CASE REPORT

Epstein-Barr virus encephalitis presenting with brain mass lesions in a patient with human immunodeficiency virus infection

António Martins[1], Cláudio Silva[1], Filipa Ceia[1], Francisco Moreira[2], Carina Reis[3], António Sarmento[1,4], Margarida Tavares[1,5]

[1]Department of Infectious Diseases, Centro Hospitalar Universitário de São João – Alameda Prof. Hernâni Monteiro, Porto, Portugal
[2]Department of Anatomic Pathology, Centro Hospitalar Universitário de São João – Alameda Prof. Hernâni Monteiro, Porto, Portugal
[3]Department of Neuroradiology, Centro Hospitalar Universitário de São João – Alameda Prof. Hernâni Monteiro, Porto, Portugal
[4]Nephrology and Infectious Diseases R&D, i3S – Instituto de Investigação e Inovação em Saúde da Universidade do Porto, Porto, Portugal
[5]EPI Unit – Instituto de Saúde Pública da Universidade de Porto, Porto, Portugal

Abstract

Epstein-Barr virus (EBV) disease of central nervous system (CNS) in human immunodeficiency virus (HIV) patients is mostly associated with primary CNS lymphoma (PCNSL). In patients who cannot undergo biopsy and have typical clinical and radiographic findings, detection of EBV deoxyribonucleic acid in CSF may provide enough evidence to start treatment for PCNSL. Here, we described a case of EBV encephalitis presenting with fever, memory, and psycho-motor deficits in a patient with HIV infection and severe immunosuppression who started antiretroviral therapy (ART) one month earlier. Brain magnetic resonance imaging showed periventricular lesions with nodular enhancing pattern and restricted diffusion, and CSF was positive for EBV. Brain biopsy revealed inflammatory lesions and lymphoid infiltrate without signs of malignancy. After three months of ART, patient improved significantly and MRI showed a marked reduction of lesions. Two years later, patient's condition remains stable. PCNSL is the leading diagnosis in HIV patients with CNS mass lesions and positive CSF for EBV. In the case described, starting treatment for PCNSL could have been considered if the patient could not undergo biopsy, or if there was no improvement under ART. However, EBV encephalitis can be a differential diagnosis in patients with compatible histopathology and clinical course.

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Introduction

In the context of human immunodeficiency virus (HIV)-associated immunosuppression, Epstein-Barr virus (EBV) is most commonly associated with central nervous system (CNS) lymphoma. Primary CNS lymphoma (PCNSL) is a well-recognized, almost exclusively EBV-driven neoplasm, affecting up to 10% of HIV-infected patients with acquired immunodeficiency syndrome (AIDS) [1]. EBV-CNS disease may also manifest as encephalitis that usually has no distinctive imaging features, and this fact makes differential diagnosis with CNS lymphomas unlikely. In this case report, we describe a rare case of EBV encephalitis presenting

Address for correspondence: António Martins, Department of Infectious Diseases, Centro Hospitalar Universitário de São João – Alameda Prof. Hernâni Monteiro 4200-319, Porto, Portugal, e-mail: antonio.rm626@gmail.com

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with CNS mass lesions in AIDS patient that raised concerns about diagnostic and therapeutic approach.

Case description

A 41-year-old Portuguese man, who had returned from Mozambique, was admitted to infectious diseases in-patient department, with low-grade fever, memory, and psycho-motor deficits appearing for four weeks. He had been diagnosed with HIV infection one year earlier, with a CD4+ T cell count of 70 cells/µl, and showed poor adherence to antiretroviral therapy (ART) with tenofovir, emtricitabine, and efavirenz.

Physical examination revealed psycho-motor slowing and memory loss, but no further neurological deficits, and remaining examination was unremarkable. Blood tests showed a C-reactive protein of 20 mg/dl and no other relevant results. Head computed tomography (CT) revealed rounded hyperdense lesions in the caudate nuclei and septum pellucidum, with marked edema. Cerebrospinal fluid (CSF) analysis showed 10 cells/µl, proteins 1.62 g/l, and glucose 51 mg/dl (blood glucose 105 mg/dl). At this point, cerebral toxoplasmosis was considered, the most plausible diagnosis, and sulfadiazine and pyrimethamine were started while continuing ART.

