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Case report

Relapsing EBV encephalitis in a renal transplant recipient

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ABSTRACT

In solid organ transplant recipients, Epstein-Barr virus (EBV) can cause active central nervous system (CNS) infection or malignant transformation of latently infected cells in the CNS, known as post-transplant lymphoproliferative disease (PTLD). Reduction of T-cell immunosuppression is the cornerstone of management. The role of antivirals with *in-vitro* activity against herpesviruses in EBV-related CNS syndromes is controversial, as they have no effect on latent virus. We report an unusual case of relapsing EBV encephalitis in a donor-positive, EBV-negative renal transplant recipient, with response to valganciclovir. Our report supports the utility of antiviral treatment for EBV encephalitis, as adjunct to reducing immunosuppression, and highlights the need for a systematic approach and long-term, multi-disciplinary follow-up of such patients.

Case report

A 53-year-old women with history of living, unrelated donor kidney transplant one year prior, due to diabetic nephropathy, was admitted to the hospital with decline in executive functioning. The patient was previously independent, but in the weeks leading to admission had difficulty calculating her insulin dose, recognizing the day of the week, and using the telephone or the microwave. The patient also experienced frequent falls. For her transplant, the patient had received induction immunosuppression with anti-thymocyte globulin (ATG), as part of steroid-sparing regimen due to diabetes. Cytomegalovirus (CMV) and EBV serology status were donor positive, recipient negative. The patient had completed 6 months of CMV prophylaxis with valganciclovir. Maintenance immunosuppression consisted of tacrolimus, with an admission level of 13.5 ng/dL, and mycophenolate 720 mg twice daily. The patient had no history of recent travel, sick contacts, or rural exposures.

On admission, the patient was febrile to 101.3 °F, perseverative and inattentive, and not oriented to person, place or time. There were no cranial nerve or other focal deficits. Laboratory work-up is summarized in Table 1. Lumbar puncture (LP) revealed pleiocytosis with lymphocyte predominance and elevated protein (Table 1). Magnetic resonance imaging (MRI) with gadolinium contrast showed abnormal signal in the left insular region, left pons, and right cerebellum (Fig. 1A–C), but no enhancing lesions. Electroencephalogram (EEG) showed left frontotemporal slowing with occasional embedded sharp waves. The patient was empirically started on intravenous (IV) acyclovir and ampicillin, for herpetic and *Listeria* encephalitis, respectively. On day 2, the patient had a generalized tonic-clonic seizure and was started on levatiracetam. Mycophenolate was decreased to 360 mg bid and tacrolimus dose was also reduced, to a trough goal of 5–7 ng/mL. Plasma EBV viral load (VL) was 285 IU/mL. EBV serologies were negative for both antiviral capsid antigen IgM and nuclear antigen (NA) IgG. EBV VL in the CSF was 1100 IU/mL. CSF cytology and flow cytometry were negative for lymphoma.

The patient's mental status improved and she was discharged, after a 2 week course of IV acyclovir, on oral acyclovir 800 mg 5 times daily. Re-admission was prompted 11 days later by mental status decline without changes in immunosuppression (Fig. 2). EEG was consistent with nonconvulsive status epilepticus, and the patient was loaded with phenytoin. MRI revealed worsening diffuse periventricular hyperintensities with more extensive pontine and cerebellar involvement (Figs. 1D–F, 2). Repeat EBV viral load in the CSF was 37,300 IU/mL. Intravenous ganciclovir was initiated with resultant improvement in mental status and decrease in CSF EBV VL (Fig. 2). The patient was discharged on oral valganciclovir 900 mg two times daily.

One month later, valganciclovir was discontinued as her mental status had returned to baseline and the patient had developed neutropenia. CSF EBV VL had decreased to 5400 IU/mL, CSF pleiocytosis had resolved, MRI was improved (Figs. 1G–I & 2), and the patient had

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Table 1
Admission laboratory results.

