV viral load of 1400 copies/μl. Although the CD4 count remained stable, treatment with HAART was initiated after 3 years, following treatment of *Pneumocystis carinii* pneumonia. An increase in CD4+ cell number to 441 cells/μl was detected following HAART initiation. Two years later, while maintaining CD4 counts at 300 to 400 cells/μl, she developed an optic neuritis (ON) that spontaneously resolved. A second episode of contralateral ON occurred 2 years later, and HAART was held as patient maintained CD4+ cell count of $>$ 300/μl. Four months after the ON, the patient experienced a subacute onset of right-sided weakness and a visual field cut, accompanied by an additional transient episode of right monocular visual loss precipitated by heat. A brain magnetic resonance imaging (MRI) scan revealed a left temporoparietal tumefactive lesion with an irregular T2-hyperintense rim and a central hypointense, necrotic area (Figure 1A) with contrast enhancement at the posterior lesion margin (Figure 1E). Cerbrospinal fluid (CSF) studies revealed 13 nucleated cells/μl, a protein level of 2080 mg/dl, no malignant cells, negative polymerase chain reaction (PCR) studies, and cultures for viral, fungal, and bacterial opportunistic infections. The differential diagnosis included an infiltrating glioma, primary CNS lymphoma, PML, and other opportunistic infections, justifying a sterotactic biopsy of the enhancing portion of the lesion. Histopathological examination revealed diffuse macrophage and perivascular T-lymphocytic infiltrates (Figure 2A, B). Near-complete loss of myelin (Figure 2C) and relative axonal sparing (Figure 2D) were present within this well-demarcated lesion, with a reactive astrocytosis in the surrounding areas. Immunostaining for T cells (CD3) and B cells (CD20) revealed that the infiltrating lymphocytes were mainly T cells. Detailed pathological examination revealed no evidence of PML, toxoplasmosis, lymphoma, or malignant astrocytoma. Because the patient's CD4+ count remained above 300/μl, HAART was discontinued. The patient continued to experience worsening of her right-sided motor deficit, loss of sensation, followed by the acute onset of expressive aphasia. On examination 1 month after the biopsy, she was disoriented, with right-sided hemiplegia, hyperreflexia, hemisensory deficit for all modalities, global aphasia, left eyelid ptosis, and a right central facial palsy. An magnetic resonance imaging (MRI) scan at that time revealed an interval increase in the size of the left temporoparietal lesion, with new appearance of mass effect and a midline shift (Figure 1B). Additional signal abnormalities were detected in the left frontal lobe, left cerebellar peduncle, and midbrain, possibly related to the wallerian degeneration of fibers passing through the left temporoparietal lesion. Small hyperintense T2 and fluid attenuated inversion recovery (FLAIR) lesions were detected in subcortical areas and centrum semiovale of the contralateral hemisphere. More prominent contrast enhancement was detected along the anterior and posterior lesion margin (Figure 1F). A course of intravenous corticosteroids led to improvement in mental status and the regained right leg strength, allowing the patient to ambulate without assistance.

Immunomodulatory therapy with high-dose interferon (IFN)β-1a led to the stabilization of clinical progression and imaging studies over the following 4 months. However, the patient then experienced a progressive left arm weakness that culminated after 5 months in paraplegia, bilateral blindness, and acute mental status change. An MRI at that time revealed dramatic extension of the inflammatory changes to the left frontal lobe. The previously noted inflammatory changes in the left temporoparietal and occipital lobes had now progressed to encephalomalacia. The progression of the enhancing changes and the extent of T2-weighted signal abnormalities revealed a pattern consistent with a spreading ''front'' of demyelination in the left hemisphere. There was a new involvement of the corpus callosum, as well as the right frontal, parietal, and occipital lobes (Figure 1C). The newly detected signal abnormalities in the left frontal lobe and the right hemisphere enhanced with contrast (Figure 1G). In contrast to the prior scan, which had shown midline shift to the right, there was now a midline shift to the left due to massive edema surrounding the right hemispheric lesions and the contralateral encephalomalacic changes. A course of intravenous corticosteroids resulted in the improvement of patient's mental status, but the remaining neurological deficits persisted. Immunomodulatory therapy was discontinued. Subsequently, the patient's CD4+ count dropped for the first time below 200 (137 cells/μl). HAART was then resumed, and over the subsequent 3 years, the patient maintained CD4+ cell counts above 400 cells/μl, without evidence of progression of the disease. The recent MRI scan revealed focal encephalomalacia corresponding to

