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CASE REPORT

Epstein-Barr virus hemorrhagic meningoencephalitis: case report and review of the literature

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Abstract Neurologic complications related to *Epstein-Barr virus* (EBV) in immunocompetent adults are rare and most commonly self-limited. However, severe cases have been previously reported in the literature. We describe a case of meningoencephalitis with frontal bilateral hemorrhage in a non-immunocompromised adult following an EBV infection of the central nervous system confirmed by the presence of EBV-DNA in the cerebrospinal fluid. During the patient's hospital stay, there was a favorable clinical and radiologic evolution and the patient was discharged asymptomatic. To our knowledge, this is the fourth case of hemorrhagic meningoencephalitis related to EBV and the first one in an immunocompetent patient with a favorable outcome.

Keywords Meningoencephalitis · EBV · Hemorrhage

Case description

The *Epstein-Barr virus* (EBV), a member of the *Herpesviridae* family (subfamily *Gammaherpesviridae*, genera *Lymphocryptovirus*) was described for the first time in 1964 by Epstein et al. (1964). However, it was not before 1968 that Henle et al. (1968) demonstrated the correlation between EBV and infectious mononucleosis, a common condition affecting mostly children and young adults, usually a self-limited and benign disease.

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EBV infection can present in two different ways the acute primary form or the reactivation of a latent/chronic form.

In the acute form of the infection, up to 5 % of all patients present neurologic complications such as meningitis, encephalitis, acute demyelinating encephalomyelitis, cerebellitis, transverse myelitis, and Guillain-Barré syndrome (Häusler et al. 2002). Although this disease has frequently a benign course, it can result in more serious complications. Previous reports have described cases of severe acute invasive EBV in young males with X-linked lymphoproliferative disorder, a rare genetic disorder caused by a mutation in the gene SH2D1A (Xq25). The protein coded by SH2D1A is an important natural killer (NK) cell mediator and involved in both T lymphocyte activation and B cell proliferation/differentiation. When present, the mutation affects the immune response to EBV, causing severe necrotic hepatic failure and hematologic dysfunction associated with a high mortality rate (Chadha and Amrol 2010).

Latent EBV infection is prevalent in more than 90 % of the adult population (Patil et al. 2012). However, neurologic symptoms are rare during reactivation of latent EBV infections in immunocompetent adults (Mizutani et al. 1993).

In general, neurologic manifestations caused by EBV-like encephalitis in immunocompetent patients are a self-limited condition usually associated with complete recovery (Todman 1983). Nonetheless, severe and even fatal cases after central nervous system (CNS) EBV infection have previously been reported, namely hemorrhagic meningoencephalitis in immunocompetent adults (Francisci et al. 2004; Takeuchi et al. 2010).

We report a confirmed case of CNS EBV infection with rare neurologic and systemic manifestations and an unexpected outcome.

A 58-year-old otherwise healthy male with no previous history of medication or relevant family medical history was admitted in our emergency department after presenting

10 days before with global headache, fever (38 °C), vomiting, and diarrhea (without blood or mucus). He also had muscular, joint, and back pain which limited his walking and that were unrelated to recent trauma.

The physical exam revealed fever (38.2 °C) and a painless elastic cervical posterior lymphadenopathy measuring 2 cm. The neurologic exam revealed neck stiffness and no mental confusion or other abnormalities.

The preliminary blood tests were unremarkable with no inflammation marker elevation and normal hepatic, renal, and metabolic function. The cranial computerized tomographic scan (CT-Scan) revealed a bilateral frontal hemorrhage with mass-effect. A lumbar puncture was performed and the cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis (40 leucocytes with 98 % mononuclear cells) and the absence of red cells, elevation of protein levels (55 mg/dl) and glucose level within the normal range. The patient was admitted with the diagnosis of hemorrhagic lymphocytic meningoencephalitis of an unknown etiology and empirical treatment was started with acyclovir (10 mg/kg tid) and systemic corticosteroids.

During the observation period, the patient's condition improved, neurologic symptoms subsided, and fever was absent. An encephalic magnetic resonance imaging (MRI) was performed and confirmed the presence of a frontal bilateral (albeit, larger on the right side) hemorrhage (Fig. 1).

The immune protein electrophoresis, autoimmunity study (including rheumatoid factor), platelet count, and the clotting factor evaluations were otherwise normal. The serologic assessments for *Human Immunodeficiency Virus* (HIV), *Rickettsia conorii* and *Borrelia burgdorferi* were also negative. The CSF PCR was positive for EBV DNA while being negative for other relevant neurotropic viruses, specifically HSV 1, HSV2, VZV, CMV, HHV6, HHV7, HHV8, and Enterovirus (multiplex herpesvirus PCR assay). Furthermore, bacterial cultures (including mycobacterial) were also negative and no neoplastic cells were detected. Serial serologic EBV testing subsequently confirmed a reactivation of a chronic EBV infection with positive EBNA-IgG/VCA-IgG (460 and >750 U/ml, respectively) and an increase in VCA-IgM (from negative at admission to 68.5 U/ml after 3 months). We were not able to perform EBV viral load in serum and CSF in a timely manner. CD4/CD8 counts and immunoglobulin levels were unremarkable and ruled out underlying immunodeficiency.

