Case Report

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Intracranial Epstein–Barr virus infection appearing as an unusual case of meningitis in an immunocompetent woman: a case report

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Abstract

Epstein–Barr virus (EBV) is a member of the herpesvirus family, which infects most of the world's population. EBV infection usually occurs asymptomatically. However, there are subsets of the population, such as juveniles and immunocompromised patients, among whom EBV may manifest symptomatically. In some cases, symptomatology involves the central nervous system. One such manifestation of EBV is meningitis. We report a unique case of EBV infectious meningitis in an immunocompetent adult female patient who showed unconventional clinical features. These features included afternoon fever, high intracranial pressure, low cerebrospinal fluid glucose levels, and an absence of blood monocytosis. Because this case involved a unique symptomatology, our findings broaden the symptom profile of EBV infection as presently understood.

Keywords

Central nervous system, Epstein–Barr virus, infection, meningitis, intracranial pressure, cerebrospinal fluid, glucose

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Introduction

Although Epstein–Barr virus (EBV) infects numerous populations worldwide, this infection occurs without any symptoms in most cases. Immunocompromised patients or juveniles are more prone to have various peripheral symptoms that are derived from infectious mononucleosis (IM) and lymphoproliferative disorders.[1] Nervous system involvement of EBV infection is rare in adults, especially in immunocompetent patients.[1]

In this report, we describe an intracranial EBV infection in an immunocompetent woman with symptoms of unconventional meningitis, which is different from classic EBV meningitis.

Case report

A 35-year-old woman presented to Beijing Chao-Yang Hospital complaining of a 6-day history of intermittent high fever, headache, periodic vomiting, profuse sweating, and fatigue. Her symptoms appeared after she caught a cold, and were more serious in the afternoon and night. The only noteworthy finding on a neurological examination was neck rigidity. No other abnormality was found in routine blood examinations, except for a high high-sensitivity C-reactive protein level and erythrocyte sedimentation rate, and positive EBV immunoglobulin G with negative immunoglobulin M in serum (Table 1). A lumbar puncture was completed and the intracranial pressure was 320 mmH_2O. The cerebrospinal fluid (CSF) glucose level was lower than normal blood glucose levels by a factor of more than three. Other CSF parameters were also consistent with central nervous system (CNS)-involved EBV infection (Day 1, Table 2). Combined with the absence of an abnormal signal on contrast-enhanced magnetic resonance imaging (Figure 1), these findings led to a preliminary diagnosis of infectious viral meningitis, despite doubts caused by the atypical symptom profile (high intracranial pressure, and low CSF glucose level). Treatments were then applied in accordance with the diagnosis as follows. Antiviral therapy with acyclovir was provided, dexamethasone was administered to reduce inflammation, and mannitol was provided to decrease intracranial pressure. Symptoms were alleviated for 6 days, but the patient then experienced new-onset fever up to 40°C, headache, and another

Table 1. Hematological examination results.

Item	Result	Reference value
WBC count	7.13×10^9/L	$3.5–9.5 \times 10^9$/L
NE	64.9%	40–75
LY	29.0%	20–50
MO	6.0%	3–10
EO	0.0%	0.4–8
BA	0.1%	0–1
HGB	132.0 g/L	115–150 g/L
PLT	298×10^9/L	$125–350 \times 10^9$/L
hs-CRP	10.35 mg/L	0–3 mg/L
ESR	31 mm/hour	2–20 mm/hour
EBV IgG	(+)	(−)
EBV IgM	(−)	(−)
EBV DNA	<500 IU/mL	<500 IU/mL
T-spot A/B	0/0	<24/24
TB antibodies (16 kD)	(−)	(−)
TB antibodies (38 kD)	(+)	(−)
PCT	<0.05 ng/mL	<0.05 ng/mL
G-test	<10 pg/mL	<10 pg/mL
TPPA	(−)	(−)
HIV	(−)	(−)

WBC, white blood cell; NE, neutrophils; LY, lymphocytes; MO, monocytes; EO, eosinophils; BA, basophils; HGB, hemoglobin; PLT, platelets; hs-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; EBV, Epstein–Barr virus; IG, immunoglobulin; T-spot A/B, T cell spot test of tuberculosis with the antigens early secreted antigenic target 6 and culture filtrate protein 10; TB, tuberculosis; PCT, procalcitonin; G-test, glucan test; TPPA, *Treponema pallidum* particle assay; HIV, human immunodeficiency virus.

