Neuroendocrinology Letters Volume 40 No. 5 2019
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

CASE REPORT

Progressive Multifocal Leukoencephalopathy associated to treatment with natalizumab in Mexican patient Multiple Sclerosis. Case report, analysis and update

Sandra Quiñones-Aguilar[1], Sergio Sauri-Suárez[1], Sofía Lizeth Alcaraz-Estrada[2], Silvia García[3]

1 Neurologist, Neurology Department, National Medical Center "20 de Noviembre" ISSSTE, México City;
2 Division of Genomic Medicine, National Medical Center "20 de Noviembre" ISSSTE, México City;
3 Neurologist, Master Degree, Clinical Research Department, National Medical Center "20 de Noviembre" ISSSTE, México City; Mexico.

Correspondence to: Silvia García
Clinical Research Department, National Medical Center "20 de Noviembre" ISSSTE; San Lorenzo 502, Del Valle Neighborhood, Benito Juárez, CP 03100, Mexico City, Mexico.
tel.: 55 52 00 50 03 ext. 14604 y 14609; e-mail: rolasil@yahoo.com.mx

Submitted: 2018-11-15 Accepted: 2019-10-10 Published online: 2019-10-10

Key words: **Multiple Sclerosis; Natalizumab; Progressive multifocal leukoencephalopathy in a Mexican patient**

Neuroendocrinol Lett 2019; **40**(5): 222–226 **PMID:** 32112546 NEL400519C01

Abstract

One of the most dreaded complications in Multiple Sclerosis (MS) patients treated with natalizumab is the appearance of the Progressive Multifocal Leukoencephalopathy (PML). A 54-year-old Mexican woman diagnosed eight years before with MS, received natalizumab for the last three years. The patient developed PLM that was confirmed by clinical, radiological, blood and CSF tests. Her treatment included methylprednisolone, plasmapheresis, immunoglobulin and mirtazapine. Risks, causes, treatments, preventive measures and opportune diagnosis for these patients are analyzed in this report.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic, inflammatory demyelinating and degenerative disease of the Central Nervous System (CNS) and its etiology is still unknown (Freedman *et al.* 2018). This disease is characterized by recurrent episodes of reversible multifocal neurological signs and symptoms and recovery and disability in various degrees. It usually affects women more in early adulthood, causing a large functional and economic impact and a decrease in the quality of life of the patient.
There's no cure available for this disease, (Vargas & Tyor, 2017) however, there are treatments that focus on the management of the acute event or the decrease of symptoms (symptomatic) that can modify the natural history of the disease, these are called – disease-modifying therapies (DMT). These therapies reduce the number of relapses, the progression of the disease as well as the accumulation of focal lesions in white matter (Mills & Mao-Draayer, 2018).

DMTs act on different targets that decrease the immune and inflammatory response in the CNS and clinical relapse in MS, however, at the same time, it increases the risk for Progressive Multifocal Leukoencephalopathy (PML) in these patients, particularly the use of new generation DMTs.

PML is caused by reactivation and mutation of John Cunningham virus (JCV); it´s a DNA virus that cohabitates with humans; most people acquire it during childhood. JCV is present in 70-90% of general population (Motte, 2018). Initial infection occurs in the tonsils or in the gastrointestinal tract, remaining latent in kidneys or lymphoid tissue (Horn & Greene, 2012). In immunocompromised patients with MS, treated with new generation of DMT (e.g. natalizumab, fingolimod or dimethyl fumarate), JCV can be reactivated to produce PML (Berger *et al.* 2018).

The National Medical Center "20 de Noviembre" ISSSTE is a governmental hospital in Mexico of national concentration for care of patients with MS, so use of new generation DMTs is routinely applied according to management guidelines of MS.

CASE PRESENTATION

A 54-year-old woman with no significant medical history was diagnosed with MS 8 years before; her initial DMT was IFN-β1-A 12 million for 24 months, she displayed elevation of hepatic transaminases thereby SMT was modified to glatiramer acetate. She remained clinically stable for 38 months; however, because of her lesions and raised radiological activity, it was decided to modify her treatment to natalizumab. She remained without clinical-radiological activity for 36 months, her EDSS was 0.

