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ORIGINAL ARTICLE

Four cases of natalizumab-related PML: a less severe course in extended interval dosing?

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Abstract

Background Progressive multifocal leukoencephalopathy (PML) is a severe adverse event of natalizumab (NTZ). The administration of NTZ with extended interval dosing (EID) has been proposed as a strategy to potentially reduce the incidence of PML while maintaining its therapeutic efficacy.

Methods In the current paper, we describe 4 cases of NTZ-PML in EID included in the Italian PML cohort.

Results The patients developed PML after at least 38 NTZ infusions. Their John Cunningham virus (JCv) index was > 1.5, and patients had not previously used immunosuppressant. Two patients were asymptomatic at PML onset, while two had mild motor impairment of the right hand and anomia, respectively. All of them had undetectable viral load but one (37 JCv copies/ml). In all patients, MRI revealed unilobar lesions with deferred contrast enhancement suggestive of immune reconstitution. The clinical course ended with a favorable clinical outcome (ΔEDSS up to 1).

Conclusions Although PML in EID seems to occur less frequently than in conventional dosing regimen, strict monitoring of high-risk patients contributed to the indolent course observed in the four described cases, characterized by a prolonged pre-symptomatic phase, paucisymptomatic onset, low JCv load, less severe functional impairment during immune reconstitution, and a mild disability burden.

Keywords Multiple sclerosis · Progressive multifocal leukoencephalopathy · Extended doses regimen · Natalizumab · Early diagnosis

Introduction

Natalizumab (NTZ), a monoclonal antibody used to treat multiple sclerosis (MS), is highly effective in reducing both clinical and radiological MS activity [1]. However, the use of NTZ is limited by its association with progressive multifocal leukoencephalopathy (PML), a lytic infection of oligodendrocytes caused by John Cunningham virus (JCv) [2], which has a severe impact on patients' disability course, functional outcome, and quality of life.

The recognized risk factors for PML include JCv seropositivity, drug exposure length, and previous treatment with immunosuppressant drugs [2, 3]; based on these factors, a risk stratification algorithm was created with the aim to estimate the PML risk for each patient [3]. Although these strategies are supposed to reduce PML insurgence, cases of PML continue to be reported [2]. As the majority of NTZ-treated patients have a high NTZ concentration at the time of re-dosing [4], extended interval dosing (EID; NTZ infusions from every 4 weeks and 3 days to every 8 weeks and 5 days [5]) has been proposed as a strategy to maintain therapeutic efficacy [5] while potentially reducing PML incidence [6]. Compared with conventional dosing, the rationale for EID is to reduce saturation of α4β1 integrin, thereby allowing improved immunesurveillance of the CNS [7]. As few data are actually available on EID efficacy, additional evidences are needed to reach

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definite conclusions. However, data publishes so far are promising [5, 6, 8].

To date, only two NTZ-PML clinical cases involving the EID regimen have been reported [7, 9]. Further description of NTZ-PML events in EID is critical to identify differences in the clinical course, immune reconstitution inflammatory syndrome (IRIS) severity, and outcome compared with cases treated with standard interval dosing (SID; NTZ infusions every 4 weeks [5]).

Methods

In Italy, 56 NTZ-PML cases have been reported up to May 2018. Five of these cases (8.95%) occurred in patients treated with the EID regimen. Clinical and radiological data were stored in a centralized dataset [10]. Here, the clinicoradiological features of four NTZ-PML cases during EID are presented, in accordance with the CARE guidelines [11]. Data were not completely available for the fifth case.

