Journal of NeuroVirology, 14: 574–578, 2008

ISSN 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280802345715

informa
healthcare

Case Report

Epstein-Barr virus encephalitis presenting with a tumor-like lesion in an immunosuppressed transplant recipient

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Epstein-Barr virus (EBV) associated central nervous system (CNS) infection is a rare disease. We report an atypical manifestation of EBV encephalitis initially presenting with a tumor-like lesion of the optic tract in an immunocompromised patient 8 years after a combined kidney and pancreas transplantation had been performed. Polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF) and antibody testing confirmed the diagnosis of EBV encephalitis, most likely as a consequence of a reactivated persistent EBV infection. After cessation of the immunosuppressive therapy and induction of treatment with ganciclovir, clinical and magnetic resonance imaging (MRI) findings rapidly improved. *Journal of NeuroVirology* (2008) **14,** 574–578.

Keywords: brain tumor; Epstein-Barr virus; encephalitis; transplantation

Background

Epstein-Barr virus (EBV), a member of the herpes virus family, has been associated with a wide spectrum of human diseases (Cohen, 2000). Neurologic complications of EBV infection, such as encephalitis, transverse myelitis, polyradiculomyelitis, seizures, and cranial nerve palsies, have been described (Fujimoto *et al*, 2003; Hausler *et al*, 2002; Volpi, 2004). There is a wide range of magnetic resonance imaging (MRI) findings in patients with EBV encephalitis and encephalomyelitis, which also depend on the timing of the MRI scan (Shian and Chi, 1996). Polymerase chain reaction (PCR) of the cerebrospinal fluid (CSF) is considered the method of choice for diagnosing CNS viral infections, but has only recently become available for the detection of EBV (DeBiasi, 2002). Here we describe an unusual case of EBV encephalitis in a 49-year-old kidney and pancreas transplant recipient who initially presented with a tumor-like lesion of the optic tract.

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Received 5 March 2008; revised 30 May 2008; accepted 8 July 2008.

Case report

On 9 February 2007, a 49-year-old female was admitted to another hospital because of a 14-day history of progressive visual deterioration and vertigo. The patient had had type I diabetes associated with renal insufficiency since 1960 and was on immunosuppressive treatment with tacrolimus and mycophenolat mofetil subsequent to a combined pancreas and kidney transplantation in 1999. Ophthalmologic examination revealed a synchysis on the left eye and a senile cataract on the right eye, which could not completely explain her symptoms.

Neurologic examination at the time of admission indicated a disturbance of the right visual field and a visual deterioration on the left eye. Furthermore, she showed decreased sense of vibration on both lower extremities and a bilaterally reduced ankle-jerk reflex. A complete blood cell count showed white blood cell WBC $4.06 \cdot 10^9$ cells/l (neutrophils 72%, eosinophils 1% basophils 0%, monocytes 13%, and lymphocytes 14%), red blood cell RBC $3.72 \cdot 10^{12}$ cells/l, hemoglobin 11.2 g/dl, and hematocrit 33.4%. There were no clinical signs of infection and levels of the C-reactive protein were normal. A computed tomography scan of the brain was read as normal. Further examinations including

magnetic resonance imaging (MRI) of the brain were deemed necessary, which was performed 5 days later. It showed high signal intensity and swelling of predominantly the left optic tract (Figure 1A). In addition, confluent periventricular white matter lesions suggested cerebral microangiopathy. No acute ischemic lesions were detected. Subsequently, the patient progressed to a complete visual loss on the left eye. The ophthalmologist suspected posterior ischemic opticopathy as a possible cause and had a MRI of the orbital region performed on 23 February. This scan revealed a 1.7×1.5 cm large expansion in the chiasma opticum with weak gadolinium enhancement (Figure 1B, C). With the tentative diagnosis of a glioma of the optic nerves, the patient was subsequently admitted to the University Clinic of Neurosurgery to undergo a craniotomy and partial extirpation of the lesion. Histopathological analysis of the specimen demonstrated tissue necrosis, but no signs of neoplasia (Figure 2). A vasculitic process was suspected. Postoperatively, the condition of the patient continuously worsened, with further deterioration of visual function of the right eye and signs of diencephalic alteration, including impaired vigilance and neuropsychological dysfunctions.

