

Case Report

Natalizumab-Related Progressive Multifocal Leukoencephalopathy-Immune Reconstitution Inflammatory Syndrome: A Case Report Highlighting Clinical and MRI Features

Bela PUROHIT^{1,2} Eranga GANEWATTE¹ Spyros S. KOLLIAS¹

Submitted: 20 Aug 2015

Accepted: 5 Dec 2015

Online: 5 Oct 2016

¹ Institute for Neuroradiology, University Hospital of Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland

² Dept. of Neuroradiology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore-308433

To cite this article: Purohit B, Ganewatte E, Kollias SS. Natalizumab-related progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome: a case report highlighting clinical and MRI features. *Malays J Med Sci.* 2016;**23**(5):91-95. <http://dx.doi.org/10.21315/mjms2016.23.5.12>

To link to this article: <http://dx.doi.org/10.21315/mjms2016.23.5.12>

Abstract

Multiple sclerosis (MS) patients treated with natalizumab often face the uncommon but severe complication of developing progressive multifocal leukoencephalopathy (PML). PML may be further complicated by immune reconstitution inflammatory syndrome (IRIS) after the removal of the drug. Since both PML and IRIS are associated with high morbidity and mortality rates, early clinical and radiological diagnosis of these complications is of paramount importance. Here, we report a case of an adult male patient who was diagnosed with PML after receiving natalizumab therapy for 6 years for the treatment of MS. Upon cessation of natalizumab, he presented with a paradoxical worsening of clinical and radiological findings consistent with an inflammatory brain injury due to IRIS. He was treated with high dose corticosteroid therapy followed by a gradual improvement in clinical and imaging findings. This article illustrates the magnetic resonance imaging (MRI) features of natalizumab-associated PML-IRIS, along with a brief overview of its clinical features, complications and management strategies.

Keywords: magnetic resonance imaging, natalizumab, multiple sclerosis, progressive multifocal leukoencephalopathy, immune reconstitution inflammatory syndrome

Introduction

Natalizumab is a monoclonal antibody used to treat relapsing multiple sclerosis (MS). Its mode of action is to produce a blockage of an integrin adhesion molecule, thereby preventing white blood cells from crossing the blood-brain barrier and restricting the inflammatory response. It is administered intravenously once every 4 weeks (dose: 300 mg) in adult patients with relapsing MS in whom it is known to substantially decrease disease activity and prevent disease progression. However,

its therapeutic efficacy has to be weighed against a serious associated side effect: the likelihood of developing progressive multifocal leukoencephalopathy (PML). PML is an opportunistic infection of the brain parenchyma caused by the JC virus and is known to show high morbidity and mortality rates (1–7).

Case Report

An adult male patient (aged 40 years) was being treated at our hospital (1) for relapsing MS since 1998. He had been on natalizumab

therapy for 6 years until being diagnosed with PML in April 2014, after which natalizumab was discontinued. Magnetic resonance imaging (MRI) of the brain in April 2014 showed a large, poorly marginated, T2 hyperintense lesion involving the left middle cerebellar peduncle (MCP) and left cerebellar hemisphere (Figure 1).

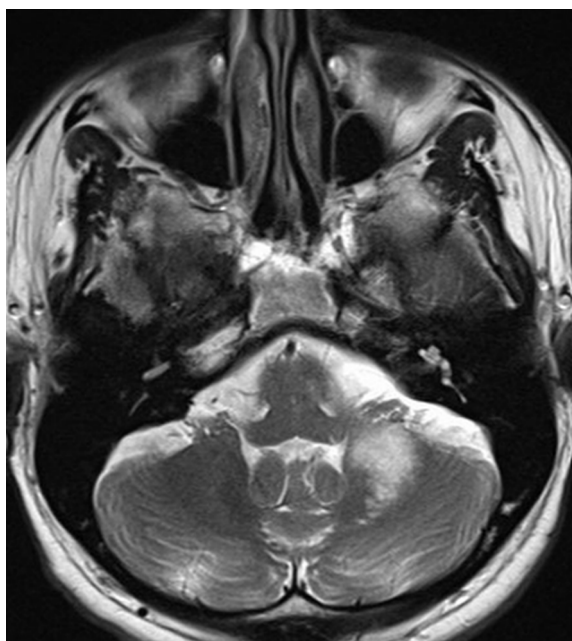


Figure 1: An axial T2W MRI of the brain at the level of the ponto-medullary junction (April 2014 study) shows a large, poorly-marginated, T2 hyperintense PML lesion involving the left MCP and left cerebellar hemisphere.