Results

Case 1 was an asymptomatic patient with an occipital lesion, who was tested negative to CSF-JCv by PCR in two consecutive sample. Due to the benign course, the patient refused a third lumbar puncture. Symptoms (phosphenes) emerged during IRIS. Case 2 was an asymptomatic patient with a frontal lesion. JCv DNA copies were undetectable in three consecutive CSF samples and additional lumbar punctures were refused. Retrospectively, the PML lesion was confirmed in an MRI scan performed 3 months prior to diagnosis. The patient remained asymptomatic throughout the disease course, consistent with a small lesion in the frontal non-motor regions [12] and in accordance with the 57.9% of asymptomatic patients previously described [13]. Case 3 was a patient with slight motor impairment of the right hand and a lesion in the left frontal cortex. In the CSF, JCv was undetectable in five consecutive samples. Case 4 was a patient who presented mild anomia, a left temporoparietal lesion, and 37 JCv viral copies/ml in the CSF. Retrospectively, the PML lesion was detectable 4 months prior to the actual diagnosis. Clinical and radiological features are reported in Table 1 and Fig. 1. As case 2 is the most controversial, the longitudinal evolution of the lesion is shown in Fig. 2.

Although case 4 was the only case that met the American Academy of Neurology (AAN) diagnostic criteria for definite PML [14], cases 1–3 met the recently proposed PML diagnostic criteria [15, 16], which are based on the most updated and advanced knowledge of PML evolution over time and its early diagnosis. Interestingly, 17.9% of patients included in the Dutch-Belgian PML cohort were asymptomatic, with no detectable JCv DNA copies in the CSF, similar to cases 1–3 described here. All cases displayed the longitudinal clinical and radiological course expected after a PML diagnosis, and immune reconstitution emerged 2/3 months after the last NTZ infusion, as previously reported [10, 17]. The observed immune reconstitution was compatible with the definition of "full blown" PML-IRIS [10, 17, 18] in cases 1, 3, and 4 as the "wave-like" contrast enhancement or contrast enhancement at the periphery of the PML lesion was coupled with sudden worsening of the clinical condition, manifesting as phosphenes (case 1), impaired movement of one hand and hemianopia (case 3), and clear aphasia (case 4). The immune reconstitution was compatible with the definition of inflammatory reaction to viral infection [17, 18], or physiological immune reconstitution, in case 2, as the contrast enhancement observed on the MRI was not associated with worsening of the patient's clinical condition. "Full-blown" PML-IRIS was treated with high-dose corticosteroid injection.

The MRI surveillance plan was carried out every 3 or 4 months, as all patients had a JCv index > 1.5 and had been treated with NTZ from more than 2 years, consistent with the guidelines [19]. Despite identification of the PML lesions with a delay of 3 and 4 months in patients 2 and 4, respectively, JCv was still undetectable (case 2) or present in a very low quantity (case 4), and these patients remained asymptomatic (case 2) or presented a very mild symptomatology (case 4). Furthermore, none of these patients were submitted to plasma exchange (PLEX) upon PML lesion identification [17].

Discussion

There is growing interest in finding approaches to minimize the risk of PML in patients treated with NTZ. Among these strategies, the administration of NTZ with extended interval dosing (EID) has been shown to maintain therapeutic efficacy [5] while potentially reducing PML incidence [6].

Recent publications pointed out that EID does not prevent PML [6, 7, 9]. We speculate that PML in EID might have a different clinical course and outcome compared with PML in SID, particularly when strict monitoring is maintained. Indeed, recent case reports have hypothesized a more insidious clinical and imaging course for EID than typically seen in NTZ-PML [7, 9], as the diagnostic delay was 3 and 12 months [7, 9] but the viral load at diagnosis was still low (20 and 10 copies/ml, respectively [7, 9]). The PML evolution of the four cases presented here supports this hypothesis, as despite diagnostic delay of 3 and 4 months in two cases, the symptomatology at PML diagnosis was absent or very mild and the JCv load was absent or low. Thus, it is not surprising that in cases with no diagnostic delay (as in our cases 1 and 3), JCv was undetectable. This clearly differs from patients in the Italian cohort treated with SID, as only a small percentage (21.9%) of cases [20] were asymptomatic at PML diagnosis. Furthermore, despite the diagnostic delay, 3 out of 4 EID patients had a unilobar lesion at

