

# Proven Epstein–Barr encephalitis with negative EBV-DNA load in cerebrospinal fluid after allogeneic hematopoietic stem cell transplantation in a child with acute lymphoblastic leukemia

Barberi W, Perrone S, Iori AP, Torelli GF, Testi AM, Moleti ML, Ceglie T, Papoff P, Caresta E, Antonelli M, Gianno F, Melone A, Badiali M, Giangaspero F, Foà R, Gentile G. (2015) Proven Epstein–Barr encephalitis with negative EBV-DNA load in cerebrospinal fluid after allogeneic hematopoietic stem cell transplantation in a child with acute lymphoblastic leukemia. *Pediatr Transplant*, 19: E19–E24. DOI: 10.1111/ptr.12386.

**Abstract:** We report a case of EBV encephalitis in a seven-yr-old child with Ph+ ALL. Two months after an allogeneic HSCT from his HLA mismatched mother, the patient showed an altered sensorium, generalized seizures, and a left hemiparesis. Brain MRI demonstrated multiple lesions highly suggestive for viral encephalitis. Blood and CSF PCR analyses were negative for the most common viruses involved in immunocompromised patients including EBV. A cerebral biopsy was performed, which showed intense gliosis and perivascular lymphocytic cuffing. PCR analysis performed on brain tissue was positive only for the EBV genome, while extensive investigations for other viral infections were negative. The patient's neurological symptoms rapidly worsened and he died two months later. This case report suggests that in patients presenting neurological and radiological signs of encephalitis after an HSCT, an EBV involvement should be considered, even in the absence of CSF and blood PCR virus detection.

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**Key words:** encephalitis – Epstein–Barr virus – cerebrospinal fluid – hematopoietic stem cell transplantation – leukemia

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Accepted for publication 15 October 2014

**Abbreviations:** ADC, apparent diffusion coefficient; ALL, acute lymphoblastic leukemia; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; EBV, Epstein–Barr virus; EEG, electroencephalogram; FLAIR, fluid attenuating inversion recovery; GFAP, glial fibrillary acid protein; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LMP, latent membrane protein; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; Ph+, Philadelphia chromosome-positive; PTLN, post-transplant lymphoproliferative disorder; Q-PCR, quantitative polymerase chain reaction.