This lesion did not show post-contrast enhancement (Figure 2).

The imaging features were typical of PML. The patient then underwent three sessions of plasmapheresis followed by a brief clinical response. He again presented in June 2014 with progressively increasing unsteadiness and left facial hypoaesthesia. A clinical examination showed left cerebellar dysfunction and left trigeminal nerve involvement. A cerebrospinal fluid (CSF) study showed elevated levels of protein (609 mg/dL) and IgG (34.7 mg/dL) without pleocytosis. A polymerase chain reaction (PCR) test for the JC virus (JCV) DNA was positive. The subsequent MRI on June 2014 showed an interval increase in the size of the previous PML lesion and an interval appearance of post-contrast enhancement along the margins of the lesion (Figures 3 and 4), which was not seen in the April 2014 MRI. Imaging findings confirmed the clinical diagnosis of PML-associated immune reconstitution inflammatory

syndrome (IRIS) occurring due to the suspension of natalizumab therapy.

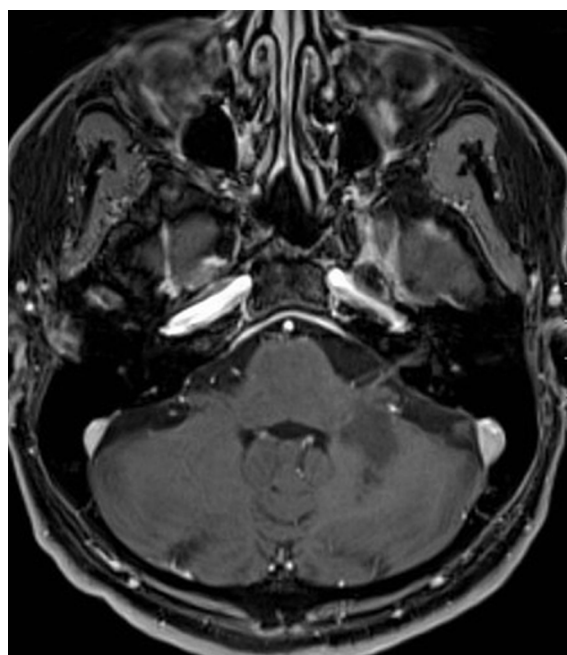


Figure 2: Contrast-enhanced axial T1W MRI at the level of the MCP (April 2014 study) shows no evidence of enhancement in the PML lesion.

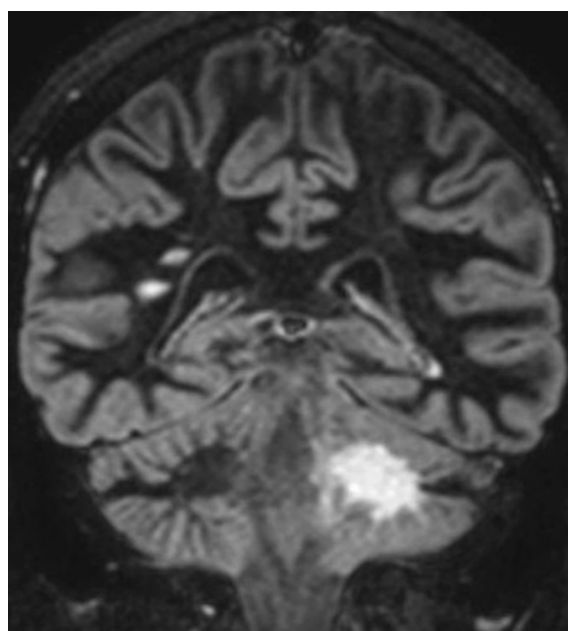


Figure 3: Coronal double inversion recovery image at the level of the ventricular trigones (June 2014 study) shows a slight interval increase in the size of the PML lesion since the previous April 2014 study. Typical small ovoid hyperintense MS plaques are noted in the right periventricular region.



Figure 4: Contrast-enhanced axial T1W MRI at the level of the MCP (June 2014 study) shows an interval appearance of gadolinium enhancement at the margins of the PML lesion in keeping with IRIS.

The patient was subsequently treated over one week with intravenous methylprednisolone. A follow-up MRI after 6 weeks showed a decrease in the size and a decrease in the previously noted contrast enhancement of the PML-IRIS lesion. The patient showed parallel clinical improvement. He is presently on oral maintenance steroid therapy.