Table 1 Demographic and clinical data of the four Italian cases and the cases described in literature

	Case 1	Case 2	Case 3	Case 4	Hervas [7]	Baldassari [9]
Age at PML onset	29	48	33	46	51	53
Gender	♀	♀	♂	♀	♂	♂
Diagnostic delay (months)	0	3	0	4	3	12
Number of NTZ total infusions	74	50	47	38	55**	77**
Number of NTZ infusions in extended dose	22	9	26	22	9**	17**
Extended dose interval (weeks)	7	6	5.5	6	6	6
Prior immune suppression	No	No	No	No	No	n/a
Prior DMT	Interferon fingolimod	Interferon fingolimod	Glatiramer acetate	Interferon fingolimod	Drug-naïve	n/a
Reason for therapy switching to NTZ	Inefficacy	Inefficacy	Inefficacy	Inefficacy	n/a	n/a
JCv index prior to PML onset	3	3.18	2.3	3.13	3.19	2.8
MRI lesion at PML onset	Occipital	Frontal	Frontal (rolandic)	Temporoparietal	Frontal (Broca area)	Frontoparietal
Lesion volume (mm3)	975	554	309	4781	n/a	n/a
JCv DNA copies at PML onset/ml	0	0	0	37	20	10
Symptoms at PML onset	No	No	Motor impairment of the right hand	Very mild anomia*	Aphasia	Paresthesia, aphasia
Anatomo-clinical correlation	n/a	n/a	Yes	Yes	Yes	Yes
EDSS at NTZ beginning	2	3	4	6	3	n/a
EDSS at PML onset	1.5	3	4	6	3**	n/a
Therapies after PML diagnosis	None	None	None	None	Plasma exchange, cidofovir, mirtazapine, mefloquine, proST	Plasma exchange, maraviroc, mirtazapine
Full-blown PML-IRIS	Yes	No	Yes	Yes	Yes	Yes
Symptoms of IRIS	Phosphenes°	n/a	Worsening of the movement of the right hand + hemianopia	Clear aphasia (both production and comprehension)	"Condition deteriorated"	Aphasia worsened
Time from last NTZ and IRIS onset (days)	110	n/a (118)	90	77	30**	30**
Time from PML onset to last follow-up (months)	12	12	12	7	9	n/a
EDSS at last follow-up	2	3	5	6	6	3.0
ΔEDSS	0.5	0	1	0	3**	n/a
Functional outcome	Occasional phosphenes	No impairment	Impaired writing abilities	Mild anomia	n/a	n/a
Post-PML therapy	Glatiramer acetate (GA) for 1 year. Then, rituximab	Glatiramer acetate from 2 years	Glatiramer acetate from 2 years	None so far	n/a	n/a
Number of relapses with the new therapy	1 during GA	2	2	n/a	n/a	n/a

♂ = male; ♀ = female. *DMT* disease modifying therapy; *MRI* magnetic resonance imaging; *EDSS* Expanded Disability Severity Scale; *IRIS* immune reconstitution inflammatory syndrome; *ΔEDSS* difference of EDSS score between PML onset and the last follow-up. The empty circle (°) denotes that the symptom emerged a patient suffering from migraine with visual aura. The asterisk (*) denotes a symptom the patient was not aware of, but revealed at the neuropsychological assessment. Two asterisk (**) denote that the information is not clearly stated in the original paper but it was deduced by the information provided. *n/a* Not available