She began with numbness of lower limbs, blurred vision, confusion, and difficulty to nomination and slowness in her mental processing; two weeks later, right facio-corporal hemiparesis was added and was admitted to the hospital. In her brain MRI, hyper intense lesion in the frontal left T2/ FLAIR (Imagen 1) was found; natalizumab was discontinued and pulses of methylprednisolone (1 g for 5 days) were started followed by 5 plasmapheresis sessions. In CSF, JC virus was detected, blood viral load was 589.47 copies and lymphocyte subpopulation were quantified (see table 1 and 2).

Two weeks later, her awareness decreased, gaze fixes in primary position and clonal movements of the right arm become convulsive-status epilepticus. The patient was treated with diazepam and phenytoin with success and magnesium valproate for maintenance. A new brain MRI with gadolinium uptake was performed and a persistent hyper intense lesion was observed in T2/FLAIR of the left hemisphere (Image 2. The following treatment consisted of IgG immunoglobulin IV 400 mg/k/d for five days, and a new cycle of methylprednisolone; for maintenance amantadine and mirtazapine. The patient had clinical improvement, physical and cognitive rehabilitation treatment is still ongoing. She has been free of epileptic seizures with magnesium valproate monotherapy, but still shows persistence of anomia, right corporal spastic paresis and sporadic myoclonic movements in both arms. She has not had MS relapses.

DISCUSSION

Natalizumab is a humanized monoclonal antibody that acts against α4β1 and α4β7 subunits of integrins in lymphocytes, blocking the migration of inflammatory cells to CNS, producing a suboptimal immune response thereby prevents MS progression. However, simultaneously a diminished immune response favors commensal microorganisms, such as JCV, to become pathogenic and produce PLM as a complication of the use of natalizumab. PML frequency associated to the use of natalizumab in MS is 1:1000; its mortality up to 20% but high risk of morbidity in survivors (Major *et al.* 2018; Landi el al. 2017).

Clinical manifestations of PML depend of the brain areas involved, however disease or underlying treatment have not been associated to a clinical manifestation; broadly cognitive and behavioral symptoms are the most commonly observed in 30-50% of the patients; abnormalities of motor, gait, language, epileptic seizures and motor incoordination occur less frequently (Maas *et al.* 2016; Berger el al. 2013).

Around 650 cases of PML associated to use of natalizumab have been reported until 2017 and its estimated incidence is 4.2 cases per 1000 patients treated (Schwab *et al.* 2017); the use of Fingolimod and dimethyl fumarate has been associated to lymphocytopenia, but only

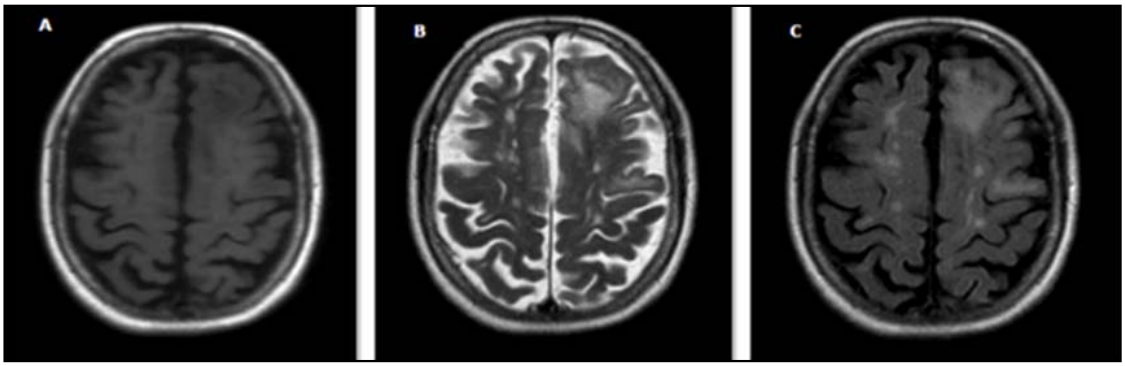

Fig. 1. MRI to two weeks after clinical manifestations began; in axial T1 (A) it observed hypo intense lesion right frontal of diffuses borders, in T2 (B) and FLAIR (C) the same lesion is observed hyper intense.

