Case Report

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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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Summary **We reported the case of a John Cunningham virus (JCV) and human herpesvirus 6 (HHV-6) mediated progressive multifocal leukoencephalopathy (PML) after human stem cell transplant, reactivated 6 months later in absence of immunosuppressive therapy, successfully treated with anti-5HT2A receptors agents and antiviral therapy. Few cases of JCV and HHV-6 coinfection associated PML are described in literature and the role of HHV-6 in the pathogenesis and prognosis of PML is not completely clear. Our case suggests that, in a possible PML, the research of HHV-6 and JCV should be always performed on cerebrospinal fluid (CSF) and on blood samples and in case of detection of HHV-6 DNA a "chromosomally integrated human herpesvirus 6" (ciHHV-6) should be excluded. Furthermore we recommend to start an appropriate therapy with antiviral and anti-5HT2A receptors agents in case of possible PML due to JCV and HHV-6 coinfection.**

Keywords: Neurovirology, human herpesvirus 6, CNS infection

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 departmet 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

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partial response.

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 leucocyties), 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 dischrged 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*).

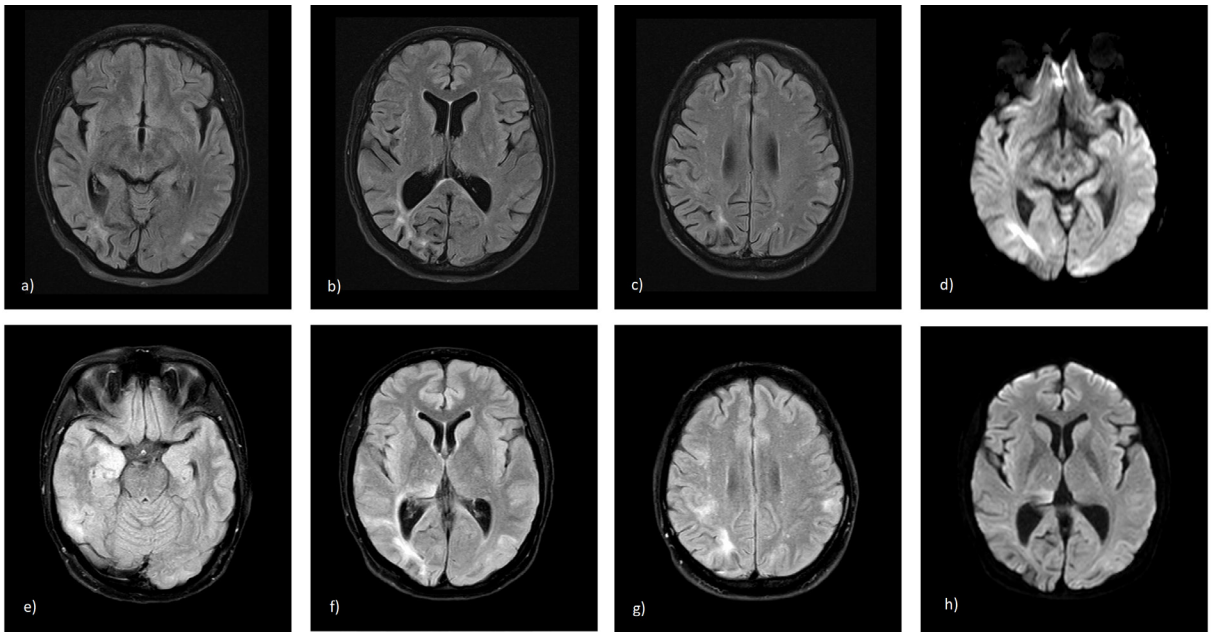

Figure 1. MR imaging of brain of the second hospitalization (**e, f, g, h**), when compared with first hospitalization (**a, b, c, d**) showed an increase in number and volume of the multifocal areas of high signal on FLAIR sequence (**a, b, c, e, f, g**) with restricted patchy diffusion on the axial DWI sequence (**d, h**).

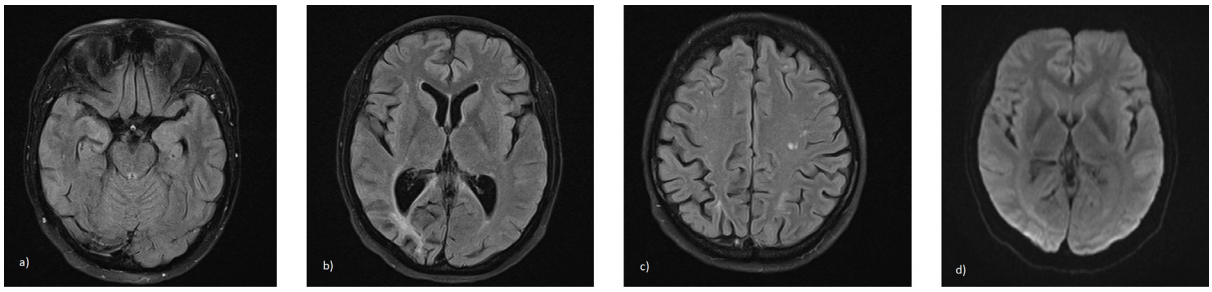

Figure 2. Brain MRI performed after the second hospitalization, showed a reduction of the pathological areas on FLAIR sequences (a, b, c) and absence of pathological activity on DWI sequences (d).

In some case reports JCV and HHV-6 coinfection was demonstrated by two-step in-situ PCR procedure performed on brain tissue samples, and single cases of coinfection of JCV and HHV-6 have been described in PML affected patients (*7,8*). Futhermore, a great frequency of HHV-6 and JCV genomes was present in numerous positively stained cells of oligodendroglial morphology in PML lesional white matter, and no HHV-6 antigens were detectable in adjacent uninvolved tissue in brain tissues of PML patients and in control tissues (*9,10*). Finally Yao demonstrated that superinfection with HHV-6 resulted in increased JCV copy number over time compared to JCV-infected SV40- transformed human glial cell line (SVG cells) alone (*2*).

CSF detection of HHV-6 is an unusual evenience in PML, Nakamichi *et al*. did not find HHV-6 DNA in any of the 299 CSF samples of 255 patients suspected of having PML, 31 of which were JCV positive on CSF (*11,12*). When HHV-6 DNA is detected on blood or other biological fluid, a "chromosomally integrated human herpesvirus 6" (ciHHV-6) must be excluded, this is a condition in which the complete HHV-6 genome is integrated into the telomere of a host cell chromosome, and it can be inherited in a Mendelian manner. Individuals with ciHHV-6 have one or more HHV-6 genomic copies per white blood cell, which corresponds to > 5.5 log10 copies/mL of whole blood, in absence of leukopenia, and the high viral DNA loads persist over time. DNA PCR testing of hair follicles or nails can confirm ciHHV-6 status, because only ciHHV-6 individuals have detectable HHV-6 DNA in these tissues (*13*).

Current prophylaxis and treatment of PML are focused on immune reconstitution, restoration of immune responses to JC virus infection, and eventual suppression of immune reconstitution inflammatory syndrome (*14*). There have been some case reports that have reported successful treatment with antipsychotic agents, such as Ziprasidone, Risperidone, and Olanzapine, as these agents can block the serotonin 5HT2A receptor, which has been shown to be a cellular receptor for JCV on glial cells, according to Elphick and colleagues (*15*).

In our case a brain biopsy and DNA PCR testing 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 foscernet associated with anti 5HT2A receptor drugs, namely olanzapine and mirtazapine, with a good clinical outcome, despite the important hematologic comorbilities.

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.

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