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Natalizumab-Associated Progressive Multifocal Leukoencephalopathy After Natalizumab Extended Interval Dosing Therapy in Japan

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Abstract

Objective

To describe 5 confirmed cases of natalizumab-associated progressive multifocal leukoencephalopathy (NTZ-PML) in Japan.

Methods

The Nationwide PML Surveillance Committee requires mandatory registration of all natalizumab cases and reporting by affiliated facilities conducting JC DNA testing. Suspected PML cases were reviewed by the committee and classified as definite, probable, possible, or non-PML based on established diagnostic criteria.

Results

From 2016 to 2024, the nationwide PML surveillance committee identified 8 NTZ-PML cases, of which 5 (all women and relapsing-remitting types) were registered as clinically definite PML cases. Four cases involved a switch from other disease-modifying drugs, while one involved natalizumab as the first-line treatment for multiple sclerosis (MS). In all cases, extended interval dosing therapy (EID) every 6–8 weeks was administered for at least 1 year before PML onset, and 3 cases had received EID from the outset. At PML onset, the viral DNA levels in the CSF were ≤100 copies/mL in 3 cases.

Discussion

Given the high prevalence of JC virus antibody positivity in Japan, additional risk factors may contribute to NTZ-PML susceptibility. Although EID of natalizumab is expected to reduce PML risk, its effectiveness may be limited, particularly in Japanese individuals with high JC virus antibody titers.

Introduction

Natalizumab is highly effective in preventing relapses in multiple sclerosis (MS)[1]; however, natalizumab-associated progressive multifocal leukoencephalopathy (NTZ-PML) is a concern.[2] Recently, an extended interval dosing (EID) regimen, involving natalizumab administration every 6–8 weeks, has been introduced to reduce the risk of NTZ-PML without compromising therapeutic efficacy.[2,3]

In Japan, the Japanese PML Surveillance Committee's nationwide surveillance has identified 8 confirmed cases of NTZ-PML between September 2016 and the end of 2024, 5 of which were

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classified as clinically definite cases.[4,5] We aimed to elucidate the clinical characteristics of those 5 clinically definite NTZ-PML cases.

Methods

Nationwide PML Surveillance Committee

The Nationwide PML Surveillance Committee's reports follow 2 pathways. The first involves mandatory registration of all natalizumab cases in Japan. Suspected PML cases are reported to a pharmaceutical company, which informs the PML Surveillance Committee. The second involves facilities affiliated with committee members, where JC DNA testing is conducted. The PML Surveillance Committee is notified on receiving the test request.

When a suspected PML case is reported through either pathway, the attending physician is asked to support surveillance by obtaining the patient's written informed consent for data sharing, which the committee reviews to confirm the diagnosis.

Diagnostic Criteria for PML

The PML diagnostic criteria are (1) subacute progressive neurologic symptoms, (2) characteristic imaging findings of PML, (3) detection of JC virus DNA in the CSF, and (4) exclusion of other diseases. Cases are classified as definite PML, probable PML, possible PML, or non-PML based on these.

By the end of 2024, the committee had confirmed 8 cases of NTZ-PML, among which 5 were registered as clinically definite cases that met all 4 criteria, and no probable or possible cases.

Information From the Patient Sheets

Data collected included age at PML onset, sex, type of MS, EDSS score before PML onset, prenatalizumab treatment, dosing interval, CSF cell count, JC DNA levels, peripheral blood IgG concentration, peripheral blood lymphocyte count, JC antibody titers, MRI lesion locations, clinical symptoms, and outcome information.

Institutional Review Board Statement

This study was approved by the Institutional Review Board (IRB) at the Jichi Medical University (Rindai 17–162) and Iou National Hospital (Iou 2024-25).

Data Availability

Anonymized data will be shared on request to the corresponding author.

Results

Baseline Characteristics

All 5 confirmed cases were women. At the onset of NTZ-PML, one patient was in her 40s and 4 patients were in their 50s. The MS subtype relapsed and remitted in all cases. MS duration was ≥16 years, except for one case of ≤5 years. Prior MS treatments before NTZ administration included interferon beta 1a (IFNb1a) in 2 cases, fingolimod (FNG) in one, a switch from IFNb1a to FNG (for 2 months) in one, and initial treatment with NTZ in another case. One patient was administered azathioprine for 1 year before NTZ treatment (Table 1).

The interval between NTZ doses, including cases initially managed with standard interval dosing therapy every 4 weeks (1–8 years), was extended to >6 weeks in all patients for at least 1 year (2–5 years) before NTZ-PML onset.

Virologic Characteristics

All patients were JC virus antibody-positive at natalizumab initiation, with 3 showing high titers (index ≥3.0). In two of these, serial measurements revealed increases from baseline. At PML onset, 4 patients had high antibody titers (index ≥3.0). At PML diagnosis, JC virus DNA in the CSF was <1,000 copies/mL in all cases, with 3 cases showing levels <100 copies/mL, as measured by an ultrasensitive PCR assay (lower detection limit: 10 copies/mL) (Table 1).