Tab. 1. Subpopulation of lymphocytes

Sub-population	%	Reference value
CD4	21.88	45 – 56
CD8	18.12	17 – 33
CD3+	41.2	59 – 85
CD2+	52.34	62 – 92
NK	2.2	3 – 7
B CD19+	33.64	3 – 10

Tab. 2. Serum and Cerebrospinal Fluid tests

Serum viral load of JC	589.47 copies/ml
JC virus DNA in CSF	Detectad

in less than 10 cases reported. Lymphocytopenia associated to use of these drugs has not been consistent for predicting PML development; therefore, monitoring the number absolute of lymphocytes has been proposed as better predictor, although, there is not solid evidence to support this practice (Berger, 2017).

Risk factors associated to developing PML in MS patients treated natalizumab include: immunosuppression history, prolonged treatment (> 24 months) and serum antibodies anti-JCV (It's sensitivity > 98% for development of PML but highly nonspecific). It has been observed seroconversion to anti-JCV antibodies in up to 10% of patients treated natalizumab per year, however, it does not mean de novo infection, neither confer an additional risk to develop PML (Berger *et al.* 2013).

Sero-reversion may occur but its meaning is uncertain, however, sero-reversion patients have similar risk to developing PML as to undetectable antibodies patients. Quantitative anti-JCV index could have a greater predictive value to PML development versus qualitative antibody level; from this, a proposal for actuarial tables has been designed as an attempt to stratify patients risk to devolvement PML (Epstein *et al.* 2018).

There is no effective PML treatment associated to use of natalizumab, thereby its indication must be always preceded by a reasonable assessment of benefits versus potential risks in each particular case (McGuigan *et al.* 2016). Determination of serum anti-JCV antibodies before beginning the natalizumab treatment is recommended with repetition every 6 months. If the antibody index is higher than 1.5, risk is high enough to consider stopping medication.

Interestingly, Magnetic Resonance Imaging (MRI) provides an early PML diagnosis, were changes in the brain precede clinical PML manifestations. Serial MRI

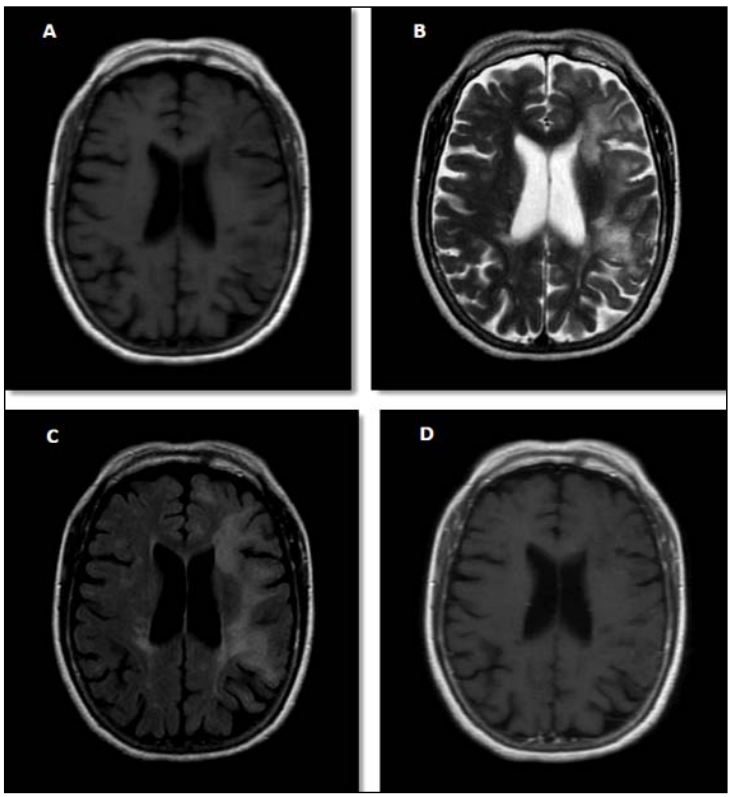

Fig. 2. MRI to four weeks after clinical manifestations began; in axial T1 (A) it observed hypo intense lesion right frontal of diffuses borders it had extension to left hemisphere, in T2 (B) and FLAIR (C) the same lesion is observed hyper intense. (D) Gadolinium is arrested and the lesion enhance

