Chronic meningitis and central nervous system vasculopathy related to *Epstein Barr virus*

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Abstract

Chronic active *Epstein Barr virus* (EBV) infection causes a wide spectrum of manifestation, due to meningeal, parenchymal and vascular involvement. An 11-year-old boy presented with chronic headache, fever and seizures of 18 months duration. His magnetic resonance imaging Brain showed fusiform aneurysmal dilatations of arteries of both the anterior and posterior cerebral circulation. Cerebrospinal fluid (CSF) showed persistent lymphocytic pleocytosis, raised proteins and low sugar with positive polymerase chain reaction for EBV. He later developed pancytopenia due to bone marrow aplasia, with secondary infection and expired. From clinical, imaging and CSF findings, he had chronic lymphocytic meningitis with vasculopathy, which was isolated to the central nervous system. He later had marrow aplasia probably due to X-linked lymphoproliferative disorder related to EBV infection. Vasculopathy, especially diffuse fusiform aneurysmal dilatation associated with chronic EBV infection, is rare, but has been described, similar to our case report.

Key Words

Epstein Barr virus, fusiform aneurysmal dilatations, lymphoproliferative disorder, vasculopathy

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Introduction

Epstein Barr virus (EBV) is one of the most common viral infections. Most primary infections occur during childhood without or with only nonspecific symptoms. After acute infection, EBV becomes latent in the lymphocytes of peripheral blood. The latent virus can become active, especially in immunocompromised states, causing a spectrum of diseases: chronic active infection and epithelial, mesenchymal or lymphoid malignancies.[1] EBV-related central nervous system (CNS) lymphocytic vasculitis/vasculopathy has been reported in few case reports.[2-5] Here, we describe an 11-year-old boy with EBV-related chronic meningitis and isolated CNS vasculopathy.

Case Report

An 11-year-old boy presented to us in December 2009 with fever, headache and seizures. In July 2008, he had headache with vomiting and photophobia. He was evaluated elsewhere and was found to have aneurysmal dilatation of intracranial segments of anterior, middle and posterior cerebral arteries on magnetic resonance imaging (MRI) and catheter angiogram of brain [Figure 1]. With the possibility of CNS angitis, he was treated with one pulse of intravenous Methylprednisolone and intravenous Cyclophosphamide, which was not continued further. He continued to have intermittent headache and fever. In November 2009, he had worsening of headache with seizures. He was admitted elsewhere and again received pulse intravenous Methylprednisolone and intravenous Cyclophosphamide, followed by a tapering course of oral steroids. In December 2009, he presented to us with headache, fever and recurrent right-side focal seizures with secondary generalisation. He was the first child of two siblings, born to nonconsanginous parents. There was no history of similar illness in the other sibling, with no other remarkable family history. MRI brain showed fusiform aneurysmal dilatations of arteries of anterior and posterior circulation with ectasia of the terminal internal carotid arteries (ICAs), proximal anterior cerebral arteries (ACAs), proximal middle cerebral arteries (MCAs) and their cortical branches. There was loss of flow void in right vertebral artery suggesting thrombosis. There was leptomeningeal enhancement [Figures 2a–d]. Cerebrospinal fluid (CSF) analysis showed 200 WBC/mm^3 (100% lymphocytes), protein of 2.2 g/dL and sugar of 29 mg/dL. CSF cultures (bacterial and fungal) were negative. CSF

