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CASE REPORT

Epstein-Barr virus encephalitis in solid organ transplantation

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SUMMARY

Epstein-Barr virus (EBV) is typically associated with post transplant lymphoproliferative disease (PTLD) after solid organ and stem cell transplantation. However, it is rarely associated with neurological complications. We report a case of severe encephalitis complicating primary EBV infection six months post renal transplantation, and review the literature on EBV encephalitis in solid organ transplantation in adults.
A 55-year-old male presented 6 months post cadaveric renal transplant with headache, fever and confusion. Neuroimaging was unremarkable, but an electroencephalogram was consistent with diffuse encephalopathy. EBV DNA was detected in both cerebrospinal fluid (13,177 copies/ml), and plasma (14,166 copies/ml). Management included reduction of immunosuppression, intravenous ganciclovir and intravenous immunoglobulin, and resulted in a reduction in EBV viral load in both plasma and cerebrospinal fluid. The patient made a full recovery with no long-term neurological deficits and preservation of the graft.
This case highlights the importance of knowing donor and recipient EBV serostatus at time of transplant, and closely monitoring EBV DNA when there is a mismatch. Ganciclovir or valganciclovir prophylaxis has also been shown to reduce the incidence of primary EBV infection in renal transplantation in these recipients. Treatment options for EBV infection post-transplant include reduction of immunosuppression, antiviral therapy, IVIg, and monoclonal antibody therapy directed toward infected B lymphocytes.

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INTRODUCTION

Epstein-Barr Virus (EBV) infection can cause serious complications following solid organ transplantation, including post-transplant lymphoproliferative disorder (PTLD) (Walker *et al.*, 1995). We describe a case of encephalitis associated with primary EBV infection 6 months post renal transplant. The infection was managed with reduction of immunosuppression and ganciclovir with resolution of his encephalitis. We then review the literature on EBV encephalitis in solid organ transplantation in adults.

CASE REPORT

A 55-year-old male with end stage renal failure secondary to IgA nephropathy and a more recent history of small renal cell carcinoma treated with left nephrectomy, underwent cadaveric renal transplant. Induction immunosuppression consisted of 1g methylprednisolone on day 0, and 500 mg on day 1 post transplant, and basiliximab 20 mg on day 0 and day 4 post transplant, with ongoing tacrolimus, mycophenolate mofetil (MMF) and prednisolone. Transplantation was complicated by delayed graft function, but no evidence of graft rejection on biopsy. Serum creatinine was 166 μmol/L 4 months post transplant. Medications included tacrolimus 5.5 mg twice daily (trough level pre-admission of 4.6 mcg/L), MMF 1g twice daily, and prednisolone 7.5 mg daily, as well as trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg twice weekly and valacyclovir 500 mg daily for pneumocystis and herpes simplex virus prophylaxis respectively. The patient was seronegative for cytomegalovirus, as was the transplant donor.
Six months following transplantation, he presented with ill-defined symptoms of abdominal pain and headache. Baseline neurological examination was unremarkable. The headache worsened and he became delirious and febrile (38°C), requiring admission to the Intensive Care Unit for monitoring of decreased conscious state and confusion. Neurological examination revealed hyperreflexia, hypertonia of both lower limbs and upper limbs, and neck stiffness. Investigations revealed neutropenia $1.10x10^9$/L and lymphopenia $0.30x10^9$/L, with a C-reactive protein (CRP) of 18 mg/L (normal range: 0-5 mg/L). In view of the leukopenia, TMP/SMX and valacyclovir was withheld, and MMF dose was halved. Serum CMV IgG and IgM remained negative.
Cranial CT and MRI (with contrast) were normal, but

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an electroencephalogram revealed diffuse delta slowing with periodic generalised triphasic waves consistent with diffuse encephalopathy. Cerebrospinal fluid (CSF) examination demonstrated a white cell count of $40x10^6$/L (34 lymphocytes, 6 polymorph nuclear cells), decreased glucose 1.4 mmol/L (2.5-5.0 mmol/L), increased protein 2.5 g/L (0.1-0.3 g/L), and increased lactate 6.2 mmol/L (0-3.0 mmol/L). Cerebrospinal fluid Gram stain revealed no organisms.

