A case of recurrent progressive multifocal leukoencephalopathy after human stem cell transplant, with detection of John Cunningham virus and human herpesvirus 6 on cerebrospinal fluid, treated with Mirtazapine, Olanzapine and Foscarnet

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1. Introduction

John Cunningham virus (JCV) and human herpesvirus 6 (HHV-6) are two ubiquitous viruses which can be reactivated in conditions immunosuppression, such Natalizumab therapy, HIV or human stem cell transplant (HSCT) (1-3). Although HHV-6 reactivation may be common after allogeneic HSCT, it only rarely causes central nervous system (CNS) complications (4).

Progressive multifocal leukoencephalopathy (PML) is a rare but fatal disease of the CNS secondary to JCV infection and reactivation (5), with an incidence of 35.4 per 100,000 person-years in transplanted patients (6), one-year mortality rate of the cases present in literature is 65.4% and mean time of death in the first year estimated at 4.1 months (3).

We present a case recurrent PML due to a possible JCV with HHV-6 coinfection after HSCT, successfully treated with Mirtazapine, Olanzapine and Foscarnet.

2. Case Report

A 44 year old Caucasian woman was admitted to our department on July 2017 for gradual onset of posterior headache, hearing loss and left homonymous hemianopia.

Remote pathological history was significant for a diagnosis of subcutaneous panniculitis-like T-cell lymphoma in 2013, treated with allogeneic HSCT from an HLA-identical sister in 2015 (conditioning regimen: Tiotepa; Busulfan and Fludarabine), complicated with Chronic Graft versus Host Disease (GVHD), treated with Corticosteroids, Mycophenolate Mofetil, Cyclosporine-A, FEC (Fluorouracil, Epirubicin, and Cyclophosphamide) and Imatinib with no clinical benefit. Tacrolimus, started in February 2017, with a...
A brain magnetic resonance imaging (MRI) showed non-enhancing T2 hyperintensities in the right occipital lobe, ipsilateral temporal lobe, thalamus and internal capsule with restricted diffusion signal (Figure 1a, 1b, 1c, and 1d). Cerebrospinal fluid (CSF) examination demonstrated total protein of 0.75 g/L, normal cell count (2 leucocytes), Polymerase Chain Reaction (PCR) on CSF detected HHV-6 (< 350 copies/mL) and JCV (< 350 copies/mL), PCR on blood sample detected HHV-6 (< 240 copies/mL). PML was diagnosed, a possible JCV and HHV-6 coinfection was suspected, Tacrolimus therapy was discontinued and Mirtazapine and Foscarnet were administered. Immunophenotype on blood serum showed an inversion in CD4/CD8 ratio (790/uL÷1710/uL). On discharge from the hospital only left homonymous hemianopia persisted.

Her clinical picture remained stable for over six months and an MRI performed in October 2017 didn't show any PML pathological activity. On December 2017 she was hospitalized for Influenzavirus B pneumonia and discharged after 7 days, without sign of infection. On February 2018 she presented to our department symptomatic for headache, chest pain, left arm numbness, nausea and vertigo, nystagmus on left lateral gaze, weakness of both upper limbs, apraxia, dysmetria and left homonymous hemianopia followed by two episodes of myoclonic movements of the left side of the face and left arm occurred. On EEG a focal motor status epilepticus was recorded and successfully treated with Levetiracetam.

A brain MRI showed increased areas of pathological signal, compared to the MRI of October 2017. Besides, new lesions showing restricted diffusion were found, suggesting a re-activation of the pathological process (Figure 1e, 1f, 1g, and 1d).

Immunophenotype on blood serum showed a reduction in CD4+ count, an inversion in CD4/CD8 ratio (330/uL÷1000/uL), severe depression of B lymphocytes (100/uL) and normal NK count. CSF analysis showed hyperproteinorrachia at 1.57 g/L and normal white blood cell count and oligoclonal bands (OCB) in a 'mirror-pattern'. CSF PCR showed presence of JCV (< 350 copies/mL) and absence of HHV-6. PCR for JCV was also positive in both serum and urine samples. A diagnosis of PML reactivation was established and Olanzapine was administered.

Later she developed respiratory failure due to Pneumocystis Carinii pneumonia, successfully treated with intravenous Trimethoprim/Sulfamethoxazole. There was partial resolution of neurological symptoms as well, on discharge from the hospital only left homonymous hemianopia, left arm weakness and numbness persisted.

A brain MRI performed in April 2018, showed a reduction of the pathological areas on FLAIR sequences and absence of pathological activity on DWI sequences, the MRI performed in November 2018 and April 2019 were stable (Figure 2).

3. Discussion

Although data are limited, some evidence suggest that HHV-6, in conjunction with JCV, infection or reactivation is associated with the demyelinating lesions of PML (2).
of hair follicles or nails was not performed but, the relatively low number of HHV-6 copies in serum and CSF let us suppose an absence of ciHHV-6. For the presence of HHV-6 and JCV on CSF, a PML due to JCV and HHV-6 coinfection was considered and the patient was treated with foscarnet associated with anti 5HT2A receptor drugs, namely olanzapine and mirtazapine, with a good clinical outcome, despite the important hematologic comorbidities.

The relatively low number of HHV-6 copies in CSF and serum during the first hospitalization, the good response to therapy with foscarnet and anti 5HT2A receptors drugs and the absence of HHV-6 in CSF in the second hospitalization, associated with literature’s findings, can indicate a pathogenetic role of HHV-6 in this patient.

In a possible PML due to HHV-6 and JCV coinfection, brain biopsy and PCR testing of hair follicles or nails are suggested to confirm the diagnosis, but not always possible. In these cases we recommend to consider an ex juvantibus antiviral therapy.

References

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Figure 2. Brain MRI performed after the second hospitalization, showed a reduction of the pathological areas on FLAIR sequences (a, b, c) and absence of pathological activity on DWI sequences (d).


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