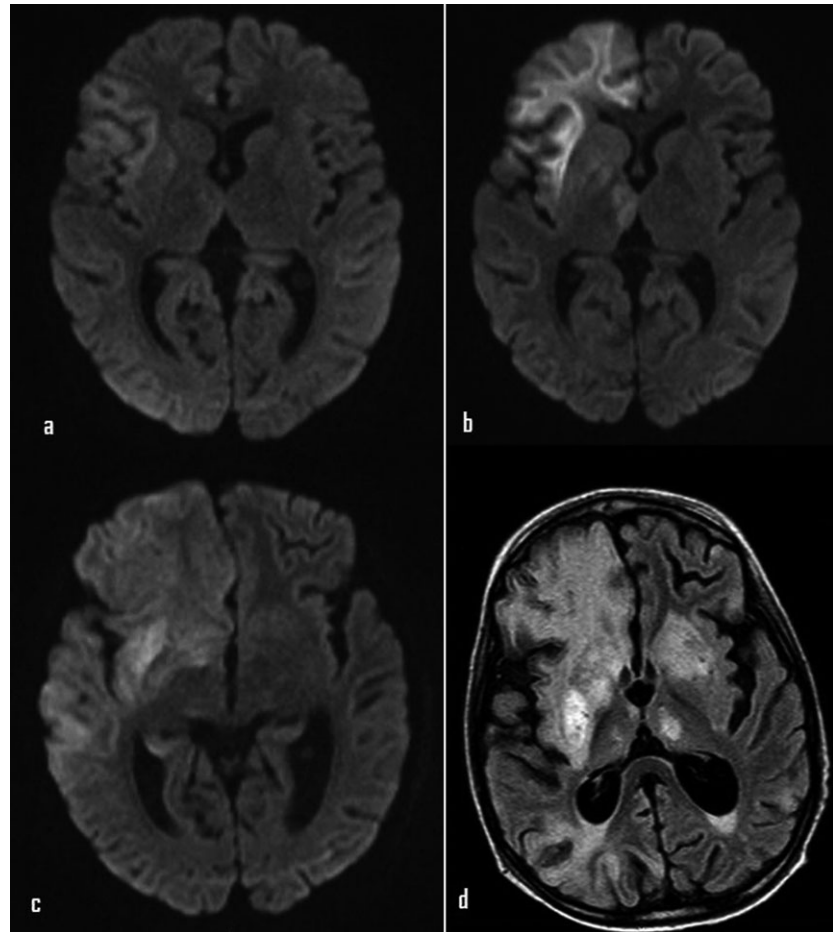
A wide range of pathogens, including viruses, can cause encephalitis in HSCT patients (1–3). EBV encephalitis has been described as a rare event in the post-HSCT setting, with a reported frequency of 19% among the other viral etiologies (4). PTLD is a well-known life-threatening disease that can be restricted to the CNS and which represents the most frequent neurological complication of EBV infection following transplant; nonetheless, encephalitis must be considered in the differential diagnosis (5–9). Encephalitis is suspected if patients present typical clinical signs, inflammatory cells are present in the CSF or changes in brain imaging are suggestive of inflammation (2–4). Over the last few years, detection of the EBV DNA in the CSF has become the gold standard for the diagnosis of EBV CNS infections and EBV-associated CNS lymphomas (10–12). The viral DNA detection in the CSF represents a diagnostic standard in the clinical practice considering that a brain biopsy may be associated to a significant morbidity (intracranial hemorrhage or biopsy site edema), although the incidence of serious adverse events has diminished with the use of modern stereotactic approaches (2–4, 13). Herein, we present the case of a leukemic child who developed an EBV encephalitis after HSCT that was diagnosed only by brain biopsy, while virological investigations in the CSF were repeatedly negative and only low levels of EBV DNA were detected in the peripheral blood. To our knowledge, this is the first observation reporting a similar discrepancy in EBV infections.

### Case report

A seven-yr-old child with Ph+ ALL in second complete hematological remission underwent an HSCT from his mother (10/12 HLA compatible; HLA-A and HLA-DPB1 mismatched) in November 2011. Both recipient and donor were EBV-IgG seropositive and IgM seronegative. The conditioning regimen included thiopeta (5 mg/kg/day, days –8, –7), fludarabine (40 mg/m<sup>2</sup>/day, days –6 to –3), busulfan (3.2 mg/kg/day, days –6 to –3), and ATG (2.5 mg/kg/day, days –3, –2, –1). A T-cell repleted bone marrow graft containing  $2.86 \times 10^8$  total nuclear cells/kg,  $1.65 \times 10^6$  CD34<sup>+</sup> cells/kg, and  $0.34 \times 10^8$  CD3<sup>+</sup> cells/kg was infused on day 0. Cyclosporine A and a short course of methotrexate were given as GVHD prophylaxis. Engraftment was achieved on day +18, with a full donor chimerism. On day +8, an asymptomatic CMV viremia was detected by a quantitative real-time PCR method; the CMV DNA level in the blood was

