Journal of NeuroVirology, 10: 414–417, 2004

ISSN: 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280490521050

Taylor & Francis
Taylor & Francis Group

Case Report

Acute fatal necrotizing hemorrhagic encephalitis caused by Epstein-Barr virus in a young adult immunocompetent man

Daniela Francisci,[1] Alessandra Sensini,[2] Daniela Fratini,[3] Maria Vittoria Moretti,[1] Maria Laura Luchetta,[1] Antonino Di Caro,[4] Giuliano Stagni,[1] and Franco Baldelli[1]

[1]Clinica di Malattie Infettive, [2]Istituto di Microbiologia, and [3]Istituto di Anatomia Patologica, University of Perugia, Perugia, Italy; [4]Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani, Rome, Italy

Epstein-Barr Virus (EBV) encephalitis is a rare (<1%) and generally self-limited disease with few sequelae. This neurological complication has been reported almost exclusively in the course of acute primary infection and in paediatric patients. We describe a case of a young adult immunocompetent man who developed an acute fatal necrotizing haemorrhagic encephalitis as the only manifestation of an acute EBV infection. EBV-DNA was tested positive in several CSF samples by qualitative and quantitative PCR. Serological profile showed: absence of IgM against Viral Capsid Antigen (VCA) in three different consecutive samples, presence of IgG against VCA and IgG seroconversion for Epstein Barr Nuclear Antigen (EBNA). EBV-DNA was detected by qualitative PCR in autoptic brain material. Clinical course was not influenced by antiviral therapy with acyclovir. In conclusion to our knowledge, this is the only case of acute necrotizing haemorrhagic EBV encephalitis with a fatal outcome, in an adult immunocompetent man. *Journal of NeuroVirology* (2004) **10,** 414–417.

Keywords: EBV; fatal encephalitis; immunocompetent man

Epstein-Barr virus (EBV) has been associated in rare cases (<1%) with a variety of central nervous system (CSN) manifestations such as transverse myelitis, meningitis, cerebellitis, and encephalitis (Connelly and De Witt, 1994; Hausler *et al*, 2002). These neurological complications have been reported almost exclusively in the course of acute primary infections, usually in pediatric patients (Domachowske *et al*, 1996).

Most often neurological disturbances accompany the classic clinical picture of infectious mononucleosis; occasionally they are the first or the only clinical manifestation of EBV infection (Silverstein *et al*, 1972; Grose *et al*, 1975).

In general, encephalitis caused by EBV has been considered a self-limited illness, with a mild course, and usually associated with a complete recovery at least in immunocompetent patients (Bernstein and Wolf, 1950; Todman 1983).

Here we describe a case of a young immunocompetent adult man who developed a fatal acute necrotizing hemorrhagic encephalitis as the only manifestation of an acute EBV infection with atypical EBV-specific antibodies pattern.

Case report

On November 7, 2001, a 28-year-old, previously healthy man was admitted to our clinic because of a 2-day history of fever, bilateral frontotemporal headache, mental confusion, and projectile vomiting. The patient was born in Tunisia and had been living in Saudi Arabia until 3 months before admission, when he moved to Italy. The patient's history was collected thanks to the translation (English-Arabian) of his partner because the patient did not speak nor understand Italian or English.

Evaluation of the patient's medical history disclosed no relevant abnormal findings. At the time of admission the physical examination revealed

Address correspondence to Professor Daniela Francisci, Clinica Malattie Infettive, Policlinico Monteluce, 06122 Perugia, Italy. E-mail: francisd@unipg.it

Received 17 May 2004; revised 9 July 2004; accepted 21 July 2004.

mental confusion, neck stiffness, disorientation, hepatomegaly, and splenomegaly. There were no lymphadenopathy or pharyngitis.

His vital signs were as follows: temperature 38°C; blood pressure 110/70; pulse rate 76 beats/min, and respiratory rate 20 breaths/min. Erythrocyte sedimentation rate was 11 mm/h, C-reactive protein concentration was 0.4 mg/L. White blood cell were 4,300/mm^3 and differential white count was N 72%, L 18%, M 6%, E 3%, B 1%; no atypical lymphocytes were seen. Hepatocellular enzymes (aspartate aminotransferase, alanine aminotransferase, and lactic dehydrogenase) were elevated (three times the upper limit of normal). Immunoglobuline profile showed IgG 545 (range 751–1560), IgA 191 (range 82–453), IgM 53 (range 46–304). IgG subclasses analysis was not performed.