On 15 March the patient was subsequently transferred to the intensive care unit of our department. A control MRI of the brain showed further increase of the area of signal abnormality, which now also demonstrated more extensive peripheral gadolinium enhancement preferentially in the hypothalamus, thalamus, basal ganglia, and dorsolateral frontal region bilaterally (Figure 3A). As these alterations were felt to possibly represent an immune-mediated inflammatory process, the patient was started on methylprednisolone intravenously. A complete blood count showed a hematocrit of 32.8%, hemoglobin of 10.8 g/dl, RBC $3.71 \cdot 10^{12}$ cells/l, WBC $3.51 \cdot 10^{9}$ cells/l (87% neutrophils, 8% lymphocytes, 4% monocytes), and a Platelet count of $100 \cdot 10^{9}$ cells/l. C-reactive protein was normal at the time of MRI acquisition. A lumbar puncture showed 5 cells/μl, glucose level of 174 mg/dl, with a CSF/serum glucose quotient of 0.71, and an immunoglobulin G (IgG) index of 0.60. Anti-EBV virus capsid antigen (VCA) IgM antibodies were elevated in the blood and EBV DNA was detected in the CSF and blood using PCR technique (Table 1). CSF PCR was negative for *Mycobacterium tuberculosis, M. Avium, M. intracellulare,* and cytomegalovirus (CMV). A combined treatment of ganciclovir and prednisolone was initiated and immunosuppression with tacrolimus and mycophenolat mofetil was stopped.

The clinical condition of the patient improved markedly, which was paralleled by substantial regression of the lesions on a control MRI of the brain performed on 11 April 2007, around 3½ weeks after adaption of therapy according to the diagnosis of EBV encephalitis (Figure 3B). Despite this clinical stabilization, EBV DNA was still detectable by PCR in the blood of the patient. EBV-DNA load of the peripheral blood was then monitored monthly, revealing a positive EBV-PCR result throughout every analysis until December 2007 (Table 1). Due to the persistent EBV infection, the immunosuppressive treatment with tacrolimus and mycophenolat mofetil was not reconvened up to now. Renal function was normal throughout the whole length of inpatient admission. The patient was discharged from our clinic on 15 May 2007. Clinical examination at this time showed an amaurosis on the left eye and an alteration of the visual fields on the right eye.

