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LETTER TO THE EDITORS

Intense immunosuppression for the treatment of an immune reconstitution inflammatory syndrome-like exacerbation after natalizumab withdrawal: a case report

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Dear Sirs,

Immune reconstitution inflammatory syndrome (IRIS) after natalizumab (NTZ) treatment interruption not associated with progressive multifocal leukoencephalopathy (PML) is an uncommon complication [1, 2]. Whereas there are recommendations on how to treat IRIS in the setting of PML [3, 4], the therapeutic approach in its absence is not well defined. We report the use of intense immunosuppression in a patient who failed to the standard recommended therapy, and the remarkable improvement despite the severity of the clinical and MRI manifestations.

A 43-year-old woman diagnosed with relapsing–remitting multiple sclerosis (MS) in 2002, started NTZ infusions in 2008 due to continuing relapses, radiological and disability progression despite previous treatments with glatiramer acetate and β-interferon. During 42 NTZ infusions, the patient improved [Expanded Disability Status Scale (EDSS) 2.0], and did not experience new relapses or MRI activity (Fig. 1a-A). In September 2011, she tested positive for serum JC virus antibodies and declined to continue on NTZ due to concern of PML. Pulses of intravenous methylprednisolone (IVMP) and resuming glatiramer acetate were offered, but patient refused any therapy. Thirteen weeks later (January 2012), she developed a severe visuospatial deficits and cognitive impairment. Brain MRI showed multiple new lesions, some of them with gadolinium enhancement (Fig. 1a-B). JC virus PCR resulted negative in two serial CSF samples. Patient received 3 g of IVMP but few weeks later she developed right hemiparesis and hemineglect (EDSS 5.5). A new MRI (Fig. 1a-C) displayed increased number of enhancing lesions. Despite another 5 g of IVMP, patient's condition worsened leading to tetraparesis (EDSS 9.0) that did not improve after six sessions of plasma exchange (PLEX). A brain MRI showed enlargement of previous lesions with new ones in brainstem and left caudate (Fig. 1a-D). Because of this, we decided to treat her with 1 g of IV cyclophosphamide followed by a cycle of rituximab (1 g administered 2 weeks apart). A month later, the patient's condition improved clinically (EDSS 5.0) and radiologically (Fig. 1a-E–G). In October 2012 her EDSS was 3.0, and in July 2013 patient resumed glatiramer acetate therapy after 16 months of being free of activity.

NTZ constitutes one of the most effective drugs in controlling MS activity. However, NTZ management has become increasingly complex, given the risk of PML and the MS activity return and/or rebound (increase of disease activity beyond pretreatment levels) after NTZ interruption [1, 5]. IRIS, a worsening of neurologic deficits and severe inflammatory changes on neuroimaging during the immune reconstitution, (Fig. 1c: increase in choline/*N*-acetylaspartate, creatine and lactate peak in MR spectroscopy [6]) has been described virtually in all cases of NTZ-associated PML [3, 4]. However, our case and few others [6–8], illustrate that IRIS can develop in the absence of PML. In the context of NTZ-associated PML, the use of PLEX to more rapidly remove NTZ and to speed reconstitution, and