Test	Laboratory Value	Reference Range
Blood		
White blood cell count	3.9 × 10^9/L	3.5–11.0 × 10^9/L
Hemoglobin	13.1 g/dL	11.0–15.0 g/dL
Platelets	240 × 10^9/L	150–400 × 10^9/L
Glucose	306 mg/dL	67–99 mg/dL
Sodium	122 mEq/L	135–145 mEq/L
Potassium	4.5 mEq/L	3.6–5.1 mEq/L
Chloride	88 mEq/L	98–110 mEq/L
Carbon dioxide	26 mEq/L	22–32 mEq/L
Blood urea nitrogen	14 mg/dL	6–24 mg/dL
Creatinine	0.87 mg/dL	0.44–1.03 mg/dL
Magnesium	1.4 mEq/L	1.3–1.9 mEq/L
ALT	21 IU/L	6–45 IU/L
AST	20 IU/L	10–42 IU/L
Alkaline phosphatase	38 IU/L	34–104 IU/L
Total bilirubin	0.7 mg/dL	0.2–1.3 mg/dL
Ammonia	34 μmol/L	2–50 μmol/L
Osmolality	274 mOsm/kg	290–300 mOsm/kg
Uric acid	2.8 mg/dL	2.6-6.0 mg/dL
TSH	0.894 μIU/mL	0.350-5.500 μIU/mL
Vitamin B12	1647 pg/mL	211–911 pg/mL
Rapid plasma reagin	Nonreactive	Nonreactive
Tacrolimus level	13.5 ng/mL	5.0-20.0 ng/mL
Blood culture ×2	No growth	
Lyme reflex	0.1	0.00 – 0.91
EBV IgG	0.3	0.0 – 0.8
EBV IgM	0.2	0.0 – 0.8
EBV qPCR (Viracor)	285 IU/mL	TND, 49-1.69 × 10^8 IU/mL
Cryptococcal antigen	Negative	Negative
HIV 1 and 2 antibodies	Negative	Negative
JC virus qPCR	TND	40–1 × 10^8 copies/mL
CSF		
Cell count, 1st tube	191 cells/μL	0–5 cells/μL
Cell count, last tube	157 cells/μL	0–5 cells/μL
RBC, 1st tube	8 cells/μL	0–5 cells/μL
RBC, last tube	3 cells/μL	0–5 cells/μL
Differential	84% lymphocytes	63–99%
	2% polys	0–2%
	14% monocytes	3–37%
Protein	136 mg/dL	15–45 mg/dL
Glucose	141 mg/dL	38–85 mg/dL
Gram stain	No organisms	
Bacterial culture	No growth	
Enterovirus PCR	Negative	
HSV I and II PCR	Negative	
West Nile IgG	< 1.3	< 1.3
West Nile IgM	< 0.9	< 0.9
CMV PCR	Negative	
JC virus qPCR	TND	72–1 × 10^8 copies/mL
VZV PCR	Negative	
EBV qPCR	1100 IU/mL	52-1.69 × 10^8 IU/mL
Fungal stain and culture	No fungus isolated	
AFB stain and culture	No AFB isolated at 6 weeks	

AFB, acid-fast bacilli; ALT, alanine aminotransferase, AST, aspartate aminotransferase; CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein-Barr Virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; (q)PCR, (quantitative) polymerase chain reaction; RBC, red blood cells; TND, target not detected; TSH, thyroid-stimulating hormone; VZV, varicella-zoster virus.

developed anti-EBV nuclear antigen IgG. After discontinuation of valganciclovir, progressive mental status changes and gait instability ensued. Three months later, MRI and LP findings were consistent with progressive infection (Figs. 1J–L & 2), and the patient was found to be viremic with EBV viral load of 900 IU/mL. Mycophenolate was discontinued, and oral valganciclovir 900 mg two times daily was resumed. The patient soon returned to her functional baseline, with resolution of viremia and MRI improvement (Fig. 1 M-O). Treatment was complicated by neutropenia, so therapy was transitioned to high-dose oral valacyclovir (1 gm three times daily). This was followed by lethargy and confusion three weeks into the course. The patient was restarted on valganciclovir with rapid recovery; after one month, the dose was decreased to 450 mg two times daily. After six additional months, she underwent repeat lumbar puncture that showed normalization of cell count and protein, and EBV viral of 61 IU/mL (limit of detection: 52 IU/mL), at which point valganciclovir was discontinued. Serum creatinine has been < 1 mg/dL, and she is receiving tacrolimus single-agent immunosuppression with trough levels of 5–7 ng/dL. Plasma EBV viral load has remained undetectable with monthly checks. The patient is off anti-epileptics, without clinical evidence of relapse, and she is able to drive.

