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Biopsy-proven case of Epstein-Barr virus (EBV)-associated vasculitis of the central nervous system

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Type: Case report

A biopsy-proven case of acute encephalopathy with Epstein-Barr virus (EBV)-associated vasculitis

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Abstract

A 75-year-old woman was admitted to our hospital with rapidly deteriorating consciousness disturbance. She had a seven-year history of rheumatoid arthritis (RA), which had been treated with methotrexate (MTX) and prednisolone. Brain T2-weighted magnetic resonance imaging (MRI) showed diffuse high intensity lesions in the cerebral subcortical and deep white matter, bilateral basal ganglia, and thalamus. A cerebrospinal fluid examination revealed elevated protein levels and positive Epstein-Barr virus (EBV) DNA. Human immunodeficiency virus was negative. Brain biopsy showed perivascular lymphocytic infiltration in the parenchyma and meninx with EBV-encoded small RNA (EBER). Since this case did not fulfill the criteria for chronic active EBV infection (CAEBV), she was diagnosed with encephalopathy with Epstein-Barr virus (EBV)-associated vasculitis. High-dose methylprednisolone, acyclovir, ganciclovir, and foscarnet were not effective. Although EBV is a causative agent of infectious mononucleosis (IM), lymphomas, and nasopharyngeal carcinomas, vasculitic pathology of the central nervous system with EBV reactivation in the elderly is rare. Immunosuppressive drugs such as steroids and methotrexate (MTX) are widely used to treat autoimmune disorders, but may exacerbate the reactivation of EBV. This is the first case of biopsy-proven EBV-positive/HIV-negative vasculitic encephalopathy during the treatment of RA with MTX and steroids. This case indicates that EBV-associated vasculitis needs to be considered as a differential diagnosis of CNS vasculitis and encephalopathy.

Key words: Epstein-Barr virus (EBV), encephalopathy, vasculitis

Introduction

Epstein-Barr virus (EBV) is a human herpes virus and 90-95% of the adult human population carries EBV as a chronic latent infection. Most EBV infections are asymptomatic; however, EBV sometimes causes a systemic infection or reactivation that may directly involve the central nervous system (CNS). Up to 7% of EBV-infected patients develop neurological symptoms, and the most common CNS complications of EBV infection include encephalitis, cerebellitis, meningitis, cranial nerve palsies/neuritis, and myelitis (1). The virus may also cause chronic active EBV infection (CAEBV) characterized by chronic or recurrent infectious mononucleosis (IM)-like symptoms, abnormal increases in specific anti-EBV antibodies, and hypersensitivity or skin ulceration caused by mosquito bites (2). However, there have been no reports of encephalopathy/vasculitis associated with EBV infection, except for rare cases of co-infection by human immunodeficiency virus (HIV) (3, 4, 5, 6, 7, 8). We herein report the first case of EBV infection involving encephalopathy and vasculitis without HIV infection.

Clinical summary

A 75-year-old woman was admitted to our hospital with consciousness disturbance. She had a 7-year history of rheumatoid arthritis (RA) that was treated with prednisolone 8 mg/day and methotrexate (MTX) 6 mg/week. Although she had general malaise for one month, her communicative competence was maintained at that time. Her consciousness deteriorated in a few days, and, thus, she was referred to us. On admission, her Glasgow Coma Scale (GCS) was 13 (E4V3M6) and voluntary activity was markedly decreased. Her body temperature was 39.2°C and blood pressure was 172/99 mmHg. A physical examination revealed rheumatic

arthritic changes in the extremities, but no specific skin changes, hepatosplenomegaly, or lymphadenopathy. A neurological examination showed that both eyeballs mildly turned upward and she also exhibited roving eye movement. The tendon reflexes of the limbs were aggravated and bilateral Babinski and Chaddock signs were positive; however, meningeal signs were not detected. Brain magnetic resonance imaging (MRI) revealed diffuse high intensity lesions in the cerebral subcortical and deep white matter, bilateral basal ganglia, and thalamus on T2-weighted images (T2WI). Small T2WI-hypointense lesions were also observed, suggesting microbleeding. T1-weighted imaging with gadolinium contrast material showed an enhancement in the right parietal lobe (Figure 1). Electroencephalography (EEG) displayed diffuse slow theta-delta background activity. Whole-body computed tomography did not detect any specific abnormalities.