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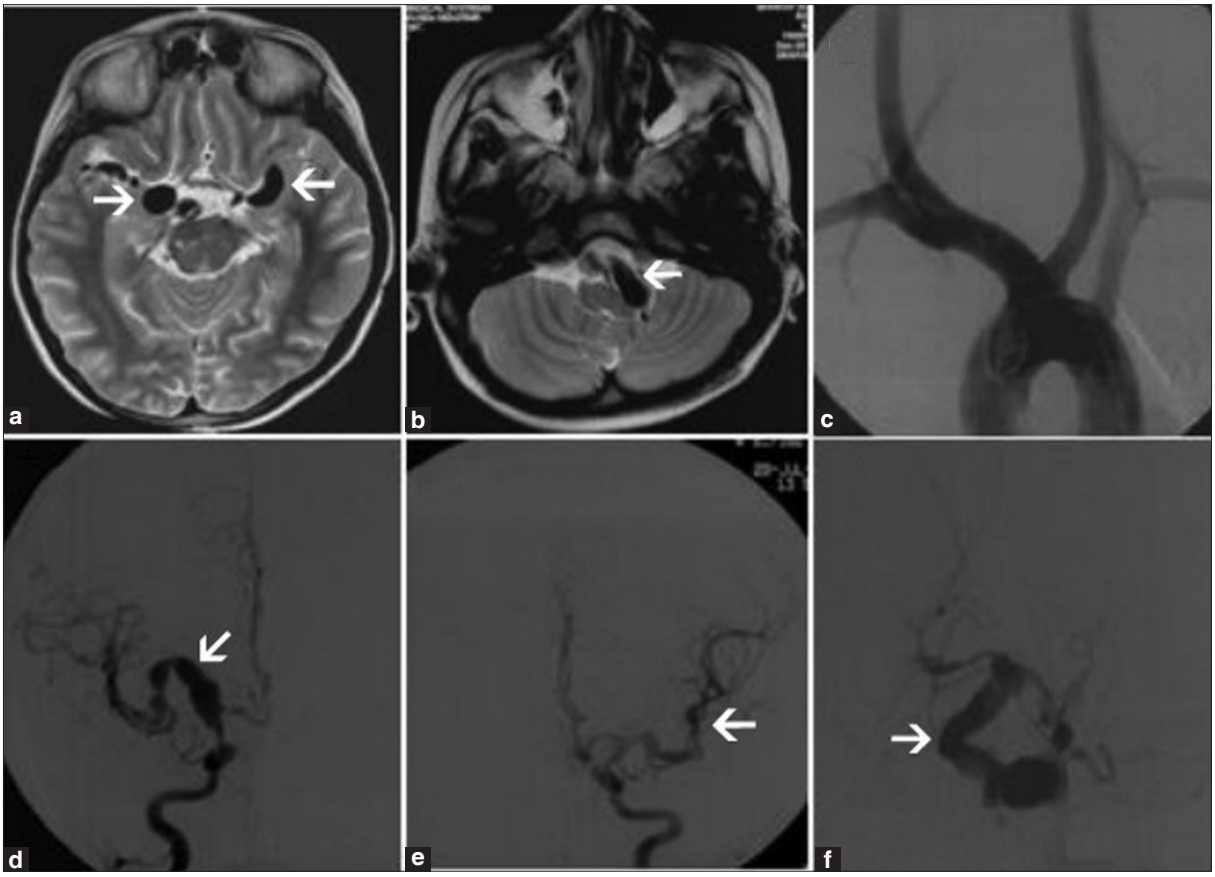

Figure 1: T2 magnetic resonance imaging of the brain shows aneurysmal dilatation of the right terminal internal carotid arteries (ICA), the left middle cerebral arteries (MCA) (a, arrows) and the left vertebral artery (b, arrow). Catheter angiogram shows normal aortic arch and its branches (c), aneurysmal dilatation of the right terminal ICA and the right MCA (d, arrow), aneurysmal dilatation of the left MCA (e, arrow) and the basilar artery (f, arrow)

multiplex polymerase chain reaction (PCR) was positive for EBV and negative for other viruses screened (herpes simplex 1 and 2, adeno, varicella and CMV viruses). Blood virus screening (HIV, hepatitis B and C viruses) was negative. Work up for lymphoproliferative disorder including screening for lymphadenopathy, CSF flow cytometry and bone marrow examination were negative. Quantitative immunoglobulin assay was normal (IgG – 1275 mg%, IgA – 201 mg% and IgE – 12.5 IU/ml). His peripheral blood lymphocyte subset analysis showed CD4+ T cells - 1091/μL and CD3+ T cells - 6060/μL. Positron emission tomography (PET) scan was unremarkable. The markers for systemic vasculitis were negative. Nerve conduction study and a muscle, nerve and skin biopsy were normal. During the hospital stay, he had worsening of headache; repeat MRI brain showed T2 hyperintensity in right caudate nuclei, bilateral frontal and hippocampal areas [Figure 2e and f]. Repeat CSF analysis showed persistent lymphocytic pleocytosis, raised proteins, low sugars and EBV PCR positive status. He was discharged on oral anticoagulation and oxcarbamazepine. In June 2010, he had fever, pancytopenia and bone marrow aplasia, probably due to EBV-associated X-linked lymphoproliferative disorder (XLP). His peripheral blood lymphocyte subset analysis showed CD3+ T cells - 3888/μL, CD4+ T cells -756/μL, CD8+ T cells - 3074/μ L, CD19+ T cells - 108/μL and CD56+ T cells - 150/μL, suggestive of mild B cell deficiency. He was treated with antibiotics for respiratory infection and also growth factors. He continued to deteriorate and succumbed to sepsis within 2 weeks. A molecular diagnosis looking for mutation in the SH2D1A/DSHP/SLAM-associated protein (SAP) gene could not be done for the lack of availability of the test.

