

Rapidly progressive and fatal EBV-related encephalitis in a patient with advanced HIV-1 infection at presentation: a case report and review of the literature

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SUMMARY

Epstein-Barr virus (EBV) has been associated with primary central nervous system lymphoma and other EBV-related malignancies in HIV infected patients, and detection of EBV DNA in cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) has been demonstrated to be a good marker of PCNSL. Conversely, EBV has been rarely associated with encephalitis in HIV patients. Here we describe for the first time the case of an HIV-infected, late presenter Caucasian man, diagnosed with a rapidly progressive diffuse encephalitis at presentation. A very high viral load for EBV was detected in CSF by PCR. The patient died 12 days after the onset of encephalitis in spite of supportive, antiviral and antiretroviral therapy. Our experience would suggest that in profoundly immunosuppressed HIV patients EBV may cause severe encephalitis in the absence of lymphoproliferative disorders.

KEY WORDS: HIV, Late-presenter, EBV, Encephalitis

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INTRODUCTION

Human immunodeficiency virus (HIV) infected individuals are known to be at higher risk of developing severe central nervous system (CNS) infections caused by herpes viruses as well as herpes virus-related malignancies, although a more favorable course of such conditions has been more recently reported for patients treated with highly active antiretroviral therapy (HAART) (Kennedy *et al.*, 2005; Martínez *et al.*, 2007; Serraino *et al.*, 2005).

In HIV patients, cytomegalovirus (CMV) is the most frequently identified cause of CNS infections among herpes viruses, while fewer cases

have been described as related to Epstein-Barr virus (EBV), human herpes virus 6 (HHV-6) and mixed herpes virus infections (Martínez *et al.*, 2007).

EBV is a B-lymphotropic virus that was initially associated with a variety of lymphoid malignancies in immune-compromised patients, as Burkitt's lymphoma, Hodgkin's disease, B-cell lymphoma, primary central nervous system lymphoma (PCNSL), as well as with CNS infections as encephalitis, meningo-encephalitis and Guillain-Barré syndrome (Serraino *et al.*, 2005; Domachowske *et al.*, 1996; Takahashi *et al.*, 2005; Kleinschmidt-DeMasters *et al.*, 2008).

Detection of EBV DNA in cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) has been demonstrated to be a good marker of PCNSL in HIV patients in several studies (Bossolasco *et al.*, 2002; De Luca *et al.*, 1995). Indeed, the detection of EBV DNA by PCR in CSF from HIV-infected patients with PCNSL has a very high diagnostic sensitivity, approximating 80

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to 100% in recent series (Bossolasco *et al.*, 2002; De Luca *et al.*, 1995; Cinque *et al.*, 1996). EBV was undetectable in most patients without PCNSL in such series.

While the presence of EBV DNA in CSF has been related with later development of PCNSL in some studies (Al-Shahi *et al.*, 2000; Brink *et al.*, 1998), others failed to demonstrate an increased risk of developing PCNSL in patients with detectable EBV DNA in CSF (Tachikawa *et al.*, 1999; Wang *et al.*, 2007).

This report describes the case of an HIV-infected man, who was diagnosed with HIV infection and AIDS due to *Pneumocystis jiroveci* pneumonia and soon after presented a rapidly progressive and lethal deterioration of consciousness, which was related to a high EBV viral load in CNS, in the absence of any other evidence of CNS infection, apart from HIV.

The patient died 12 days after the onset of signs of encephalitis in spite of prompt introduction of HAART and combined treatment with ganciclovir and foscarnet.

CASE REPORT

The patient, a 40-year-old heterosexual Caucasian, came to our attention for the first time in February, 2008, transferred from another Institute due to worsening dyspnea not responsive to antibiotics. Severe pulmonary interstitial disease was molecularly diagnosed by real-time PCR as *Pneumocystis Jiroveci* pneumonia. HIV infection was documented for the first time; CD4 T-cell count was 56 mm³ and HIV viral load was 555,000 cp/mL.