Discussion

In solid organ transplant (SOT) recipients, symptoms and signs of encephalopathy, such as altered mental status, motor or sensory deficits, behavioral or personality changes, speech or movement disorders, and seizures are common. The differential diagnosis is broad, and causes classified as infectious and non-infectious. Non-infectious causes are drug toxicities (neurotoxicity from calcineurin inhibitors), vascular events (stroke, uncontrolled hypertension) and metabolic abnormalities (hepatic or uremic encephalopathy) [1,2]. Encephalitis is the term describing encephalopathy from viral [3], bacterial (bacterial meningoencephalitis or *Listeria* rhomboid encephalitis), fungal (*Cryptococcus*) or parasitic (*Toxoplasma*, *Trypanosoma*) infection of the CNS [1]. CSF evaluation is paramount to diagnosis and, in viral encephalitis, reveals pleiocytosis with lymphocytic predominance, elevated protein, and normal glucose (Table 1) [3]. Imaging findings may depend on the etiology, but often include nonspecific white matter changes, as demonstrated in our case (Figs. 1 and 2) [3]. Specific serologies and PCR are used to identify the causative agent [3]. It should be noted that, in the setting of immunosuppression, EBV viremia and positive PCR in the CSF can be reactive. Therefore, if another pathogen has been identified, the clinical significance of EBV in the CSF is unclear.

Primary EBV infection occurs in over 90% of the world population and is either asymptomatic, or manifests as infectious mononucleosis (IM), followed by latency of the virus in B-lymphocytes [4]. EBV affects the central nervous system (CNS) in 1–18% of patients [2]. Up to 22% of viral encephalitis cases have been reported as EBV-related [5]. Neurologic sequelae of EBV infection are due to the virus-host immunity interaction, and include encephalitis, meningitis, cerebellitis, polyradiculomyelitis, transverse myelitis, and cranial and peripheral neuropathies [2,6]. Outside of primary EBV infection, reactivation of latent virus is a prerequisite for CNS involvement and is most likely to occur in T-cell immunosuppressed hosts [1,2,7–9]. In the current case, donor derived primary EBV infection is most likely, given the serodiscordance at time of transplantation.

EBV latently infected B-cells can be oncogenically transformed, giving rise to lymphoproliferative disorders, especially post-transplant lymphoproliferative disorder (PTLD) in the setting of decreased immune surveillance secondary to T-cell immunosuppression [10,11]. Therefore, an important diagnostic consideration in SOT recipients with CNS manifestations is EBV-related CNS-PTLD [12]. In renal transplant recipients, the incidence of PTLD is approximately 1% [12]; CNS involvement is estimated in 10–15% of all PTLD cases [12,13], 12% among renal transplant recipients with PTLD [13]. The World Health Organization classifies PTLD into early, polymorphic and monomorphic lesions [11]. These conditions lie along a continuum of disease. Early lesions can have relatively nonspecific manifestations such as IM-type illness and no signs of space-occupying malignancy. Both polymorphic and monomorphic lesions demonstrate malignant transformation, but only the latter meets all the diagnostic criteria for a B-cell lymphoma recognized in immunocompetent patients [11].

