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Case Report

Progressive Multifocal Leukoencephalopathy and Immune Reconstitution Inflammatory Syndrome after Discontinuation of Fingolimod

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Keywords
Fingolimod · Immune reconstitution inflammatory syndrome · Magnetic resonance imaging · Multiple sclerosis · Progressive multifocal leukoencephalopathy

Abstract
Progressive multifocal leukoencephalopathy (PML) is a rare complication of immunosuppressive treatment in MS patients. Immune reconstitution inflammatory syndrome (IRIS) appears after the withdrawal of certain drugs such as natalizumab (NTZ) or fingolimod. The development of PML-IRIS after NTZ treatment has been described, and its diagnosis is made by clinical and radiological criteria and the determination of the John Cunningham virus in CSF. We present a clinical case of a patient with MS who, after the withdrawal of fingolimod, developed PML-IRIS despite sustained lymphopenia. This is important for pharmacovigilance purposes, not only for NTZ but also for alternative drugs used in MS treatment.

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Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the CNS due to reactivation of John Cunningham virus (JCV). The prevalence is estimated to be around 0.2 cases per 100,000 inhabitants in the general population, increasing in patients who are immunosuppressed by HIV infections or by chronic treatment with immunosuppressants. In 2005, the cases associated with natalizumab (NTZ) appeared in patients with MS [1] or Crohn's disease, and there are currently risk stratification programs and early detection of PML in patients treated with NTZ.

Fingolimod is an oral disease-modifying drug approved for the treatment of relapsing-remitting MS. It modulates the sphingosine-1-phosphate receptor, and it produces a "sequestration" of lymphocytes in lymph nodes, reducing the number of circulating lymphocytes available to enter the CNS, and predisposes to the appearance of bacterial infections (respiratory, nasopharyngeal, and urinary) and viral infections such as herpes zoster virus, in addition to opportunistic infections such as PML [2].

A complication of PML treatment is the development of immune reconstitution inflammatory syndrome (IRIS). It appears weeks or months after withdrawal of immunosuppressant, caused by going from acquired immunodeficiency to a state of immune reconstitution. This leads to an increased transit of $CD4^+$ and $CD8^+$ lymphocytes through the blood-brain barrier, causing excessive cytotoxic damage after activation of T lymphocytes upon contact with cells infected by JCV. Radiologically, an increase in the size of the lesions was observed with edema, mass effect, and gadolinium (Gd) enhancement. The clinical presentation of IRIS is characterized by a neurological worsening of previous deficits as a consequence of the predominant inflammatory phenomena and destruction of neuronal and glial cells [3]. We present a clinical case of PML-IRIS in a patient treated with fingolimod and sustained lymphopenia after its withdrawal.

Case Report

A forty-year-old female has a medical history of lithium-treated bipolar disorder. At 30 years old, she was diagnosed with MS according to McDonald 2010 criteria. Initially, she was treated with Copaxone, but it was suspended due to allergy. Subsequently, treatment with interferon B1a (Rebif) was started, and it was withdrawn due to intense skin reaction and suboptimal response. She begins treatment with fingolimod with good tolerance and analytical controls with persistent lymphopenia (between 250 and 670 lymphocytes/μL) and the last known count being 380 lymphocytes/μL. JCV antibody index value was 2.74. She continued treatment with fingolimod for 4 years with good clinical and radiological control. She had EDSS 2.5 six months before the current income.

Initially, she was admitted for suspected decompensation of the psychiatric process. She was found at home with a low level of consciousness, motor agitation, and a sparse response to stimuli, disoriented, with repetitive and inadequate responses. The family reported behavioral disorder several weeks earlier and abandonment of treatment 2 months earlier.

Neurological examination highlighted preserved state of alertness, without gaze fixation. The spontaneous language was not very fluent, with a tendency to silence. She had tetraparesis with a left predominance and an extensor plantar response. She had decreased left response to painful stimulus.

The laboratory test revealed lymphopenia of 180 lymphocytes/μL, and lymphocyte subpopulations stood out with $CD4^+$ count of 106 lymphocytes/μL, $CD8^+$ count of 85 lymphocytes/μL,

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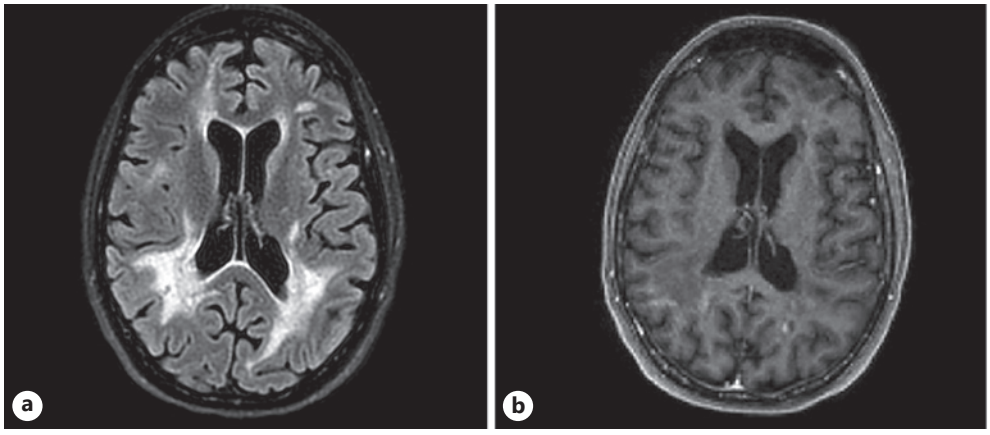

Fig. 1. MRI showing the T2 FLAIR sequence (**a**) extensive lesions in periventricular and subcortical white matter located at frontal and parietal lobes. T1 following Gd administration (**b**) shows peripheral and dotted enhancement of lesions.

and CD19 B lymphocytes count of 95 lymphocytes/μL. The CD4/CD8 ratio was 1.25. Autoimmunity and serology resulted in negative or normal.