studies are useful for monitoring natalizumab treatment (McGuigan *et al.* 2016). MRI must be performed every 6 months after stopping natalizumab treatment. Radiological patterns can suggest early stage PML: subcortical diffuse lesions (100%), U-fibers involvement, white matter hyper intense lesions in T2 (100%) hypo intense in T1 (94%); well-defined lesions in gray substance and diffuses in white substance (100%) (Harrison *et al.* 2011; Yousry *et al.* 2012). Zhang *et al.* 2018 reported a woman with MS diagnose, natalizumab treated, who development PML with radiological changes without PML clinical manifestations, thereby this report supports the importance of a regular and serial MRI importance in natalizumab treat patients.

There is no effective treatment for PML, (Pavlovic *et al.* 2015; Williamson & Berger, 2017) methylprednisolone pulses have been proposed for immune reconstitution syndrome, (Zhang *et al.* 2018; Giacomini *et al.* 2014) plasmapheresis also has been used however there is no consensus in its usefulness. There are reports of mirtazapin can improvement survivor of these patients. IG immunoglobulin IV has been used in immune reconstitution syndrome but its effectivities is limited (Jamilloux *et al.* 2016). PML patients associated to natalizumab treatment used to survival of 72% at 16.1 months after diagnosis.

Anti-JCV antibody prevalence in MS patients ranged from 47% to 68% across these countries: Norway, 47.4%; Denmark, 52.6%; Israel, 56.6%; France, 57.6%; Italy, 58.3%; Sweden, 59.0%; Germany, 59.1%; Austria, 66.7% and Turkey, 67.7%. It increased with age in 66.5%, in patients of ≥ 60 years of age; it was lower in females than in males and was not affected by prior immunosuppressant or natalizumab use (Olsson *et al.* 2013). Latin America countries were not included in this review and before this report, only a 32 year old man with MS diagnostic, natalizumab treated, whom devolvement PML was reported in Colombia (Triana et. al. 2014). Thereby it could be a lower frequency of this complication in this geographically area or all cases are not reported.

This report on a Mexican woman with PML due to natamiumab treatment, adds to similar reports, and confirms PML as an appalling complication to natalizumab treatment that can occur in different populations regardless of their genetic background. Therefore, it is of utmost importance to take preventive measures in all patients (Calic *et al.* 2015).

CONCLUSIONS

There is a great need for guidelines in management of MS patients, particularly strategies for patients who will be treated with natalizumab, which include: previous determination of anti-JCV Ab, its periodic follow-up; periodical MRI studies once the medication is started, and six months after it is stopped.