Testing for a range of pathogens was negative, including PCR testing of CSF for HSV 1 and 2, CMV, VZV, enterovirus, adenovirus, virus, flaviviruses (including West Nile Virus, Murray Valley encephalitis and Yellow Fever virus), respiratory virus multiplex PCR including influenza A and B, and *Mycobacterium tuberculosis* culture and PCR. Multiple sets of blood and urine cultures were negative. HIV serology was negative. Interferon- release assay for tuberculosis was negative. Serum cryptococcal antigen was not detected. Culture of CSF for common bacterial pathogens, mycobacteria and fungi was negative.

EBV DNA was detected in CSF (13,177 copies/ml) and plasma (14,166 copies/ml). Intravenous (IV) ganciclovir 5 mg/kg 12 hourly was commenced, tacrolimus and MMF were withheld, and intravenous immunoglobulin (IVIg two doses of 68 g, 3 days apart) was also administered, in conjunction with IV methylprednisolone 20 mg daily. The patient showed gradual neurological improvement, and was discharged from intensive care after 8 days. Anti-rejection medication was recommenced 9 days later with everolimus 1.5 g BD and 20 mg daily prednisolone, which was slowly weaned. Ganciclovir was ceased after 14 days due to neutropenia (neutrophil count $0.14x10^9$/L) and valaciclovir 500 mg daily was recommenced. Plasma EBV viral load fell to 166 copies/mL after 16 days.

The patient made a full recovery with no neurological sequelae and undetectable serum EBV viral load at 18 months follow-up. There has been no radiological evidence of lymphoproliferative disease on PET scan, and serial CT chest, abdomen and pelvis in this time period. Interstitial rejection was reported on graft biopsy 12 months after resolution of EBV infection. Tacrolimus being recommenced in the patient, in addition to everolimus, however this had no effect on serum EBV viral load, which remained undetectable. He remains on everolimus 0.5 mg mane, 0.75 mg nocte, and tacrolimus 1g daily. Renal function remains stable at a creatinine of 96 μmol/L at 18 months follow up.

EBV INVESTIGATIONS

EBV serological assignments were derived from combined analysis of the three Novagnost EBV enzyme immunoassays (VCA IgM, VCA IgG, and EBNA-1 IgG) (Siemens Healthcare Diagnostics GmbH, Marburg, Germany). EBV nucleic acid testing was performed using real time (rt) PCR with in-house primers targeting EBNA-1 and viral load calculated by Droplet Digital PCR (Bio-Rad, Pleasanton, CA, USA).

A summary of the EBV laboratory results is presented in *Table 1*. EBV VCA IgG and EBNA IgG was negative pre-transplant, and EBV seroconversion was demonstrated following his encephalitis, however this is masked by administration of IVIg. Subsequent retrospective testing of the donor's blood at time of organ retrieval confirmed past EBV infection (EBV VCA IgG and EBNA-1 IgG both positive), without evidence of active infection (EBV DNA not detected by rt-PCR).

DISCUSSION

EBV encephalitis has been reported in children and young adults, and post hemopoetic stem cell transplants. However, on reviewing all published reports in adult solid organ transplant patients, where EBV virus was reported as a cause of encephalitis and other pathogens were excluded we found only seven reports of EBV encephalitis, without evidence of PTLD (*Table 2*) (Khalil *et al.*, 2008; Munang *et al.*, 2013; Garamendi *et al.*, 2002; MacGinley *et al.*, 2000; Shafiq *et al.*, 2011; Babik *et al.*, 2015; Lahmer *et al.*, 2010). Six patients had received kidney transplants, and one had received a liver graft. Time from transplant ranged from 5 months to 10 years. The most common immunosuppressive agents were tacrolimus, MMF and corticosteroids. One patient developed encephalitis 11 days after receiving muromonab-CD3 (OKT3) for acute graft rejection.

Neurological symptoms included headache, dizziness, limb weakness, confusion and seizures. Two cases required intensive care admission for altered conscious state. Symptoms were mainly subacute, occurring weeks

Table 1 - *EBV serology and nucleic acid test results.*

Days post transplantion	*Specimen*	*EBV serology*			*EBV DNA*	
		EBV VCA IgG	*EBV VCA IgM*	*EBNA IgG*	*rt-PCR (ct)*	*Viral load, copies/ml (log10)*
0	serum	Negative	Negative	Negative	Not detected	-
99	serum	Negative*	Negative*	Negative*	Not detected	-
154	serum	Negative	Negative	Negative	Detected (32)#	1,615 (3.21)#
155	serum	-	-	-	Detected (30)	8,750 (3.94)
167	CSF	-	-	-	Detected (30)	14,166 (4.15)
168	plasma	-	-	-	Detected (30)	13,177 (4.12)
172	CSF	-	-	-	Detected (30)	11,458 (4.06)
181	plasma	Positive	Negative	Positive	Detected (33)	2,500 (3.40)
188	plasma	-	-	-	Detected (35)	166 (2.22)
198	plasma	Positive	Negative	Positive	Not detected	-

nd, not detected.
#not tested in parallel with the other specimens; viral load calculated by standard curve method.

prior to presentation in most cases. Visual symptoms were reported in three of the cases. MRI findings ranged from unremarkable, to multiple high intensity lesions and oedema.