Discussion

EBV infection is prevalent in more than 90% of the adult population as latent infection. In CNS, chronic active EBV infection can cause recurrent meningitis, chronic meningoencephalitis and acute disseminated encephalomyelitis.[1] Rare manifestations reported include diffuse CNS vasculopathy/lymphocytic vasculitis with aneurysmal dilatations of arteries.[2-5] Our case had presented with features of chronic meningitis, with chronic headache, fever and seizures. Initial MRI brain had showed fusiform aneurysmal dilatations of anterior and posterior cerebral circulation with right vertebral artery thrombosis and leptomeningeal enhancement. MRI brain done later had showed T2 hyperintensity of right caudate nuclei, bilateral frontal and hippocampal areas with persistent vascular dilatation. Weeks *et al*. reported MRI brain of a 17-year-old boy with XLP related to EBV, which showed fusiform dilatation of the bilateral cisternal segments of the anterior/middle cerebral, supraclinoid segments of the internal carotid arteries and distal portion of the basilar artery. Subsequent MRI had showed T2

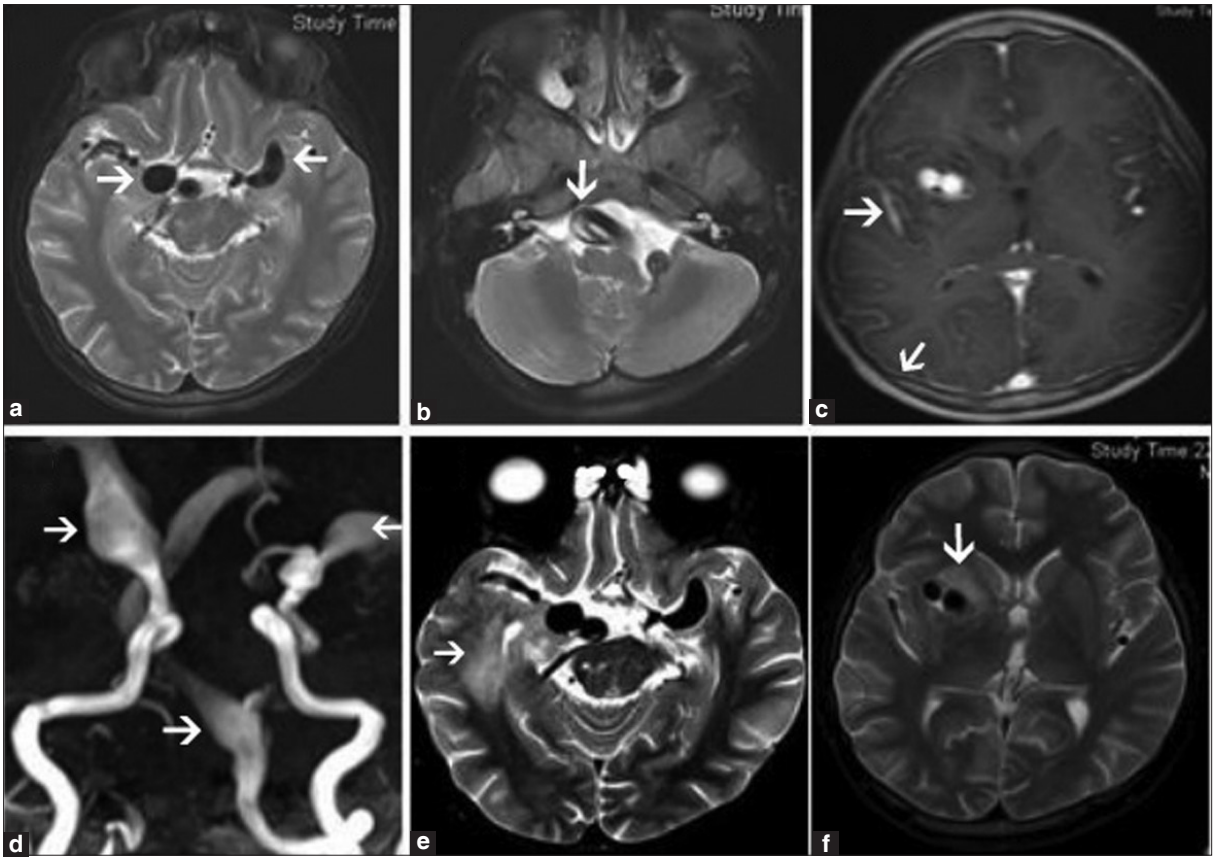

Figure 2: T2 magnetic resonance (MR) imaging of the brain shows aneurysmal dilatation of the right terminal internal carotid arteries (ICA), the left middle cerebral arteries (MCA) (a, arrows) and the left vertebral artery (b, arrow). T1 gado image shows meningeal enhancement (c, arrows). MR angiogram shows aneurysmal dilatation of ICA, MCA, vertebral and basilar arteries (d, arrows). T2 images shows hyperintensity in the right hippocampal area (e, arrow) and right caudate nucleus (f, arrow)