CSF polymerase chain reaction (PCR) test was positive for EBV deoxyribonucleic acid (DNA) (2.4×10^6 copies/ml), and negative for *Toxoplasma gondii* (TG), human polyomavirus 2 (JC), cytomegalovirus (CMV), *Mycobacterium tuberculosis* (MT), and *Nocardia* spp. DNA. TG serology was also negative. Further blood tests showed CD4+ T-cell count of 35/µl (11.84%, ratio CD4/CD8: 0.17), and HIV viral load of 3,270 copies/ml (3.51 log10). Brain magnetic resonance imaging (MRI) revealed rounded lesions in the caudate nucleus, septum pellucidum, and left periventricular parietal white matter, with a nodular and peripheral enhancing pattern, restriction on diffusion-weighted imaging (DWI) in the enhancing areas, and micro-hemorrhages, along with vasogenic edema and ependymal enhancement (Figure 1). Considering these results, EBV-associated PCNSL was presumed.

During second week in the hospital, the patient still complained of neurological impairment. TG serology was repeated and results was negative once again, and head CT revealed no reduction in the size of lesions. Cerebral toxoplasmosis treatment was interrupted and PCNSL was still considered the most plausible diagnosis. Patient was discussed in a multidisciplinary team, which included hematology and neurosurgery, and a brain biopsy was performed. PCR test was positive for EBV-DNA in the biopsy sample, and negative for TG, JC, CMV, MT, and *Nocardia* spp. Histologic examination revealed glioneuronal tissue with reactive astrocytosis and gliosis, inflammatory infiltrate with macrophages and lymphoid cells with perivascular arrangement, and focally EBV-encoded small ribonucleic acid (EBER)-positive lymphocytes (Figure 2). No signs of neoplastic process were found. The diagnosis of EBV encephalitis was assumed.

The patient remained in stable condition and was discharged at week four after admission. Follow-up evaluations were conducted every week during the first month. ART regimen was changed to dolutegravir, abacavir, and lamivudine. During this time, the patient reported progressive improvement in memory and psycho-motor deficits. CSF analysis showed a reduction in EBV viral load (1.7×10^6 copies/ml), blood tests showed an increase in CD4+ T cell count to 167/µl (12.6%, ratio CD4/ CD8: 0.18) and a decreased HIV viral load of 1,160 copies/ml (3.06 log10). Two months after discharge, CSF analysis was repeated and showed an EBV viral

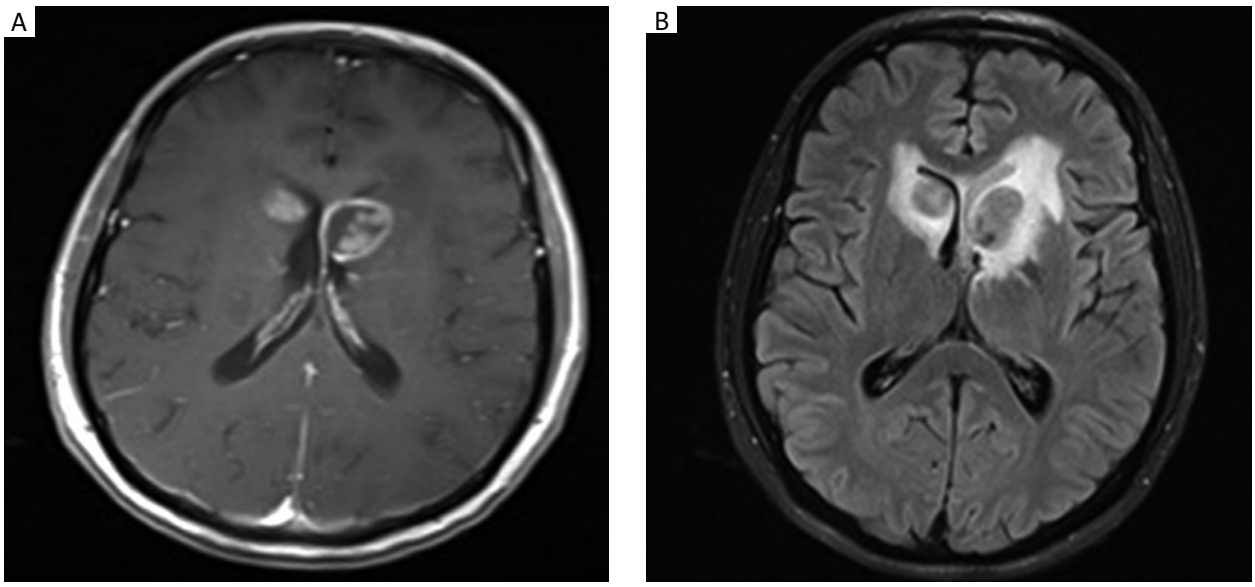

Figure 1. Brain MRI. Focal lesions in caudate nuclei with nodular and ring enhancement pattern. **A**) Axial T1 GAD and surrounding edema. **B**) Axial T2 FLAIR