MRI Findings

Some patients had an interval of >6 months between the MRI study. The last MRI study before NTZ-PML onset was performed 1–10 months prior. In some cases, a retrospective review by the committee identified NTZ-PML lesions based on the final preonset MRI finding that had previously been interpreted as no NTZ-PML lesions (Table 1).

NTZ-PML Characteristic

The EDSS scores before NTZ-PML onset ranged from 1.0 to 6.0, with half of the cases having scores ≥4.0, indicating moderate-to-severe disability. The clinical manifestations of PML included muscle weakness in 4 cases, ataxia in one, and visual disturbances in one. No patient had abnormal CSF lymphocyte counts at NTZ-PML onset. MRI revealed cerebral white matter lesions in all cases, thalamic lesions in three, and brainstem lesions in one. Contrast-enhanced gadolinium lesions were observed at PML onset in one case. After discontinuation of natalizumab treatment, 2 cases developed immune reconstruction inflammatory syndrome. Mirtazapine and mefloquine were used as therapeutic agents for PML in 2 cases; however, no clinical improvement was observed. At the final follow-up, the EDSS ranged from 6.0 to 9.0 (Table 1).

Discussion

As of February 2024, natalizumab has been administered to over 260,000 individuals worldwide, with 927 cases of NTZ-PML reported.[9] The overall risk of developing NTZ-PML is 3.43 cases per 1,000 natalizumab-treated patients.[9] Prior use of immunosuppressive agents and elevated JC virus antibody titers may increase the risk of PML[10]; however, the adoption of EID therapy is expected to significantly reduce this risk, and

Table 1 Clinical Information[4-8]

	Total (n = 5)
Age at PML onset (y)	
40–49	1
50–59	4
Sex, female	5
MS type	
RRMS	5
SPMS	0
PPMS	0
MS duration at PML onset (y)	
0–5	1
6–10	0
11–15	0
16–20	2
>21	2
EDSS pre-PML	
0–3.5	2
4.0–6.0	2
6.5–	1
EDSS post-PML	
0–3.5	0
4.0–6.0	1
6.5–	4
Prior MS therapy	
GA, IFN	2
DMF	0
FNG	2
Ofatumumab	0
Non	1
Prior use of immunosuppressive agents	1 (AZA)
NTZ interval	
SID	0
SID→EID	2
EID	3
Duration of NTZ infusions (m)	
0–24	0
25–48	2
49–72	1
≥73	2
Clinical symptom at PML	Muscle weakness (4), ataxia (1)
Anti-JC virus index at the start of NTZ treatment	
Negative	0
Positive <1.0	1
1.0–1.99	0
2.0–2.99	1
≥3.0	3
Lymphocyte number in the peripheral blood at PML onset	
≤1,000	0
>1,000	5
Serum IgG concentration at PML onset	
≤700	1
701–999	2
≥1,000	2
CSF cell number at PML onset	
<5	5
≥5	0
CSF protein concentration at PML onset	
<40	4
≥40	1
JC virus DNA copy number in the CSF at PML onset (copies/mL)	
<100	3
100–999	2
≥1,000	0
Location of PML lesion	
Cerebral white matter	5
Thalamus	3
Brainstem	1
Cerebellum	0
PML treatment	
Mirtazapine + mefloquine	2
None	3

Abbreviations: AZA = azathioprine; DMF = dimethyl fumarate; EDSS = expanded disability status score; EID = extended interval dosing; FNG = fingolimod; GA = glatiramer acetate; IFN = interferon; NAT = natalizumab; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive MS; RRMS = relapsing-remitting MS; SID = standard interval dosing; SPMS = secondary progressive MS.

many natalizumab-treated patients are now receiving this therapeutic approach.[3,11,12]

In Japan, all patients receiving natalizumab are registered, with approximately 2,000 individuals listed by the Biogen Corporation as of the end of November 2023. To date, 8 cases of NTZ-PML have been confirmed in Japan, corresponding to an estimated risk of approximately 4 cases of NTZ-PML per 1,000 natalizumab-treated patients, which is consistent with global reports. Notably, all 5 clinically definite PML cases registered by the nationwide PML surveillance committee in Japan underwent EID therapy. Following the study by Ryerson et al., the efficacy of EID became widely recognized. Thus, patients starting natalizumab therapy after 2019 were likely initiated on EID.[3] As natalizumab became commercially available in Japan only in 2014, SID use was likely limited to clinical trials or early postmarketing. Many of these early patients may have subsequently transitioned to EID. Had SID been more prevalent, PML risk in Japan might have been higher. Nevertheless, the observed PML incidence—over 2.5 per 1,000 patients—suggests that the EID-associated risk reduction reported by Ryerson et al.[3] (<10% of SID) may have been less pronounced in the Japanese cohort.