EBV serostatus and the depth of T-cell immunosuppression are risk factors for the development of PTLD: EBV sero-negative recipients of an EBV sero-positive organ have a 10- to 76-fold greater incidence of PTLD, compared to those who are seropositive [12]. EBV-infected B-

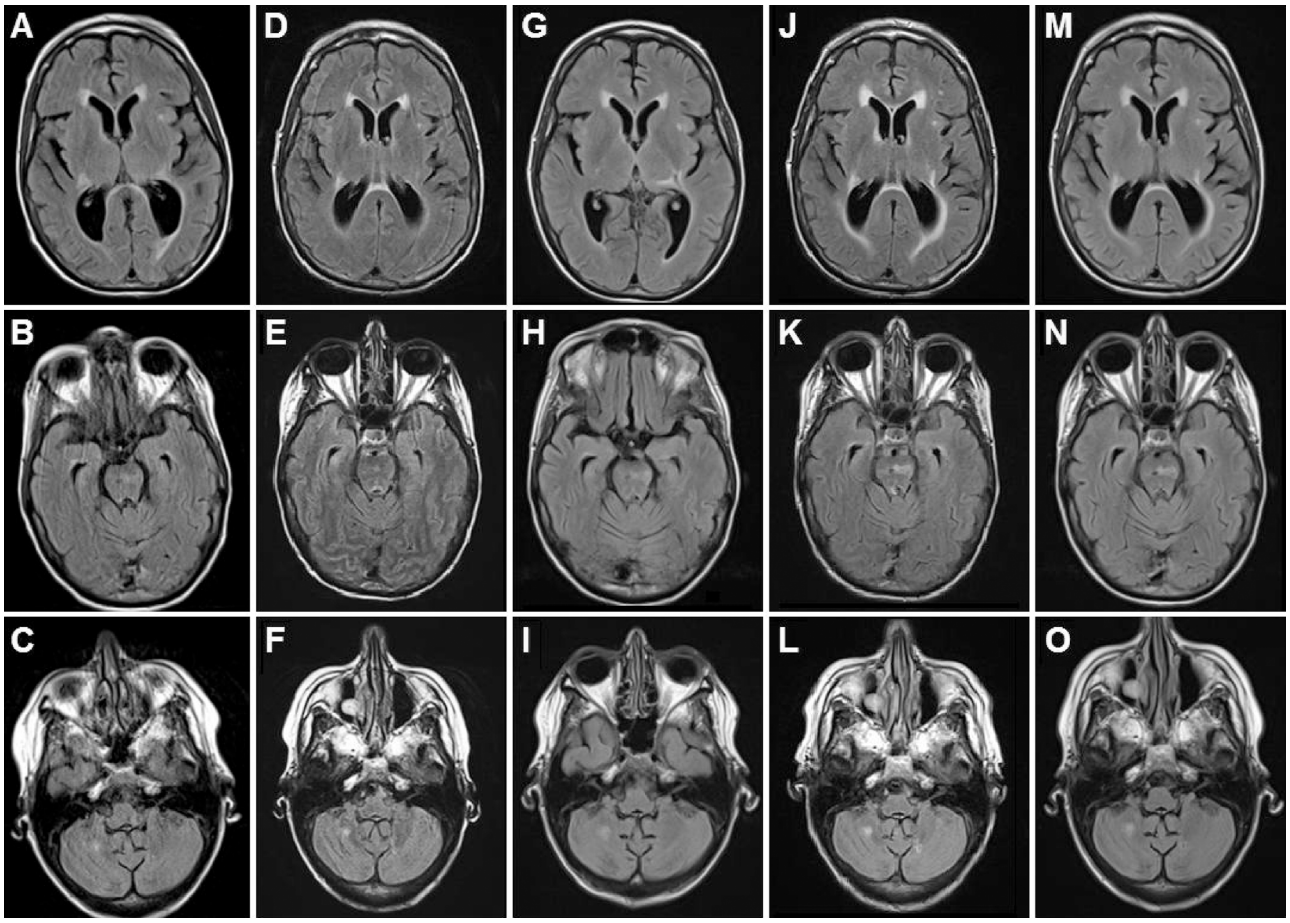

Fig. 1. Magnetic resonance imaging (MRI) showing diffuse multi-focal hyperintense lesions on axial T2 fluid-attenuated inversion recovery (FLAIR) sequences on initial presentation (A–C), 3 weeks after presentation (D–F), 6 weeks after presentation (G–I), 5 (J–L) and 8 (M–O) months after presentation.

lymphocytes are controlled by cytotoxic T-cells [14]. ATG induction therapy depletes T-cells and has been associated with 5-fold increase in the incidence of PTLD [13]. Calcineurin inhibitors (i.e. tacrolimus) inhibit T-cell activation and therefore add to the risk. Mycophenolate targets both T and B-cells, but does not confer significant risk for development of PTLD [15].