Discussion

After the first 2–3 years of treatment with natalizumab, the PML incidence increases with increased duration of drug exposure. Patients develop symptoms approximately 17–25 months after treatment (3,4). The approximate risk of developing PML in MS patients treated with natalizumab is about 3–4/1000 (4). Cumulative increased exposure to natalizumab increases the risk of developing PML. The risk is significantly higher in patients who have previously received immunosuppressive treatments or in combination with natalizumab. In our patient, the delayed appearance of PML after 6 years may be explained by the fact that he was not treated with other immunosuppressants. Reports in the literature also mention a low viral load and high

anti-JCV antibody titre as possible causes for decreased susceptibility to PML (5,6).

The presenting symptoms of PML in MS patients include progressive clinical deterioration, changes in cognition and personality, aphasia, hemiparesis, seizures and visual disturbances. The pathological hallmark of PML is a progressive demyelination of oligodendrocytes without a significant inflammatory response. Its clinical diagnosis is aided by a MRI evaluation and the detection of JCV DNA on CSF analysis. Early diagnosis of PML is crucial because a delay in the diagnosis has a negative impact on the overall prognosis (1–8).

An awareness of the MRI features of PML is of paramount importance. The common sites for the development of PML lesions are the supratentorial subcortical white matter, with occasional involvement of the deep grey matter. The brainstem and cerebellum are often involved; however, spinal cord involvement is rare. The MRI diagnosis of PML in patients with MS and the decision of whether a new lesion is MS or PML is challenging, especially as it affects therapy. Characteristic MRI features of PML in MS include large, diffuse and asymmetric (> 3 cm), unifocal or multifocal, subcortical white matter lesions (affecting “U” fibres) that are hyperintense on T2W and FLAIR sequences and hypointense on T1W sequences. The lesions typically show a well-margined border towards the grey matter and a poorly-margined border towards the white matter. On the other hand, MS lesions are smaller, typically ovoid or flame-shaped, commonly seen in the periventricular white matter, often seen in the spinal cord, may show restricted diffusion, have mild mass effect and have a ring-like enhancement in the acute/active phase. PML lesions typically do not show mass effect. PML is characterised histologically by paucity of inflammation and hence, contrast-enhancement is uncommon (4–11).

PML linked to natalizumab treatment is associated with 20% mortality rates with survivors sustaining moderate to severe disabilities. It is treated by the immediate discontinuation of the drug and often, plasmapheresis is performed to rapidly remove the drug from the circulation. Adjuvant immunomodulatory therapy with mefloquine and mirtazapine has been reported to show favourable responses (1–11).

Unfortunately, as in our patient, the sudden removal of natalizumab or the use of plasmapheresis may lead to the development of

IRIS, which is defined as a paradoxical clinical and radiographic worsening after a period of stability. PML-IRIS typically presents with a worsening of earlier PML symptoms; this occurs a few days to weeks after natalizumab discontinuation or the start of plasmapheresis. Immune reconstitution is characterised by intense perivascular CD4 lymphocytic infiltration and inflammatory brain damage. IRIS is associated with mortality rates of 20–30%. Important MRI features of PML-IRIS include the development of new inflammatory changes with an increase in PML lesion size. There may be an interval appearance of contrast-enhancement, oedema and mass effect. PML-IRIS has also been described in HIV-positive patients being treated by highly active antiretroviral therapy, in which case, infection and lymphoma are likely imaging differentials for PML-IRIS lesions. However, a correlation between the clinical scenario of MS post-natalizumab therapy and the typical MRI findings of PML lesions showing enhancements clinches the IRIS diagnosis. PML-IRIS can lead to substantial long-term sequelae with more extensive necrotic tissue damage than just the JCV infection with severe residual parenchymal and cortical atrophy (4–11).

Corticosteroid therapy in high doses, which is usually intravenous methylprednisolone (1 g per day) for 5 days, is the recommended treatment for PML-IRIS. This is followed by oral steroids with tapered doses. Prednisolone in a dose of 0.75 mg/kg has been suggested by some authors as an acceptable taper dose for some forms of IRIS (12). IRIS can persist for several months and hence, long-term steroid therapy may be necessary along with close clinical and MRI monitoring (2,3). Favourable responses to treatment are associated with a gradual regression of the acute inflammatory features on MRI (8).