Lymphocyte subsets tested by flow cytometry (FACSCalibur, Becton Dickinson) were CD3+ 85% (range 55%–84%), 633 cells/μl (range 690–2540 cells/μl); CD4+ 47% (range 31%–60%), 372 cells/μl (range 410–1590 cells/μl); CD8+ 35% (range 13%–41%), 250 cells/μl (range 190–1140 cells/μl). Antibodies to HIV1/2 and plasma HIV1 RNA (Cobas Amplicor HIV-1 Monitor; Roche) were tested negative.

Analysis of a cerebro spinal fluid (CSF) sample, performed at the time of admission, showed a white blood cell (WBC) count of 24 cells/ml (90% mononuclear cells), a protein level of 65 mg/dl, and a glucose level of 51 mg/dl. CSF was found to be negative for bacteria, mycobacteria, and fungi.

A brain MR done on admission showed multiple focal areas of increased signal on T2-weighted imaging sequences on bilateral temporal lobes. There were also signs of hemorrhage within the lesions on left thalamus, parahippocampal, and peri-insular left areas (Figure 1).

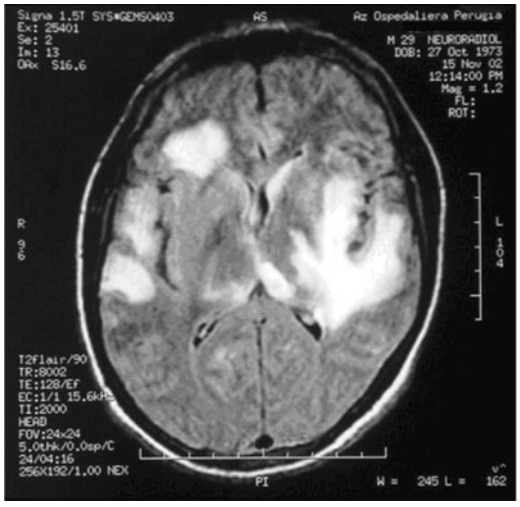

Figure 1 Brain imaging of the patient (MRI, T2-weighted FLAIR), 8 days after admission, showing multiple focal areas of increased signal with hemorrhagic component within the lesions.

CSF was found to be positive for EBV DNA and negative for herpes simplex virus (HSV1, HSV2), cytomegalovirus (CMV), varicella-zoster virus (VZV), human herpesvirus (HHV)6 DNAs by commercially available polymerase chain reaction (PCR) (Herpes Consensus; ARGENE-Biosoft). A plasma sample was tested negative for all herpesviruses DNA. On admission, serum antibodies to viral capsid antigen (VCA) measured by immunofluorescence assay revealed absence of immunoglobulin (Ig)M and presence of IgG at titer of 1280; antibodies to virus-associated nuclear antigen (EBNA) were absent.

On day 2 of hospitalization, treatment with acyclovir was started (10 mg/kg twice daily, intravenous [i.v.]). Because of deterioration of mental status, despite therapy, on day 11 of hospitalization, dexamethasone (4 mg four times daily, i.v.) and foscarnet (90 mg/kg twice daily, i.v.) were given.

The patient initially improved and on day 20 of hospitalization he was alert, able to concentrate and to memorize, and to normally relate with the hospital personnel. Antiviral drugs (acyclovir, foscarnet) and dexamethasone were given until December 5, 2002.

On January 5, 2003, 30 days after antiviral and steroid therapy withdrawal, the patient gradually worsened with drowsiness, disinhibition, mental confusion. A brain magnetic resonance imaging (MRI) done on January 22, 2003, showed remarkable increase of supratentorial lesions in the grey matter, with clear hemorrhagic component, and lesions of thalamus, right lenticular nucleus, cerebellar cortex; angiographic sequences were normal (Figure 2). At this time serum antibodies to VCA measured by immnunofluorescence assay confirmed the IgM absence and IgG presence at titer of 1280. There was appearance of antibodies to EBNA, and EBV VCA IgG avidity test was 68.9%. The patient's serological data are summarized in Table 1.

On January 22, 2003, dexamethasone (4 mg four times daily, i.v.) and foscarnet (90 mg/kg twice daily, i.v.) were started again. However, his neurological conditions continued to deteriorate and he developed generalized seizures. On February 5, 2003, foscarnet was replaced by gancyclovir (5 mg/kg twice daily).

Nevertheless, his conditions did not improve and the patient fell into deep coma.

