

Encephalitis by Epstein Barr Virus in a Transplant Immunosuppressed Patient

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Encefalitis por virus de Epstein Barr en una paciente trasplantada inmunosuprimida. Reporte de caso

ABSTRACT

Encephalitis due to Epstein-Barr Virus (EBV) is a rare condition that primarily affects children and immunosuppressed patients. Diagnosing EBV encephalitis can be challenging due to its nonspecific clinical presentation and the lack of confirmatory tests. We present the case of a 66-year-old woman with a history of kidney transplantation who was admitted due to progressive subacute mental deterioration, preceded by vertigo and without fever. Physical examination revealed no cranial nerve abnormalities, focal neurological deficits, or meningeal signs. Cerebrospinal fluid (CSF) analysis showed a mild increase in protein and pleocytosis (13/ μ L) without hypoglycorrhachia. Brain magnetic resonance imaging (MRI) revealed multiple bi-hemispheric supratentorial hyperintensities associated with mild vasogenic edema, most prominent at the cortico-subcortical interface, hippocampal regions, and basal ganglia. An extensive search for microorganisms identified EBV by RT-PCR in the CSF (1,650 copies/mL). The patient initially received acyclovir without improvement but achieved rapid recovery after switching to ganciclovir. The patient was discharged, and outpatient follow-up visits demonstrated full recovery. This case supports the effectiveness of ganciclovir, as observed in previous reports. Overall, patients with EBV encephalitis generally have a benign course with complete recovery or mild sequelae.

Keywords: Encephalitis; Epstein-Barr Virus Infections; Ganciclovir; Immunocompromised Host; Transplantation.

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RESUMEN

La encefalitis por virus de Epstein-Barr (VEB) es una afección rara que afecta principalmente a niños y pacientes inmunodeprimidos. Su diagnóstico puede ser un desafío debido a la presentación clínica inespecífica y la falta de pruebas de confirmación. Presentamos el caso de una mujer de 66 años inmunodeprimida con un trasplante renal previo, que ingresa por deterioro mental subagudo progresivo precedido de vértigo y sin fiebre. El examen físico no indicó alteraciones de los pares craneales, signos neurológicos focales ni meníngeos. Un estudio del LCR destacó un leve aumento de proteínas y pleocitosis (13/ μ L), pero sin hipoglucorraquia. La resonancia magnética cerebral mostró múltiples hiperintensidades supratentoriales bihemisféricas asociadas a edema vasogénico leve, más evidente en la interfaz cortico-subcortical, regiones del hipocampo y en los ganglios basales. Una búsqueda exhaustiva de diferentes microorganismos sólo mostró VEB mediante PCR a tiempo real en el LCR (1.650 copias/mL). La paciente recibió inicialmente tratamiento con aciclovir sin mejoría, pero logró una rápida recuperación tras un cambio a ganciclovir. Fue dada de alta y las visitas de seguimiento ambulatorias demostraron una recuperación completa. Este informe respalda la utilidad del ganciclovir observada en informes anteriores. En general, estos pacientes tienen un curso benigno con recuperación ad integrum o secuelas leves.

Palabras claves: Encefalitis; Ganciclovir; Huésped Inmunocomprometido; Infecciones por Virus de Epstein-Barr; Trasplante.

Epstein-Barr virus (EBV) encephalitis is a rare condition primarily observed in the pediatric population and in immunocompromised adults, associated either with primary infection or viral reactivation¹. Its clinical presentation is nonspecific², and conventional diagnostic tests often do not provide definitive guidance³, necessitating a high index of suspicion to establish the diagnosis.

In this paper, we report a recently observed case of EBV encephalitis and discuss the challenges encountered in the diagnostic process, the confirmation of etiology, and current therapeutic concepts based on the available literature.

Clinical case

A 66-year-old female patient with a history of kidney transplantation for polycystic kidney

disease (performed 10 years prior) was initially admitted due to kidney graft failure, vertigo, and vesicular lesions in the oral cavity. She was receiving prednisone (5 mg/day), mycophenolate mofetil (750 mg/day), and everolimus (2.5 mg every 12 hours). Everolimus had replaced tacrolimus following a diagnosis of lip carcinoma a year earlier. Additionally, she was taking diltiazem, folic acid, atorvastatin, omeprazole, and NPH insulin for post-transplant diabetes. The stomatitis was attributed to an adverse drug reaction to everolimus, which was subsequently replaced with sirolimus (1 mg/day). Kidney graft failure reversed after hydration (serum creatinine decreased from 1.85 to 1.5 mg/dL), and oral lesions resolved following the switch to sirolimus. An Ear-Nose-Throat specialist diagnosed benign paroxysmal positional vertigo,

but an examination of the VIII nerve could not be completed due to the patient's impaired concentration. After 10 days, she was discharged with reduced vertigo but continued difficulties with concentration and attention.

