Epstein–Barr virus infection and central nervous system involvement after orthoptic liver transplant

Kamran Shafiq,¹ Ahamad Hassan,² Mervyn H Davies,³ Rebecca L Jones³

¹City Hospitals Sunderland, Sunderland, UK

²Department of Neurology, Leeds General Infirmary, Leeds, UK

³Liver Transplant Unit, St James's University Hospital, Leeds, UK

Correspondence to

Kamran Shafiq, Consultant Gastroenterologist, City Hospitals Sunderland, Kayl Road, Sunderland SR4 7TP, UK; kshafiq2003@yahoo.co.uk

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Abstract

Epstein–Barr virus (EBV) infection presenting as encephalitis in seronegative adults in the context of solid organ transplantation is rarely reported. EBV seroconversion illnesses in the adult population after organ transplantation are quite uncommon. This report describes a case of encephalitis due to EBV infection after liver transplantation in an adult patient. The patient was seronegative for EBV pretransplant. She showed persistent viral replication indicated by high levels of EBV DNA in the serum, which raised concerns for future development of post-transplant lymphoproliferative disorder. The report discusses the management of such patients, awareness of EBV infection and earlier diagnosis by use of EBV PCR in adult immunocompromised individuals where infection may cause particular problems.

Case history

A 58-year-old woman was admitted to our transplant clinic in October 2005. She complained of non-specific symptoms of feeling unwell with lethargy, nausea and headache for a few weeks. She had no weight loss or night sweats.

A year prior, she had received a liver transplant for primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome. Her initial post-transplant immunosuppression included prednisolone plus ciclosporin 150 mg twice a day and azathioprine 150 mg once a day. She had an episode of acute moderate rejection in January 2005, which resulted in a switch of ciclosporin and azathioprine to tacrolimus 3.5 mg twice a day and mycophenolate mofetil 1 g twice a day. Her liver function tests had remained stable thereafter.

She was admitted for further investigation. On examination, she was febrile with a temperature of 38°C, dehydrated and had mild epigastric tenderness.

The rest of the examination including neurological examination was normal. Subsequently, she had an episode where she was found unresponsive and aphasic that lasted about 10 min. Following this, she was drowsy for 2–3 h, consistent with a post-ictal state.

Investigations revealed normal full blood count but low lymphocyte count of 0.82×10^9 ($1\text{--}4.5 \times 10^9$). Routine biochemistry, coagulation tests and C reactive protein were all normal. Tacrolimus level was 4 (target range in our unit 4–8 ng/ml at 12 months after transplant). Blood and urine cultures were negative. Chest x-ray was normal as was a brain CT scan. She went on to have a lumbar puncture (see table 1). Cerebrospinal fluid (CSF) showed 10×10^6 /l white blood cells of which 8×10^6 /l were monocytes. No organisms were seen on microscopy. Tests for atypical organisms including fungi and tuberculosis were negative as was a PCR battery for CSF viruses (herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV) and enterovirus). The CSF protein was elevated at 1.82 g/l with a borderline low glucose (1.8 mmol/l) and oligoclonal bands restricted to spinal fluid. Brain MRI with gadolinium revealed a couple of tiny foci of high signal within deep white matter of frontal lobes, not thought to be significant. An EEG showed moderate generalised excess of slow wave activity consistent with encephalopathy, but no focal or epileptiform abnormalities were seen.

A viral encephalitis was suspected, possibly related to her immunocompromised state, and she was started on intravenous acyclovir for possible HSV, which was continued for 14 days.

The episode of aphasia was thought to be a complex partial seizure secondary to viral

Table 1 CSF analysis over time

Day	WBC/mm ³	RBC/mm ³	Glucose (mmol/l)	Protein (g/l)	Gram staining and culture	CSF PCR	Cytology
7	10 (2 poly, 8 mono)	56	1.8 (serum glucose 5.6)	1.82	Negative	Negative for enterovirus, HSV, VZV, CMV and Mycobacterium	Negative
14	8 (2 poly, 6 mono)	29	2.2	2.17	Negative	Negative for enterovirus, HSV, VZV, CMV and Mycobacterium	Atypia
19	<1	48	1.9	2.98	Negative	Bacterial DNA negative	Negative
34	57 lymphocytes	5	2.3 (serum glucose 7.1)	2.4	Negative	Negative for enterovirus, HSV, VZV, CMV and Mycobacterium Positive for EBV DNA (6490 copies/ml) oligoclonal bands present	Negative
64	4 (all lymphocytes)	166	2.7 (serum glucose 4.7)	1.17	Negative	Negative for enterovirus, HSV, VZV, CMV and Mycobacterium Positive for EBV DNA (4950 copies/ml)	Negative

CMV, cytomegalovirus virus; CSF, cerebrospinal fluid; EBV, Epstein–Barr virus; HSV, herpes simplex virus; RBC, red blood cell; VZV, varicella zoster virus; WBC, white blood cell.

encephalitis and carbamazepine was also commenced. Over the next few days, both confusion and persistent headache gradually improved while investigations continued.