hyperintensities in the bilateral basal ganglia, internal capsules, thalami and medial temporal lobes.[2] These findings were similar to those in our patient, including the arterial dilatations and parenchymal hyperintensities. Dutz *et al.* reported autopsy findings of a 13-year-old boy with chronic systemic vasculitis and XLP related to EBV infection, which had showed focal, widespread, asynchronous microscopic necrotizing arteritis with aneurysmal dilatation. There was medium/small vessel arteritis affecting the CNS.[3] Loeffel *et al.* reported autopsy findings of an 8-year-old boy with XLP and recurrent episodic intracerebral hemorrhages, which had showed necrotizing vasculitis and aneurysms involving the cerebral arteries. EBV genome was demonstrated in tissues obtained at autopsy.[4] Murakami *et al.* described features of mesoarteritis in large systemic vessels on autopsy in a 13-year-old girl related to EBV infection.[5] The case report by Weeks *et al.* described the imaging and histopathology findings,[2] whereas the other three reports (Dutz *et al.*, Loeffel *et al.* and Murakami *et al.*) described predominantly histopathology findings of vasculopathy associated with EBV infection on autopsy.[3-5] An autopsy was not done in our case and the nerve muscle and skin biopsy was unremarkable. These patients had features of vasculopathy, but were different from our case in terms of focal involvement and, in addition, extracranial vasculature involvement. In our case, CSF study had shown lymphocytic pleocytosis with raised protein and decreased sugar. CSF multiplex PCR was positive for EBV. Subsequent CSF analysis had shown persistent pleocytosis, raised proteins and reduced sugars. In the case report by Weeks *et al.*, CSF analyses had shown recurrent pleocytosis, persistently elevated protein and positive EBV DNA PCR, similar to that in our case.[2] CNS vascular pathology in EBV infection is considered to involve direct invasion, infiltration of EBV-infected lymphocytes and endothelial deposition of antibody–antigen complexes.[2,6] Our case had shown features of chronic lymphocytic meningitis with vasculopathy, which was localized to the brain. The salient features noted were a positive PCR for EBV DNA, gross CSF abnormality (persistent pleocytosis, proteins in grams/dL and low sugars), fusiform aneurysmal dilatation of intracranial cerebral vessels and bone marrow aplasia with no other obvious explanation other than XLP.

Conclusion

EBV can cause a wide spectrum of manifestations, from tumors, immunodeficiency states to vasculopathy. Vasculopathy/vasculitis, especially diffuse fusiform aneurysms associated with chronic EBV infection/XLP, is rare, but has been described in few case reports, similar to ours. There needs to be a high index of suspicion of such an association that would help diagnosis, look for the spectrum of lymphoproliferative disorder, study the probable mechanisms for the vascular changes and avoid treatment as noninfectious immune-

mediated vasculitis/vasculopathy. These patients have a poor prognosis due to the immune-deficient status.

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References

1. Maeda E, Akahane M, Kiryu S, Kato N, Yoshikawa T, Hayashi N, *et al*. Spectrum of *Epstein-Barr virus*-related diseases: A pictorial review. Jpn J Radiol 2009;27:4-19.
2. Weeks JK, Helton KL, Conley ME, Onciu M, Khan RB. Diffuse CNS vasculopathy with chronic *Epstein-Barr virus* infection in X-linked lymphoproliferative disease. AJNR Am J Neuroradiol 2006;27:884-6.
3. Dutz JP, Benoit L, Wang X, Demetrick DJ, Junker A, de Sa D, *et al*. Lymphocytic vasculitis in X-linked lymphoproliferative disease. Blood 2001;1:95-100.
4. Loeffel S, Chang CH, Heyn R, Harada S, Lipscomb H, Sinangil F, *et al*. Necrotizing lymphoid vasculitis in X-linked lymphoproliferative syndrome. Arch Pathol Lab Med 1985;109:546-50.
5. Murakami K, Ohsawa M, Hu SX, Kanno H, Aozasa K, Nose M. Large vessel arteritis associated with chronic active *Epstein-Barr virus* infection. Arthritis Rheum 1988;41:369-73.
6. Volpi A. *Epstein-Barr virus* and human herpesvirus type 8 infections of the central nervous system. Herpes 2004;11(suppl 2):120A-27A.

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