EBV-associated CNS Infection in an Immunocompetent Adult: A Case Report and Literature Review

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Verbal and written consent was obtained from the patient to publish his case.

Abstract

Epstein-Barr virus (EBV) infections typically manifest with respiratory symptoms, lymphadenopathy, and, rarely, central nervous system (CNS) involvement. We report an uncommon case of an immunocompetent 18-year-old male with altered mental status due to EBV-associated CNS infection. The patient, with a recent history of infectious mononucleosis, presented with fever and meningeal irritation signs. Initial investigations revealed leukocytosis, atypical lymphocytes, and positive heterophile antibodies, but a head CT scan was normal. Empirical treatment for bacterial meningitis was initiated. Results of further assessments, including a positive EBV serology, a consistent cerebrospinal fluid analysis and positive EBV DNA in the CSF led to the diagnosis of EBV-associated CNS infection-more specifically meningoencephalitis. Neuroimaging, including MRI, showed no abnormalities. The patient improved with supportive care and a four-day course of acyclovir. We discussed the challenges in diagnosing EBV-associated CNS infection, emphasizing the role of CSF PCR in confirming the diagnosis. The importance of ruling out other infections is highlighted, and the heterogeneity in the mechanism of infection is explored. The case underscores the significance of recognizing an isolated, active EBV infection in young adults with altered mental status, especially when more common causes have been excluded.

Keywords: Epstein-Barr virus, CNS infection, aseptic meningitis, altered mental status, CSF PCR, viral encephalitis.

Introduction

EBV infection is commonly characterized by fever, malaise, sore throat, upper respiratory symptoms, headache, and lymphadenopathy. CNS involvement is uncommon, occurring in 0.5-7.5% of all EBV infections [1], and can present with a wide spectrum of symptoms, including encephalitis, meningitis, myelitis, cranial neuropathy, mononeuritis multiplex, brachial plexopathy, acute psychosis, Guillain Barré syndrome, to acute cerebellar ataxia or seizures [1-3]. These neurological symptoms usually manifest 1-3 weeks after the onset of respiratory symptoms [1,4] but could also manifest much later, as in the case of our patient. Interestingly, EBV-related CNS infection tends to occur in younger adults, with an average age of 36, as reported in Japan [4]. We report a case of EBV-associated CNS infection in an immunocompetent adult.

Case Presentation

An 18-year-old Caucasian male with a past medical history of infectious mononucleosis eight weeks ago presented with altered mental status. His friends found him lying on the floor with a fever, groaning, combative, and not able to be calmed with verbal measures. He was alert and oriented as recently as the day prior. Emergency medical services (EMS) brought him to an outside facility, where he was sedated and intubated to protect his airway and transferred to our facility. Physical examination demonstrated a fever of 39.16 (102.5), no lymphadenopathy, mild hepatosplenomegaly, and nuchal rigidity. Initial neurological examination under sedation was otherwise non-focal.

Methods

The patient had elevated leukocytosis with no left shift. Atypical lymphocytes were detected. A mononucleosis screen (heterophile antibodies) test was positive. The glucose level was mildly elevated. Serum salicylate, alcohol, and acetaminophen levels were negative. His serum creatinine, creatinine kinase, and aldolase levels were elevated (Table *1*). The urine drug screen test was negative (Table *2*). A computed tomography (CT) scan without contrast of the head showed no intracranial abnormalities. He was treated empirically with piperacillin-tazobactam and intravenous fluid resuscitation before being transferred to the intensive care unit (ICU).

On the first day of arrival to the ICU, the patient remained sedated due to severe agitation. Piperacillin-tazobactam was switched to Ceftriaxone and Vancomycin, and Dexamethasone was added for suspected bacterial meningitis. Serum HIV, HSV, and Syphilis screen were negative. The patient tested positive for serum Epstein Barr Virus (EBV) Viral Capsid Antigen (VCA) IgG, EBV VCA IgM, and EBV Nuclear Antigen (EBNA) IgG. His serum creatinine kinase remained elevated (Table *1*). Urinalysis was positive for blood and red blood cells (RBC) (Table *2*). He received aggressive fluid hydration for rhabdomyolysis due to combative behavior and sedation.

The magnetic resonance imaging (MRI) of the head was normal, with no restricted diffusion in the diffusion-weighted image (DWI), and the apparent diffusion coefficient (ADC) map. The electroencephalography (EEG) only showed continued generalized slowed activity and absent post-dominant rhythm consistent with encephalopathy (Figure *1*).

A lumbar puncture was performed to obtain cerebrospinal fluid (CSF) for analysis. The opening pressure was elevated, and the CSF was clear. CSF analysis demonstrated increased WBC with lymphocytes predominance, increased protein, and mildly increased glucose, which was consistent with aseptic meningitis (Table *3*).