Following discharge, her mental state deteriorated over the next 3 weeks, with symptoms including confusion, lethargy, disorientation, and behavioral changes, leading to rehospitalization. Upon admission, her vital signs were normal; she had no fever or dehydration and weighed 40 kg. Physical examination revealed no abnormalities in cranial nerves, focal neurological deficits, or meningeal signs. Laboratory results showed a blood glucose level of 181 mg/dL, normocytic normochromic anemia (hemoglobin 8.3 g/dL) with no leukocytosis or platelet abnormalities. C-reactive protein was mildly elevated (2.63 mg/dL; reference <0.5 mg/dL). Kidney function was at baseline values (serum creatinine 1.61 mg/dL; Glomerular Filtration Rate 30 mL/min/1.73 m²). Liver profile and coagulation tests were normal;

there were no electrolyte or acid-base imbalances, nor hypoxemia or hypercapnia, and thyroid hormone levels were normal. An HIV-ELISA test was negative.

A non-contrast-enhanced brain CT scan showed no acute lesions but indicated an old left thalamic lacunar infarction. Brain MRI revealed multiple bi-hemispheric supratentorial hyperintensities on axial FLAIR sequences, associated with mild vasogenic edema, most prominent at the cortico-subcortical interface, hippocampal regions, and basal ganglia (Figure 1), top row panels A-D). No hemorrhages or associated restriction phenomena were identified.

A lumbar puncture was performed, and extensive CSF analysis revealed a mild increase in protein (78 mg/dL) and pleocytosis (13/μL) with no hypoglycorrachia. No microorganisms were detected in Gram stain, routine or fungal cultures, or in the meningitis-encephalitis molecular panel (FilmArray, BioMerieux). PCR studies for JC and BK viruses, *Mycobacterium tuberculosis*, atypical

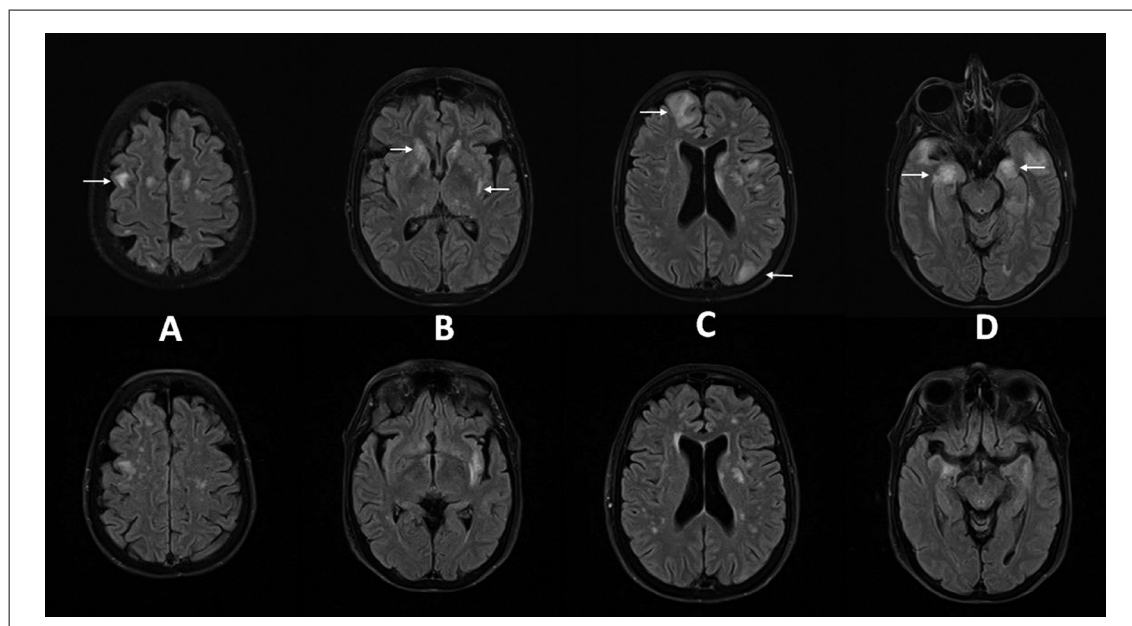


Figure 1: Top Row. Axial FLAIR sequence images demonstrating multiple bihemispheric supratentorial hyperintensities associated with mild vasogenic edema, most evident at the cortico-subcortical interface (arrows in panel A and C), at hippocampal regions (arrows in panel D) and in basal ganglia (arrows in panel C). No hemorrhages or associated restriction phenomena were identified. There was no contrasted study. Bottom row. Follow-up brain MRI (FLAIR) at 6 weeks reveals significant regression of lesions, most evident when comparing images, A and C.

Mycobacteria, and *Toxoplasma spp.* were negative. *Cryptococcus spp.* antigen and VDRL tests were also negative. Flow cytometry did not reveal a clonal profile suggestive of neoplasm. A complementary PCR for viral agents (Allplex Meningitis Panel Assay; Seegene Inc.) was positive for EBV with 1,650 copies/mL in the CSF. Attempts to detect EBV in blood by PCR were negative. EBV IgM-VCA serology was also negative. An EEG study was normal, and the panel of paraneoplastic antineuronal antibodies showed no reactivity.