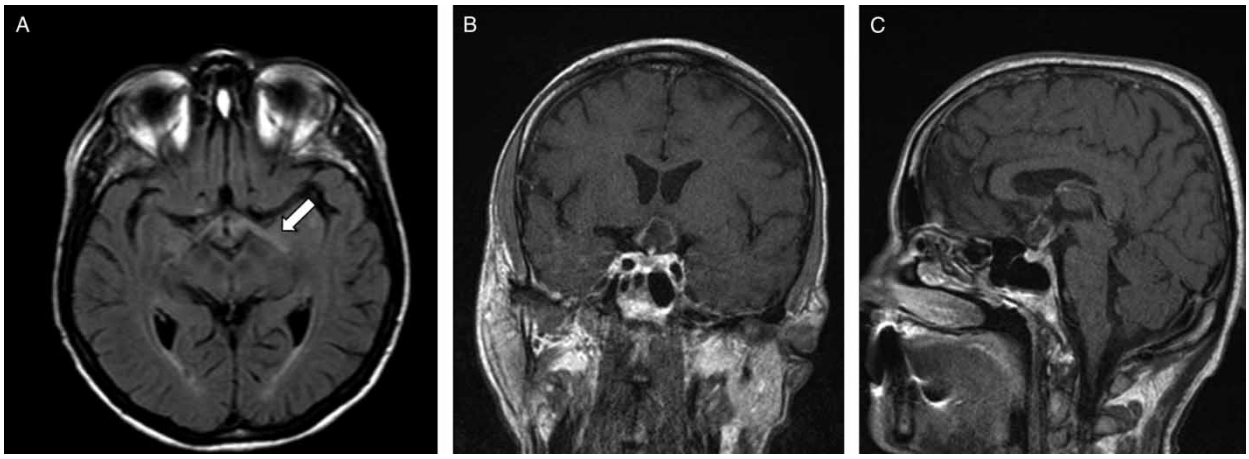

Figure 1 Representative MRI slices demonstrating the temporal dynamics of lesion evolution in one panel. MRI performed on 14 February 2007 showed high signal intensity and swelling of predominantly the left optic tract (*arrow*) (**A**). MRI performed on 23 February 2007 showed development of a mass lesion within and above the optic chiasm with extension into the left basal ganglia; contrast enhancement at the borders of the expansile lesion (**B** and **C**).

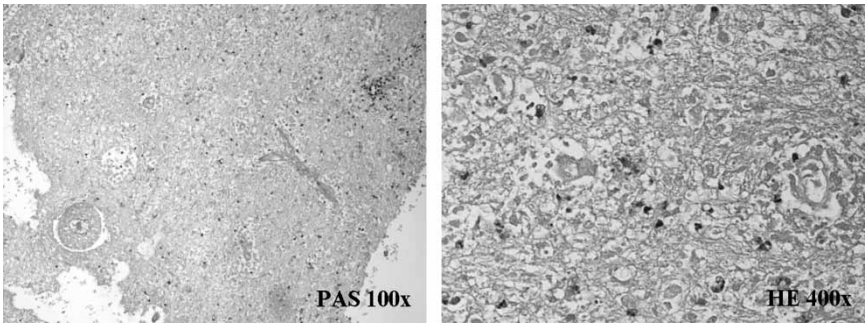

Figure 2 Histopathological analysis of the biopsy specimen obtained from the 1.7 × 1.5 cm large expansion in the chiasma opticum revealed brain tissue necrosis, interspersed by neutrophils and granulocytes, necrotic vessels, but no signs of neoplasia. PAS = periodic acid–Schiff stain; HE = hematoxylin and eosin stain.

