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Case Report Open Access

Neurological Deterioration in a PML-HIV Patient in the Absence of Immune Reconstitution Inflammatory Syndrome

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Abstract

Following the initiation of HIV treatment AIDS patients with progressive multifocal leukoencephalopathy (PML) may clinically worsen because of either: 1) Immune Reconstitution Inflammatory Syndrome (IRIS) which is supported by marked deterioration of their MRI findings or 2) progressive JC virus (JCV) CNS infection, often characterized by stable or minimally changed MRI findings. We present a 35-year-old PML-HIV patient with neurological deterioration and death despite early and successful highly active antiretroviral therapy (HAART), in the absence of IRIS. We hypothesize that HIV induced irreversible depletion of T-cells leading to an inability to mount an effective response to the JCV infection.

Keywords: Viral infection; Molecular microbiology; Immune reconstitution; HIV infection; Central nervous system infection

Introduction

Progressive multifocal leukoencephalopathy (PML) is a CNS demyelinating disease secondary to JC virus (JCV), a member of the polyomavirus family. JCV infects oligodendrocytes causing intranuclear viral inclusions and lysis with subsequent demyelination. JCV also infects astrocytes, but in this case does not cause cell lysis. PML occurs in the setting of immune compromise or immunomodulatory drugs, such as Natalizumab. AIDS accounts for 55%-85% of all PML cases. Classically the presenting symptoms are sub-acute onset of focal neurological symptoms, typically hemiparesis, visual field deficits and cognitive dysfunction. Antiretroviral therapy (ART) is the most effective therapy available, prolonging survival and decreasing neurological deficits when immune reconstitution is achieved. However, patients may initially deteriorate neurologically despite ART therapy due to the immune reconstitution inflammatory syndrome (IRIS). Our case provides clinical, radiologic and histopathologic evidence of progressive JCV infection in an HIV patient. Highly active antiretroviral therapy (HAART) resulted in complete control of the HIV infection but T cell counts and function failed to recover. Failure to show early immune reconstitution is a poor prognostic sign in PML until effective treatment for JCV infection is identified.

Case Report

A 35 year old male with a past medical history of multi-substance abuse, depression, treated syphilis, gonorrhea and HIV (diagnosed 10 days prior) presented with 4 months of progressive ataxia, dysarthria, left facial numbness, headaches and blurred vision. Physical exam illustrated diffuse hyperreflexia, abnormal cerebellar signs and oculomotor findings, which included: a brief ocular flutter on fixation, saccadic horizontal pursuit, bilateral horizontal gaze paretic nystagmus and upbeat nystagmus in up gaze. In addition, he had right ocular lateropulsion (Video 1) and diplopia due to skew deviation in left lateral gaze. MRI on admission showed increased white matter signal intensity in T2 and FLAIR scans, compatible with demyelination and gliosis predominantly involving the left pons, middle/inferior cerebellar peduncles and cerebellum (Figure 1).

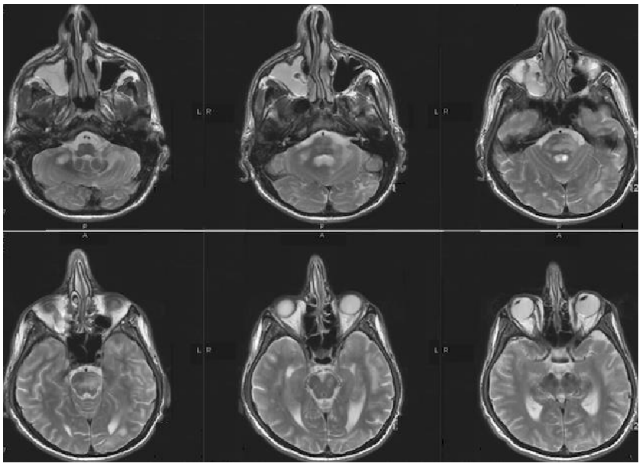

Figure 1: Serial Axial: T2 and FLAIR MRI scans. Increased signal is noted primarily in the left pons, middle and inferior peduncles and cerebellum.