Cranial magnetic resonance imaging (Fig. 1a) showed extensive lesions in the white matter of the periventricular and subcortical located at the bilateral periatrial level, around the temporal horns in the lateral ventricles and the frontal lobes. They presented a central zone with hypointense halo, punctate Gd enhancement (Fig. 1b), and an area of peripheral edema. We can see a mild restriction in diffusion at the periphery of some lesions, without mass effect and demyelinating lesions around the fourth ventricle, similar to previous studies. We can see mild restriction in diffusion at the periphery of some lesions, without mass effect and demyelinating lesions around the fourth ventricle, similar to previous studies.

With suspicion of IRIS, treatment with 1 g of methylprednisolone was started. Due to the lack of improvement, plasmapheresis was initiated 4 days after starting corticosteroids. After DNA-JCV detection (113 UI/mL) in CSF, plasmapheresis was stopped after 4 sessions, and treatment was started with mirtazapine 15 mg per day, mefloquine 250 mg per day, and corticosteroids. The patient showed a subsequent progressive clinical and neuroimaging partial improvement. After 2 months, she worsened with the appearance of new CNS lesions on MRI.

Discussion

The incidence of PML in patients treated with fingolimod is infrequent. The majority of PML-IRIS cases occurred after withdrawal of NTZ with positive JCV antibodies [4]. Twenty-one cases of PML have been described in patients treated with fingolimod without previous exposure to NTZ, estimating an incidence of 3.17 (95% CI 2.29–5.67) per 100,000 patients/year, until May 2019 and has been related to the presence of JCV antibodies and the immunosuppression time. There are also published cases of PML in patients taking dimethyl fumarate [5], ocrelizumab, or alemtuzumab [6] without having previously been exposed to NTZ. The association of PML-IRIS with fingolimod is very rare or perhaps not reported due to the lack of information on clinical cases [7, 8]. Four patients with PML-IRIS

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and fingolimod have been reported in association with previous NTZ therapy. It usually appears after normalization of lymphocyte levels, as in the case described by Sinnecker et al. [9], although it may appear with sustained lymphopenia as happened in our case. The diagnosis of PML is not always easy since the initial symptoms can be nonspecific and overlap with the symptoms of a relapse of MS. In our case, in addition, the coexistence of a bipolar disorder caused confusion of the behavioral symptoms of PML with a decompensation of its psychiatric disorder.

Magnetic resonance imaging is essential for the diagnosis of suspected PML, although the difference between PML, IRIS, and new active demyelinating lesions is often controversial. Despite this, Gd uptake patterns, the nature and location of lesions, the presence of a SWI hypointense signal, and echo gradient sequence lesions are more frequent in PML [10].

PML lesions tend to be subcortical with restriction in diffusion images and with Gd enhancement in 40–50% with a variable pattern (linear, nodular, accurate, or peripheral), although we can find more atypical findings that delay their diagnosis. A study has recently been published showing that irregular and dotted contrast enhancement on the periphery of PML lesions suggests more PML-IRIS, appearing in up to 86% of patients treated with NTZ and PML [11].

The low incidence of PML-IRIS with fingolimod may be related to several factors [12]. Plasmapheresis in patients with PML and NTZ predisposes to the development of an early IRIS, with a high morbidity-mortality rate. Rapid elimination of the drug, with faster immune reconstitution kinetics than patients with fingolimod (week-month), could be related to the onset of PML-IRIS. On the other hand, a low level of DNA-VJC in the CSF and slight pathological changes in the CNS can underestimate the cases, and neuroimaging is the most useful and sensitive technique for diagnosis.

In the absence of consensus for the treatment of PML, the use of plasmapheresis, mirtazapine (blocks the entry of the virus into cells), and mefloquine (antireplicative effect of JCV) has been proposed. Intravenous immunoglobulins have been tested in some cases. To avoid IRIS in patients with PML, there are series that use filgrastim as an immunoactivator. For the treatment of IRIS, corticosteroids have been used in high doses and the receptor antagonist CCR5 maraviroc, although the latter has been debated for its usefulness [13]. In our case, we treated her with megadoses of corticosteroids associated with mirtazapine and mefloquine, which had a partial clinical and radiological response.

Conclusions

Diagnosis of PML-IRIS is difficult, especially when immune reconstitution and reactivation of JCV are unclear in patients with fingolimod, without other prior immunosuppressive treatments [14]. Accelerated clinical worsening after cessation of fingolimod with contrast-enhancing MRI lesions may suggest PML-IRIS, even in patients with sustained lymphopenia, as in our case happened. This is important for the pharmacovigilance of the various immunosuppressive treatments used in MS.

Statement of Ethics

Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images. Ethical approval was not required for this study in accordance with local/national guidelines. In

addition, the author confirms that he has accepted the journal's position on issues related to ethical publishing and states that this work is consistent with those guidelines.

Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could represent a potential conflict of interest.

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Author Contributions

R.P.M. and F.J.B.H. have contributed to the conception and design of the work. R.P.M. and M.C.G. have contributed to the acquisition, analysis, and interpretation of data for the work. L.G.R. and F.J.B.H. have contributed to drafting the work and revising it critically. All the authors have approved the version to be published.

Data Availability Statement

The data sets used and/or analyzed during the current study are available from the corresponding author, upon reasonable request. The data are generally not accessible because it contains information that could compromise the privacy of the research participant.

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