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Use of interleukin-2 for management of natalizumab-associated progressive multifocal leukoencephalopathy: case report and review of literature

Divyanshu Dubey, Yinan Zhang, Donna Graves, Allen D. DeSena, Elliot Frohman and Benjamin Greenberg

***Abstract*:** A 51-year-old woman with relapsing–remitting multiple sclerosis (RRMS) and 3-year history of natalizumab use developed expressive aphasia. A brain magnetic resonance image (MRI) showed left frontotemporal and right parietal lesion with mild contrast enhancement and cerebrospinal fluid (CSF) was positive for John Cunningham virus (JCV) by polymerase chain reaction (PCR). The patient received five cycles of plasmapheresis followed by intravenous immunoglobulin. Despite this intervention, her speech deteriorated and she developed right hemiparesis. Upon referral to our institution, CSF quantitative JCV PCR was notable for 834 copies/ml. The patient was given an initial dose of 50,000 units of interleukin-2 (IL-2) subcutaneously (SQ) followed by 1 million units IL-2 SQ daily. Due to concern for immune reconstitution inflammatory syndrome (IRIS), the patient also received intravenous methylprednisone weekly. The regimen was tolerated well by the patient with no severe adverse effects. Clinically, the patient showed some improvement, and became more responsive and regained right lower extremity antigravity strength. After 12 weeks of IL-2 therapy, JCV quantitative PCR was notable for 31 copies/ml and the patient was more responsive. Due to persistence of JCV, IL-2 therapy was changed to mefloquine. At follow up after 6 months, the patient showed no clinical deterioration.

Keywords: Progressive multifocal leukoencephalopathy, Interleukin-2, Natalizumab, Multiple sclerosis, Immune Reconstitution Inflammatory Syndrome

Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection caused by John Cunningham virus (JCV) in immunocompromised patients [Aksamit, 2012]. PML has been described in acquired immune deficiency syndrome (AIDS) patients, hematological malignancies, rheumatoid arthritis, systemic lupus erythematosous and sarcoidosis, and in patients receiving immunomodulatory therapies such as rituximab, natalizumab and efalizumab [Aksamit, 2012]. So far, more than 400 cases of PML have been reported among patients on natalizumab. Among these patients, progression of neuropathology due to JCV infection is gradual, but many of these cases are complicated by development of immune reconstitution inflammatory syndrome (IRIS) which requires administration of high dose corticosteroids [Calabrese, 2011].

We report a case of a patient who received natalizumab for prolonged duration, even after JCV serology was positive. Unfortunately she developed PML and was transferred to our facility for a higher level of care. We attributed her clinical deterioration to extension of PML rather than IRIS based on high copy number JCV. We attempted interleukin-2 (IL-2) as a therapeutic agent for PML based on the pathophysiologic principle of IL-2 promoting reconstitution of T lymphocytes to fight the infection.

Correspondence to:
Divyanshu Dubey, MD
Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, 5323 Harry Hines Blvd. Dallas, Texas-75235, USA
divyanshudubey87@gmail.com

Yinan Zhang, MD
Donna Graves, MD
Elliot Frohman, MD, PhD
Benjamin Greenberg, MD
Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, Dallas, Texas, USA

Allen D. DeSena, MD, MPH
Department of Neurology, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