EBV DNA was detected by PCR in CSF in all cases, with a viral load ranging from 6,490-23,000 copies/mL (when reported). Four cases represented EBV reactivation, with the recipient being EBV IgG positive pre-transplant. In one case presenting 13 years post renal transplant, EBV serology was not reported (Munang *et al.*, 2013). There is only one other report of encephalitis associated with primary EBV infection, one year following liver transplant (Shafiq *et al.*, 2011).

All of the reported patients were treated with antiviral therapy (ganciclovir or aciclovir) and immunosuppression was reduced or ceased in the majority of cases. All cases had favourable outcomes, with complete recovery, graft preservation, and no long-term neurological deficits.

Approximately 90-95% of adults are EBV seropositive (Sumaya *et al.*, 1975), therefore primary EBV infection is un-

Table 2 - *Case reports of EBV encephalitis in adult solid organ transplant patients.*

Case	*Age/ Gender*	*Underlying disease*	*Immuno-suppression*	*Duration post transplant*	*Clinical presentation*	*Neuroimaging Findings*
(1)	49F	Simultaneous kidney pancreas transplant 2 to T1DM and ESRF	Tacrolimus and MMF,	8 years	14-day history of progressive visual deterioration and vertigo	1st MRI (brain): high signal intensity and swelling predominantly the left optic tract MRI (orbital): 1.7x1.5 cm large expansion in the chiasma opticum with weak gadolinium enhancement
(2)	54M	Renal transplant 2 to Ig A nephropathy	MMF and prednisolone	13 years	1 week history of right leg weakness, headaches and blurring of vision, associated with 3month history of isolated dysphagia	MRI: Restricted diffusion in the left medulla and left occipital lobe
(3)	55F	Renal transplant for IgA nephropathy	Prednisolone, MMF and cyclosporine	8 years	4 weeks history of vertigo, flu-like illness. Then developed visual hallucinations, ataxia and altered conscious state in hospital, seizures.	MRI: high signal-intensity regions indicating lesions on the bulb, protuberance, mesencephalon, left thalamus and parenchyma adjacent to the corpus calosum
(4)	43F	Renal transplant for diabetic nephropathy OKT3 (acute rejection)	Cyclosporin, and azathioprine OKT3 for acute rejection	10 years 11 days after OKT3 course	Confusion, nausea, vomiting and fevers Altered conscious state developed in hospital	Unremarkable
(5)	58F	Liver transplant for primary sclerosing cholangitis/ autoimmune hepatitis	Prednisolone, tacrolimus, MMF	1 year	Lethargy, nausea, headache, fever, seizure	MRI: several tiny foci of high signal within deep white matter of frontal lobes, not thought to be significant
(6)	26M	Renal transplant for reflux nephropathy	Prednisolone, tacrolimus, MMF	11 years	Headaches, vomiting, dysphasia, visual disturbances, confusion, fever	Extensive multifocal white matter lesions, including all cerebral lobes, cerebellum, and brainstem with some lesions demonstrating micro-haemorrhage Repeat MRI: rapid progression of prior lesions, post-gadolinium images showed were ring-enhancing lesions
(7)	51M	Not reported	Prednisolone, tacrolimus, MMF	2 years	Confusion, nausea, vomiting, headache, ataxia	Signal altera- tions and white matter lesions of the cortical and sub- cortical substance
Our patient	55M	Renal transplant 2 to Ig A nephropathy	Prednisolone, tacrolimus, MMF	5 months	Generalised abdominal pain and intermittent vague headache. Fevers, altered conscious state developed while in hospital	Unremarkable

MMF: mycophenolate mofetil.

