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Short communication

Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: A clinical, neuroradiological and virological response after treatment with risperidone

Daniele Focosi [a,*], Rita Fazzi [a], Domenico Montanaro [b], Michele Emdin [c], Mario Petrini [a]

[a] *Division of Hematology, Azienda Ospedaliera Universitaria Santa Chiara, via Roma 56, 56100 Pisa, Italy*
[b] *Department of Neuroradiology, National Research Council, Pisa, Italy*
[c] *Department of Cardiovascular Medicine, National Research Council, Pisa, Italy*

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Abstract

JC virus (JCV) is a double-stranded DNA virus belonging to family Polyomaviridae. It causes progressive multifocal leukoencephalopathy (PML), mainly in immunosuppressed people. JCV had been shown to require the serotonin 2A receptor for host cell entry. We report a case of clinical, neuroradiological and virological response of biopsy-proven PML in a 33-year-old comatose woman after treatment with the anti-psychotic drug risperidone. Since risperidone is the tightest binding of current drugs to this receptor we think this may have blocked JCV entry in our patient, allowing her immune recovery and viral clearance.

Keywords: Immunosuppression; Leukemia; Progressive multifocal leukoencephalopathy; Risperidone; Ziprasidone

1. Introduction

Progressive multifocal leukoencephalopathy (PML), is a demyelinating disease caused by the JC virus (JCV), occurring mainly in immunosuppressed states (Koralnik, 2006; Khalili et al., 2006). In HIV-negative patients it is usually fatal, and therapeutic options are few and often ineffective (Roskopf et al., 2006). We report here the first patient who developed histology-confirmed PML in the setting of haploidentical allogeneic hematopoietic stem cell transplantation: we believe she has been cured of PML and we explain how we think this may have happened.

The spectrum of diseases caused by JCV is unknown but this may be broader than previously thought. For example JCV is implicated in pathogenesis of cancer of brain and meninges (Delbue et al., 2005), stomach (Shin et al., 2006), colon (Goel et al., 2006) and others. An apparent cure of JCV-mediated disease therefore potentially has wider treatment implications.

1.1. Clinical presentation

In April 2003, a 33-year-old HIV-negative female diagnosed with Philadelphia-positive B-cell acute lymphoblastic leukemia was treated with 4 courses of R-hyper-CVAD [rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone] plus imatinib. In April 2004, while in complete remission, consolidation with haploidentical T-cell depleted allogeneic hematopoietic stem cell transplantation from her brother was performed. She remains in complete remission as of August 2006.

In October 2004 she developed rituximab-refractory autoimmune hemolytic anemia, treated with splenectomy and prednisone maintenance until April 2005. In October 2005 she experienced right hemiparesis, progressing to motor aphasia within 2 months when white blood cell count was 13,800 μL^{-1}, with 1500 $CD4^+$ lymphocytes/μL and serum IgG 700 mg/dL.

Polymerase chain reaction (PCR) for JCV DNA was positive on peripheral blood, negative on cerebrospinal fluid, as commonly reported in other case series. Blood PCR for all herpesviruses, adenovirus and tuberculosis was negative. MRI showed a left frontal lobe demyelinating lesion suggestive of

* Corresponding author. Tel.: +39 050993085; fax: +39 0583975869.
E-mail address: focosi@icgeb.org (D. Focosi).

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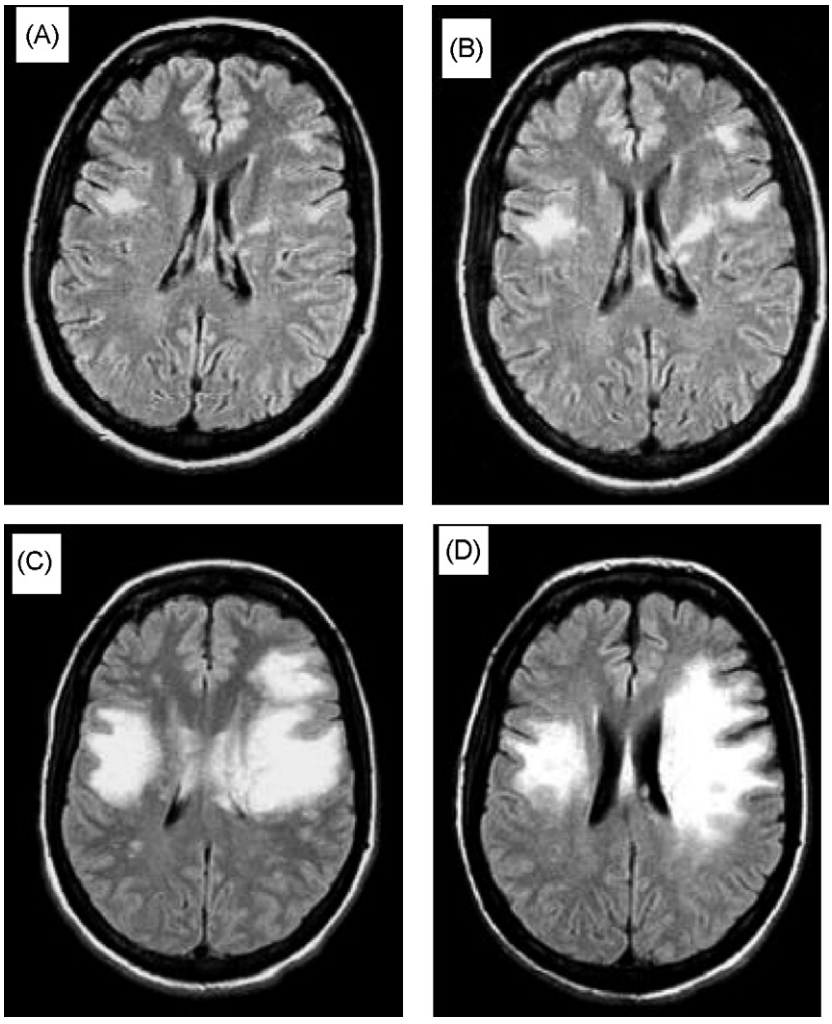

