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Letter to the Editor

EBV-NMDA double positive encephalitis in an immunocompromised patient

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1. Introduction

In the past years rare cases of double positive Epstein-Barr virus (EBV) and anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis in post solid organ transplant (SOT) patients, were reported [1–3]. We highlight the fact that clinicians should consider autoimmune encephalitis in SOT patients despite treatment with immunosuppressants and would like to highlight the good outcome in this case with antiviral treatment and adjusted immunotherapy.

2. Case report

A 64-year-old male patient presented to an outside hospital with nausea, malaise and a 'strange' sensation in the head after an episode of increased alcohol abuse. Past medical history is noticeable for chronic kidney disease leading to renal transplantation in 2013, hypertension, hypercholesterolaemia, abdominal aortic aneurism, gout, diabetes mellitus and major depressive disorder. He was on Tacrolimus (1 mg) and Mycophenolate Mofetil (MMF - 750 mg) for his renal transplant. During hospitalization, he developed hallucinations and delusions. Later focal seizures with impaired awareness occurred. An electroencephalogram (EEG) showed slow basic activity (5–6 Hz) without epileptiform abnormalities. Brain magnetic resonance imaging (MRI) was unrevealing. Levetiracetam was initiated. Subsequently, clinical deterioration occurred with a fluctuating level of consciousness, confusion and dysarthria. Clinical neurological examination showed no signs of lateralisation. Lumbar puncture (LP) demonstrated a mild lymphocytic leucocytosis (48/µl WBC) with mild hyperproteinorrhachia (56 mg/dl), raising suspicion of herpes simplex virus (HSV) encephalitis, for which acyclovir IV (750 mg, thrice daily) was initiated. When polymerase chain reaction (PCR) results for HSV and Herpes Zoster virus were found to be negative, acyclovir was discontinued. A further LP revealed an increasing leucocytosis (84/µl) and a proteinorrhachia of 33 mg/dl. The MRI remained normal. On suspicion of autoimmune encephalitis, methylprednisolone 125 mg IV was administered for three days and then discontinued due to absence of clinical improvement and the already immunocompromised state of the patient. Since PCR results for EBV DNA in the cerebrospinal fluid (CSF) were repeatedly positive, acyclovir was restarted. Subsequently, NMDAR antibodies in CSF were repeatedly positive. Possible underlying neoplasms were excluded with PET/CT and scrotal ultrasound. However, a pulmonary embolism was detected for which enoxaparin 80 mg was started. The patient was transferred to a tertiary centre for further treatment. For more than three weeks, Acyclovir was continued, decreasing EBV DNA copies in the serum (1436 < 1744 copies/µg DNA). After cessation of acyclovir, the number of EBV DNA copies reincreased to 9232 copies/µg DNA. Antiviral therapy was restarted, MMF temporarily reduced and tacrolimus ceased, since this primarily targets the T cells needed in the defence against EBV-infected B cells. After clearance of three episodes of urosepsis, plasmapheresis was started. After four treatments, the patient recovered remarkably, but his clinical condition deteriorated again a few weeks later. Rituximab (two courses of 1000 mg) was started with slow but marked improvement. The patient left the hospital in good condition, with acyclovir PO 400 mg, prednisolone 6 mg and MMF 750 mg at discharge. At three months follow-up, he dramatically improved clinically, presenting only slight concentration deficits (Montreal Cognitive Assessment (MoCA 23/30)) and mild balance problems. Fig. 1 details the clinical evolution and treatment of our patityent.

3. Discussion

Our patient's clinical presentation is consistent with anti-NMDAR encephalitis: a prodromal phase of days to weeks with general malaise, followed by psychiatric symptoms, epileptic seizures and autonomic instability (blood pressure fluctuations). Choreiform movements were absent in this case but are known to be a feature rather seen in children than in adults with post-HSV anti-NMDAR encephalitis [4–6]. Given the low prevalence of EBV encephalitis, no typical clinical pattern is described in the literature. Possible characteristics include: psychiatric symptoms, cognitive dysfunction, aphasia or dysarthria, focal deficits, epileptic seizures, with most cases described in SOT patients [7,8].