Table 2. Cerebrospinal fluid examination results.

Item	Result	Reference value
Day 1		
Total cells	138/μL	/
WBC count	138/μL	0–8/μL
MO	87.0%	/
M-TP	145 mg/dL	15–45 mg/dL
CSF Glu (BG)	2.44 mmol/L (7.87)	2.5–4.5 mmol/L
Day 8		
Total cells	52/μL	/
WBC count	52/μL	0–8/μL
MO	85.0%	/
M-TP	49 mg/dL	15–45 mg/dL
CSF Glu (BG)	2.74 mmol/L (5.86)	2.5–4.5 mmol/L
Day 15		
Total cells	9/μL	/
WBC count	9/μL	0–8/μL
MO	67.0%	/
M-TP	35 mg/dL	15–45 mg/dL
CSF Glu (BG)	2.40 mmol/L (5.59)	2.5–4.5 mmol/L
Etiological results		
EBV DNA (Day 15)	4980 IU/mL	<500 IU/mL
TB DNA	(–)	(–)
Acid-fast staining	(–)	(–)

WBC, white blood cell; MO, monocytes; M-TP, micro total protein; CSF Glu, glucose level of cerebrospinal fluid; BG, blood glucose level at lumbar puncture; EBV, Epstein–Barr virus; TB, tuberculosis.

bout of intermittent vomiting in the afternoon. The most recent CSF analyses showed persistent improvement in all parameters at Days 8 and 15 (Table 2), although intracranial hypertension was 330 and 335 mmH_2O, respectively. This symptom also ultimately dissipated after continual application of antiviral therapy.

Therefore, there appeared to be a mismatch between CSF results and symptoms in this case. While CSF results showed continuous improvement, the symptoms appeared to fluctuate in an unrelated manner. Because we considered that further exploration of the etiology for this mismatch was warranted, we searched the CSF for possible pathogenic evidence. EBV DNA was detected at a level that exceeded the reference value by a factor of almost 10 at Day 15, rather than Days 1 and 8 (Table 2). This finding was accompanied by negative results for other pathogens, such as other viruses (herpes simplex virus types 1 and 2, cytomegalovirus and rubella virus, adenovirus, enterovirus 71, and coxsackievirus A16), culture and smear results (bacteria, fungus, and mycobacterium tuberculosis), syphilis, human immunodeficiency virus, Brucella, and the full analytic complement of parasites (lung flukes, schistosomes, *Angiostrongylus*, *Sparganum mansoni*, *Toxoplasma gondii*, hepatic hydatids, *Borrelia burgdorferi*, and cysticercus). Taking into consideration these negative results in conjunction with the absence of extra-neurological symptoms and continuous remission of CSF indicators after antiviral therapy, we finally diagnosed

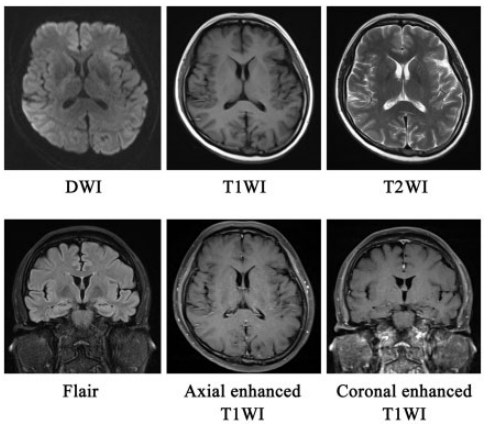

Figure 1. Magnetic resonance imaging of the patient.
Magnetic resonance imaging of the patient, including various sequences and contrast-enhanced scans, did not definitely show an abnormal signal in brain parenchyma and the meninx. DWI, diffusion-weighted imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; FLAIR, fluid-attenuated inversion recovery; enhanced, gadolinium contrast-enhanced.

the patient with EBV infectious meningitis. After remission, the patient left the hospital asymptomatically and achieved full recovery in a subsequent follow-up.

This case report was approved by the Beijing Chao-Yang Hospital of Capital Medical University Ethics Committee and conformed with the principles of the Declaration of Helsinki. Verbal and written informed consent was obtained from the patient before submission. The case report contained no direct patient identifiers and no relevant indirect identifiers (as specified in the journal policy). However, the patient was explicitly and adequately informed by the corresponding author regarding the potential publication of this case and the photographs used in the report.