A laboratory examination revealed an increased white blood cell count (16200/μl) (neutrophils 93.0%, lymphocytes 3.0%, monocytes 0.0%, eosinophils 0.0%, basophils 0.0%, and atypical lymphocytes 0.0%) and mild elevations in serum C-reactive protein (0.60 mg/dl) and serum soluble interleukin-2 receptor (sIL-2R) (1834 U/ml; normal range 127-582). A cerebrospinal fluid (CSF) analysis detected elevated protein (106.4 mg/dl), lactic acid (17.3 mg/dl), interleukin (IL)-6 (7.9 pg/ml; cut-off ≦4.0 pg/ml) and sIL-2R (140.0 U/ml; cut-off <50.0 U/ml) levels without pleocytosis. Bacterial, fungal, and mycobacterial cultures of the CSF were all negative. Polymerase chain reaction-based tests for EBV deoxyribonucleic acid (DNA) were positive (EBV-DNA levels, 760 copies/ml) in the CSF, whereas those for herpes simplex virus (HSV) 1 and 2, varicella-zoster virus (VZV), cytomegalovirus (CMV), and JC virus were negative. A cytological examination of CSF detected no malignant cells (Table). Serological tests for EBV showed positive VCA-IgG (80x), negative VCA-IgM and IgA,

negative EADR-IgG, negative EADR-IgA, and positive EBNA (40x), which suggested previous infection. A blood serological test for HIV was negative. The rapid plasma reagin test (RPR) for syphilis and the treponema pallidum hemagglutination test (TPHA) were negative. Rheumatoid factor, other anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), and anti-toxoplasma IgG and IgM antibodies were also negative.

Pathological and Immunohistochemical findings

Brain biopsy of the right parietal lobe lesion was performed on the 13th day for a differential diagnosis of malignant lymphoma, encephalitis, and encephalopathy. Hematoxylin-Eosin (HE) staining showed perivascular lymphocytic infiltrates and most of the vascular wall was thickened (Figure 2 HE-A). In addition, fibrinoid necrosis was observed within the thickened vascular wall (Figure 2 HE-B). Perivascular lymphocytic infiltrates existed not only in the brain parenchyma, but also on the meninges side. The inflammatory infiltrate was dominantly composed of CD3+ and CD8+ T-lymphocytes (Figure 2). CD4- and CD20-positive cells were also observed, whereas CD56-positive cells were not (data not shown). EBV-encoded small RNA (EBER) positivity was observed in one third of perivascular lymphocytes by *in situ* hybridization (Figure 2). There was neither monoclonal proliferation nor malignant cell in the lesion specimen.

Clinical course

On admission, MTX was discontinued and the patient was treated with steroid pulse therapy (intravenous administration of 1000 mg methylprednisolone for 3 days) followed by prednisolone 8 mg/day. Although acyclovir (1000 mg/day), clindamycin

(1200 mg/day), and trimethoprim-sulfamethoxazole (1 g/day) were also administered, the patient's clinical condition gradually worsened (GCS E3V1M4). Since her consciousness had not improved on the 8th hospital day and IL-6 (11.9 pg/ml) and sIL-2R (448 U/ml) levels in the CSF were elevated, steroid pulse therapy was performed again. Clindamycin was stopped on the 12th hospital day because bacterial tests were negative. On the 13th day, we performed brain biopsy and diagnosed EBV-associated encephalopathy. On the 15th hospital day, we changed acyclovir to ganciclovir (300 mg/day). IL-6 and sIL-2R levels in the CSF gradually decreased, whereas consciousness disturbance persisted. On the 40th hospital day, we shifted ganciclovir to foscarnet (6480 mg/day); however, her consciousness and EBV-DNA in the CSF did not improve. Foscarnet therapy was discontinued on the 57th hospital day and she was moved to a medical long-term care institution. Her level of consciousness slightly improved at the end of medication, but her clinical state remained bed-ridden.

