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LETTER TO THE EDITOR

Epstein–Barr virus encephalitis after kidney transplantation and successful treatment with brivudine

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Viral infections are one of the major complications in patients with immunosuppressive therapy after kidney transplantation with an incidence rate of 34% [1]. Common are infections with herpes simplex virus (HSV) in 23% and cytomegalovirus (CMV) in 36% of patients under immunosuppressive therapy [1]. We report about a 51-year-old male kidney transplanted recipient who was admitted to the emergency room with reduced alertness, mental confusion, nausea, vomiting and headache, as well as walk and stand ataxia of the trunk for 10 days. Kidney transplantation had become necessary 2 years back in 2006. Our patient had been found to be Epstein–Barr virus (EBV) seropositive without any symptoms before transplantation. After the latest EBV-polymerase chain reaction (PCR) findings in peripheral blood leucocytes (PBL), we stopped the immunosuppressive medication with mycophenolate mofetil (MMF); however, tacrolimus and low-dose steroids were continued.

Laboratory findings presented nearly normal white blood cells (leucocytes 3.9×10^9 cells/l) but an elevated C-reactive protein up to 21 mg/dl. Serum creatinine and urea were stable at 1.5 mg/dl and 27 mg/dl. Cranial computed tomography (CT) scan recorded no pathological findings. Magnetic resonance imaging (MRI) recorded signal alterations and some white matter lesions of the cortical and subcortical substance as a possible indicator of encephalitis.

Current quantitative PCR revealed a positive match of 7300 genome equivalents (Geq)/10^5 cells of EBV copies in blood (Fig. 1) and 16 100 Geq/ml in cerebrospinal fluid (CSF). Cerebrospinal fluid had clear colour (cell count 88/3 cells, lymphocytes 91%, monocytes 8%, neutrophils 1%, protein 84 mg/dl and glucose 79 mg/dl). Cytomegalovirus and HSV were not detected, therefore we diagnosed EBV encephalitis.

Antiviral therapy was started with the virostatic agent ganciclovir and switched after 14 days to foscarnet, because of increasing EBV-load up to 18 040 Geq/10^5 cells (Fig. 1). Seven days later, we stopped foscarnet because symptoms increased and EBV load in PBL only decreased marginally from 5000 to 4086 Geq/10^5 EBV copies. Thus, we decided to start empirically a therapy with Brivudine, as well a virostatic agent, and the patient's symptoms improved steadily within a few days. Initially, Brivudine was administrated for 7 days. Neurological symptoms declined steadily and ceased completely. Epstein–Barr virus load became negative in CSF and viral load in PBL declined to 320 Geq/10^5 EBV copies.

Upon reducing Brivudine the patient developed the same symptoms within a few days again. Thus, we decided to continue the therapy for 4 weeks under control of liver-, blood- and kidney parameters and clinical presentation. The overall tolerability was good. The patient suffered no side-effects. The liver and peripheral blood parameters were stable within the normal range. The transplanted kidney maintained a stable function (creatinine 1–1.3 mg/dl). After 4 weeks, Brivudine treatment was stopped; the patient was stable, with EBV DNA still detectable in PBL.

In literature, there are only a few reports of cases of EBV encephalitis in adult renal transplant recipients. Neurological complications caused by EBV after transplantation normally appear within a few weeks or months and are rare [1,2]. They occur in 1–18%, and sometimes they are the first and unique manifestations of EBV infection [3]. The cerebellum is a predilection site for EBV infections [3]. Typical common symptoms of EBV encephalitis are headaches, vomiting and alterations in consciousness. These symptoms can be accompanied by ataxia, nystagmus, dysarthria and cranial nerve palsies [4]. Sometimes

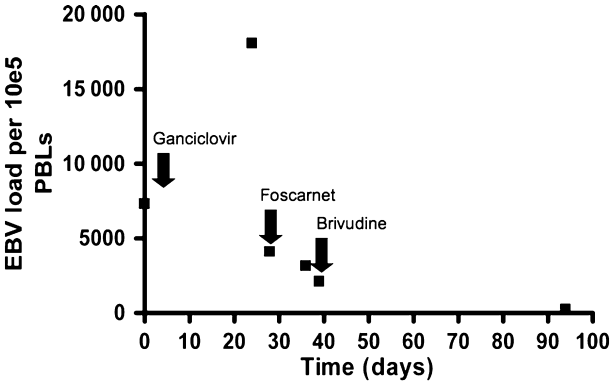

Figure 1 The figure shows the time of treatment on the *x*-axis and the PCR EB Virus load (Geq/10^5 cells) on *y*-axis with the corresponding antiviral agent.

an acute hydrocephalus, with herniation of the cerebellar tonsils and obstruction of the fourth ventricle can appear, and make an emergency decompression necessary [5].

To prove a viral encephalitis or meningitis, CSF has to be examined [6]. However, a negative viral PCR does not fully exclude a central nervous system (CNS) infection [7]. In addition to clinical manifestations and laboratory tests, a MRI or CT scan is indicated to prove or to exclude other aetiologies for encephalitis. In most cases initial CT scans present no pathological findings. With an MRI scan an increasing diffusion weighted signal in cerebellar grey matter is sometimes visible. This and the absence of contrast enhancement, indicating there is no significant vasogenic oedema, are specific for viral encephalitis [3].

The relative rarity of EBV encephalitis has not permitted clinical trials to determine the efficacy and safety of different therapies. Thus, drugs in current use are largely empiric and most based on case reports. There are some reports using a virostatic medication with ganciclovir, a nucleoside analogue, and foscarnet, a pyrophosphate analogue, which is also inhibiting viral DNA polymerases [8,9]. Drug-resistance testing of antiviral agents has currently been established only for CMV and HSV and not for EBV.

Brivudine is a nucleoside analogue targeting two viral enzymes: deoxythymidine kinases and polymerases. The dosage is 125 mg per day. Brivudine is mainly effective against herpes simplex and the varizella zoster virus, but there are also good results against EBV [9,10]. The potential effect against EBV could be shown in the early 1980s with *in vitro* experiments [11]. The issue whether Brivudine could be used for the treatment of EBV encephalitis has largely been unestablished so far, and now it can be safely assumed based on our case.

Another advantage of this antiviral agent is that an adaptation to kidney function is not necessary if the recommended dosage of 125 mg per day is not exceeded [12,13].

Biotransformation takes place with the pyrimidine phosphorylases, an enzyme which separates a sugar component from Brivudine and diminishes Brivudine to bromovinyl uracil a metabolite without any virostatic activity [13]. Elimination runs to 65% via the urine as a uracil acid metabolite. Comparative examinations of patients with reduced kidney and liver function to patients with normal kidney and liver function reported no difference in elimination of Brivudine [13].

Brivudine should be avoided in patients during chemotherapy, especially with 5-fluorouracil or related substances [13]. Other interactions are not described. An induction of the liver cytochrome P450 system could not be detected; Brivudine is with more than 95% attached to plasma proteins [12,13].

In conclusion, Brivudine can be a helpful agent in selected cases, especially in cases with a neurological EBV affection, if the more commonly used antiviral agents ganciclovir or foscarnet show no effect. This case demonstrates that EBV should be considered in kidney transplant recipients, especially in patients with neurological symptoms.

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