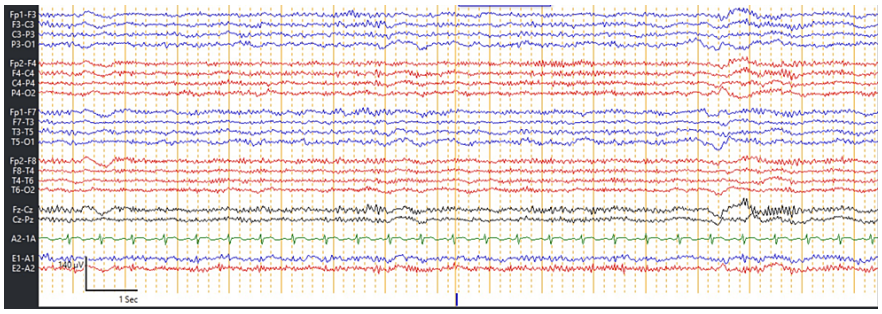

Figure 1: Routine EEG showing generalized slowing with absent PDR

Intravenous Acyclovir was added to cover for possible herpes meningoencephalitis. The CSF panel came back later, and EBV DNA was detected. The central nervous system viral panel, bacterial meningitis panel, and other micro-organism panels were all negative (Table*4*).

The acid-fast bacilli (AFB) stain and mycobacterium culture were also negative. He was diagnosed with viral meningoencephalitis due to EBV infection.

Investigation	Normal Range	Results
Blood count		
WBC count	4.5-11 K/uL	17.5 K/uL
Neutrophils	37-80%	46%
Lymphocytes	10-50%	39%
Atypical lymphocytes	0%	6%
Monocytes	2-9%	8%
Eosinophils	0-4%	1%
RBC count	4.7-6.1 M/uL	5.26 M/uL
Hemoglobin	14.0-18.0 g/dL	15.7 g/dL
Hematocrit	42.0-52.0 %	46.5%
MCV	80-94 fL	86.7%
Platelets	140-450 K/uL	359 K/uL
Serum chemistries		
Glucose	65-115 mg/dL	138 mg/dL
BUN	8-21 mg/dL	18 mg/dL
Creatinine	0.8-1.5 mg/dL	1.5 mg/dL
AST (SGOT)	17-59 units/L	35 units/L
ALT (SGPT)	21-72 units/L	34 units/L
Alkaline phosphatase	38-126 units/L	68 units/L
Creatinine kinase	26-308 IU/L	2,953 IU/L
Aldolase	≤ 8.1 units/ml	138.8 units/ml
Alcohol Screen	Negative	Negative
Salicylate	Negative	Negative
Acetaminophen	Negative	Negative
Serology/Immunology		
Anti-Nuclear Antibody (ANA)	Negative	1:40
Syphilis screen	Non-reactive	Non-reactive
HIV screen	Non-reactive	Non-reactive
Mononucleosis screen	Negative	Positive
Epstein Barr Nuclear Ag IgG	-	Positive
EBV VCA IgG and IgM	-	Positive
Coccidioides Ab	-	Negative
Coccidioides Ab complement fixation	-	<1:2 (antibody not detected)
CMV IgM and IgG	-	Negative
CMV DNA Qualitative PCR	-	Not detected
Antibody to TP antigen IgM	-	Negative
Antibody to T F antigen IgG	-	Negative
HSV1 and HSV 2 DNA Qualitative PCR	Not detected	Not detected

Table 1: Basic Bloodwork: Complete Blood Count (CBC), Serum Chemistries, and Serology/Immunology

Table 2: Urinalysis and Urine Drug Screen

Investigation	Normal Range	Results
Urinalysis		
Glucose	Negative	Negative
Bilirubin	Negative	Negative
Ketones	Negative	Negative
Blood	Negative	2+
pH	5.0-8.0	6.0
Protein	Negative	20 mg/dL
Urobilinogen	Negative	<2.0 mg/dL
Nitrite	Negative	Negative
Leukocyte Esterase	Negative	Negative
Specific Gravity	1.003-1.025	1.035
Color	Yellow	Yellow
Clarity	Clear	Cloudy
RBC	0-3/HPF	78
WBC	0-3/HPF	2
Squamous Epithelial	0-5/HPF	None
Bacteria	None	None
Mucous	None	None
Hyaline Cast	None	None
Amorphous Crystals	None	Trace/HPF
Uric Acid Crystals	None	Trace/HPF
Urine Drug Screen		
Urine Amphetamine	Negative	Negative
Urine Barbiturate	Negative	Negative
Urine Benzodiazepine	Negative	Negative
Urine Cannabinoid	Negative	Negative
Urine Cocaine	Negative	Negative
Urine Opiate	Negative	Negative