She underwent repeated CSF examinations that were persistently consistent with aseptic meningitis. This led to concerns about the development of leptomenigeal infiltration secondary to post-transplant lymphoproliferative disorder (PTLD) involving the central nervous system (CNS). Evidence of infection with Epstein–Barr virus (EBV) was sought. Her pretransplant EBV serology was negative. It was positive when checked again during this current illness, consistent with seroconversion. She showed a rising titre of EBV in both CSF and serum. The cells in the CSF were reported initially as monocytes although in hindsight they were atypical lymphocytes.

A final diagnosis of primary EBV infection with a seroconversion illness presenting with encephalitis was made. Her immunosuppression doses were reduced without deterioration of her liver function tests. We looked for and excluded PTLD with a further brain MRI scan and single photon emission CT study showing no evidence of CNS deposits. CT scans of the chest, abdomen and pelvis were normal with no signs of lymphadenopathy or unexplained mass lesion. Clinically she remained well at 5 years follow-up with no further seizure or episodes of confusion.

Discussion

EBV is a double-stranded DNA herpes virus. It is usually spread by intimate contact involving salivary exchange and the majority of primary EBV infections throughout the world are subclinical. Antibodies to EBV have been demonstrated in all population groups with a worldwide distribution; approximately 90–95% of adults are EBV seropositive.¹ EBV seroconversion

illnesses in the adult population after organ transplantation are therefore uncommon.

Clinical EBV infection most commonly manifests as infectious mononucleosis in young adults, but infection can also lead to lymphoma, nasopharyngeal carcinoma and, in the organ transplant population, post-transplant lymphoproliferative disease. Reported neurological manifestations include encephalitis, meningitis, myelitis, peripheral and cranial neuritis as well as primary CNS lymphoma in immunosuppressed individuals.^{2,3} EBV encephalitis in an immunocompetent Asian population has been reported to have an annual incidence of approximately 0.05–0.56 cases/1 000 000.^{3,4} EBV CNS infections can occur as a result of acute primary infection or reactivation of the virus, which remains in tissues, following the initial infection. Neurological features can occur with or without the typical symptoms and signs of infectious mononucleosis.⁵

The pathogenesis of EBV-associated CNS diseases is not completely understood; it may be due to direct invasion or may be immunologically mediated. CSF shows increased levels of protein and lymphocytes. High viral EBV load in CSF (4.2 ± 0.3 log DNA copies/ml) may be observed.⁶ No EBV antiviral therapy is as yet available although both acyclovir and ganciclovir may have antiviral activity against EBV.^{7,8}

Our patient was seronegative for EBV prior to transplant while the donor is likely to have been positive, given the population prevalence of virus seropositivity. Latent virus may have been transmitted at the time of transplantation resulting in recipient infection. We think that this presentation represented a seroconversion illness although this might usually be expected in the earlier post-transplant period. Two alternative explanations have been considered: EBV infection may have been community acquired, but we consider this

less likely. Alternatively, seroconversion may have been subclinical and this presentation may have been due to reactivation of the latent virus.

The causes of viral encephalitis to consider in the immunocompromised patient include HSV, VZV, enteroviruses and also less known viruses such as human herpes virus 6, CMV and EBV, which are not available on routine PCR viral screens. Therefore, the clinician needs to be aware of these possibilities for the differential diagnosis of encephalitis in the immunosuppressed patient and specifically request testing. Subacute encephalitis running for a few weeks should also make one think of an atypical virus (as was true in our case).

The prognosis remains good for most EBV-related neurological complications in immunocompetent individuals,⁹ although fatal cases have been reported.¹⁰ Our case highlights the need for awareness of EBV infection in adult immunocompromised individuals such as recipients of solid organ transplants, where infection may cause particular problems. It is likely that EBV infection is underestimated as a cause of encephalitis in both immunocompetent and immunocompromised patients, although more cases are likely to be detected in the future with the availability of sensitive PCR techniques.^{11 12}

Persistent viral replication indicated by high levels of EBV DNA in the serum of our patient raised concerns for future development of PTLT. PTLT is one of the most feared post-transplant complications and contributes to significant morbidity and mortality. It occurs in 1–20% of transplanted patients with almost all cases related to latent EBV infection. Seronegative recipients of organs from seropositive donors seem to be at highest risk for the development of PTLT.¹³ Primary EBV infection after transplantation increases the risk of PTLT.¹⁴ Our patient was both seronegative for EBV and acquired primary infection after transplantation therefore posing a high risk for development of PTLT. Serial monitoring of EBV load using quantitative PCR may allow early detection of asymptomatic viral replication and guide pre-emptive reduction of immunosuppression to reduce the risk of developing PTLT.¹⁵ The patient has been under follow-up for the last 5 years since her initial presentation. Her immunosuppression has been reduced to a level (tacrolimus 1 mg in the morning and 2 mg in the evening with mycophenolate 500 mg once a day) that has maintained good liver function without recurrent late acute rejection. On diagnosis, her serum EBV PCR rose to >600 000 copies/ml. Subsequently, it has reduced to between 7600 and 39 220 copies/ml. Although EBV has never cleared from her serum, it now runs at a much lower level, suggesting that it has come down

with our approach, and there has been no evidence for the development of PTLT.

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