It also involved the left temporo-parieto- occipital lobes. Mild mass effect was noted along with several discrete non-enhancing frontoparietal white matter nodules. There was no evidence of active

breakdown of the blood brain barrier. At baseline JCV DNA quantitative PCR showed 797 copies of the JCV (normal reference range <500) and the patient was started on highly active antiretroviral treatment (ART): emtricitabine/tenofovir/efavirenz single dose combination medication. Throughout the admission the patient developed suicidal ideations and neurological function deterioration. Rapid plasma reagin with an elevated titer of 1:32, but CSF VDRL was nonreactive, thus ruling out neurosyphilis. The patient was started on mefloquine due to suspicion of IRIS with an improved $CD4^+$ count and elevated JCV quantitative count in the CSF. Over the course of the next four months the patient was frequently re-admitted and his neurological function slowly deteriorated, despite compliance with ART and undetectable HIV virus count. Last lumbar puncture performed showed an increase in JC viral load to 5124, HIV quantitative PCR detected less than 48 copies/mL, and $CD4^+$ 78 / mm^3. Throughout these re-admissions features included worsening ataxia, weakness progressing to right hemiparesis, worsening dysarthria and increasing nystagmus (R gaze>L gaze). Mirtazapine was started and mefloquine was discontinued due to lack of improvement. Serial brain MRIs remained stable with minor changes throughout, until close to the time of death when it showed interval increase in abnormal signal involving the left thalamus, dentate nuclei and eventually left posterior limb of the internal capsule. Mild cerebral and cerebellar atrophy were present.

Brain necropsy was performed. Patchy areas of discoloration and softening were noted grossly throughout the brain, but most severe in the cerebellum (Figure 2a) and brainstem. Histologically, these areas showed demyelination as evidenced by loss of staining with the myelin stain Luxol-fast blue (Figure 2b). Viral nuclear inclusions were seen in some oligodendrocytes (Figure 2c), and in situ hybridization for the JC virus was positive in many cells (Figure 2d). Extensive gliosis, macrophage infiltration, foci of necrosis, and many astrocytes with giant bizarre nuclei were also observed. Notably, however, there was a paucity of lymphocytic infiltrates.

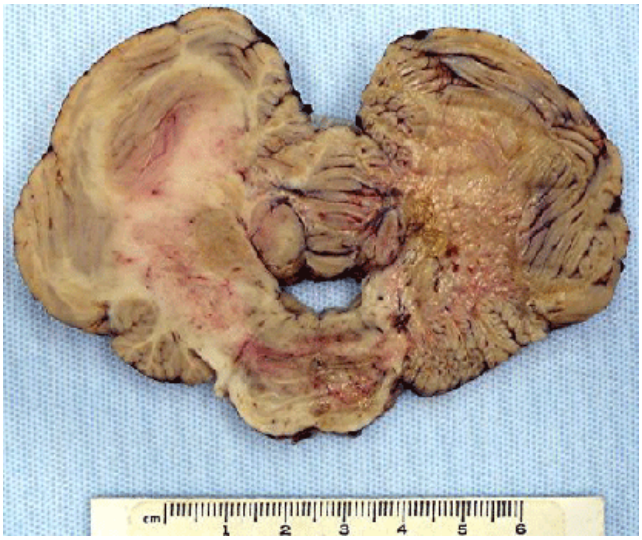

Figure 2a: Gross examination reveals patchy areas of discoloration and softening throughout the brain, including in the cerebellum.