Table 3: Lumbar Puncture Opening Pressure and CSF Analysis

Investigation	Normal Range	Results
Opening Pressure	6-25 cmH2O	26 cmH2O
CSF Analysis		
WBC	0-5	42
Neutrophils	0-6%	12%
Lymphocytes	40-80%	85%
RBC	-	98
Protein	12-45 mg/dL	90 mg/dL
Sugar	40-70 mg/dL	72 mg/dL
LDH	-	26 units/L

Results

The patient's mental status started to improve over the next 24 hours; he became more cooperative, started responding to commands, and was successfully extubated. The neurological examination after extubating which included cranial nerves, muscle strength and sensation, and tendon reflexes were all unremarkable, although he still has neck stiffness and limited hip flexion due to muscle pain. The patient remained slightly confused and exhibited some degree of unusual behavior and language use noticeable by his parents. He complained of some muscle aches and headaches. The decision to discontinue antibiotics, acyclovir, and dexamethasone was made after 4 complete days of treatment as the etiology of his illness was likely from EBV infection.

His clinical and mental status gradually improved with supportive and symptomatic treatment. By the fourth day of admission, his mental status was back to normal baseline. He was able to walk around with minimal muscle aches and a mild posterior headache. The patient continued to exhibit no neurological deficit. Eventually, he was discharged home by the seventh day.

Table 4: CSF Microbiology Panel

CSF Micro-organism panel	Normal Range	Results
Viral panel		
EBV DNA quantitative	Not Detected	<200 DETECTED copies/mL
	Not Detected	<2.3 log10 DNA copies per milliliter.
PCR Enteroviruses	Not Detected	Not Detected
Herpes simplex virus 1 and 2 (HSV-1, HSV-2) IgG	Not Detected	<0.01 (not detected)
Echovirus type 4, 7, 9, 11, and 30 Ab	Not Detected	<1:1 (not detected)
Coxsackie virus A2, A4, A7, A9, A10, A16 Ab	Not Detected	<1:8 (not detected)
West Nile Virus IgG	Not Detected	<1.30 (not detected)
West Nile Virus IgM	Not Detected	<0.9 (not detected)
Lymphocytic choriomeningitis virus (LCMV) IgG and IgM	Not Detected	<1:1 (not detected)
Varicella zoster virus (VZV) IgM and total Ab	Not Detected	Not Detected
Mumps virus IgG and IgM IFA	Not Detected	Not Detected
Measles virus IgG and IgM IFA	Not Detected	Not Detected
Bacterial meningitidis panel		
Haemophilus influenzae type B	Negative	Negative
Neisseria meningitidis types A, B, C, Y, W13	Negative	Negative
E. Coli	Negative	Negative
Streptococcus pneumoniae	Negative	Negative
Group B Streptococcus antigen	Negative	Negative
Others		
Coccidioides Ab immunodiffusion	Negative	Negative

Discussion

The mechanism underlying EBV-associated CNS infection is not well established. Current evidence suggests that EBV gains access to the CNS by utilizing infected lymphocytes to traverse the blood-brain barrier. Post-mortem studies in specific cases have identified infiltrated lymphocytes containing EBV DNA in meninges and perivascular areas, with their absence in neurons indicating inflammatory brain damage resulting from an immune response rather than direct viral invasion, in contrast to herpes simplex virus (HSV) infection [5-9]. An in-vitro study provides an intriguing alternative perspective, demonstrating EBV's capacity to infect various neural cells, generating progeny virus through lytic replication and causing host cell destruction, potentially infecting other neurons and mononuclear cells [10]. In a rat encephalitis model, anti-neuronal antibodies have been detected [11]. Despite these controlled laboratory findings, demonstrating this phenomenon in vivo remains inconclusive with current knowledge.

EBV-associated CNS infection can occur in 1-3 weeks following an acute infection [12], but can also occur in the absence of acute infection, potentially attributed to reactivation. There is currently no established diagnostic criteria of EBV-associated CNS infection. While a possible diagnosis has been suggested based on positive serologic findings alongside compatible neurological symptoms [13], the rarity of this condition dictates the exclusion of more common viruses in suspected cases among young immunocompetent patients [8]. Further support for diagnosis may be provided by a positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for EBV DNA [6, 13], yet the specificity and sensitivity of this test remain undetermined. In a review of 23 cases diagnosed with EBV-associated CNS infection, 20 tested positive on the CSF PCR [11]. However, even when CSF PCR for EBV DNA is positive, co-infection is prevalent, found in 22% of patients with compatible symptoms. In such cases, it has been suggested that, instead of being the primary pathogen, EBV may be reactivated secondary to inflammatory responses from other pathogens, or even contamination from EBV-infected lymphocytes [9]. While direct isolation of the virus in brain biopsy or culture from the CSF could support the diagnosis [6], such approaches are less practical in clinical practice.