Discussion

We herein report a rare pathologically-proven case of brain vasculitis associated with EBV reactivation under immunosuppressive treatment. Vasculitic changes in the CNS may be caused by various disorders such as collagen disease or fungal or mycobacterial infection; however, these conditions were excluded in the present case. Positive EBER in the lesion suggests pathogenic viral activation, not latent infection.

The involvement of EBV in our case was observed in the CNS, but no other organs. This case does not fulfill the criteria for CAEBV because of the absence of hepatosplenomegaly and significant elevations in anti-EBV VCA-IgG and EA-IgG antibodies (2). However, Kobayashi et al. (9) reported an autopsy case of CAEBV with

CNS lesions showing perivascular CD3+ and EBER1+ lymphocyte infiltration, which resembles the CNS pathology of our case. These cases suggest the disease spectrum of EBV vasculitic pathology in the CNS; however, further investigations are needed. Angiitis of the CNS may have previously been categorized as primary angiitis of the CNS (PACNS) when its cause was unknown; however, Pagni et al. reported two cases of PACNS, among which one had a possible EBV relationship (10). These findings suggest that testing for EBV needs to be considered for the accurate diagnosis and classification of CNS vasculitis. Only one study has reported a case of chronic active EBV infection with the features of granulomatosis with polyangiitis because it is very rare (11). Other studies have described encephalitis due to EBV with HIV infection (3, 4, 5, 6, 7, 8); on the other hand, our case was HIV-negative, and, thus, EBV may have played a more significant role in the development of vasculitis. A limitation of this study is that we were unable to identify the type of lymphocytes infected by EBV in the histopathological examination; therefore, it was not possible to elucidate the precise mechanisms underlying the activation of EBV in this case. Previous findings on CAEBV infection indicate that the up-regulated expression of vascular cell adhesion molecule-1 (VCAM-1) on cytokine-stimulated endothelial cells is important for the adhesion of EBV-positive natural killer (NK) cells (12).

The treatment of CNS vasculitis due to EBV is still challenging because of the rarity of this disease and, thus, a lack of evidence. Most EBV infections are self-limiting and EBV-specific antiviral therapy is unnecessary in common conditions; however, treatments have not yet been established for EBV-related complications in the nervous system or lymphoproliferative diseases. In this case, steroids and anti-herpesvirus agents did not appear to have any significant effects on EBV infection. Previous studies suggested the use of high-dose antiviral therapy with

azidothymidine and ganciclovir in patients with EBV-positive primary CNS lymphomas (13). In addition, anti-herpes viral therapy with acyclovir or foscarnet sodium may be proposed and corticosteroid therapy also appears to be reasonable when vasculitis is suspected. Ganciclovir and valganciclovir inhibit the replication of EBV *in vitro*, but have limited efficacy in treating acute EBV infection or EBV-associated malignancies (14). Both drugs have been shown to reduce the incidence of EBV-encephalitis or prevent EBV infection (3, 4, 15, 16, 17, 18); however, these findings have not been consistently replicated. Furthermore, no studies have directly compared these drugs for the treatment of EBV. Since our case was suspected of having encephalitis due to viral infections such as HSV1, HSV2, VZV, and EBV on admission, we initiated the administration of acyclovir. Antiviral therapy and steroids appear to be acceptable as an initial treatment for CNS vasculitis due to EBV; however, alternative treatments need to be considered for resistant cases. Although plasmapheresis (PA) or intravenous immunoglobulin (IVIg) may be candidate treatments (19, 20), systematic research has not yet been conducted. Based on the treatment of CAEBV, hematopoietic cell transplantation may be an emerging strategy (21, 22, 23, 24).

In conclusion, we herein report the first biopsy-proven case of CNS vasculitis associated with EBV reactivation without HIV infection. This case suggests that CNS vasculitis related to EBV needs to be considered as a rare complication during immunosuppressive therapy, and brain biopsy may contribute to an accurate diagnosis, elucidation of the underlying mechanism, and development of more effective treatments.

The authors state that they have no Conflict of Interest (COI).

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Figure legends

Figure 1

Magnetic resonance imaging (MRI) and MRI with gadolinium contrast findings of the brain on admission.