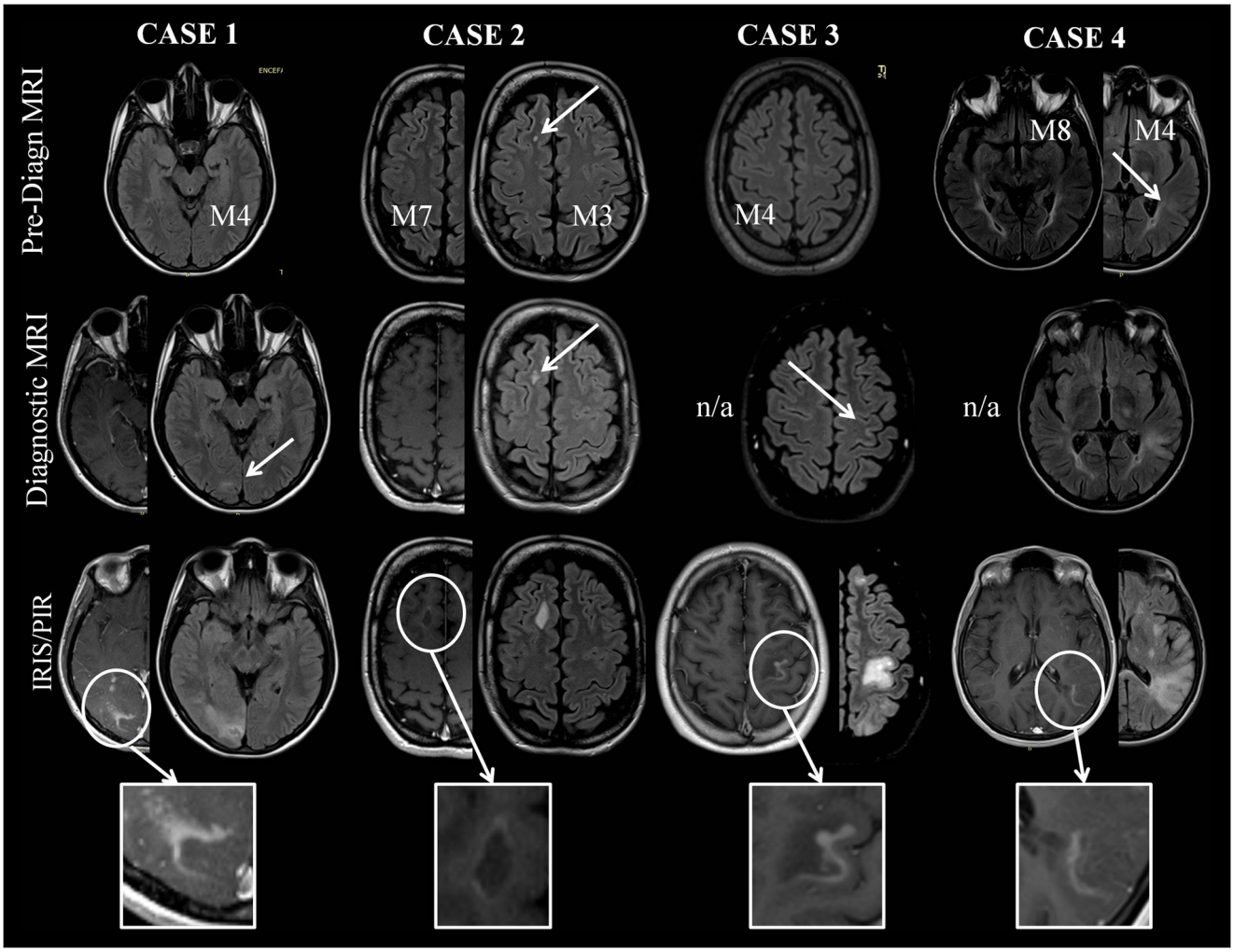

Fig. 1 Radiological evolution of PML the PML lesion in the four cases (columns). Upper line: axial FLAIR images: pre-diagnostic MRI = MRIs prior to the diagnostic one. We presented all MRI defined as the pre-diagnostic as the last one without the possibility PML lesion's identification. The letters and numbers superimposed to each MRI refers to the number of months prior to diagnosis, e.g., M4: MRI performed 4 months prior to PML diagnosis. Middle line: diagnostic MRI = MRI done in concomitance with PML diagnosis. For each patient, both FLAIR (on the right) and GD T1 W (on the left) are reported if available. n/a = not available. Lower line: IRIS/PIR = MRI performed in concomitance with the immune reconstitution both pathological/excessive (IRIS), as in cases 1, 3, and 4, and physiological/expected (PIR), as in case 2. For each patient, both FLAIR (on the right) and GD T1 (on the left) are shown

diagnosis, while only 33% of SID patients had a unilobar lesion at diagnosis [10].