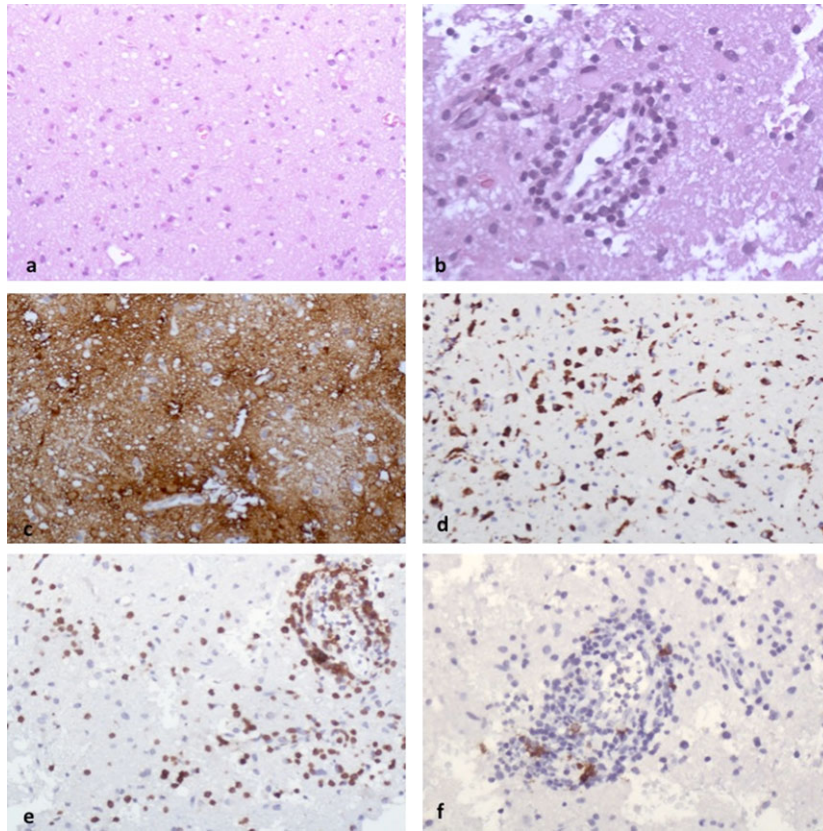
$4 \times 10^3$  cp/mL. Preemptive therapy with foscarnet (60 mg/kg every 12 h) was started. On day +20, because of a persistent blood viral replication ( $2.29 \times 10^3$  cp/mL), treatment was modified by adding ganciclovir (5 mg/kg/day) to foscarnet (60 mg/kg/day). The blood CMV DNA level became undetectable from day +32, and one wk later, the antiviral treatment was discontinued. On day +39, the patient presented biopsy-proven bilateral testicular relapse. Bone marrow aspirate showed morphological remission; full donor chimerism was still maintained. Bilateral testicular radiotherapy was started, with an initial response. In January 2012, on day +61, the child developed fever, headache, and dysuria. At that time, the white blood cell count was  $5.79 \times 10^9$ /L with 67% neutrophils and 19% lymphocytes; the hemoglobin level was 8.8 g/dL and platelet count  $86 \times 10^9$ /L. The chemistry panel and liver function tests were within the normal range. Baseline serum cyclosporine level was 52 ng/mL. No active GVHD was present. Intravenous antibacterial treatment with piperacillin–tazobactam and ciprofloxacin was promptly started. The day after, he presented with vomiting and an altered sensorium, followed by generalized tonic–clonic seizures, successfully treated with midazolam. Left hemiplegia was present on clinical examination. Brain MRI, performed on the same day, revealed multiple lesions in the right hemisphere; in particular, an area involving the cerebral cortex and ipo-cortex of the frontal-insular region was characterized by a restricted diffusion with hypointensity in ADC images and a normal intensity in FLAIR images; other lesions that displayed T2 hyperintensity and T1 hypointensity involved the basal ganglia with associated compression of the lateral ventricle; another area with the same features was present in the mid-brain. The lesions did not show an abnormal contrast enhancement (Fig. 1a). The MRI images were highly suggestive of a viral encephalitis. CSF examination showed a lymphocytic pleocytosis (200 cells/μL), increased protein levels (92 mg/dL, normal range 10–45), and slightly increased glucose levels (79 mg/dL, normal range 40–70); no malignant cells were found by cytological and flow-cytometry analysis; oligoclonal IgG bands were absent. Based on a suspicion of viral encephalitis, cyclosporine was stopped and treatment with dexamethasone (4 mg/m<sup>2</sup>/every six h) and foscarnet (60 mg/kg every 12 h) was immediately started with the addition of valproic acid as anticonvulsant drug; intravenous antibacterial treatment was continued; polyvalent immunoglobulins (400 mg/kg/dose) were administered and planned every two wk. During the

*Fig. 1.* Brain MRI performed at the time of initial presentation and during clinical progression of neurological symptoms. (a) Area of restricted diffusion with low ADC values, involving the cerebral cortex and hypocortex of the frontal-insular region (DWI-weighted, axial image); (b) extension of the frontal-insular lesion, with hypointensity in ADC (DWI-weighted, axial image); (c) lesions involving frontal-insular region, basal ganglia with associated compression of the lateral ventricle and mid-brain (DWI-weighted, axial image); (d) progression of lesions also involving left frontal-insular region (FLAIR-weighted, axial image). DW, diffusion weighted.