A, B: Brain MRI revealed diffuse high intensity lesions in the cerebral subcortical and deep white matter, bilateral basal ganglia, and thalamus on T2-weighted images (T2WI). Small T2WI-hypointense lesions were also observed, which suggested microbleeding.

C, D: MRI with gadolinium contrast material showed a lesion with an irregular ring enhancement in the right parietal lobe.

Figure 2

Histopathological findings

HE-A and B (×200): H & E-stained sections showed perivascular lymphohistiocytic infiltrates (arrows: fibrinoid necrosis).

CD3 and CD8 (×200): The inflammatory infiltrate was dominantly composed of CD3+ and CD8+ T-lymphocytes.

CD20 (×200): CD20-positive cells were observed.

EBER (×200): Immunostaining analysis with an anti-EBER antibody showed EBV-positive cells in the perivascular site.

Figure 2

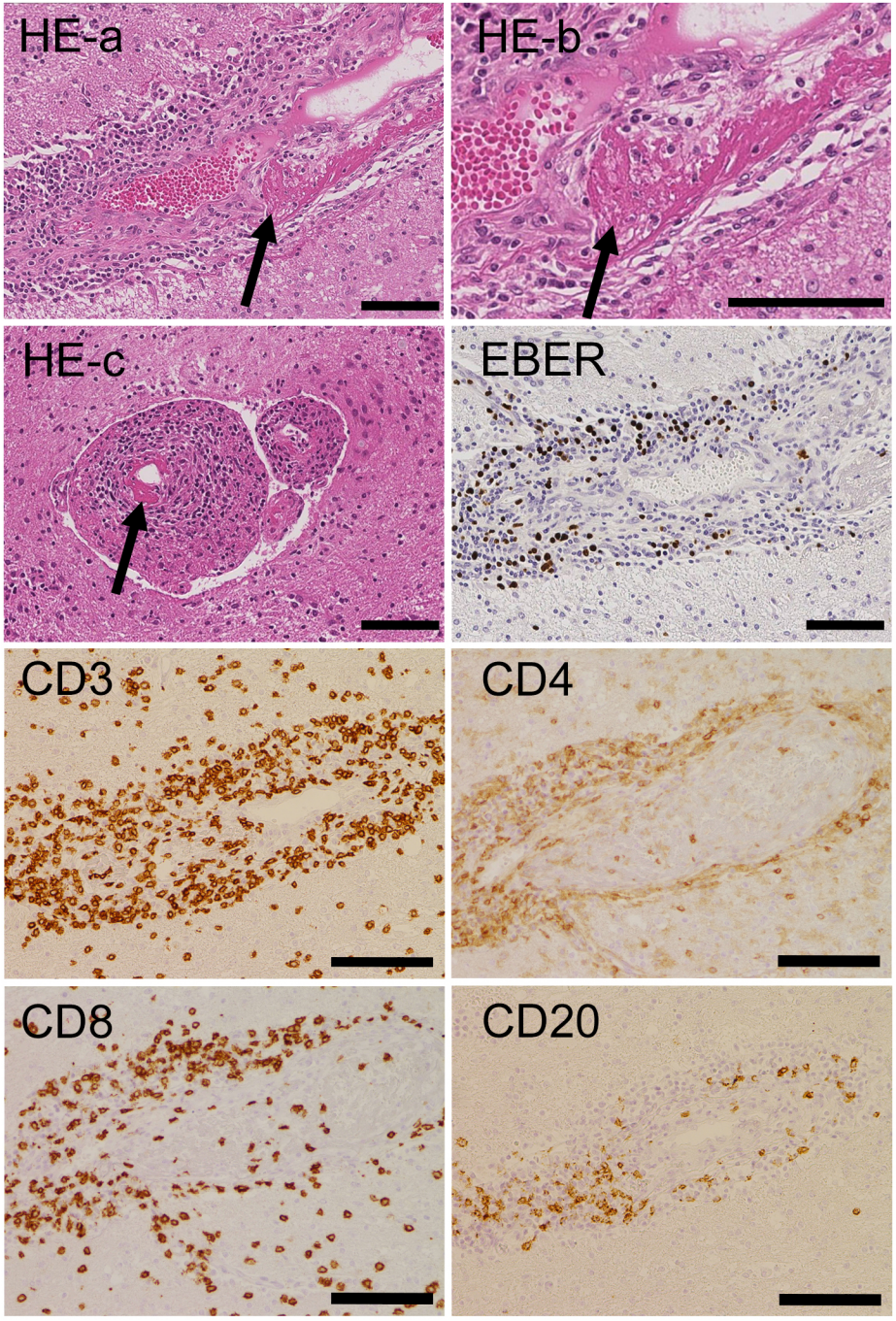

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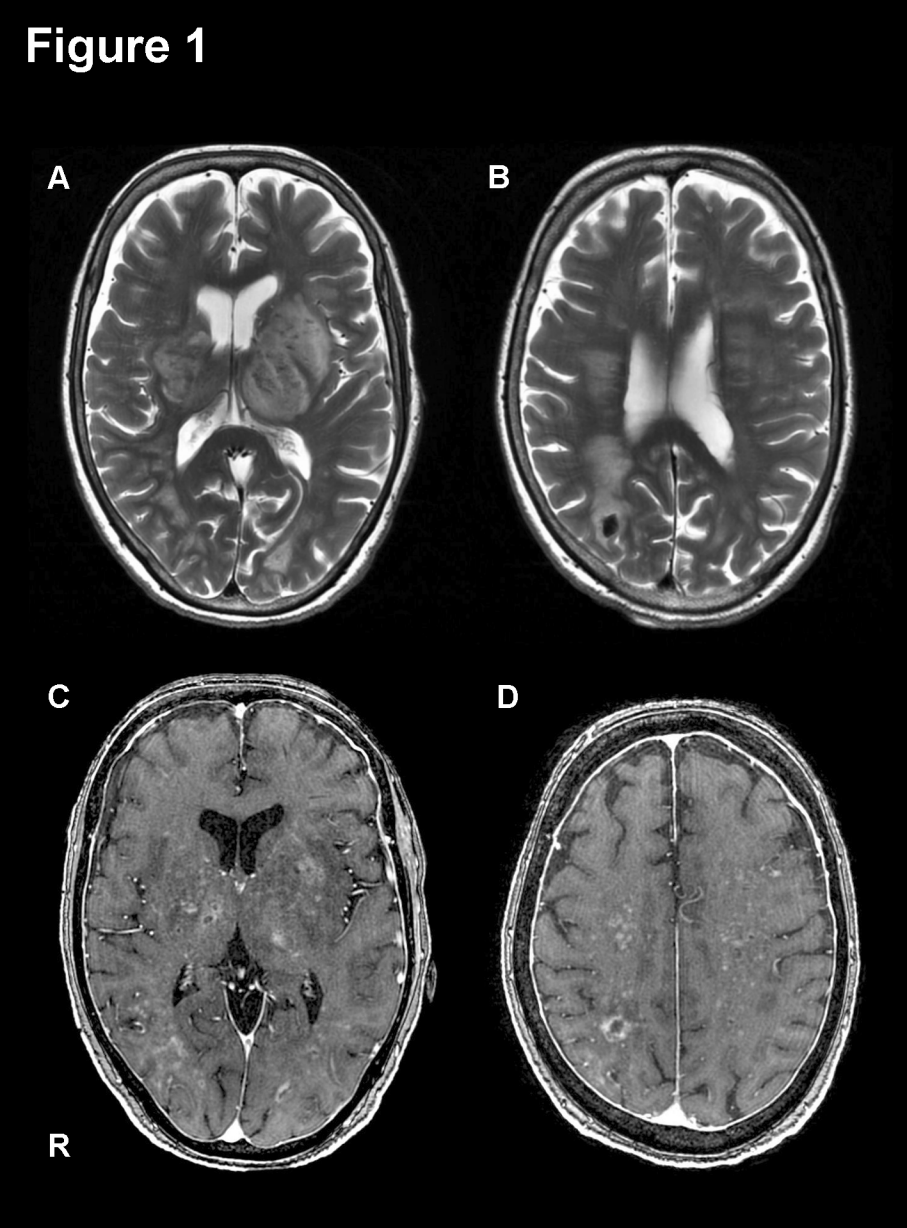
Figure 1



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