Taken together, these data suggest that the pre-symptomatic phase might be prolonged in these patients, who might manifest clinical symptoms only during "full-blown" PML-IRIS. This raises the interesting hypothesis that JCv replication and spread might be slower or more restrained in EID, as immune surveillance against the virus might be increased compared with conventional interval dosing [7].

In addition, the four patients described in the current paper had a positive outcome, as their disability score increased by up to 1 EDSS point from PML diagnosis to the final follow-up. Comparatively, only 38% of patients in the total Italian PML cohort had an increase in disability score up to 1 EDSS point, while the remaining patients accumulated more than 2 EDSS points [10]. The frequent MRI surveillance probably contributed to early detection of the PML lesion.

Moreover, the insurgence of full-blown IRIS did not severely affect the longitudinal disability score. Indeed, although the clinical manifestation of IRIS was sudden, abrupt, and acute according to the definition [17], it was not characterized by the severity observed in the Italian SID cohort [10]. We speculate that EID might lead to reduced saturation of NTZ receptors, allowing for a greater migration of CD4 and CD8 T cells into the CNS, a crucial element to control the lysis of JCv-infected oligodendrocytes. The increased immune surveillance and associated reduction in antigen burden might have contributed to the decreased IRIS severity.

A strict comparison of outcome of these four cases and previously described EID cases is not possible as the four