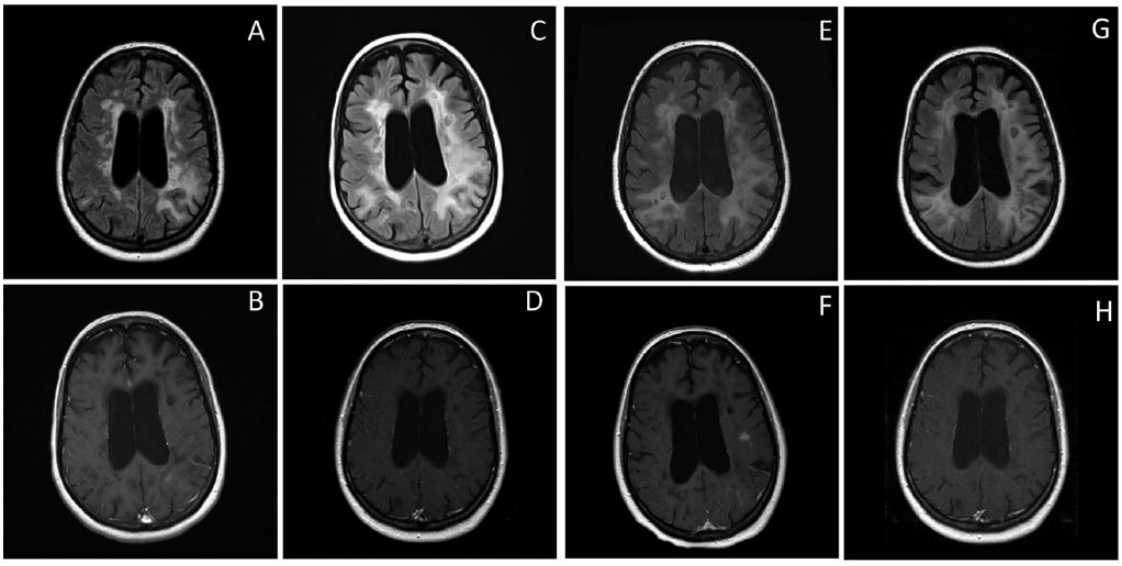

Figure 1. (A–H): Initial magnetic resonance imaging (MRI) fluid attenuation inversion recovery (FLAIR) and post contrast T1 images (A,B) of the patient from outside facility showing subcortical, periventricular, left frontoparietal and right parietal FLAIR hyperintensity (A) with mild contrast enhancement in left parietal lesions (B). Images obtained at our institution 16 weeks into clinical course, showing increase in size of biparietal lesions (C) but no contrast enhancement (D. Images (E,F) obtained after 4 weeks of IL-2 therapy showing area of contrast enhancement left frontal subcortical area concerning for IRIS. Images obtained following completion 12 weeks of IL-2 therapy (G,H).

Case presentation

A 51-year-old woman with relapsing–remitting multiple sclerosis (RRMS) and a 3-year history of natalizumab use developed progressive expressive aphasia in March 2013. A brain magnetic resonance image (MRI) revealed new left frontoparietal and right parietal lesions with mild contrast enhancement (Figure 1a and b), and natalizumab was discontinued. The patient's cerebrospinal fluid (CSF) was positive for the JCV *via* polymerase chain reaction (PCR) testing and she received five cycles of plasmapheresis in June followed by intravenous (IV) immunoglobulin (2 g/kg body weight, divided over 5 days). Despite this intervention her speech deteriorated and she developed right hemiparesis. Upon referral to our institution in August, she had global aphasia, right sided neglect and right sided hemiparesis. Another brain MRI was obtained which showed subcortical, periventricular, left frontoparietal and right parietal lesions (increased in size compared with the previous MRI) with no contrast enhancement (Figure 1c and d). Lumbar puncture was performed, which was consistent with mild lymphocytic pleocytosis (total nucleated cells 20 cells/dl, 85% lymphocyte). Quantitative PCR of JCV showed 834 copies/ml. Serum flow cytometry analysis showed 319 cells/µl CD8 positive cells (normal range: 330–920 cells/µl) and 570 cells/µl CD4 positive cells (normal range: 530–1300 cells/µl).

Over the next few days her clinical condition worsened. She also had starring spells with automatisms concerning of complex partial seizures. She was started on levetiracetam 1 g twice a day. Additional therapies for JCV were considered. The patient was given an initial dose of 50,000 units of IL-2 subcutaneously (SQ) on 25 August followed by 1 million units IL-2 SQ daily. Due to increased risk for IRIS with use of daily IL-2, the patient also received IV methylprednisone weekly. The effect of the off-label therapy was monitored with daily clinical assessments, weekly brain MRI and quantitative CSF JCV PCR. Subsequent CSF JCV PCR showed the JCV copy number had reduced to 240 copies/ml after 1 week of therapy and to 43 copies/ml at 2 weeks. Clinically, the patient showed some improvement and became more responsive and regained right lower extremity antigravity strength. A brain MRI obtained after 4 weeks of therapy showed some contrast enhancement in the left frontoparietal region, which was concerning for development of IRIS (Figure 1e and f). The patient was given IV methylprednisone 1 g

Table 1. Case reports of use of IL-2 therapy for management of PML.

	Age (years)/ sex	Clinical presentation	MRI findings	Dose	Duration of therapy	Underlying predisposing factor	JCV CSF PCR/brain biopsy	Improvement in neurological status
Dubey *et al.* (in press)	51/F	Global aphasia, right sided neglect, right hemiparesis, complex partial seizure	Left frontoparietal and right parietal lesions hyperintense on T2-WI and mild contrast enhancement	IL-2: 50,000 units/ m^2 initial dose, then 1 million units/m^2 daily, SQ Methylprednisone: 1 g weekly	84 days	Natalizumab therapy for RRMS	+	Decrease in JCV quantitative PCR, improvement and stabilization of neurological status
Buckanovich *et al.* [2002]	29/F	Ataxic, decreased, visual acuity, bilateral inferior,visual field deficits	Irregular diffuse noncontrast enhancing lesions in bilateral parietal lobes, hyperintese on T2-WI	IL-2: 0.5 million units/m^2 per day, IV	116 days, followed reinitiation of therapy 20 days later, duration of therapy NS	Hodgkin's lymphoma treated with NMASCT status post radiation therapy, MOPP/ABV chemotherapy, cyclosporiene for GVHD prophylaxis	–	Neurological deficits completely resolved; patient able to perform all activities of daily living
Kunschner and Scott [2005]	58/F	Cognitive deterioration, dysarthria, right hemiparesis	Irregular no contrast enhancing 3–4 cm lesion in the left centrum semiovale, hyper-intense on T2-WI	IL-2: 0.5 million units /m^2 per day for 5 weeks, 1.0 million units /m^2 per day for a sixth week, IV	42 days	Myelodysplastic syndrome	+	5-year follow up Improved cognition, mild dysarthria, and moderate right hemiparesis
Przepiorka *et al.* [1997]	46/F	Vertigo, aphasia and right hemiparesis	Contrast nonenhancing T2 hyperintense lesion in left frontoparietal region	IL-2: 0.5 million units/m^2 per day, IV	182 days	Low-grade lymphoma status post etoposide, cyclophosphamide, total body irradiation, and autologous marrow and blood stem cell transplantation	+	Improvement in speech and motor function