In addition to clinical features, the diagnosis of CNS-PTLD is supported by imaging and evidence of malignant transformation. In our patient, no brain biopsy was performed and the possibility of PTLD could not be excluded. MRI imaging features favoring encephalitis rather than PTLD were absence of well-circumscribed lesions and, most importantly, lack of contrast enhancement (Figs. 1 and 2) [12]. CSF cytology was negative, though it can be negative in up to 60% of primary CNS lymphomas in immunocompetent hosts [16]. Most convincingly, our patient responded to antiviral treatment, which is only active against lytic virus, and should, therefore, have no effect on CNS-PTLD [12].

Distinguishing between EBV encephalitis and CNS-PTLD in SOT recipients could be important for initiation of appropriate treatment. For both, reduction of immunosuppression should be attempted, to the maximum feasible degree without endangering vital transplant organ function that cannot be replaced otherwise. Additional treatment options for PTLD include rituximab, radiation, and combination chemotherapy [12]. In our patient, tacrolimus was dose-reduced and mycophenolate dose-reduced and eventually discontinued, in order to remove an additional myelo- and immunosuppressive agent and to help maintain a higher neutrophil count while on treatment with valganciclovir.

Treatment with antivirals has no role in management of PTLD, as it does not affect latently-infected tumor cells [12]. Antivirals are not routinely recommended for primary EBV infection, including encephalitis [4], given their lack of efficacy in IM [7]. In immunocompetent hosts however, there are case reports [6] and small case series [17] of the use of antivirals for the treatment of EBV-related neurologic complications, often with adjunct steroids [6–8]. Based on this limited data and the experienced gained from the current case, antiviral treatment against actively proliferating, lytic virus should be considered as an adjunct to decreased immunosuppression in cases of EBV-encephalitis in immunocompromised hosts. Both acyclovir and ganciclovir target the viral DNA-polymerase, potentially halting active EBV infection. Valganciclovir would be the preferred drug of choice, given its ten-fold increased *in-vitro* activity against EBV compared to valacyclovir [9,18]. Myelosuppression may occur after prolonged valganciclovir treatment. Contingent upon clinical circumstance, treatment discontinuation, growth factor administration, or dose adjustment can be considered. Given the paucity of published data available for review, optimal antiviral treatment duration is unknown. In the current case, the decision for maintenance therapy was based on clinical, radiographic and virologic relapse or persistence, with valganciclovir discontinuation despite reduced maintenance immunosuppressive therapy (Fig. 2).

The risk of developing CNS-PTLD in the future for a patient with EBV-encephalitis is unclear, as both syndromes are rare. EBV-positive CNS lymphoma, 10 years after EBV encephalitis has been reported in a renal transplant recipient. Prospective monitoring of EBV PCRs on blood [19] and monoclonal protein secretion in serum or urine have been proposed [20].