subsequent few days, the results of CSF PCR analysis showed the absence of DNA of CMV, EBV, HSV-1, HSV-2, HHV-6, HHV-8, VZV, JCV, BKV, and of RNA of enteroviruses. In addition, all CSF cultures and serologic tests for bacteria, mycobacteria, fungi, and toxoplasma were negative. At that time, EBV-PCR from peripheral blood was negative; EBV-DNA load was monitored every two wk; it displayed only low levels in two circumstances ( $1.3 \times 10^2$  and  $2.45 \times 10^2$  copies/mL, on days +69 and +87, respectively). Four days later, the child presented continuous epilepsy and a progressive consciousness impairment; he was referred to pediatric ICU. Repeated MRI documented an extension of the frontal-insular lesion, with hypointensity in ADC and slight hyperintensity in FLAIR images (Fig. 1b); EEG showed diffuse slowing, consistent with encephalitis. Anticonvulsant phenytoin was added to the treatment. Despite the treatment with foscarnet and dexamethasone, the patient did not show any clinical improvement. On day +75, two wk after the onset of neurological symptoms, a second lumbar puncture was performed in an attempt to identify the causative

agent of encephalitis. CSF examination was normal, with no cellular sediment, a glucose level of 60 mg/dL, and a protein level of 30 mg/dL; PCR-CSF analyses confirmed the absence of DNA of CMV, EBV, HHV-6, HSV-1, HSV-2, and VZV. The patient experienced progressive deterioration of the neurological function and required intubation and mechanical ventilation. EEG monitoring documented a worsening of the bioelectric patterns and MRI revealed an extension of inflammatory lesions also involving the right parietal cortex and left frontal-insular region (Fig. 1c,d). On day +83, in the absence of any neurological improvement, foscarnet was stopped and treatment with aciclovir (10 mg/kg every eight h, intravenously) was started. On day +98, the irreversible progression of brain damage without a recognized viral etiology led us to perform a stereotactic biopsy that showed damage to the parenchyma, reactive gliosis, microglial activation, and inflammatory cellular infiltration (Fig. 2a,b). The alterations were highlighted by the intense immunoreactivity for GFAP and CD68 (Fig. 2c,d). An infiltrate of small lymphocytes not showing any features of atypia (e.g.,



*Fig. 2.* Immunohistochemical study performed on brain tissue. (a,b) Cerebral parenchyma shows gliosis and lymphocyte infiltrate; (c) reactive gliosis is positive for GFAP; (d) CD68<sup>+</sup> evidences marked microglial reaction; (e) most lymphocytes are CD3<sup>+</sup>; (f) B-lymphocytes (CD20<sup>+</sup>) are scant.

irregular to folded nuclei, condensed chromatin, inconspicuous nucleoli, or scant cytoplasm) was present as single cells and around the vessels. The majority of the cells were positive for CD3 and CD8, while CD20-positive B-lymphoid cells were scant (Fig. 2e,f). Morphologic and immunophenotypic features of the T-cell infiltrate and the markers of glial activation were consistent with an infectious/inflammatory process while were not compatible with the diagnosis of EBV-associated T-cell PTLD. The immunohistochemical study with a monoclonal antibody for EBV (LMP-1) was positive. The presence of EBV in the brain tissue was assessed by Q-PCR. DNA was extracted from the FFPE tissue specimen using QIAamp DNA Blood Mini kit (by QIAGEN, Hilden, Germany), and the presence of EBV per cells was established using the EBV R-gene kit and the Cell Control R-gene obtained by Argene (Verniolle, France). The analysis detected 116 copies/35 cells of EBV on brain tissue. At the same time, nucleic acid detection on the brain tissue of CMV, HSV 1/2, VZV, HTLV, parvovirus B19, BKV, JCV, measles, mumps, enteroviruses, respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, rhinovirus, adenovirus, novel human coronavirus) was negative. PCR analysis from parallel peripheral blood samples was nega-

