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A game of viral hide and seek: miliary PML masquerading as EBV encephalitis in an HIV+ patient

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INTRODUCTION

Primary CNS lymphoma (PCNSL) occurring in the setting of HIV disease is always associated with Epstein-Barr virus (EBV). However, the presence of EBV DNA in the cerebrospinal fluid without CNS mass lesion does not necessarily indicate the presence of PCNSL or EBV-encephalitis (1). We present the case of an AIDS patient initially treated for EBV-encephalitis who was finally diagnosed with a miliary form of progressive multifocal leukoencephalopathy (PML).

CASE REPORT

A 37-year-old man, with a 14 year history of HIV infection complicated by herpes zoster and CMV retinitis in the context of poor medication adherence, presented with a six week history of frontotemporal headaches and personality changes. Neurologic examination revealed flat affect, impulsive behavior, attention deficit and mild bilateral appendicular ataxia. Brain MRI showed subtle hyperintensity on FLAIR around the frontal and occipital

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COMPETING INTERESTS

None

CONTRIBUTORSHIP

Dr Sarah Gheuens was involved in reviewing the files, doing the immunological assays, preparing the manuscript and figure. Dr Brian Buggy was involved in patient care, preparing and reviewing the manuscript, Dr Wieslawa Tlomak was involved in the autopsy, pathological and histological examination, and reviewing the manuscript, Dr Christian Wuthrich was involved in the histological examination and preparing the figure, Dr Igor Koralnik was involved in reviewing the files, preparing the manuscript and figure.

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horns and bilateral centrum semiovale, consistent with HIV encephalopathy (Figure, A). These were new findings compared to an MRI performed 5 years prior as part of a headache work-up. Following the administration of gadolinium, there were approximately 75 punctate areas of focal enhancement measuring 1–3 mm in T1-weighted images within the deep white matter of bilateral frontal, temporal, parietal and occipital lobes (Figure, B). Single lesions were also present in the left pons and right cerebellum.

CT of the brain, chest and abdomen and electroencephalogram were normal. CD4⁺ count was 129/uL (21%) and plasma HIV viral load (VL) was 1863 copies/ml. Serological testing revealed past exposure to cytomegalovirus (CMV), EBV and Toxoplasma gondii. Peripheral blood flow cytometry showed no malignant cells. Cerebrospinal fluid (CSF) exam showed 0 red blood cells (RBC)/uL, 26 white blood cells (WBC)/uL with 93% lymphocytes and 7% monocytes. Total protein and glucose were 54 mg/dl and 48 mg/dl respectively. Lactate dehydrogenase (LDH) was 162 units/L. A qualitative polymerase chain reaction (PCR) for EBV DNA was positive in serum and CSF. Bacterial, fungal and acid-fast cultures, CSF PCR for JC virus (JCV) (Focus Diagnostics, Cypress, CA), Toxoplasma gondii, CMV, Herpes simplex (HSV) and Varicella zoster virus (VZV) DNA were negative. CSF VDRL was non-reactive and cytology revealed no abnormal cells. CSF HIV VL was not measured.

Left frontal brain biopsy revealed only mild gliosis with no perivascular lymphocytic infiltrate. There was sparse detection of CD45⁺, CD3⁺, CD20⁺ lymphocytes in the parenchyma. Brain tissue was positive by qualitative PCR for EBV DNA and negative for Toxoplasma, CMV, HSV and VZV DNA. PCR for HIV and JCV were not performed.

The patient was discharged home. Over the next nine months, HIV plasma VL became undetectable and CD4⁺ T-cell count increased to 325/uL (24%) on combined antiretroviral treatment (cART) with tenofovir, emtricitabine, fosamprenavir and ritonavir. EBV DNA was intermittently detected by serum PCR at low levels, but quantitative PCR performed nine months after his initial presentation showed 86,300 copies/ml (log 4.90). Repeat MRI showed an increase of hyperintense lesions on FLAIR (Figure, C) and an increased number of enhancing lesions to >100 (Figure, D).

He was hospitalized and treated with intravenous foscarnet 60 mg/kg TID for seven days for presumed EBV encephalitis. Serum EBV PCR was positive, but CSF PCR for EBV, CMV, and Human herpesvirus 6 (HHV-6) DNA were negative. He was given prednisone 0.6 mg/kg daily. However, he became more lethargic and this treatment was discontinued. Repeat MRI showed persistence of numerous punctate enhancing lesions in the white matter of both hemispheres. CSF exam showed 4 WBC/uL, but JCV PCR was positive for the first time at 10,578 copies/ml. The patient gave written consent according to our institution's guidelines to participate in our ongoing immunological studies and he had a detectable JCV-specific T-cell response in his blood (2). Repeat biopsy of the left frontal lobe showed again gliosis with the presence of rare multinucleated cells together with scattered reactive astrocytes with glassy eosinophilic cytoplasm. A few blood vessels had perivascular lymphocytic infiltrate. There were no viral inclusions nor areas of demyelination. However, brain DNA was positive by qualitative PCR for JCV and EBV (Focus Diagnostics, Cypress, CA) as well as HIV (National Genetics Institute, Los Angeles, CA). The brain DNA was negative by PCR for Toxoplasma, CMV, HSV and HHV-6 (ARUP Laboratories, Salt Lake City, UT). The patient remained on the same cART regimen, but the neurological exam three months later showed continued worsening.