common in adults. This is the second reported case of primary EBV infection causing encephalitis post solid organ transplantation. EBV seroconversion after the patient's encephalitis, with negative pre-transplant EBV serology supports the diagnosis of primary infection. However the interpretation of these findings is complicated by the administration of IVIg with the early appearance of EBNA IgG antibodies, and the relative absence of EBV VCA IgM (Chan *et al.*, 2001). Given the short time frame between receiving the transplantation and developing EBV encephalitis, it is possible that this is a donor-derived infection. EBV DNA was negative pre-transplant and was detected at 154 days post transplant. In the donor, positive EBV serology was consistent with previous EBV infection, but plasma EBV DNA was not detected at time of organ retrieval. The true significance of the presence of EBV DNA in CSF is unclear in some situations, and EBV DNA is often found with other pathogens, particularly in immunocompromised hosts (Kleines *et al*., 2011; Martelius *et al*., 2011). EBV is latent in B cells, and PCR may detect EBV

EBV PCR Serum (VL if reported)	*EBV PCR CSF (copies/mL if reported)*	*EBV serology*	*Treatment*	*Outcome*
EBV PCR positive in serum 134250 DNA copies/mL	Positive for EBV DNA	EBV IgG 1:128 EBV IgM positive	Ganciclovir and prednisolone. Immunosuppression witheld	Improved. EBV DNA remained positive for a long time despite treatment so tacrolimus and MMF were not recommenced
EBV DNA not detected	Positive for EBV DNA 23000 copies/mL	EBV IgG positive.	Prednisolone, Ganciclovir and later, valganciclovir. MMF witheld.	Full recovery
Not reported	Positive for EBV DNA	EBV IgG positive pre-transplant	IV Ganciclovir	Full recovery
Not reported	Positive for EBV DNA	IgG positive IgM positive EBNA negative Serology consistent with reactivation of recent primary infection	IV Ganciclovir	Full recovery
EBV PCR positive in serum >600000 copies/ml	Positive for EBV DNA 6490 copies/ml	Pre-transplant serology negative, evidence of primary infection with seroconversion	IV Aciclovir Reduction of immunosuppresion	Full recovery
EBV DNA not detected	Positive for EBV DNA 9800 copies/mL	Pretransplant serology IgG positive, IgM negative	IV acivlovir, then IV ganciclovir and antifungals. Immunosuppression withheld	Full recovery
EBV PCR positive in serum 7300 genome equivalents (Geq)/105 cells	Positive for EBV DNA 16100 Geq/ml in cerebrospinal fluid (CSF)	Seropositive pre-transplant	IV ganciclovir, foscarnet, brivudine MMF witheld	Full recovery
EBV PCR positive in serum 10946 copies/mL	EBV viral load (CSF): 5162 copies/mL EBV PCR (CSR): positive	IgG negative IgM negative EBNA negative	IV Ganciclovir Immunosuppression witheld	Full recovery

DNA from B cells which are part of the inflammatory response to the other pathogen (Gilden *et al.*, 2007). In our case, however, no other pathogens were identified, and we demonstrated high CSF and plasma EBV viral load. Following antiviral treatment and cessation of immunosuppression, there was clinical improvement with a reduction of plasma and CSF EBV viral load.

Neurological complications have been reported in up to 5% of cases of EBV-associated infectious mononucleosis (Lennon *et al*., 2015). Neurological disorders include meningitis, cerebritis, status epilepticus, Guillain-Barré Syndrome, cranial nerve palsies, transverse myelitis, and psychosis (Kleines *et al.*, 2011; Mizutani *et al*., 1993; Connelly and DeWitt, 1994; Portegies, Corssmit, 2000). Encephalitis and meningitis are the most common neurological complication of EBV infection (Connelly and DeWitt, 1994). Although rare in adults, EBV encephalitis/meningitis can cause long-term neurological deficits after resolution of acute disease (Majid *et al.*, 2002). Most neurological complications of EBV have been reported in children under 5 or over 10 years of age associated with primary EBV infection (Doja *et al.*, 2006).

Post-transplant lymphoproliferative disorder (PTLD) is a potentially fatal complication that affects between 1-20% of solid organ transplants (Walker *et al*., 1995). Most studies have been performed in paediatric transplant populations, where seroprevalence has been reported to be as low as 50% at time of transplant (Smith and Dharnidharka, 2015). Risk factors for EBV-associated mortality include donor positive/recipient negative (D+/R−) serostatus as well as intensity of immunosuppressive therapy, however duration or degree of EBV load were not found to be risk factors (Smith and Dharnidharka, 2015). Primary EBV infection post-transplantation is the major risk factor for PTLD development in renal transplant recipients (Comac *et al.*, 2014) and there is an association between rapidly increasing EBV load and progression of PTLD in bone marrow transplants and solid organ transplants (Hoshino *et al.*, 2000; Lucas *et al.*, 1998; Green *et al.*, 1998).