Treatment with i.v. cotrimoxazole was effective in controlling fever and dyspnea, but on the third day the patient showed rapidly worsening sleepiness in the absence of focal neurological deficits and/or any sign of peripheral neuropathy. A brain CT scan with and without contrast medium did not reveal any obvious organic damage, while a first EEG showed diffuse slow discharge, consistent with severe encephalopathy.

Routine CSF analysis was normal, with no cellular sediment, and a modest increase in CSF proteins. Real Time PCR on CSF, however, amplified EBV DNA at a high titer (11,230 cp/mL), while it was negative for pathogens such as HSV1-2,

HHV6, HHV8, CMV, JC virus and Mycobacteria. Cultures for *Cryptococcus* were negative. HIV viral load in the CSF was 261,000 cp/mL. EBV DNA and other herpes viruses were not amplified from parallel peripheral blood samples.

A first brain magnetic resonance imaging (MRI) scan showed an apparently normal pattern. Antiviral therapy with i.v. aciclovir was soon established at standard doses, without benefit. Three days later, therefore, an association of i.v. ganciclovir and foscarnet was started at standard doses.

In spite of that, the patient rapidly progressed to a state of light coma, difficult to awaken. A second MRI brain scan with and without contrast medium was again normal, without any evidence of organic lesions, while EEG monitoring documented a worsening of bioelectric patterns.

On the tenth day HAART was started (lopinavir, LPV; stavudine, d4T; lamivudine, 3TC), without any improvement. A few days later the patient showed progressive focal neurological involvement (strabismus and a coarse tremor), deepening in his state of coma and necessitating relocation at an intensive care unit. A third MRI scan could not be therefore be undertaken. Thirteen days after admission, the patient died due to cardiac arrest, in spite of any attempt at resuscitation. Autoptic examination was not granted.

DISCUSSION

The rapid and irreversible neurological progression of our patient is of relevance, as it may represent the first evidence of rapidly progressive and lethal EBV-related encephalitis in an HIV patient. Indeed, his fatal course occurred in the absence of any evidence of other causative agents of encephalitis in his CSF and in spite of combination antiviral therapy for EBV and HAART, whereas treatment with cotrimoxazole controlled his presentation pneumonia. Indeed, HIV itself was amplified from CSF at high titer.

Our patient, however, did not present any of the clinical characteristics which have been reported for HIV-related meningo-encephalitis: he was a late presenter, with very low CD4 T-cell counts in his peripheral blood, did not present any sign of meningitis, and no cellular sediment was detected on CSF (Villar Del Saz *et al.*, 2008).

Furthermore, pneumonia due to *Pneumocystis jiroveci* was his presenting condition, followed by rapid deterioration of his mental state and late appearance of focal neurological signs after the start of HAART with a lopinavir-based regimen, which may well have rapidly controlled HIV replication in CSF (Letendre *et al.*, 2007). For this reason, we felt that the diagnosis of HIV-related meningo-encephalitis was not likely on a clinical basis, although a concurrent role of HIV cannot be excluded. Serial electroencephalographic evaluations showed patterns of severe encephalopathy, with progressively diffuse lateralizing epileptiform discharges, in the absence of any neuro-radiologic evidence of brain damage or PCNSL on serial MRI scans. A causative role for EBV was therefore supported by its very high titer in CSF, as well by the absence of other known pathogens such as HSV1-2, CMV, HHV-6, VZV, JC virus, HHV-8, *Cryptococcus* and *Mycobacteria* (Landgren *et al.*, 1994; Cinque *et al.*, 2003). Interestingly, EBV was not amplified on a parallel peripheral blood sample drawn at the time of CSF sampling, adding to the causative role of its reactivation in CSF (Pedneault *et al.*, 1992; Volpi, 2004).

Most members of the herpesviridae family with CNS tropism have been associated with sporadic cases of encephalitis, causing a wide spectrum of clinical manifestations (Aberle *et al.*, 2002; Quereda *et al.*, 2000). Patients with an impaired immune system, and especially patients with HIV infection, have been reported at increased risk (Kennedy *et al.*, 2005). Analysis of CSF by PCR for herpes viruses proved useful in establishing an accurate diagnosis and to monitor the efficacy of antiviral therapy in these patients (Frías *et al.*, 2001).