tive for EBV, as well as for the aforementioned viruses. These features prompted us to the final diagnosis of EBV-related encephalitis. The antiviral treatment was modified replacing aciclovir with ganciclovir (5 mg/kg every 12 h) from day +116. At the same time, hematological relapse, with 60% of bone marrow Ph+ ALL blasts, was diagnosed, for which daily dasatinib therapy, at the dosage of 80 mg/m<sup>2</sup>/day, was given by nasogastric tube. Despite antiviral and antileukemic treatment, the patient experienced further deterioration of neurological function and progression of hematological disease and expired on day +132 after transplant. Autopsy was not performed.

### Discussion

Our case shows that a diagnosis of EBV encephalitis should be hypothesized when a highly immunosuppressed patient presents unspecific neurological symptoms, even in the absence of EBV detection in the CSF and without significant systemic reactivation. The virological results obtained in our patient represent an uncommon finding according to the literature. The detection of EBV DNA in the CSF and the concomitant low levels or negative DNA results obtained from peripheral blood in patients with a deep

EBV-associated disease have been reported in patients with a diagnosis of isolated CNS-PTLD (14–17). On the contrary, it was surprising that in our patient EBV-PCR was negative in two consecutive CSF samples despite an extensive biopsy-proven EBV encephalitis. As EBV infects B cells, any tissue biopsy containing B cells may be positive for EBV by PCR and this may explain a positive PCR on tissue biopsy while negative on CSF. However, in our case, this discrepancy was not justified as pleocytosis with predominant lymphocytes was present in CSF. Moreover, the high viral load ( $\geq 1$  copies per cell) detected by PCR on brain biopsy (18, 19) was in favor of the hypothesis of a viral replication against a B-cell contamination in the brain parenchyma. Nevertheless, false-negative PCR results on CSF and peripheral blood could not be excluded. False-negative cases have been ascribed to many factors, including low amount of viral DNA in the test sample, presence of PCR inhibitors such as common components of clinical samples (e.g., hemoglobin, heparin, IgG), ineffective release of viral DNA from the cells, and poor DNA recovery after extraction and purification steps (20). Moreover, cases of early stage HSV encephalitis in children and in immunocompromised patients, where no cells were found in the CSF and HSV PCR was negative, have been occasionally reported (2–4), but this is, to our knowledge, the first observation reporting a similar discrepancy in EBV infections. As the information obtained from the examination of the CSF and of the peripheral blood may be misleading in HSCT patients with acute neurological symptoms, neuroimaging represents, currently, a key part of the investigational process for encephalitis. In fact, the location of the lesions within the brain may be useful for a differential diagnosis. Indeed, EBV has a characteristic tropism for some areas: Cerebral hemispheres, basal ganglia, cerebellum, brain stem, thalamus, and the limbic system, in this order, are frequently involved (21–23). However, when MRI imaging and CSF findings are suggestive for encephalitis, but inconclusive for the etiological diagnosis, a brain stereotactic biopsy should be considered, in order to provide direct evidence of brain involvement from specific infectious processes and to exclude many of the non-infectious alternative diagnoses (2–4).

Obtaining a diagnosis of viral encephalitis is relevant to ensure the prompt initiation of a specific treatment. Nevertheless, currently, there is limited evidence of effective therapies for EBV encephalitis post-transplant, which continues to be a challenging clinical problem with a

consistently poor outcome (24–28). In particular, efficacy of antiviral drugs in EBV encephalitis is debated (29). Successful treatment with intravenous ganciclovir has been reported in other cases of EBV-associated encephalitis (30–32) but, in this case, it was added in a stage too late to evaluate its efficacy. However, the patient had been treated from the onset of the symptoms with foscarnet, a highly active drug against EBV (33, 34). This fact argues against an efficacious effect of antiviral drugs in EBV encephalitis, at least in this patient.

In conclusion, our case shows that an aggressive diagnostic approach in transplanted patients, including a brain biopsy for selected cases, is needed to pursue an early diagnosis in the setting of clinical and radiographic evidence consistent with viral encephalitis where CSF analysis does not identify any etiology.

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