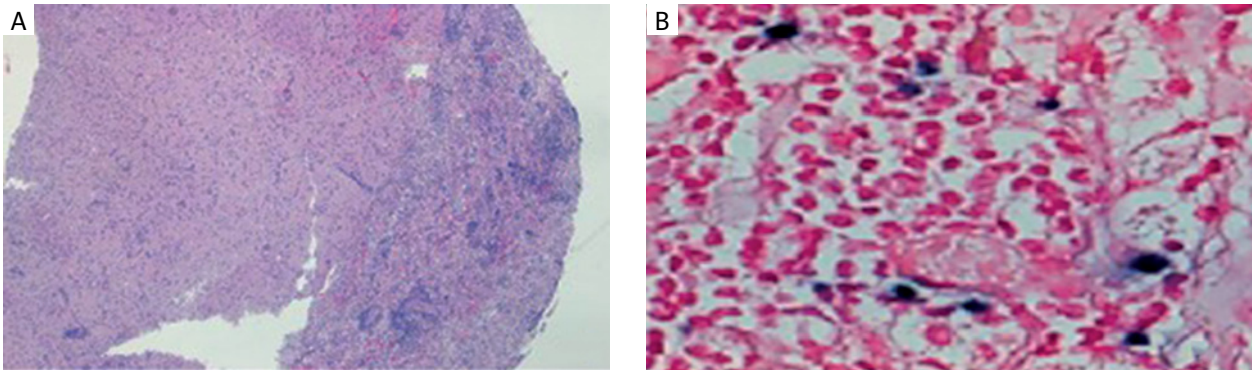

Figure 2. Brain biopsy. Glioneuronal tissue with inflammatory infiltrate (**A**: HE 40×) and scattered EBER-positive lymphocytes (**B**: EBER 400×)

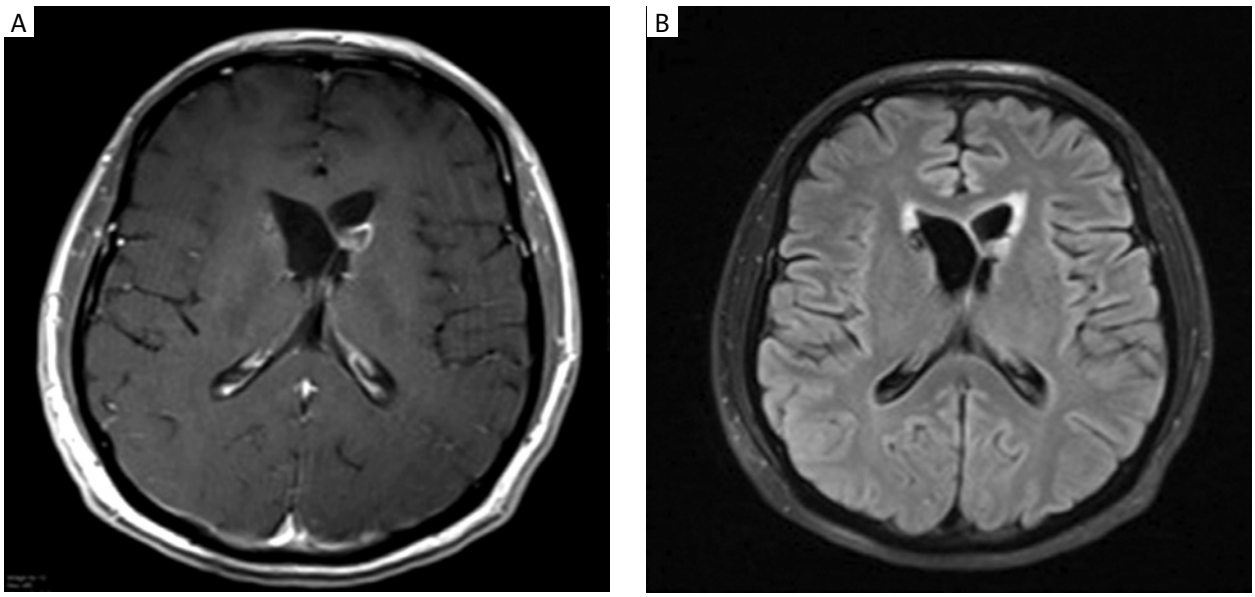

Figure 3. Two-month follow-up brain MRI. Prominent reduction of the lesions: small ring-enhancing lesions (**A**: axial T1 GAD), with minor gliosis and/or edema (**B**: axial T2 FLAIR)

load of less than 150 copies/ml. HIV viral load was undetectable, and CD4+ T cell count was 176/µl (11.5%, ratio CD4/CD8: 0.17). Brain MRI revealed a favorable evolution, with total regression of ependymal enhancement and prominent reduction of the lesions with minor gliosis/edema (Figure 3). At this time, the patient had improved significantly and was able to return to his daily routine and work in Mozambique. He remained in stable condition, with complete recovery two years after hospital discharge.