On February 14, 2003, CSF showed 10/mm^3 mononuclear cells. The CSF was found to be positive

Table 1 Patient's serological data

	Date of test		
	Nov. 15, 2002	*Dec. 12, 2002*	*Jan. 21, 2003*
VCA-IgG (IFI)	1280	1280	1280
VCA-IgM (IFA)	Neg	Neg	Neg
VCA-IgG (avidity)	45.7%	46.35%	68.9%
EBNA-IgG	Neg	Neg	Pos (serum and CSF)

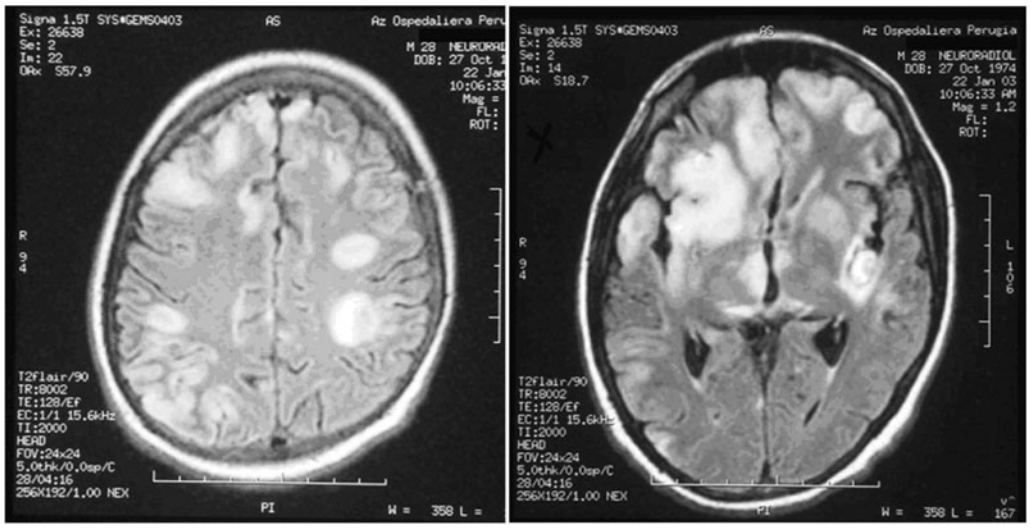

Figure 2 Brain imaging of patient (MRI, T2-weighted FLAIR), 75 days after admission, revealing relevant increase of supratentorial lesions, with clear hemorrhagic component.

for EBV DNA (26,500 copies/ml) by real time PCR (Q-EBV Ampli-Mix; Amplimedical s.p.a.) performed at the Virology Laboratory of Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani of Rome. Moreover, for the first time, and despite antiviral treatment, a plasma sample was found to be positive for EBV DNA by qualitative PCR.

The patient died on February 20, 2003. Autopsy was performed. The diagnosis of necrotizing-hemorrhagic meningoencephalitis with multiple foci was confirmed (Figure 3a, b); EBV DNA was detected by qualitative PCR in autoptic brain material.

Discussion

EBV encephalitis is a rare but generally benign, self-limited disease, with few sequelae, even in patients who exhibit severe impairment on presentation (Scully, 1974). The pathogenesis of EBV meningoencephalitis has been ascribed either to a mechanism of postinfectious encephalitis (Tardieu *et al*, 1984; Bray *et al*, 1992), or to a direct infection of the CNS (Halsted and Chang, 1979; Schiff, 1982). In our patient, the detection of EBV DNA both in CSF and in brain autoptic material confirms the direct CNS invasion. Three major histopathological patterns of EBV encephalitis have been reported: (a) acute demyelinating encephalomyelitis; (b) encephalitis with perivascular mononuclear infiltrates and occasional viral inclusions in cortical and subcortical cells, and (c) edematous-hemorrhagic encephalitis (Hausler *et al*, 2002). In particular, EBV encephalitis with an edematous-hemorrhagic pattern similar to that of our case has been only occasionally described during an acute primary infection, or in pediatric patients (Hausler *et al*, 2002).

Our patient was a young, healthy male, with no apparent congenital or acquired immunodeficiency. The only apparent immunologic anomaly we found