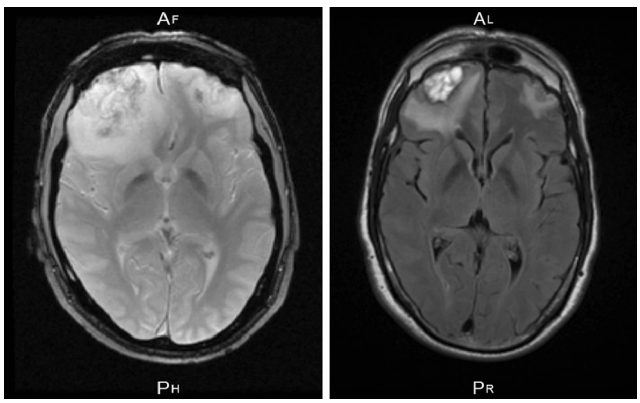

Fig. 1 Encephalic MRI at admission (axial T2 GRE) and at discharged (2 weeks lateral axial T2 flair)

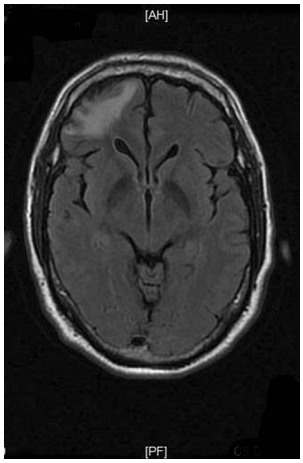

Fig. 2 Encephalic MRI 20 weeks after admission (axial T2 flair)

After 14 days of acyclovir, the patient had a complete resolution of his clinical condition. The lumbar puncture was repeated at this time and confirmed that the CSF had no relevant alterations and was negative for EBV DNA.

The patient was subsequently discharged with the diagnosis of hemorrhagic meningoencephalitis associated to EBV.

We repeated the brain MRI with spectroscopy 20 weeks later and found no evidence of aggravated frontal hemorrhage or any other relevant abnormalities (Fig. 2).

Discussion

To our knowledge, hemorrhagic meningoencephalitis associated to EBV has only been described three times in the previous literature (Table 1) (Francisci et al. 2004; Takeuchi et al. 2010; Sabat et al. 2015). Francisci et al. reported the first fatal case confirmed both by protein chain reaction (PCR) in the CSF and postmortem brain biopsy. The second case, published by Takeuchi et al., was also confirmed by both CSF PCR and brain biopsy during decompression neurosurgery. In this latter case, the patient survived. The third case, described by Sabat et al., was an immunocompromised patient with inflammatory bowel disease under methotrexate and prednisolone, the diagnosis was confirmed with a positive CSF PCR (brain biopsy was not done) and the patient had a good outcome without invasive measures.

Contrary to the previous cases, our patient was immunocompetent and had complete clinical improvement not

Table 1 Case reports of EBV meningoencephalitis

Case reports	Age	Sex	Underlying illness	Heralding symptoms	Physical examination	Outcome
Francisci et al.	28	M	Healthy	2 days of fever, headache, confusion and projectile vomiting	Confusion, neck stiffness, fever, hepatosplenomegaly	Patient died after 106 days of hospital admission
Takeuchi et al.	20	M	Healthy	1 week of fever, headache and confusion diarrhea	Confusion, neck stiffness, fever	Surgical decompression and external ventricular drainage on day 2, discharged on day 57 with no neurological abnormalities.
Sabat et al.	24	F	Immunocompromised	Headache, nausea, photophobia	Neck stiffness	Discharged after 7 days with no neurological abnormalities.
Branco Ascenção et al	58	M	Healthy	10 days of fever, headache, diarrhea, myalgia, joint, and back pain.	Fever, cervical lymphadenopathy, neck stiffness	Discharged after 14 days with no neurological abnormalities.

requiring surgery or any other invasive measures, justifying the lack of a confirmatory brain biopsy.

Neurologic manifestations associated to EBV may be due to either direct CNS EBV invasion (Imai et al. 1993) or a post-infectious inflammatory response mediated by antineuronal antibodies (Ito et al. 1994).

Three major histo-pathologic patterns in the EBV encephalitis have previously been reported (Häusler et al. 2002): (1) edematous-hemorrhagic (which would be the expected pattern for this patient if we had performed the brain biopsy), (2) perivascular mononuclear infiltrates and occasional viral inclusions in cortical/subcortical cells, or (3) perivascular lymphocyte inflammation with demyelination of the white matter and no viral inclusions (a pattern associated to an autoimmune response following an acute infection).

Similarly to the previously reported cases, the benefit of antiviral medication remains unclear, since the efficacy of acyclovir in EBV has yet to be established (Fujimoto et al. 2003).

In conclusion, this is the fourth case reported of hemorrhagic meningoencephalitis associated to EBV infection and the first one in an immunocompetent patient with a favorable outcome that did not require the use of invasive measures.

Compliance with ethical standards

Funding None.

Conflict of interest None declared.

Ethical approval Not required.

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