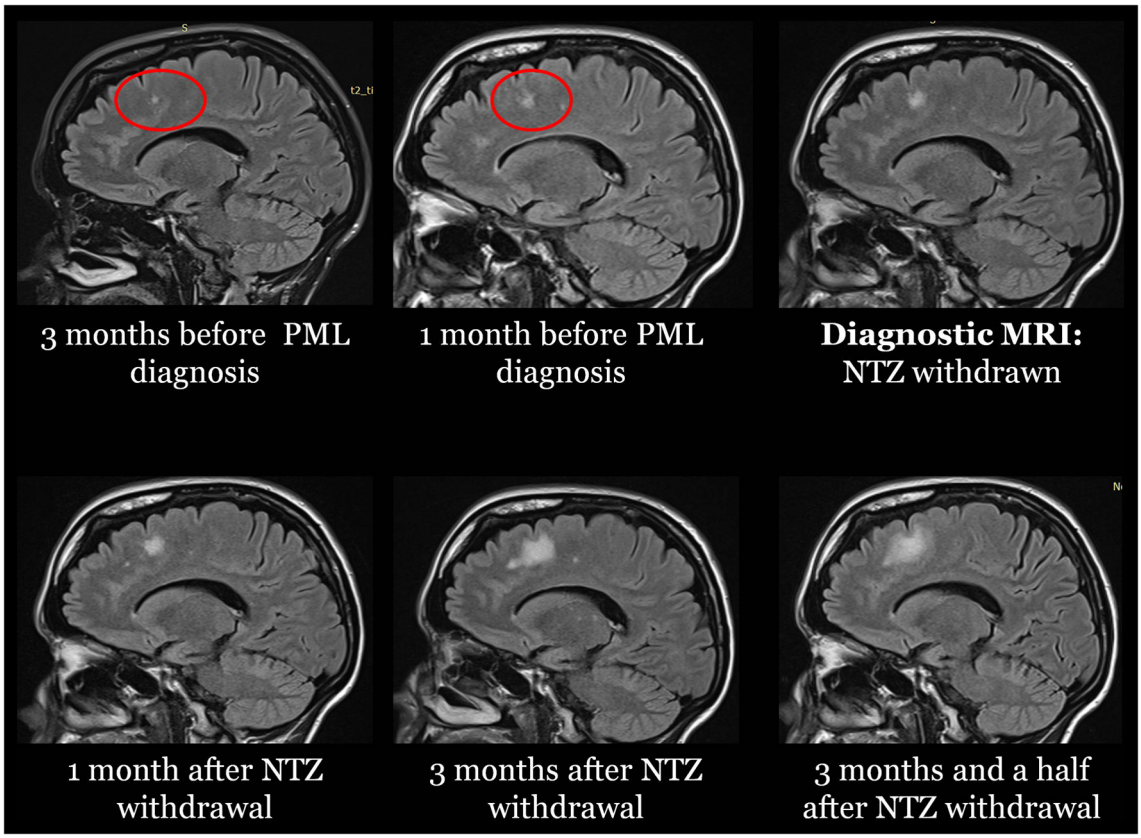

Fig. 2 Longitudinal lesion evolution for patient 2. Radiological evolution of PML lesion of patient 2. FLAIR images are reported. Three months before the diagnosis of PML, the PML lesion was already evident but was undetected, as reported in the main text. One month before PML diagnosis, the lesion was detected and neuroradiologists indicated the presence of a suspected lesion. Diagnostic MRI was performed to follow up on this lesion, and PML was recognized. The following MRIs were performed to strictly follow up on the radiological evolution of the PML lesion

Italian patients were only treated with high-dose IV corticosteroids once full blown PML-IRIS emerged, whereas the patients described by Hervas [7] and Baldassari [9] received PLEX shortly after PML diagnosis. This difference might have contributed to the positive outcome in the four cases described here, as PLEX could potentially increase IRIS damage [17] and it does not improve survival or clinical outcomes [17, 21].

This paper described four cases of EID-PML. Basing on the longitudinal clinical evolution of these four cases and the two already described in the literature, we speculate that EID might contribute to a more indolent PML presentation, prolonging the pre-symptomatic phase and reducing viral replication, possibly due to more effective immune surveillance in EID compared with SID. This would, in turn, have a positive impact on IRIS severity and on patients' functional prognosis and outcome. This hypothesis merits further investigation. Furthermore, therapeutic alternatives to NTZ are now available [22]. As these therapies are characterized by a good efficacy and a virtually absent risk of PML, they should be carefully considered in patients treated with NTZ and at high risk to develop PML. However, these new therapies might have potential adverse events other than PML that are still unknown, as long-term consequences could have not been completely elucidated during phase III clinical trials [23, 24].

In conclusion, although there are now some emerging publications suggesting that the EID regimen might be associated with lower PML risk compared to SID [6], pharmacovigilance should be maintained. As the PML diagnostic criteria are currently being revised [16], it is of extreme importance to enrich the literature with reports of cases emerging during EID and with description of cases hampering the classical PML diagnostic criteria.

Authors' contributions Conceived the study: CS, RC. Collected the data: CS, GT, NDR, MVT. Analyzed the data: CS, SG, RC. Critically reviewed the data: GT, NDR, MVT. Drafted the manuscript: CS, RC. Critically reviewed the manuscript: GT, NDR, MVT. All the authors approved the final version of the manuscript.

Compliance with ethical standards

Ethical standards This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients provided written informed consent for the publication of data. Retrospective analysis of patients' data was approved by the ethical committee of the Spedali Civili of Brescia.

Conflict of interest Dr. Scarpazza, Dr. Tabiadon, and Dr. Turrini have no conflicts of interest. Dr. De Rossi received consulting fees from Biogen, Merk-Serono, and Genzyme. Dr. Gerevini declares consulting fees or honorarium from Novartis and Biogen and payment for lectures including service on speaker bureaus from Novartis and Biogen. Dr. Capra received payment for lectures from Novartis, Biogen, and Genzyme.

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