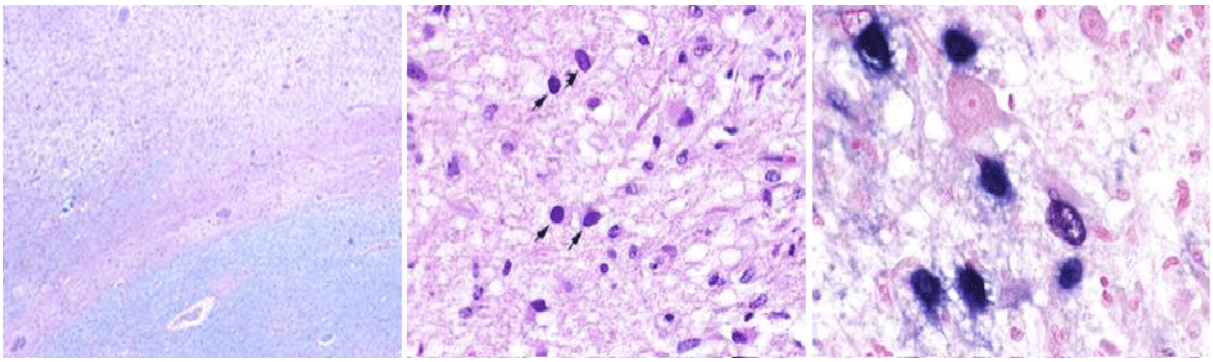

Figure 2: (b) Luxol fast blue stain for myelin highlights an area of demyelination (loss of blue staining). (c)High-power H&E-stained section of the medulla shows intranuclear viral inclusions in some oligodendrocytes (arrows). (d) In situ hybridization for the JC virus is positive (dark blue staining).

Discussion

The prevalence of JCV antibodies in the general population is 66-92% [1], however, the incidence of PML in patients with AIDS is about 5% [3]. Tonsillar stromal cells and B-lymphocytes are theorized as sites of JCV latency with primary infection occurring in childhood. B- lymphocytes may allow for viral circulation to the brain and kidney epithelial cells [1]. HIV not only affects the immune system but also has significant effects on the local cellular environment: a) changes in immune cell trafficking b) blood-brain barrier (BBB) permeability c) cytokine secretion [2] d) secretion of HIV-1 transactivator protein (Tat) which may stimulate JCV transcription and replication [2]. JCV can be present in the brain of non-PML healthy individuals. In these cases the virus was not replicating as supported by the lack of expression of VP1 protein [1].

Controlled studies have been unable to prove that drugs such as cidofovir (CDV), cytosine arabinoside (Ara-C), and mefloquine, are consistently efficacious in the treatment of PML [2]. However, early restoration of the immune system is important to control JCV replication, as supported by poor prognosis in patients with low T cell counts and high copy numbers of CSF JCV DNA at diagnosis. Also, it has been shown that CD4-ATP concentration, a marker of T-cell function, inversely correlates with risk of JCV infections in immunocompromised patients [3]. Early use of antiretroviral therapy

improves survival, but this is complicated by the development of IRIS. IRIS presents as paradoxical neurologic deterioration in the setting of immune reconstitution. IRIS can develop simultaneously with PML or after the initiation of antiretroviral therapy. PML-IRIS develops in up to18% of HIV patients with PML. In IRIS typical lesions enhance with contrast due to breakdown of the blood brain barrier and are associated with significant mass effect. Histopathology demonstrates severe inflammatory and demyelinating lesions with CD8-positive T lymphocyte and macrophage infiltration [3].

Neurologic deterioration in PML patients in the context of HIV infection therefore may be due to progressive PML despite successful treatment of the HIV infection or be the result of IRIS. MRI monitoring may define the specific cause for the worsening clinical picture. In the case of IRIS, timely steroid therapy may induce neurologic recovery. Our case showed MRI stable lesions and minimal histopathologic evidence for acute inflammation, in contrast to known pronounced inflammation in previous reports of PML IRIS.

Conclusion

The case described herein has multiple interesting aspects. First, HAART therapy resulted in decreased HIV virus levels, without corresponding improvement in immune function as measured by serial T-cell counts. In addition, our patient's clinical deterioration was not associated with evidence of increased white matter disease or destruction on serial MRI scans of the brain. Furthermore, at autopsy, minimal CNS inflammation was noted histopathologically. Despite the introduction of antiretroviral therapy, which has led to a substantial decrease in opportunistic infections in HIV infected patients, the incidence of PML, a disease that carries high mortality, decreased as much as would be expected. Better familiarity with the features specific to CNS disease progression as opposed to IRIS progression in PML patients could aid in earlier detection of the cause of neurological deterioration in these patients and earlier start of appropriate management. This would be particularly relevant when effective anti-JCV infection treatment becomes available.

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