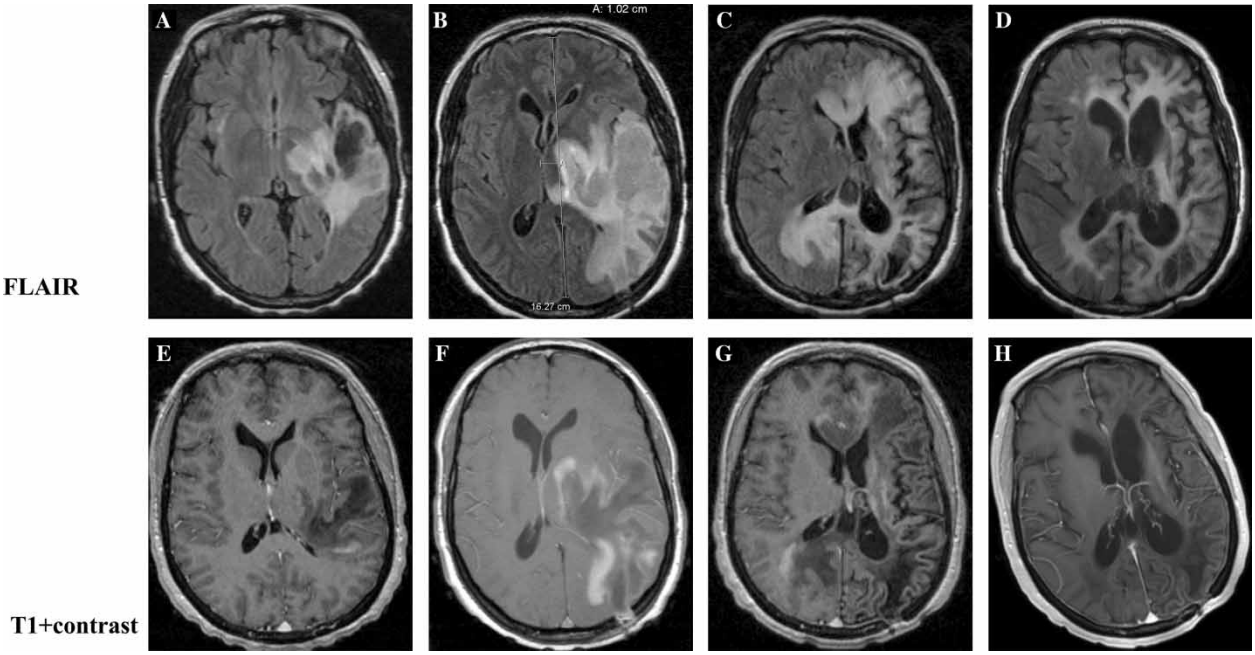

Figure 1 Serial MRI scans of tumefactive inflammatory CNS demyelinating disease in an AIDS patient treated with HAART. (**A**) Initial FLAIR MRI scan obtained 1 month after neurological symptom onset showed an infiltrative appearing lesion with irregular hyperintensity and a central hypointense region. Contrast enhancement was detected at the posterior lesion rim (**E**). (**B**) Follow-up FLAIR MRI scan 5 months after the symptom onset showed enlargement of the lesion with mass effect and a midline shift. Areas of abnormal contrast enhancement were noted at the periphery of the new lesions (**F**). (**C**) A third scan at the time of clinical worsening showed a significant interval enlargement of the lesions with extension of the previously noted signal abnormalities through the corpus callosum and involvement of the right hemisphere. The left frontal lobe demonstrated new signal abnormalities. Encephalomalacia was noted within the left temporal, parietal, and occipital lobes. Areas of irregular contrast enhancement were noted at the periphery of the new lesions (**G**). (**D**) Most recent imaging study, 36 months following symptom onset, showed stable white matter changes and atrophy, with no contrast enhancement (**H**).

the regions of previous inflammatory changes and extensive atrophy of the left cerebral hemisphere. T2-hyperintense abnormalities in the right frontal, parietal, and occipital lobe persisted without contrast enhancement (Figure 1D, H).