Our case study has limitations, specifically lack of tissue diagnosis,

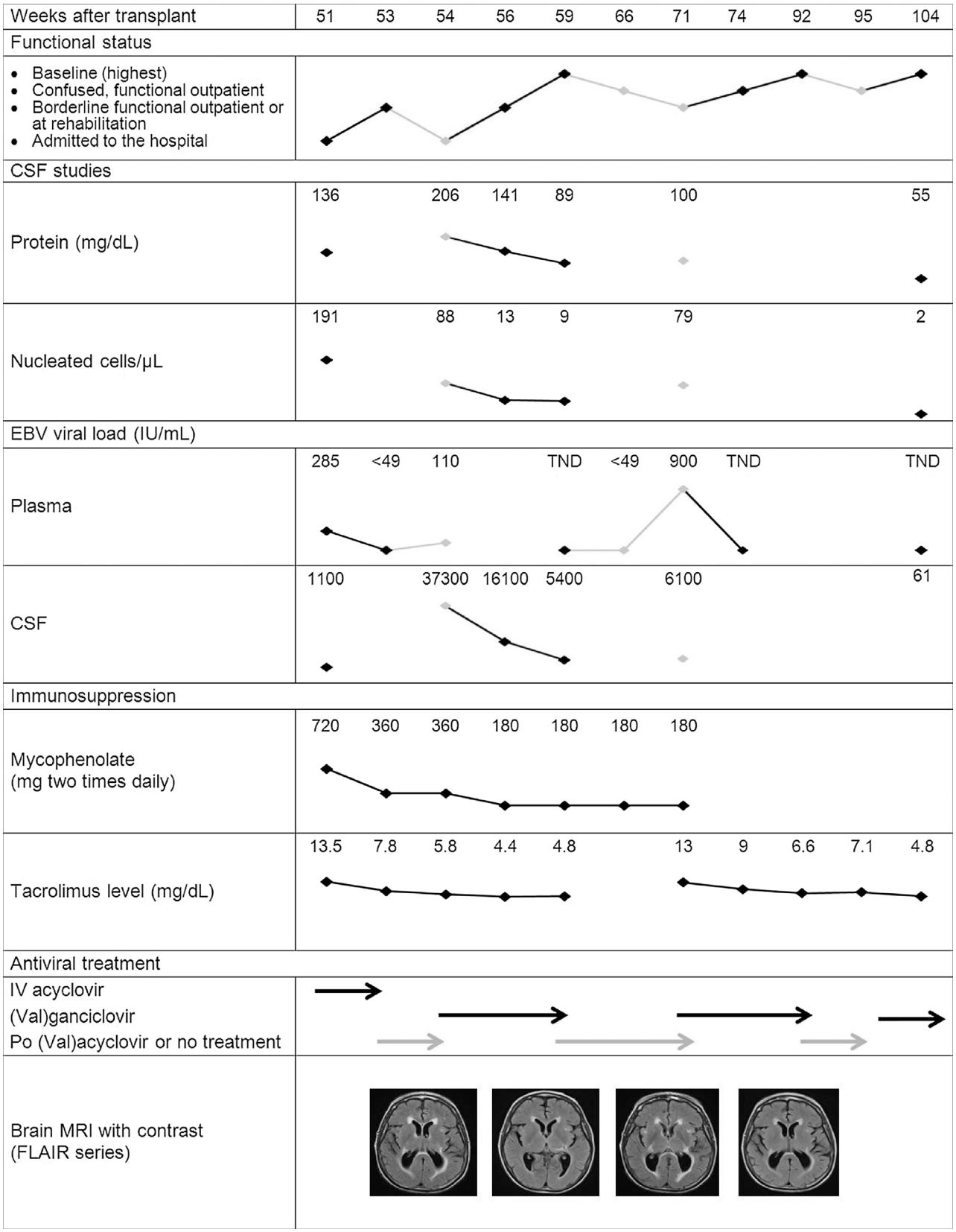

Fig. 2. Clinical course, respective interventions, laboratory values and imaging.
Laboratory values and images have been linked to the closest timepoint of clinical assessment. Grey marks represent clinical or laboratory deterioration and black ones improvement. CSF, cerebrospinal fluid; EBV, Epstein-Barr Virus; FLAIR, fluid-attenuated inversion recovery; IV, intravenous; MRI, magnetic resonance imaging; TND, target not detected; < 49 (plasma), EBV detected, below quantification cut-off.

few follow-up LPs due to patient preference, and overlap between changes in immunosuppression and antiviral treatment.

In conclusion, valganciclovir treatment for EBV encephalitis in immunocompromised patients should be considered as an adjunct to immunosuppression reduction. Transplant recipients with EBV encephalitis benefit from long-term, multi-disciplinary follow-up.

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