JCV-specific cellular immune response remained detectable in his blood. Repeat MRI 20 months after his initial presentation showed a further increase in enhancing lesions, mainly in the subfrontal regions and the posterior fossa. cART was continued throughout his course.

HIV plasma VL remained undetectable and CD4⁺ T-cell counts increased to 341/uL. Twenty-one months after the original presentation, the patient refused all food intake and died soon thereafter. An autopsy limited to his brain was performed.

On histological examination, there were numerous, small areas of softening and discoloration in the white matter, with some lesions closely located at the gray-white junction (Figure, E). These lesions were characterized by myelin loss, foamy macrophages and rare enlarged astrocytes with large, pleomorphic and bizarre nuclei. Luxol fast blue staining revealed foci of demyelination in the white matter of the cerebral hemispheres (Figure, F). CD8⁺ staining showed perivascular lymphocytes and lymphocytes around the lesions. Immunohistochemistry (IHC) staining was positive for JCV T-antigen (Figure, G), but not JCV VP1 capsid protein, indicating a restrictive, non-productive infection. IHC staining for HIV p24 antigen and EBV-encoded RNA (EBER) *in situ* Hybridization were negative. The final pathological diagnosis was of a miliary form of PML.

DISCUSSION

This patient originally presented with marked immune suppression. EBV infection was detected in the CSF first, while JCV infection was discovered subsequently. Patients who are severely immunosuppressed may be affected simultaneously by several opportunistic infections. However, detection of EBV DNA in CSF is suggestive of PCNSL in HIV⁺ patients presenting with mass lesions, but it is not a predictor of PCNSL (1). Indeed this patient had neither lymphomatous meningitis nor a tumoral lymphomatous infiltrate in his brain parenchyma. In addition, EBV DNA is increasingly found in CSF of patients with other CNS disease, and may not be pathogenic (3).

This case had unique radiological features. Serial MRIs indeed showed an increase in punctate enhancing lesions, concomitant to detection of JCV in CSF. This MRI pattern is highly unusual for classic PML, which is typically characterized by large confluent subcortical lesions, that do not enhance after contrast administration. However, the lesions of this case are very similar to a recently described case of PML in a natalizumab- treated multiple sclerosis patient (4). Conversely, enhancement in PML lesions is often seen in the setting of an immune reconstitution inflammatory syndrome (IRIS). This was likely the case in this patient, who had a marked decrease in HIV VL and increase in CD4⁺ T cell counts, indicating a recovery of the immune system after resuming cART. We can only postulate that this IRIS phenomenon was directed mainly against JCV, because JCV-specific T cells were detected in his blood on several occasions, and JCV was the only pathogen found in the CNS on postmortem exam. IRIS is further supported by the presence of T-cell infiltrates seen on the second biopsy and at autopsy, consistent with findings reported in other PML/IRIS cases (5). Interestingly, the first MRI already showed contrast enhancement. In light of the poor medication adherence of this patient, it is possible that he had episodes of waxing and waning immune reconstitution already from the start.

Although HIV replication was suppressed in the plasma, HIV was still readily detected in the second brain biopsy. This could be caused by limited penetration of antiretrovirals into the brain parenchyma. HIV RNA remained undetectable in plasma, and HIV was not detected in the brain in autopsy material, suggesting that cART was finally able to control HIV replication in all compartments. Despite improvement in immunological function and the presence of JCV-specific T-cell response (2), this patient continued to worsen and passed away 21 months after initial presentation.

CONCLUSION

Multiple pathogens can be found simultaneously in the CNS of severely immunosuppressed individuals, but may not be causing active disease. Although PML typically presents with subcortical confluent non-enhancing lesions, imaging can be atypical, especially in the setting of IRIS. The detection of JCV protein expression, documented on autopsy material taken from areas of contrast-enhancement, and the histological findings showing multifocal demyelination confirm that PML, and not EBV encephalitis, was the correct final diagnosis in this patient.

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Highlights

Many viruses can be present together in the brain of immunocompromised patients.

Unique enhancement pattern can be seen in the setting of PML-IRIS.

EBV can be present in the brain without causing disease.

Figure 1.

Figure (A–B) MRI sequences obtained 6 weeks after symptoms onset. FLAIR sequence (A) demonstrated hyperintensity around the frontal and occipital horns of the lateral ventricles. On T1-weighted images, there were several enhancing lesions (B). Repeat imaging 9 months later (C–D) showed an extension of hyperintense lesions on FLAIR (C) and increase in number of enhancing lesions on T-1 weighted-imaging post-gadolinium administration (D). (E) Coronal section of the brain showing multiple white matter lesions. The boxed area in (E) is shown in (F). (F) Immunostaining for JCV T antigen, with Luxol Fast Blue and Crystal Violet counterstaining, depicting multiple areas of demyelination at the gray-white matter junction (GWJ). A higher magnification of the boxed area in (F) is shown in (G), which demonstrates an enlarged astrocyte expressing JCV T antigen (magnified in insert). The size bars are 1mm (F) and 100 μ m (G). Abbreviations: FLAIR: fluid-attenuated inversion recovery, GWJ: gray-white junction, WM: white matter, GM: gray matter