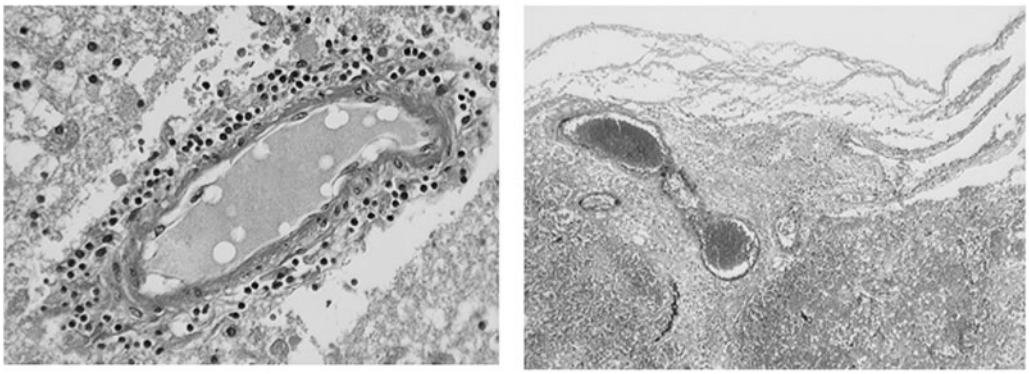

Figure 3 Autoptic brain material of patient (EE, 40×). (**a**) Perivascular mononuclear infiltrates; (**b**) mononuclear infiltrates with a necrotic-hemorrhagic focus below.

was a mild quantitative IgG deficit, which was detected on admission and confirmed after 1 month. In both occasions IgM and IgA values were normal. However, his EBV-specific antibody pattern, with VCA IgG positive, VCA IgM negative, confirmed in three different consecutive samples, was atypical for a primary infection. On the other hand, EBNA IgG seroconversion and the low VCA IgG avidity strongly support a primary infection.

In our patient, the clinical course was only transitorily influenced by antiviral therapy, which never caused a viral DNA disappearance.

Acyclovir administration in the early stages of infectious mononucleosis can reduce pharyngeal shedding, but the clinical benefits are marginal (Andersson *et al*, 1986).

Moreover, acyclovir therapy has been tried for encephalitis with conflicting results and the efficacy of the drug is not documented in clinical trials. There are only anecdotic reports on ganciclovir use in transplant recipients (Dellemijn *et al*, 1995; Garamenti *et al*, 2002). Thus, it is not possible to make recommendations on the use of antiviral drugs in the settings of complicated infection.

In conclusion, to our knowledge, acute necrotizing hemorrhagic EBV encephalitis with a fatal outcome in adult immunocompetent persons has not been described until now.

References

Andersson J, Britten S, *et al* (1986). Effect of acyclovir on infectious mononucleosis: a double blind, placebo-controlled study. *J Infect Dis* **153:** 283–290.

Bernstein TC, Wolff HG (1950). Involvement of the nervous system in infectious mononucleosis. *Ann Intern Med* **33:** 1120–1138.

Bray PF, Culp BS, *et al* (1992). Demyelinating disease after neurologically complicated primary Epstein-Barr virus infection. *Neurology* **42:** 278–282.

Connelly KP, De Witt LD (1994). Neurological complications of infectious mononucleosis. *Pediatr Neurol* **10:** 181–184.

Dellemijn PL, Brandenburg A, *et al* (1995). Successful treatment with ganciclovir of presumed Epstein-Barr meningo-encephalitis following bone marrow transplant. *Bone Marrow Transplant* **16:** 311–312.

Domachowske JB, Cunningham CK, *et al* (1996). Acute manifestations and neurologic sequelae of Epstein-Barr virus encephalitis in children. *Pediatr Infect Dis J* **15:** 871–875.

Garamenti M, Montejo M, *et al* (2002). Encephalitis caused by Epstein-Barr Virus in a renal transplant recipient. *CID* **34:** 287–288.

Grose C, Henle W, *et al* (1975). Primary Epstein-Barr virus infections in acute neurologic disease. *N Engl J Med* **292:** 392–395.

Halsted CC, Chang RS (1979). Infectious mononucleosis and encephalitis: recovery of EB virus from spinal fluid. *Pediatrics* **64:** 257–258.

Hausler M, Ramaekers VT, *et al* (2002). Neurological complications of acute and persistent Epstein-Barr virus infection in paediatric patients. *J Med Virol* **68:** 253–263.

Schiff JA (1982). Epstein-Barr virus in cerebrospinal fluid during infectious mononucleosis encephalitis. *Yale J Biol Med* **55:** 59–63.

Scully RE (1974). Case records of the Massachusetts General Hospital. *N Engl J Med* **291:** 141.

Silverstein A, Steinberg G *et al* (1972). Nervous system involvement of infectious mononucleosis. *Arch Neurol* **26:** 353–358.

Tardieu M, Brun P, *et al* (1984). Encephalite post-infectieuse due au virus d 'Epstein-Barr. *Arch Fr Pediatr* **41:** 425–427.

Todman DH (1983). Encephalitis in infectious mononucleosis. *Clin Exp Neurol* **19:** 81–86.