Fig. 1. FLAIR MRI images on the axial plane passing through the atrium of the lateral ventricles at different dates. The images at neurological onset (panel A) and 15 days later (panel B) show focal alterations of the white matter surrounding the lateral ventricles, which had progressed extensively at the time risperidone treatment was started (panel C). One month after the end of such a treatment, improvement of the alteration and the compression on the ventricles are evident (panel D).

PML (Fig. 1A). Stereotactic cerebral biopsy in January 2006 showed typical PML histology. Biopsy tissue PCR was positive for JCV. While sequentially receiving supportive intravenous immunoglobulins, 2 donor lymphocyte infusions, 3 courses of oral cidofovir, probenecid, intrathecal cytosine arabinoside, and seizure prophylaxis, MRI showed fast progression of demyelination (Fig. 1B). She was comatose, requiring intubation and ventilation.

Considering our patient's terminal state and a] recent in vitro evidence showing that JCV requires the serotonin 2A receptor, 5-HT2A, to enter glia and cannot enter glia without using the 5-HT2A receptor (Elphick et al., 2004), and b] that the commonly used anti-psychotic risperidone is the tightest binding and best suited 5-HT2A antagonist to treat PML (Altschuler and Kast, 2005) we tried risperidone for 10 days, titrating up to 8 mg a day (4 mg orally q12 h). After 2 weeks, MRI showed an arrest in progression (Fig. 1C), accompanied by a drop to normal of previously elevated inflammatory markers (transaminases, fibrinogen and alkaline phosphatase). Three months later (May 2006) MRI was improved (Fig. 1D). She now (October 2006) feeds herself, smiles, hugs her child, verbally interacts with her relatives, walks, is fully oriented and emotionally intact.

Her peripheral blood is now free from JCV DNA. Most importantly, her peripheral blood is now free from JCV DNA and her CD57 + lymphocyte count, a subset associated with immune senescence (Brenchley et al., 2003), dropped from 70% at the time of diagnosis to just 30%, suggesting that immune reconstitution contributed to JCV eradication.

2. Conclusions

Given our experience with this patient and the safety and high brain concentrations achieved with risperidone, future clinical trials are needed to ascertain risperidone's potential anti-JCV activity.

Risperidone also has urinary catabolites which are still active against 5-HT2a, which is expressed on urothelium, one of the sites of JCV latency in immunocompentent people: according to preliminary data collected by Dr. Richard Kast at Univer-

sity of Vermont, risperidone seems able to reduce JC viruria in psychiatric patients, a surrogate marker for inhibition of JCV replication in the central nervous system (personal communication). Risperidone is already approved for human use and preferentially accumulates in the brain: given the current dismal prognosis of PML, future clinical trials are anticipated. PML is a rare disease, so multicentric efforts will be required to gather enough data to confirm the utility of risperidone for this yet untreatable disease.

Ziprasidone is the other high affinity 5-HT2A receptor antagonist available in many countries and should be investigated for potential anti-JCV effects too. The full spectrum of diseases that JCV can cause is uncertain. If risperidone or ziprasidone can be shown to prevent JCV entry into host cells and thereby facilitate viral clearance, urgent delineation of these different disease states [if any other than PML] is required. Olanzapine was previously suggested (Altschuler and Kast, 2005) as potentially active against JCV as well but we think olanzapine's affinity for 5-HT2A is too weak. We suggest anti-JCV studies be confined to risperidone and ziprasidone.

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