Discussion

PCNSL is considered the second most common cause of brain mass lesions in AIDS patients after toxoplasmosis [2]. EBV expression is present in the majority of these tumors, suggesting this virus is implicated in oncogenesis. Detection of viral DNA in CSF may be the first indication to diagnosis. In the presented case, EBV-DNA detection in CSF as well as the imaging features were compatible with PCNSL. Brain biopsy is required for diagnosis, and treatment should only be started after confirmation of the diagnosis [3]. However, a brain biopsy is a complex procedure and potential risks may contraindicate it performance. In these circumstances, the diagnosis might be assumed based on typical clinical and radiographic findings for PCNSL, and detection of EBV-DNA in CSF [3]. In the patient described, he was submitted for a brain biopsy, which revealed an alternative diagnosis of EBV encephalitis.

In the context of HIV-associated immunosuppression, individuals are known to be at higher risk of CNS infections by herpes viruses, but there are few reports of EBV encephalitis [4-8]. Most cases of EBV encephalitis in patients with HIV infection have an insidious course, with progressive neurological impairment during weeks or even months. Headaches,

vertigo, limb weakness, ataxia, memory deficits, confusion, and obtundation have been described [5-8]. EBV encephalitis in HIV-infected patients usually presents with focal lesions without mass effect located in the basal ganglia, brain stem, and cerebral cortex [5-8, 9]. The very few reports on EBV encephalitis presenting as CNS mass lesions are described in children and transplant patients [10, 11]. Based on the patient's brain MRI, the differential diagnosis was mainly between toxoplasmosis and PCNSL. The last was more probable due to global restriction in right caudate nucleus lesion, percent signal recovery curve, and ependymal enhancement; although EBV encephalitis or EBV-driven B cell lymphoproliferative disorder (lymphoma precursor) could also be considered.

In HIV-infected patients, the diagnosis of EBV encephalitis may be challenging due to higher incidence of PCNSL, and because the detection of EBV-DNA in CSF by PCR is very strongly suggestive of PCNSL [12]. Despite this fact, the diagnosis of EBV encephalitis relies on a positive CSF-PCR test after exclusion of more frequent pathologies, namely EBV-driven neoplasms. We assumed the diagnosis of EBV encephalitis based on the biopsy results without evidence of neoplastic process and favorable evolution without specific treatment for PCNSL. However, the possibility of PCNSL has still to be taken into account. Some reports on HIV-infected patients with PCNSL treated only with ART have been published [13, 14].

Ganciclovir has been reported to decrease EBV viral load and to improve survival in patients with PCNSL and EBV-driven lymphoproliferative disorders [15]. Although the evidence is scarce about the role of targeted antiviral therapy in EBV encephalitis, HIV-infected patients have been successfully treated with ganciclovir and valganciclovir [5-8]. In the present case, the treatment strategy was based only on ART because during follow-up monitoring, there was a marked reduction in EBV-CSF viral load accompanied by sustained clinical and radiological improvement. EBV-CNS infections usually resolve with no recurrences or long-term sequelae; however, fatal outcomes have been described [4, 5].

Conclusions

This case report suggests that EBV encephalitis may present as CNS mass lesions in HIV-infected patients. PCNSL is the diagnosis to assume in HIV-immunosuppressed patients with brain mass lesions and positive CSF for EBV DNA, and above all, because early recognition and treatment may improve the outcomes for PCNSL patients, which otherwise is poor. However, EBV encephalitis could be a differential diagnosis in patients with compatible histopathology and clinical course, and the treatment for this condition might only be ART. This emphasizes the importance of performing a brain biopsy, whenever it is technically possible and safe, to confirm the diagnosis before treatment decision. In a scenario of differential diagnosis between these two entities, close monitoring with CSF testing and brain imaging re-assessment is mandatory.

Conflicts of interest

The authors declare no conflict of interest.

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