International guidelines recommend close monitoring of serum EBV PCR in sero-discordant renal transplantations (D+/R−) (Kasiske *et al.*, 2010; San-Juan *et al.*, 2013). EBV PCR should be assessed every 2-4 weeks in the first three months, monthly until six months post-transplantation, then every three-six months for two-three years post-transplant (Kasiske *et al.*, 2010; San-Juan *et al.*, 2013). Additional monitoring should be performed after treatment for acute graft rejection (Kasiske *et al.*, 2010). The main purpose of this is to stratify risk of PTLD, however, as evidenced by our case report, other rare complications of EBV infection can also occur.

Guidelines also recommend considering monitoring in EBV seropositive recipients of lung and intestinal transplants for EBV reactivation (San-Juan *et al.*, 2013). Published guidelines do not designate an EBV viral load cutoff at which to alter management (Allen *et al.*, 2002; Martin *et al.*, 2011). Immunosuppression should be reduced if EBV infection is diagnosed, aiming to find a dose that allows immune restoration against the EBV infection without precipitating graft rejection (Comac *et al.*, 2014). High level EBV viremia may be asymptomatic or associated with non-specific symptoms, however EBV infection post solid transplantation is associated with opportunistic infections and a higher risk of graft loss (Bamoulid *et al*., 2013). It has also been suggested that changes in EBV viral load could be used to assist titrating immunosuppression (Comac *et al*., 2014).

There are no formal guidelines for themanagement of EBV encephalitis, particularly in a transplant recipient, however management principles can be extrapolated from experience with PTLD post transplant in paediatric populations (Comac *et al*., 2014; Green, 2001). The mainstay of treatment is reduction of immunotherapy (Green, 2001), which allow T-cell mediated immune responses to suppress duplication of EBV-infected B-cells (Comac *et al*., 2014). Ganciclovir is 10 times more potent than aciclovir against EBV *in vitro* (Green, 2001; Allen and Preiksaitis, 2013), and therefore should be considered antiviral therapy. In PTLD, treatment with rituximab (San-Juan *et al*., 2014), cytotoxic T cell therapy (Comoli *et al*., 2002; Savoldo *et al*., 2006), and IVIG (Green, 2001) have been described, and there may be a role for immunomodulation in the management of EBV encephalitis (Smith and Dharnidharka, 2015). Rapamycin, and its derivative everolimus (an mTOR inhibitor), have been shown to inhibit proliferation of EBV positive B lymphoblastoid cell lines (Nepomuceno *et al.*, 2003; Majewski *et al.*, 2000), and have been described in the treatment of PTLD (Krams and Martinez, 2008). mTOR inhibitors have demonstrated antiviral activity against BK virus (Liacini *et al.*, 2010) and CMV (Kobashigawa *et al*., 2012), and may therefore have activity against EBV infection when not associated with PTLD.

Prophylactic ganciclovir or valganciclovir has been shown to reduce the incidence of primary EBV infection in renal transplantation where the donor is seropositive for EBV (D+) and the recipient negative (R-) (Höcker *et al*., 2012). Some centres consider treatment with ganciclovir +/− immunoglobulin for a period up to 12 weeks of post transplantation (Allen *et al.*, 2002). Approaches to treatment vary widely, and there is no consensus on how reduction of immunosuppression is to be implemented, but expert opinion advised two-three weeks of reduction before alternative medication is considered (Allen *et al*., 2002). Treatment options for subclinical EBV infection post-transplant include reduction of immunosuppression, antiviral therapy, IVIG, and monoclonal antibody therapy directed toward infected B lymphocytes (Green, 2001).

CONCLUSION

Epstein-Barr virus is a cause of viral encephalitis in solid organ transplant patients. EBV serostatus should be routinely checked prior to all transplantations. Seronegative patients who receive grafts from a seropositive donor should be closely monitored for EBV DNA. EBV PCR may not be included on routine CSF PCR panels, and thus must be considered and specifically requested by the treating physician, especially if the presentation is subacute and other infective causes have been excluded. Full clinical recovery can be achieved with antiviral therapy and reduction of immunosuppression.

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