To our knowledge, few reports of EBV-related encephalitis have been published in HIV-infected patients (Hirsch *et al.*, 1998; Katramados *et al.*, 2007; Cubo *et al.*, 2007). EBV infections of CNS were usually reported without recurrences and/or long-term sequelae (Fujimoto *et al.*, 2003). In a recent report, the presence of EBV-DNA in CSF was not associated with more advanced immunosuppression in HIV patients without a diagnosis of PCNSL (Wang *et al.*, 2007). Indeed, the use of HAART may protect these patients from developing PCNSL even in the presence of EBV (Astriti *et al.*, 2006). In a recent communication,

Katramados *et al.* reported a possible case of EBV-related encephalitis in a HIV patient treated with HAART and a relatively preserved immune system (Katramados *et al.*, 2007). In this case, the patient experienced early partial clinical improvement and a clinical relapse of encephalitis during maintenance therapy with oral valganciclovir. The authors reported a favorable course after restoring therapy with intravenous ganciclovir and suggested that restoration of immune control induced by HAART may have prevented development of PCNSL, thus inducing an unusual clinical expression of persistent EBV infection, that is recurrent encephalitis. Our experience would therefore suggest for the first time the occurrence of EBV-related encephalitis in an advanced, severely immunosuppressed patient at presentation of HIV infection, without any sign of lymphoma.

In spite of association therapy with i.v. ganciclovir and foscarnet and the early start of HAART, a rapid worsening of encephalitis with progression to status epilepticus ensued. This was unlikely to be due to the emergence of viral resistance, a well-known phenomenon with other herpes viruses in HIV-infected patients (Astriti *et al.*, 2006; Field *et al.*, 1994) as well as in HIV infected patients chronically treated for other EBV-related infections, as in the case of oral hairy leukoplakia (Walling *et al.*, 2003).

The rapid worsening of the clinical state of our patient, however, with the ensuing of focal signs, suggested us that further sampling of CSF might be unwise. Failure of antiviral therapy in our patient might have been rather related to uncontrollable reactivation of EBV during his state of advanced immune suppression, as evidenced by a high titer by quantitative PCR, possibly favoring clinically irreversible EBV-related brain injury.

Indeed, 2 sequential brain MRI scans did not reveal any evidence of brain damage in our patient. Acute encephalitis associated with EBV infection, however, has been frequently reported in the absence of abnormalities at neuroimaging (Shian *et al.*, 1996).

Available reports of MRI findings are limited, and describe lesions involving the basal ganglia, brainstem and cerebral cortex (Shian *et al.*, 1996; Ono *et al.*, 1998; Angelini *et al.*, 2000), consistent with the late events observed in our patient, for whom

a third MRI scan could not be performed at the time when focal signs ensued. Normal brain MRI scans, however, have also been reported in cases of other viral encephalitis (Misra *et al.*, 2008). The majority of patients with herpes simplex encephalitis have positive findings at inferomedial temporal lobes, but some 10% of them have normal MRI scans (Domingues *et al.*, 1998). Furthermore, normal MRI scans in 6 advanced HIV patients with CMV encephalitis have been related to a possible lack of sensitivity of standard MRI neuroimaging (Clifford *et al.*, 1996). Finally, abnormal findings in HHV-6 related encephalitis, characterized by low-attenuation lesions in the posterior cerebral lobes, were present only in 17% of investigated patients (Singh *et al.*, 2000). In conclusion, our experience suggests that EBV-related encephalitis may represent a rare but severe complication in severely immunocompromised patients with HIV infection in the absence of any sign of PCNSL, adding further evidence to the knowledge that late presentation in HIV infection may be a major cause of AIDS-related mortality in the HAART era (Girardi *et al.*, 2007). Further studies are needed to confirm our isolated observation and to better understand the precise role played by EBV in the development of severe neurological impairment in our patient.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

E. Polilli, G. Parruti, A. and Consorte ideated this case-report and did most of the writing, supported by F. Sozio; L. Cosentino and E. Polilli performed RNA sequencing and sequence interpretation; F. Di Masi, A. Agostinone and E. Mazzotta contributed their critical counseling and looked after the patient in his clinical course.

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