Discussion

Studies performed during the pre-HAART era have reported on the occurrence of neurological disorders consistent with multiple sclerosis (MS) (Berger *et al,* 1989; Berger *et al,* 1992) or acute disseminated encephalomyelitis (Allen *et al,* 2002) in immunocompetent AIDS patients. We present here the first case of a progressive *tumefactive* inflammatory demyelinating CNS disease consistent with the Marburg variant of MS in a patient with AIDS.

Whether the MS occurred as a consequence of IRIS is debatable, given that our patient had been on antiretroviral therapy for 2 years. In support of this possibility, Shelbourne *et al* (2005) have reported that IRIS developed up to 658 days following the initiation of HAART. Although IRIS typically develops in the context of occult opportunistic infections (Riedel *et al,* 2006), including PML (Vendrely *et al*, 2005), cytomegalovirus (CMV) encephalitis, CNS cryptococcal and mycobacterial infections, HIV encephalitis (Gray *et al,* 2005), or parasitic infections (Lawn and Wilkinson, 2006), it is possible that in patients with a genetic predisposition towards an autoimmune response (Sospedra and Martin, 2005), an inflammatory demyelinating disease may occur in the CNS secondary to a significant release of self-antigens, even in the absence of an infectious process. Our patient's clinical, pathological, and imaging findings indicated a fulminant inflammatory demyelinating disease consistent with the Marburg variant of MS. It is conceivable that the strong inflammatory response is associated with the reconstituted immune response, as documented by the increased CD4+ counts following HAART initiation. However, because our patient's neurological presentation was remotely related to the onset of HAART, which induced only a modest increase in CD4+ cell count, an alternative explanation would be that this case represents a coexisting fulminant inflammatory demyelinating disease and AIDS. Furthermore, when the HAART was restarted at a CD4+ count of 137 cells/μl, after stabilization of the neurological deficit, there was no evidence of IRIS or further neurological disease.

The differential diagnosis of demyelinating disease in an HIV-positive patient also includes PML. However, multiple negative PCR studies for JC virus