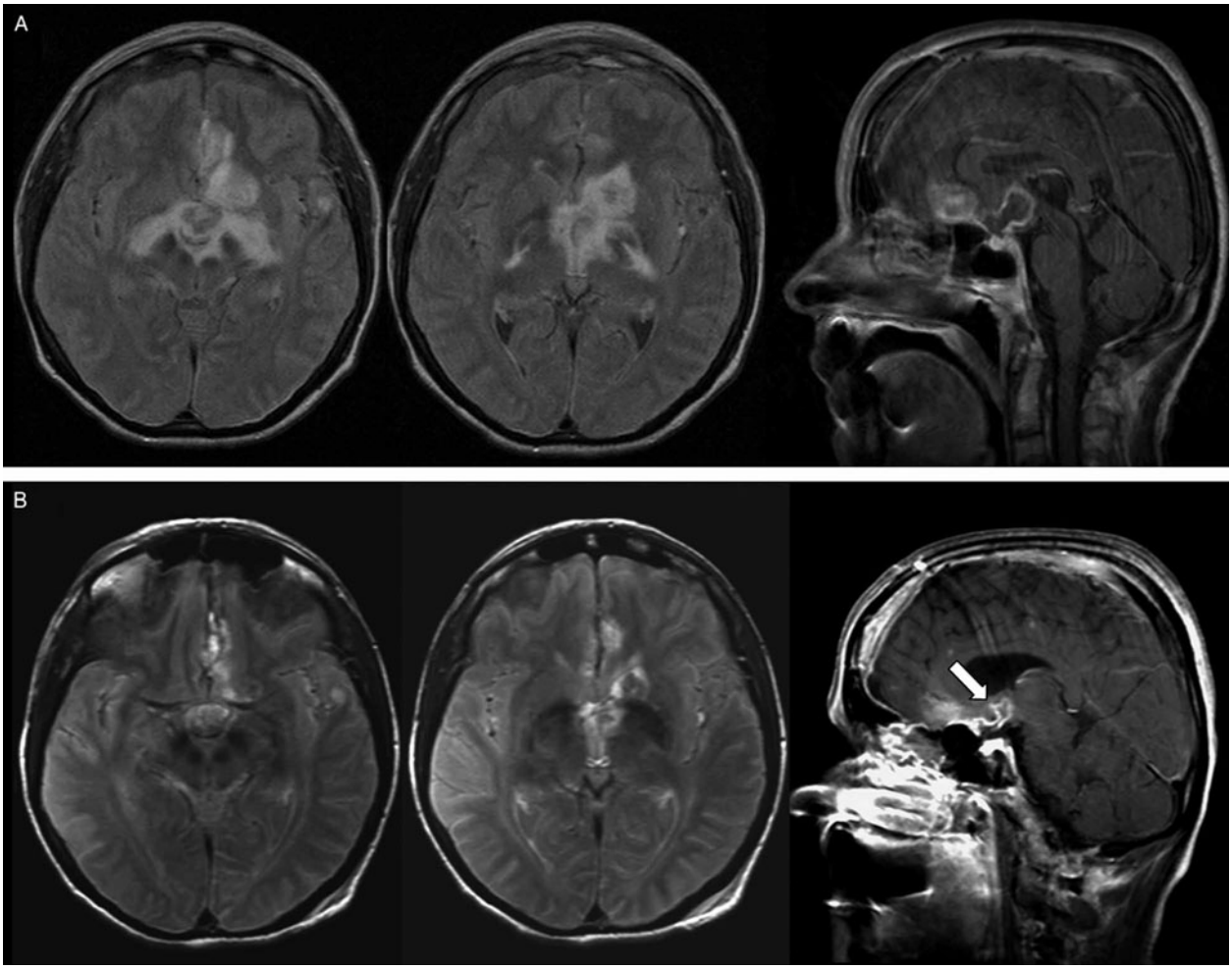

Figure 3 Postoperative evolution of MRI changes. MRI performed on 16 March 2007 (**A,** upper panels) at the nadir of the patient's clinical condition showed marked extension of the signal abnormalities with mass effect involving the basal ganglia bilaterally (especially on the left) and the left orbitofrontal gyrus. A rim of contrast enhancement bordered the area of the lesion. Follow-up MRI performed on 11 April 2007 around 3½ weeks after adaption of therapy according to the diagnosis of EBV encephalitis (**B,** lower panels) demonstrated a significant reduction of signal abnormalities with parts of the lesion appearing necrotic (*arrowhead*). This was paralleled by a significant improvement of the patient's neuropsychiatric symptoms.

Table 1 Epstein-Barr-Virus CSF and peripheral blood findings.

	Date of sample collection				
	19 March 2007	3 April 2007	13 June 2007	26 July 2007	13 December 2007
CSF					
PCR	+				
Blood					
PCR		+	+	+	+
(DNA copies/ml)		134250	11900	485	1450
EBV VCA IgG Abs		1:128	1:128		
EBV VCA IgM Abs		+	+		

Note. EBV-DNA was detected in CSF. After cessation of the immunosuppressive therapy, EBV DNA was still detectable in the peripheral blood throughout every single follow-up analysis, indicating a persistent EBV infection. Serum IgG and IgM antibodies directed against EBV virus capsid antigen were elevated.
CSF = cerebrospinal fluid; PCR = polymerase chain reaction; EBV = Epstein-Barr virus; EBV VCA = Epstein-Barr virus virus capsid antigen; IgG = immunoglobulin G; IgM = immunoglobulin M; Abs = antibodies.