REFERENCES

1 Berger JR (2017). Classifying PML risk with disease modifying therapies. Mult Scler Relat Disord. **12**: 59–63
2 Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, SejvarJJ, et al (2013). PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology. **80**: 1430–1438
3 Berger JR, Cree BA, Greenberg B, Hemmer B, Ward BJ, Dong VM, et al (2018). Progressive multifocal leukoencephalopathy after fingolimod treatment. Neurology. **90**: e1815–e1821.
4 Calic Z, Cappelen-Smith C, Hodgkinson SJ, McDougall A, Cuganesan R, Brew BJ (2015). Treatment of progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome with intravenous immunoglobulin in a patient with multiple sclerosis treated with fingolimod after discontinuation of natalizumab. J Clin Neurosci. **22**: 598–600.
5 Epstein DJ, Dunn J, Deresinski S (2018). Infectious Complications of Multiple Sclerosis Therapies: Implications for Screening, Prophylaxis, and Management. Open Forum Infect Dis. **5**: OFY1-18
6 Freedman MF, Selchen D, Prat A, Giacomin PS (2018). Managing Multiple Sclerosis: Treatment Initiation, Modification, and Sequencing. The Canadian Journal of Neurological Sciences. **12**: 1–15.
7 Giacomini PS, Rozenberg A, Metz I, Araujo D, Arbour N, Bar-Or A (2014). Maraviroc in Multiple Sclerosis–Associated PML–IRIS (MIMSAPI) Group. Maraviroc and JC virus-associated immune reconstitution inflammatory syndrome. N Engl J Med. **370**: 486–488.
8 Harrison DM, Newsome SD, Skolasky RL, McArthur JC, Nath A (2011). Immune reconstitution is not a prognostic factor in progressive multifocal leukoencephalopathy. J Neuroimmunol. **238**: 81–86.
9 Horn A, Greene JN (2012). Successful Treatment of Progressive Multifocal Leukoencephalopathy with Interferon. Infectious Disease in Clinical Practice **20**: 345–348.
10 Jamilloux Y, Kerever S, Ferry T, Broussolle C, Honnorat J, Sève P (2016). Treatment of Progressive Multifocal Leukoencephalopathy with Mirtazapine. Clin Drug Investig. **36**: 783–789.
11 Landi D, De Rossi N, Zagaglia S, Scarpazza C, Prosperini L, Albanese M, et al Italian PML study group (2017). No evidence of beneficial effects of plasmapheresis in natalizumab-associated PML. Neurology. **88**:1144–1152.
12 Maas RP, Muller-Hansma AH, Esselink RA, Murk JL, Warnke C, Killestein J, et al (2016). Drug-associated progressive multifocal leukoencephalopathy: a clinical, radiological, and cerebrospinal fluid analysis of 326 cases. J Neurol. **263**: 2004–2021.
13 Major EO, Yousry TA, Clifford DB (2018). Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. Lancet Neurol. **17**: 467–480
14 McGuigan C, Craner M, Guadagno J, Kapoor R, Mazibrada G, Molyneux P, et al (2016). Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry. **87**: 117–125
15 Mills EA, Mao-Draayer Y (2018). Understanding Progressive Multifocal Leukoencephalopathy Risk in Multiple Sclerosis Patients Treated with immunomodulatory Therapies: A Bird's eye view. Front. Immunol. **9**: 1–18.
16 Motte J (2018). Detection of JC virus archetype in cerebrospinal fluid in a MS patient with dimethylfumarate treatment without lymphopenia or signs of PML. Journal of Neurology. **265**: 1880–1882
17 Olsson T, , Achiron A, Alfredsson L, Berger T, Brassat D, Chan A, et. al. (2013). Anti-JC virus antibody prevalence in a multinational multiple sclerosis cohort. Mult Scler **19**: 1533–1538.
18 Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M (2015). Progressive Multifocal Leukeoncephalopathy Consortium. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. Therapeutic Advances in Neurological Disorders. **8**: 255–273.

19 Schwab N, Schneider-Hohendorf T, Melzer N, Cutter G, Wiendl H (2017). Natalizumab-associated PML: challenges with incidence, resulting risk, and risk stratification. Neurology. **88**: 1197–1205
20 Triana JD, Reyes M, Hernández L, Mendoza O, Salgado SA, Becerra GP (2014). Leucoencefalopatía multifocal progresiva asociada al uso de Natalizumab en un paciente con esclerosis múltiple. Primer caso en Latinoamérica. Hospital de San José - Bogotá 2013Acta Neurol Colomb. **30**: 200–220
21 Vargas DL, Tyor WR (2017). Update on disease-modifying therapies for multiple sclerosis. J Investig Med. **65**: 883–891.
22 Williamson EML, Berger JR (2017). Diagnosis and Treatment of Progressive Multifocal leukoencephalopathy Associated with Multiple Sclerosis Therapies. Neurotherapeutics. **14**: 961–973.
23 Yousry TA, Pelletier D, Cadavid D, Gass A, Richert ND, Radue EW, et al (2012). Magnetic resonance imaging pattern in natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. **72**: 779–787
24 Zhang Y, Wright C, Flores A (2018). Asymptomatic progressive multifocal leukoencephalopathy: a case report and review of the literature. Med Case Rep. **12**: 187–191