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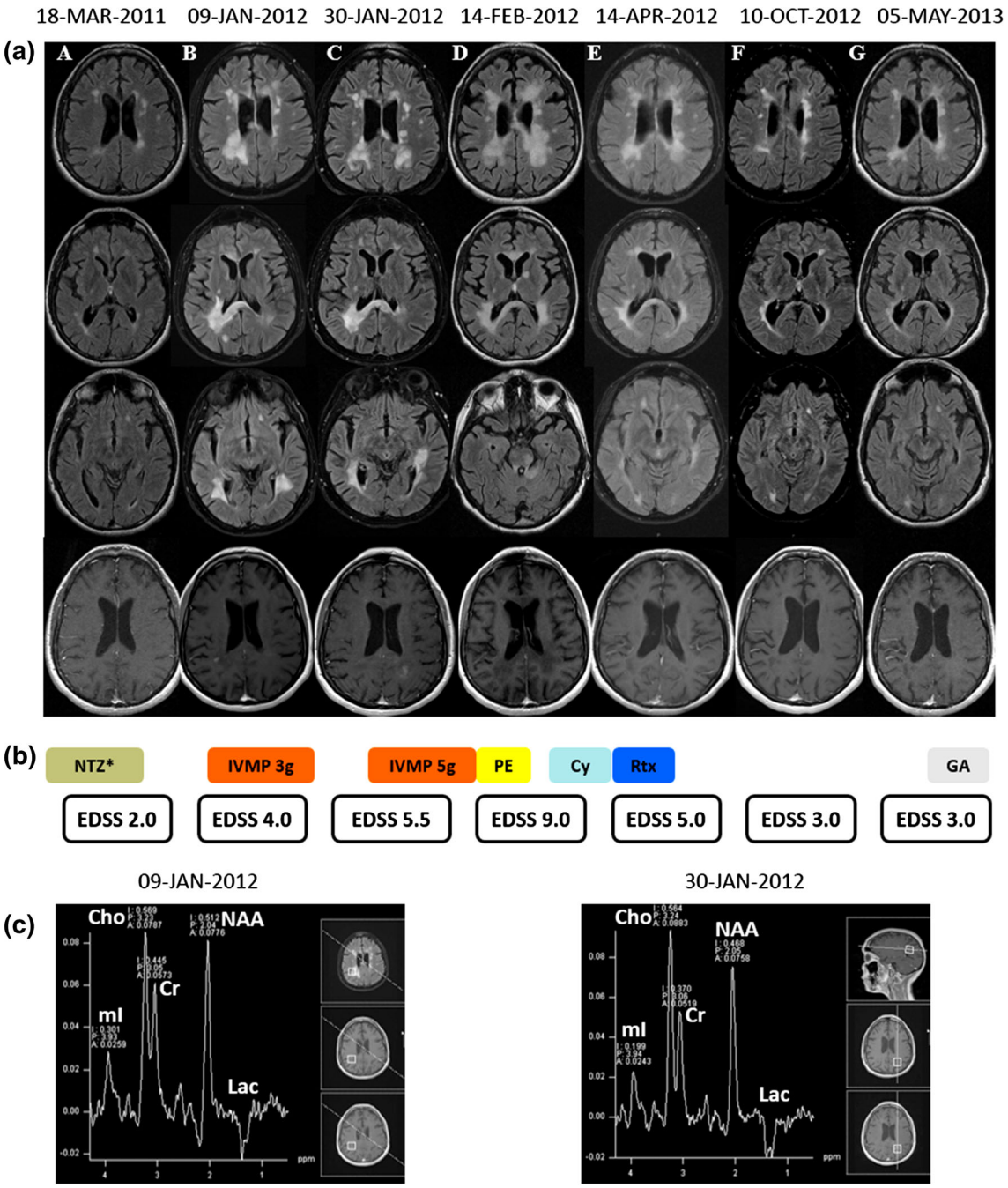

Fig. 1 **a** MRI changes after natalizumab withdrawal. Evolution of atypical brain lesions in FLAIR sequences and T1-weighted after gadolinium (Gd) administration: *A* white matter MS lesions present during NTZ treatment (at dose number 38). *B* Multiple new lesions, some with Gd enhancement. Notice a large periventricular lesion with pseudotumoral morphology in right temporal and parietal lobes extending along the splenium of corpus callosum. *C* Enlargement of a lesion in the left temporal lobe and new gadolinium enhancing lesions. *D* New lesions in brainstem and left caudate. *E–G* Follow-up at 3, 9 and 16 months after the IRIS showing decrease of the size of lesions and absence of gadolinium enhancement. Notice the increase in the ventricular volume in comparison with the first MRI. **b** Time line of disability and treatment approaches. **c** H^1-MR spectroscopy: increase in choline (Cho)/*N*-acetylaspartate (NAA), creatine (Cr) and lactate peak in univoxel spectroscopy centered in large lesions. *Asterisk* last dose NTZ: September 2011, *NTZ* natalizumab, *IVMP* intravenous methylprednisolone, *PE* plasma exchange, *Cy* cyclophosphamide, *Rtx* rituximab, *GA* glatiramer acetate, *EDSS* Expanded Disability Status Scale

high-dose steroids following IRIS development seem to be associated with a better outcome [3, 4]. High-dose steroid treatment has also been frequently used in IRIS cases without PML infection [6–8], but in general associated with worse outcome (from death to moderate-severe neurological deficits). Moreover, it has been suggested that the treatment with PLEX may aggravate IRIS [3, 9]. In our case, given the dramatic evolution, we decided to treat her with an intense immunosuppression similar to that performed as second line immunotherapy in severe autoimmune encephalitis [10], resulting in a remarkable neurological improvement. Nevertheless, different strategies have been used to reduce the risk of disease activity rebound after NTZ discontinuation [11–13], being fingolimod with a short switch period (2 months or less) the more promising one [14, 15]. In the meantime, IRIS can be a serious manifestation related to NTZ treatment interruption and the administration of intense immunosuppression, once PML is ruled out, a therapeutic option for such rapidly worsening condition. The information provided may be useful because controlled trials for this rare complication are unlikely.

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Conflicts of interest Maria Sepúlveda, Sara Llufriu, Yolanda Blanco, Núria Solà-Valls, Delon La Puma and Joan Berenguer report no disclosures. Pablo Villoslada reports having received consultancy fees in the last year from Roche, Novartis and Bionure Incorporation. Albert Saiz has received compensation for consulting services and speaking from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd. and Novartis.

Ethical standards All patients and controls provided written informed consent and the local ethics committee approved the study which has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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