Discussion

This case report illustrates an unusual presentation of EBV encephalitis in an immunocompromised pancreas and kidney transplant recipient consisting of progressive visual deterioration due to a mass lesion that involved the optic chiasm and nerves. The patient underwent regulatory clinical and laboratory monitoring during immunosuppressive treatment. At time of clinical admission, the patient only had mild neutropenia and there were no signs of infection. Impairment of cellular immunity in immunosuppressed patients can result in a proliferation of EBV-infected B cells, leading to the EBV-associated lymphoproliferative disease (Cohen, 2000). However, the expansion in the optic tract was initially suspected as a glioma and therefore treated surgically. Histopathological work-up of the specimen also revealed tissue necrosis rather than neoplastic transformation, suggesting a vasculitic process. There are only a few reports of tumor-like central nervous system (CNS) lesions caused by EBV infection (Angelini *et al*, 2000). Furthermore, a large variety of MRI findings in EBV encephalitis and encephalomyelitis can be found, including T2 prolongation over gray and white matter, periventricular leukomalacia, and brain atrophy, which are also dependent on the timing of the MRI scan during EBV infection (Shian and Chi, 1996).

Polymerase chain reaction of the cerebrospinal fluid has been developed recently for the diagnosis of EBV infection of the CNS (DeBiasi *et al*, 2002). In our patient EBV DNA was detectable in both the CSF and the blood, leading to the diagnosis of EBV encephalitis. After cessation of the immunosuppressive treatment, the patient clinically improved and signal abnormalities on MRI of the brain regressed, suggesting local resolution of the inflammatory process. Besides stopping the immunosuppressive treatment, further therapeutic interventions, such as methylprednisolone and ganciclovir therapy, might have additionally contributed to clinical improvement in our patient. However, EBV DNA was still detectable in the peripheral blood at a high level after the patient was discharged from our hospital, indicating that the patient retained an EBV infection despite antiviral therapy (Kimura, 2006). Based on the serological findings with a persistently stable EBV IgG antibody titer, clinical and PCR findings with a high EBV DNA load, it is most likely that our patient had experienced a reactivation of EBV infection as the trigger of her encephalitis (Merelli *et al*, 1997), although the possibility of an initial EBV infection cannot be completely ruled out. Importantly, even though clinical presentation, radiological, histopathological, and laboratory findings strongly support the diagnosis of EBV encephalitis in our patient, the possibility of a CNS lymphoma has still to be taken into account. The majority of primary CNS lymphomas are EBV related (Volpi, 2004). Therefore long-term follow-up of our patient regarding clinical status, magnetic resonance imaging, and laboratory findings is planned. Involvement of the optic tract as a complication of EBV infection is rare. Eight cases of optic neuritis in the context of EBV infection have recently been summarized (Phowthongkum *et al*, 2007). Another two reports of bilateral optic neuritis and papilloretinal edema associated to EBV infection have been reported in the medical literature (Blaustein and Caccavo, 1950; Bonynge and Von Hagen, 1952). In our patient the optic tract and chiasma were primarily affected (Purvin *et al*, 1988) and subsequently the basal ganglia were affected bilaterally (Phowthongkum *et al*, 2007).

Only a few reports are available in the medical literature describing cases of EBV encephalitis, either due to primary infection or reactivation, following bone marrow or solid organ transplantation. In most of these cases, neurologic complications developed within weeks or months after transplantation (Behr *et al*, 2006; Dellemijn *et al*, 1995; Kim *et al*, 1998; Ponticelli and Campise, 2005). In the present case, EBV reactivation occurred 8 years after transplantation. A similar time interval

between kidney transplantation and EBV reactivation, clinically presenting with vertigo, influenza-like syndrome, visual hallucinations, and impairment of consciousness, has been reported previously (Garamendi *et al*, 2002).

Although the prognosis of EBV encephalitis is generally good (Portegies and Corssmit, 2000; Volpi, 2004), fatal cases of EBV encephalitis, even in immunocompetent patients, have been reported (Francisci *et al*, 2004; Vince *et al*, 2007). In our patient, most neurological and psychological symptoms recovered except for the visual loss on her left eye, which might be partially caused by the neurosurgical intervention. The present case indicates that an infectious process including EBV should be considered in the differential diagnosis of a rapidly expanding cerebral mass in the context of immunosuppression. In such a scenario, PCR and antibody testing in the CSF and blood may aid in the diagnosis of an EBV infection or its reactivation and thereby guide decision making concerning appropriate treatment and adjustment or cessation of immunosuppression.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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This paper was first published online on iFirst on 6 November 2008.