In our patient, the EBV DNA in CSF is measured at less than 200 copies/ml [3,4], which falls within the previously reported range of 51-216,000 copies/ml [9][14]. The absence of other pathogens on PCR and bacterial panels makes contamination unlikely. In cases involving potential co-infections with other pathogens, we concur that utilizing reverse transcription-polymerase chain reaction (RT-PCR) for messenger RNA (mRNA) of the lytic cycle gene BZLF in the CSF may be the optimal approach to establishing the pathogenic role of EBV [9]. The BZLF gene, responsible for encoding a transcription regulator protein, is expressed by EBV only during the transition from latent to lytic infection.

Our case also demonstrated the challenging nature of determining the chronicity of an EBV-related CNS infection. For an acute infection, a positive serum EBV-specific IgM and IgG to the Viral Capsid Antigen (VCA IgG, IgM), a positive IgG to the early antigen (EA IgG), and a negative IgG to nuclear antigen (EBNA IgG) is suggestive. If follow-up serology were obtained, significant changes in EBV-specific antibodies such as a rise in IgG level, the disappearance of VCA-IgM and EA IgG, and the appearance of EBNA IgG further support an acute infection [13]. The positive EBNA IgG in the context of positive VCA IgM and VCA IgG in our patient may initially appear perplexing. VCA IgM is a marker of acute infection. At the same time, EBNA IgG is usually expressed only during latent infection, beginning from 6 weeks after the first infection, as EBNA are proteins responsible for maintaining an episomal state of EBV DNA as well as immortalizing B-cells in which EBV persists during latent infection. However, this can be reconciled by the fact that VCA IgM can be presented up to 3 months following acute infection. Our patient's reported symptoms of infectious mononucleosis 8 weeks prior and mild hepatosplenomegaly on the exam are consistent with that. Another possibility is a reactivation infection. In either case, the timing of the infection is not likely to be clinically significant, and we suggest serial follow-up serology in case chronicity needs to be elucidated.

Neuroimaging is normal in most of the patients with EBV-associated CNS infection, as in our patient. However, it is essential to perform an MRI to rule out other causes of CNS infection such as HSV encephalitis or acute disseminated encephalomyelitis (ADEM), which typically presents with lesions mostly in the deep and subcortical white matter [10]. The MRI findings in EBV-associated CNS infection can vary widely in

hyperintensity in the basal ganglia, thalamus, cerebral cortex, brainstem, optic nerves, splenium, and corpus callosum [15, 16]. These manifestations may extend to brainstem hemorrhage [5], meningeal enhancement and multi-level spinal cord involvement [13]. While most MRI abnormalities are observed in the FLAIR and T2 sequences, restricted diffusion on the DWI sequence can also be presented. Additionally, heterogeneous signals on ADC sequences can be observed, ranging from hypointensity to hyperintensity [17]. However, none of these findings is specific to EBV infection.

There is no standard treatment guideline for EBV-associated CNS infection. There have been reports of ganciclovir or acyclovir treatment with or without corticosteroids. This is due to ganciclovir's ability to suppress replication in DNA viruses and good in-vitro activity against EBV virus [16]. However, the efficacy remains unclear [9,18]. Suppose the main pathogenetic cause of EBV-associated CNS infection is the result of the inflammatory response by the body's immune system rather than direct viral invasion. In that case, systemic corticosteroids are more likely to be efficacious. While the exact pathogenesis of EBV-associated CNS infection is not yet entirely clear, we believe it is reasonable, in the absence of contraindications, to initiate treatment with both antivirals and systemic corticosteroids. Our patient received both systemic corticosteroid and intravenous acyclovir empirically and they were discontinued once the patient showed continuous improvement, and we thus believe the duration of this treatment could be guided by the patient's clinical response.

Conclusions

EBV infection involves a very heterogeneous constellation of symptoms. Isolated, EBV-associated CNS infection should be considered in young adults with altered mental status when other more common CNS viral infections have been ruled out. A positive CSF PCR for EBV DNA strongly supports the diagnosis in the absence of other pathogens in the PCR. MRI findings typical of other conditions, such as ADEM, also must be ruled out. Due to the unclear pathogenesis of EBV-associated CNS infection, we suggest the combination of antivirals and systemic corticosteroids if not contraindicated.

AUTHOR CONTRIBUTIONS

Gwyn Srifuengfung: writing-original draft, review, and editing

Pichatorn Suppakitjanusant: conceptualization, review and editing

Nattanicha Chaisrimaneepan: Resources; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

CONSENT

Verbal and written consent was obtained from the patient to publish this case.

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