ABV, doxorubicin, bleomycin, vinblastine chemotherapy; CSF, cerebrospinal fluid; GVHD, graft-*versus*-host disease; IL-2, interleukin-2; IV, intravenous; JCV, John Cunningham virus; MOPP, mechlorethamine, vincristine, procarbazine; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; NMASCT, nonmyeloablative allogeneic stem cell transplantation; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing–remitting multiple sclerosis; SQ, subcutaneous; T2-WI, T2-weighted images.

daily for 3 days and IL-2 therapy was continued. The patient's neurological examination showed no clinical deterioration. The next JCV PCR copy number 1 week after the last test was 70 copies/ml, but the contrast enhancement was reduced on subsequent MRI (Figure 1g and h). After 12 weeks of IL-2 therapy, JCV copy number was 31 copies/ml. There was also a mild increase in CSF lymphocytic pleocytosis (total nucleated cells 32 cells/dl, 97% lymphocytes). The patient was more responsive and there was improvement in right sided weakness. Due to the persistence of JCV, IL-2 therapy was changed to mefloquine. At follow up after 6 months, the patient showed no clinical deterioration.

Discussion

This case brings forth a therapeutic option for management of PML, a fatal opportunistic infection which is a complication of natalizumab infusion. Our patient was treated with daily IL-2 and weekly methylprednisone for 3 months with significant reduction in JCV PCR quantitative titers and stabilization of clinical presentation. Although there was some increase in extent of white matter involvement on MRI (Figure 1a–h), no adverse effects were reported from IL-2 administration.

Various therapies have been tried so far for management of PML, largely without success. These therapies have been reported to be effective by directly acting on viral neuronal entry or replication, or by potentiating host immune system mediated viral eradication [Aksamit, 2012]. Currently the standard approach to manage PML related to natalizumab infusion is to discontinue the monoclonal antibody and institute plasmapheresis to remove the integrin α-4/β-1 antibody from the circulation, subsequently increasing central nervous system (CNS) immunosurveillance [Calabrese, 2011].

Based on the patient's clinical deterioration following initial plasma exchange therapy, there was no definitive way to differentiate between progression of PML *versus* IRIS. However, lack of gadolinium enhancement on brain MRI and a high copy number of JCV despite conventional treatment suggested a lack of immune response to the infection. We decided to use IL-2 due to its role in potentiation of the anti-JCV cytotoxic T-cell response. IL-2 administration influences CD-8 count, and increases granzyme and perforin formation [Smith, 1984]. It has also been shown to enhance response to cytotoxic natural killer (NK) cells and to induce lymphokine activated killer cells [Lotze *et al.* 1986]. IL-2 is usually produced by antigen-activated T cells. It subsequently promotes T cells to switch from the G1 phase to the proliferative phase and increases the levels of proinflammatory cytokines leading to T-cell differentiation [Smith, 1984].

Following discontinuation of therapy, the immune system has extensive access to the CNS and patients are at a high risk of developing IRIS [Calabrese, 2011]. Therefore we also continued weekly treatment with high dose methylprednisone. The IL-2 regimen theoretically also puts the patient at increased risk of progression of multiple sclerosis, therefore extensive consenting of patient and family was performed. As the fatality and rate of progression associated with PML is significantly higher than with multiple sclerosis, we decided that the benefits of IL-2 therapy outweighed the risks.

In the past, IL-2 therapy has been utilized for treatment of PML in the patients with hematological malignancies (Hodgkin's lymphoma, myelodysplatic syndrome) [Buckanovich *et al.* 2002; Kunschner and Scott, 2005; Przepiorka *et al.* 1997]. These patients have shown stabilization or improvement in neurological status (Table 1).

So far, there are no published cases of the management of natalizumab-related PML with a regimen of daily IL-2 and weekly high dose corticosteroids. Based on our experience, this novel regimen not only was well tolerated by the patient with no severe adverse effects, but it may also have contributed to the reduction in CSF JCV copy number. Further prospective studies and randomized controlled trials are required to study IL-2 as a therapeutic agent for PML following natalizumab administration.

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