Based on these results, antiviral therapy was initiated with intravenous acyclovir at the maximum dose for her weight. However, no improvement was observed by the fourth day of treatment, and the therapy was switched to ganciclovir, adjusted for renal function (2.5 mg/kg/day). The response to this change was rapid and evident. By the fifth day of treatment, the patient was fully awake, oriented, communicative, and functional, with only mild residual lethargy. Follow-up brain MRI (Figure 1, bottom rows) showed significant regression of lesions. Involvement persisted in the left insula with an irregular focus of enhancement after gadolinium administration. Hyperintensities at the hippocampal level also persisted. The patient was discharged, and outpatient follow-up visits demonstrated full recovery.

Discussion

EBV is a ubiquitous agent typically acquired at an early age, often asymptotically, but capable of establishing a lifelong latent infection in B lymphocytes⁴. Both primary infection and viral reactivation can cause encephalitis; however, it is a rare complication, constituting less than 1% of all cases of encephalitis^{5,6}. EBV encephalitis tends to be more frequent in immunocompromised individuals compared to immunocompetent adults, although the difference is not statistically significant⁷. In immunocompetent individuals, EBV encephalitis usually occurs following primary infection and is more common in children and young adults. In contrast, it is more frequently observed in adults with compromised immune systems. Among patients with EBV encephalitis, 80% of those under 25 years of age have posi-

ve VCA IgM assays, whereas 80% of those over 25 years of age have negative VCA IgM tests, suggesting viral reactivation rather than a recent infection, as seen in our patient⁸.

The clinical presentation of EBV encephalitis is often subacute, with an average of 52 days prior to consultation, and nonspecific symptoms such as apathy (81%), vestibular syndrome (66%), or headache (58%). Classic symptoms seen in other viral encephalitides, such as focal neurological signs (27%), seizures (18%), confusion (12%), and fever (8%), are relatively uncommon⁹, complicating diagnosis. Therefore, prolonged mental alterations (weeks to months) accompanied by other non-specific neuropsychiatric symptoms in susceptible patients should raise suspicion for EBV encephalitis, particularly when associated with vertigo, as in our patient.

Brain MRI is highly sensitive and specific for detecting inflammatory changes. In EBV encephalitis, the most frequent findings are focal lesions (58%) affecting the limbic system, as well as the temporal, occipital, and frontal lobes. Diffuse lesions (31%) and even normal MRI findings (10%) can also be observed⁹. In our case, FLAIR sequences revealed multiple hyperintense focal lesions in both hemispheres, at the cortico-subcortical level, over the tentorium, as well as in hippocampal regions and the basal ganglia. These findings confirm encephalitis but do not point to a specific etiology.

CSF analysis is often unremarkable, showing mild mononuclear pleocytosis (usually less than 10 cells/ μ L), increased protein levels, and frequently normal glucose levels (83% and 95%, respectively)⁹.

Establishing a syndromic diagnosis of encephalitis can be challenging. We believe our patient meets the diagnostic criteria for confirmed encephalitis as proposed by the International Encephalitis Consortium: altered mental status with no other identifiable cause, a new onset of focal neurological findings (vertigo), CSF leukocyte count $\geq 5/\mu$ L, and neuroimaging abnormalities¹⁰. However, the etiological diagnosis of EBV encephalitis can be complex, as a positive EBV CSF amplification has limitations and must be interpreted with caution.

In a descriptive study evaluating EBV-positive CSF samples (n= 39), only 25% were associated with encephalitis¹¹. Furthermore, other pathogens were found in 22% of cases, suggesting a minor or no pathogenic role¹². Quantification of EBV copies by RT-PCR can help determine its pathogenic role. Higher numbers of copies have been associated with CNS lymphoma or EBV encephalitis (IQR 25,540-152,000 copies/mL and 8,000-64,000 copies/mL, respectively) compared to post-infectious conditions (IQR 500-1,953 copies/mL)¹¹. Nonetheless, cases of encephalitis with a viral load below 1,000 copies/mL have been reported¹¹. The exclusion of other potential pathogens, autoimmune encephalitis, and a thorough evaluation of the clinical background are crucial in determining the pathogenic role of EBV in CSF. In our case, the detection of a lower viral load (1,650 copies/mL) was atypical but, given the compatible clinical picture, immunosuppression, absence of other pathogens, and a favorable therapeutic response, strongly suggests a causal role.

Acyclovir and ganciclovir are the most commonly used antivirals for treating EBV encephalitis⁸. However, there are no prospective studies evaluating their effectiveness, and available evidence comes from case reports and series. Ganciclovir has demonstrated greater in vitro activity than acyclovir¹³ but has a less favorable side effect profile, with up to 30% of patients experiencing neutropenia due to myelotoxicity¹⁴.

Some reports have documented successful treatment with both antivirals⁸, but the majority of immunocompromised patients have received only ganciclovir^{2,15}. The overall prognosis is generally favorable, with full recovery or mild sequelae in most cases^{2,8,9}. Our patient showed progressive improvement after switching from acyclovir to ganciclovir. This experience supports the use of ganciclovir in immunocompromised patients, while balancing the associated risks.

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