Discussion

Our case was positive for EBV immunoglobulin G and negative for immunoglobulin M in serum (Table 1). This finding indicated that the patient had been infected with EBV previously and that she had not had any recent contact with the virus in blood. She showed no classic symptoms, and lacked diagnostic markers of IM, such as semiological and cytological indices. Direct central infection has been proposed as a pathogenic mechanism in CNS-involved EBV on the basis of the presence of the PCR-amplified EBV genome in CSF of patients.[2–4] In our case, CSF was examined three times and a remarkable increase in EBV DNA to 4980 IU/mL was observed. This finding suggested that EBV infection occurred locally in the brain, specifically in the meninx.

Reactivation of latent EBV of the type that was observed in our case is clinically significant in symptomatic infection. However, this reaction mainly occurs in immunocompromised patients, and tends to occur in conjunction with lymphoproliferative disease.[5] However, our patient had no immunodeficiency disease. This finding indicates that her meningitis should be attributed not to reactivation, but rather to recent direct invasion of exotic EBV into the meninx. With regard to the probability of new invasion of EVB, the patient is a basement storekeeper who had undergone substantial exertion in that environment 1 month before her disease, and she then caught her cold. These conditions are likely to have contributed to development of her disease. However, we cannot verify the clear mechanism of CNS infection only with the current evidence. There are three possible reasons for the patient's infection as follows: (1) the EBV immunoglobulin G titer in the patient gradually decreased year by year and did not provide sufficient protection for EBV infection; (2) destruction of the body's defense and immune systems, including damage of the nasal mucosa after a common cold, may have provided the opportunity for EBV infection; and

(3) EBV infection occurred without crossing the blood–brain barrier, such as entering the brain via the olfactory or optic nerve pathway.

Some features of our case resemble idiopathic intracranial hypertension. High intracranial pressure was present in our patient throughout the whole course of her disease. However, our patient lacked the symptom profile suggestive of idiopathic intracranial hypertension. This lack of finding in addition to the fact that the patient attained full recovery on follow-up led us to believe that the high pressure was secondary to EBV infection, despite the fact that we did not obtain a confirmatory baseline intracranial pressure. In the context of a diagnosis of EBV meningitis, the high intracranial pressure, low CSF glucose level, and intermittent high fever with chills in the afternoon were unusual findings. Therefore, to the best of our knowledge, this is the first case of atypical EBV meningitis that required supplementation of the symptom profile as currently understood.

There is currently little understanding or consensus about how to treat EBV infection. Treatment with acyclovir for acute IM has been studied in several trials, but these failed to show any antiviral efficacy.[6,7] In patients with CNS disease, a benefit of acyclovir had also not been clearly demonstrated for patients with CNS-involved EBV.[8] In a recent study, all of the patients with primary EBV infection and neurological complications who were treated with acyclovir recovered fully, whereas three of four patients who did not receive antiviral therapy had a complicated course.[9] Successful treatment with intravenous ganciclovir has been reported in cases of encephalitis caused by EBV.[10] Other modalities of treatment have also been investigated, such as recombinant interleukin-2 and intravenous human immunoglobulin.[11,12] Starting treatment as soon as EBV is suspected on the basis of clinical features is important because EBV encephalitis can have considerable neurological sequelae and be fatal.[13] Corticosteroids have been provided for most neurological complications related to EBV infection, including encephalitis, myelitis, cerebellar ataxia, and various neuropathies. Unfortunately, controlled studies of this therapy have not been performed. Because of the low incidence of these complications, such studies are difficult to conduct and the results of the available case trials are difficult to interpret.[8] However, despite our patient's volatile symptoms, administration of acyclovir and dexamethasone led to gradual recovery. Our case of EBV meningitis provides preliminary support for an association between antiviral/corticosteroid treatment and a good prognosis.

Conclusion

We present a case of EBV infectious meningitis in an immunocompetent woman. Despite a complicated clinical course, her prognosis was good. As indicated by the unique combination of clinical features found in our case, as well as the paucity of literature available, nervous system involvement of EBV infection is not fully understood. Therefore, more studies should be designed with the aim of yielding mechanistic and therapeutic information for more effectively diagnosing and treating this disease.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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