In conclusion, diagnosing natalizumab-associated PML-IRIS is of paramount importance. It requires regular clinical follow-up and vigilance, reliable JCV PCR testing and well-defined MRI criteria for the recognition of PML-IRIS. Optimised treatment strategies of IRIS reactions and the development of robust predictive markers for patients at risk for PML must be sought. Clinicians and radiologists must work in close collaboration to avoid a misdiagnosis of these potentially lethal conditions.

Acknowledgement

None

Conflict of Interest

No conflict of interests.

Funds

No grants were applied or received.

Authors' Contributions

Conception and design: BP
 Analysis and interpretation of the data: BP, EG
 Drafting of the article: BP
 Critical revision of the article for important intellectual content: SK
 Final approval of the article: BP, SK
 Collection and assembly of data: EG

Corresponding author

Bela Purohit
 MD, DNB, FRCR, EBHNR
 Department of Neuroradiology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore-308433
 Phone: +65-63577018.
 Fax: +65-63577039
 Email: purohitbela@yahoo.co.in
 This study originated at: Institute for Neuroradiology, University Hospital of Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland.

References

1. Chataway J, Miller D. Natalizumab therapy for multiple sclerosis. *Neurotherapeutics* 2013;**10**(1):19–28. <http://dx.doi.org/10.1007/s13311-012-0171-4>
2. Hoepner R, Faissner S, Salmen A, Gold R, Chan A. Efficacy and side effects of natalizumab therapy in patients with multiple sclerosis. *J Cent Nerv Syst Dis* 2014;**28**(6):41–49. eCollection 2014. <http://dx.doi.org/10.4137/JCNSD.S14049>
3. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovanni G, Nath A. Natalizumab associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 2010;**9**(4):438–446. [http://dx.doi.org/10.1016/S1474-4422\(10\)70028-4](http://dx.doi.org/10.1016/S1474-4422(10)70028-4)

4. Yousry TA, Pelletier D, Cadavid D, Gass AC, Richert ND, Radue EW, et al. Magnetic resonance imaging pattern in natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2012;**72**(5):779–787. <http://dx.doi.org/10.1002/ana.23676>
5. Kappos L, Bates D, Edan Gilles, Eraksoy M, Garcia-Merino A, Grigoriadis, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. *Lancet Neurol* 2011;**10**:745–758. [http://dx.doi.org/10.1016/S1474-4422\(11\)70149-1](http://dx.doi.org/10.1016/S1474-4422(11)70149-1)
6. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A et al. Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy. *N Engl J Med* 2012;**366**:1870–1880. <http://dx.doi.org/10.1056/NEJMoa1107829>
7. Wattjes MP, Richert ND, Killestein J, de Vos M, Sanchez E, Snaebjornsson P, et al. The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy. *Mult Scler* 2013; **19**(14):1826–1840. <http://dx.doi.org/10.1177/1352458513510224>
8. Gheuens S, Smith DR, Wang X, Alsop DC, Lenkinski RE, Koralnik IJ. Simultaneous PML-IRIS after discontinuation of natalizumab in a patient with MS. *Neurology* 2012;**78**(18):1390–1393. <http://dx.doi.org/10.1212/WNL.0b013e318253d61e>
9. Miravalle A, Jensen R, Kinkel RP. Immune reconstitution inflammatory syndrome in patients with multiple sclerosis following cessation of natalizumab therapy. *Arch Neurol* 2011;**68**(2):186–191. <http://dx.doi.org/10.1001/archneurol.2010.257>
10. Metz I, Radue EW, Oterino A, Kümpfel T, Wiendl H, Schippling S, et al. Pathology of immune reconstitution inflammatory syndrome in multiple sclerosis with natalizumab-associated progressive multifocal leukoencephalopathy. *Acta Neuropathol* 2012;**123**(2):235–245. <http://dx.doi.org/10.1007/s00401-011-0900-5>
11. Kleinschmidt-DeMasters BK, Miravalle A, Schowinsky J, Corboy J, Volmer T. Update on PML and PML-IRIS occurring in multiple sclerosis patients treated with natalizumab. *J Neuropathol Exp Neurol* 2012; **71**(7):604–617. <http://dx.doi.org/10.1097/NEN.0b013e31825caf2c>
12. Marais S, Wilkinson RJ, Pepper DJ, Meintjes D. *Management of patients with the immune reconstitution inflammatory syndrome*. Current HIV/AIDS Reports 2009. **6**:171–180. <http://dx.doi.org/10.1007/s11904-009-0022-z>