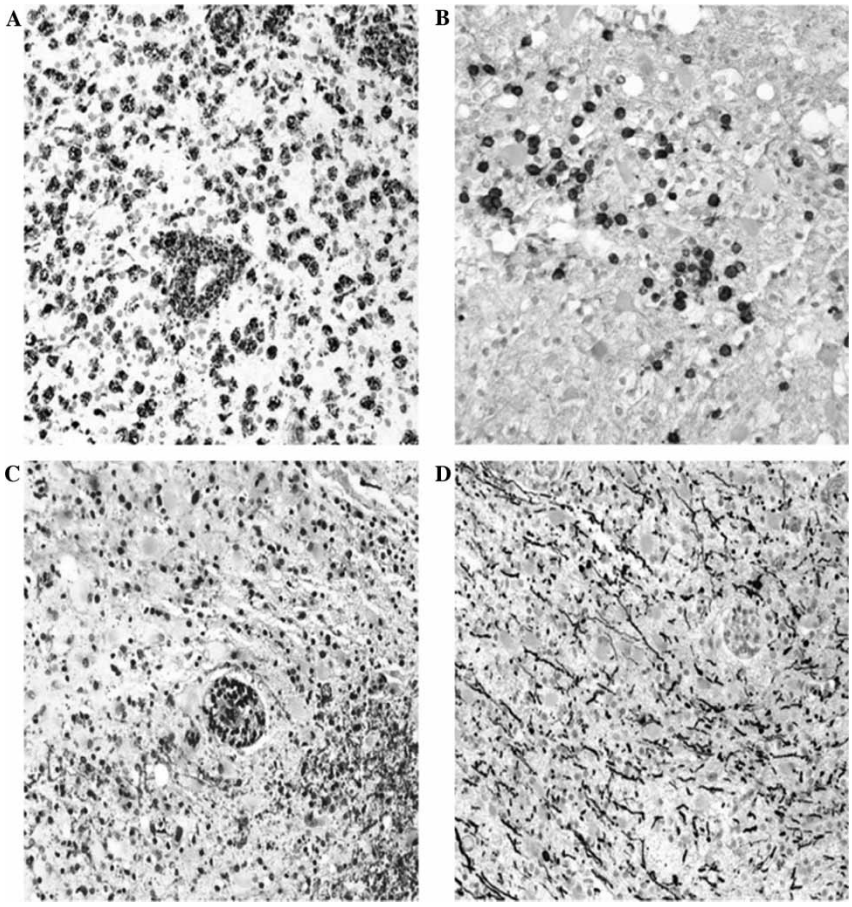

Figure 2 Histopathological studies reveal an inflammatory demyelinating disease. (**A**) CD68 immunohistochemical staining for macrophages revealed a diffuse white matter infiltration. (**B**) Immunohistochemical staining for T lymphocytes revealed numerous T lymphocytes around blood vessels and within brain parenchyma. Perivascular lymphocytic infiltrate is composed predominantly of T cells. (**C**) Luxol fast blue myelin staining detected only a small amount of remaining myelin in the right lower quadrant of the slide. (**D**) Immunohistochemical staining for neurofilament protein showed preserved axons coursing through the demyelinated cerebral white matter.

in both CSF and biopsy material, CD4+ counts above those usually seen in PML, the plateau of clinical progression, the pattern of centrifugal spread, and the lack of pathologic features of PML, such as bizarre astrocytes and viral inclusions within oligodendrocites, militated against this diagnosis in our patient. After the diagnosis of inflammatory demyelinating disease was confirmed and opportunistic infections were excluded, we initiated treatment with intravenous corticosteroids and IFNβ-1a immunomodulatory therapy.

Treatment of HIV positive patients with coexisting inflammatory disease is challenging, due to the implications of using immunosuppressive medications in the context of preexisting immune dysfunction. The resolution of an inflammatory demyelinating process after discontinuation of HAART can be observed with IRIS, but may also be seen in cases of MS-like illness in the context of HIV infection. The patient's improvement was possibly further hastened by IFNβ-1a. Although there was a temporary stabilization of disease progression with intravenous (IV) cortcosteroid therapy as well as with IFNβ-1a, the patient subsequently experienced clinical progression, with imaging evidence of significant extension of the inflammatory demyelinating process. The lesions extended in a centrifugal fashion and led to extensive bihemispheric brain involvement and subsequent atrophy.

Because HAART therapy has been suspected as a trigger of this aggressive inflammatory demyelinating disease, the decision to hold HAART was made in the context of stable CD4+ cell counts (>350 cells/μl), while immunomodulatory treatment was initiated in response to the fulminant exacerbation of her demyelinating disease. In fact, the recommendations for the AIDS treatment indicate HAART therapy for asymptomatic seropositive patients only with CD4+ cell count below 350 cels/μl (Hammer *et al,* 2006). With the exception of CNS tuberculosis, CNS opportunistic infections occur in the context of lower CD4+ counts. Multiple studies have addressed the optimal time for the initiation of HAART (Hammer, 2005), and it is conceivable that

delaying HAART may less dramatically enhance the immune response. Other treatment considerations include the use of intravenous corticosteroids for the control of life-threatening mass effect within the brain, which may provide, as in our case, short-term improvement (Venkataramana *et al,* 2006).

In conclusion, our study reports the first case of a progressive tumefactive CNS inflammatory demyelinating disease in an AIDS patient, possibly related to HAART. Therapeutic interventions included a discontinuation of HAART, the use of intravenous corticosteroids to control brain edema, and the use of IFNβ immunomodulatory therapy for suppression of the chronic inflammatory response. Further studies are required to elucidate etiologic factors and to provide definitive treatment recommendations for 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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