Technical investigations provided arguments for both conditions. Mild lymphocytosis in CSF may be consistent with both EBV and anti-NMDAR encephalitis [5]. Repeatedly positive PCR results for EBV DNA in CSF along with a high copy number, suggests EBV being the cause of the encephalitis. Since EBV replicates in peripheral lymphocytes, one could in theory doubt

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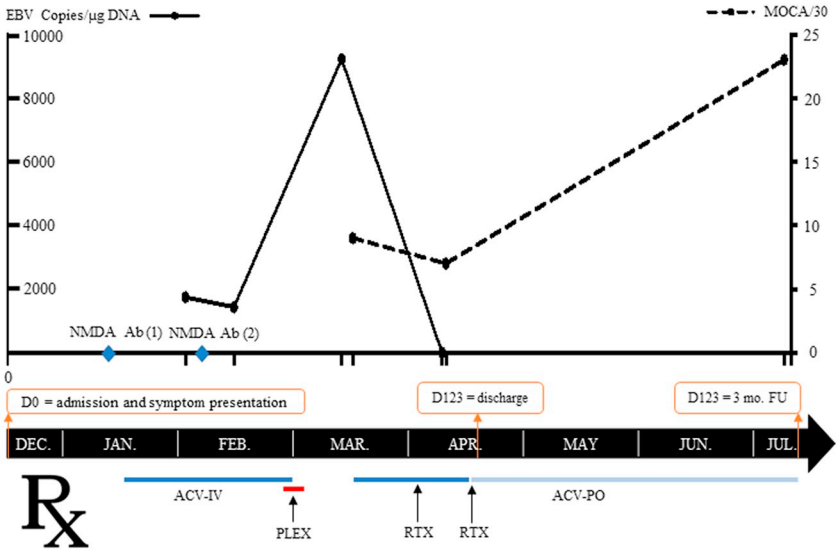

Fig. 1. Illustration of EBV viral load and MoCA over time. ACV-IV = Acyclovir intravenous 3x750mg, ACV-PO = Acyclovir oral 400 mg, PLEX = plasma exchange, RTX = Rituximab intravenous 1000 mg, NMDA Ab (1) = first NMDAR antibody determination and diagnosis of anti-NMDAR encephalitis, NMDA Ab (2) = second NMDAR antibody determination (still positive).

whether a positive PCR result effectively points to a CNS infection rather than a migration of peripheral lymphocytes to the CSF. However, the International Herpes Management Forum (IHMF) recommends the use of PCR for EBV DNA in CSF for diagnosing CNS infections. NMDAR antibodies in the CSF have a sensitivity and specificity of nearly 100%. This measurement should always be interpreted within the clinical context, which for this patient is consistent with an anti-NMDAR encephalitis [4,5,9]. MRI was negative, with a sensitivity of 60% for EBV encephalitis and 33% in anti-NMDAR encephalitis [4,5].

Standard therapy of autoimmune encephalitis consists of treating a possible causative tumour, symptomatic treatment and immunotherapy. First-line treatment consists of corticosteroids, intravenous immunoglobulin (IVIg) or plasmapheresis (PLEX). Rituximab or cyclophosphamide are often chosen as second-line immunotherapy with MMF, azathioprine or methotrexate as alternatives [4,5,9].

EBV encephalitis is treated with antivirals and a reduction of immunosuppressants (where used). Theoretically, rituximab could also be used, since EBV induces a polyclonal proliferation of B cells and, subsequently, latently persists in these cells. Although the role of Rituximab in EBV encephalitis is yet unclear, it is well established in EBV-related post-transplant lymphoproliferative disorder (PTLD) [7,8]. In this case, Rituximab was eventually used, considering the presumed double hit on both anti-NMDAR and EBV encephalitis.

Several case reports have shown the use of methylprednisolone IV combined with antibody depleting treatment (PLEX or IVIg and rituximab) to be effective in SOT patients with EBV-NMDAR encephalitis [1–3].

Based on (para)clinical findings and therapeutic response, we suspected an anti-NMDAR encephalitis triggered by the reactivation of EBV in this SOT patient. In patients with HSV encephalitis, parainfectious NMDAR encephalitis is well documented and presumably explained by molecular mimicry or antigenic release and secondary immunisation [6]. EBV, another member of the Herpes Virus family, might act in a similar way as it is known to be a potential trigger of a wide range of autoimmune disease. Recent data suggest EBV switches on autoimmunity promoting genes that might also act as a pathophysiological substrate for developing NMDAR encephalitis [10].

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Conflicts of interest

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