All 5 patients who developed PML were exposed to natalizumab for >2 years—a known risk factor for PML—although only one patient had a history of immunosuppressive therapy. A high proportion of Japanese individuals are known to be JC virus antibody-positive.[13] Before developing PML, 4 of the 5 patients had high JC virus antibody titers of >3.0. Notably, Japan has a disproportionately high number of fingolimod-associated PML cases.[6] Since the clinical features of NTZ-PML are consistent across Japan and other countries, Japanese individuals are hypothesized to be more susceptible to developing PML. The higher prevalence of JC antibody positivity and other unidentified risk factors specific to the Japanese population could have increased the risk of NTZ-PML.

Conversely, in 2 of 5 NTZ-PML cases, lesions were retrospectively identified on MRI performed before the onset of clinical symptoms. NTZ-PML diagnosis before symptom manifestation is crucial for improving prognosis. Therefore, frequent MRI examinations and advancements in imaging accuracy are essential.

Limitations

We used data from patient sheets completed by the attending physicians. Consequently, variations in the quantity and quality of information among cases hinder the acquisition of detailed data and objective evaluations.

Conclusion

The clinical symptoms of NTZ-PML were consistent with those reported previously. Although natalizumab EID is expected to lower the risk of developing PML, its effectiveness may be limited, particularly in Japanese individuals with high JC virus antibody titers.[7,8]

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Author Contributions

K. Takahashi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. J. Nakahara: analysis or interpretation of data. Y. Miura: analysis or interpretation of data. R. Ae: analysis or interpretation of data. K. Nakamichi: major role in the acquisition of data. M. Harada: major role in the acquisition of data. K. Mori: major role in the acquisition of data. N. Sanjo: analysis or interpretation of data. M. Yukitake: analysis or interpretation of data. H. Yokote: analysis or interpretation of data. T. Hamaguchi: analysis or interpretation of data. M. Yamada: analysis or interpretation of data. M. Takao: analysis or interpretation of data.

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Disclosure

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References

1. Jakimovski D, Bittner S, Zivadinov R, et al. Multiple sclerosis. *Lancet*. 2024; 403(10422):183-202. doi:10.1016/S0140-6736(23)01473-3
2. Rindi LV, Zaçe D, Braccialarghe N, et al. Drug-induced progressive multifocal leukoencephalopathy (PML): a systematic review and meta-analysis. *Drug Saf*. 2024; 47(4):333-354. doi:10.1007/s40264-023-01383-4
3. Ryerson LZ, Foley J, Chang I, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology*. 2019;93(15): e1452-e1462. doi:10.1212/WNL.0000000000008243

4. Sugimoto T, Neshige S, Aoki S, et al. A case of natalizumab-associated progressive multifocal leukoencephalopathy followed by immune reconstitution inflammatory syndrome with difficulty in the timing of immunotherapy. *Clin Exp Neuroimmunol*. 2023;14(2):110-115. doi:10.1111/cen3.12734
5. Yokote H, Mori K, Nakamichi K, Matsuda T, Miura Y. Global hyperperfusion in the brain at onset of the immune reconstitution inflammatory syndrome in a patient with natalizumab-associated PML. *Neurology*. 2024;103(7):e209874. doi:10.1212/WNL.0000000000209874
6. Nakahara J, Tomaske L, Kume K, et al. Three cases of non-carryover fingolimod-PML: is the risk in Japan increased? *Neurol Neuroimmunol Neuroinflamm*. 2019;6(3):e559. doi:10.1212/NXI.0000000000000559
7. Tanaka M. Presented at 65th Annual Meeting of the Japanese Society of Neurology. 2024. Pj-013-2 (Japanese).
8. Oiwa H Neuroinfection. 2022;27(2):212. Abstract at 26th Annual Meeting of the Japanese Society of Neuroinfection. 2022. A7-03 (Japanese).
9. BiogenLinc. Accessed December 17, 2024. biogenlinc.jp/ja/products/tysabri/risk01/
10. Moser T, Zimmermann G, Baumgartner A, et al. Long-term outcome of natalizumab-associated progressive multifocal leukoencephalopathy in Austria: a nationwide retrospective study. *J Neurol*. 2024;271(1):374-385. doi:10.1007/s00415-023-11924-7
11. Rabea EM, Belal MM, Hafez AH, et al. Safety and efficacy of extended versus standard interval dosing of natalizumab in multiple sclerosis patients: a systematic review and meta-analysis. *Acta Neurol Belg*. 2024;124(2):407-417. doi:10.1007/s13760-024-02480-6
12. Foley JF, Defer G, Ryerson LZ, et al.; NOVA study investigators. Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. *Lancet Neurol*. 2022;21(7):608-619. doi:10.1016/S1474-4422(22)00143-0
13. Watanabe M, Nakamura Y, Isobe N, et al. Two susceptible HLA-DRB1 alleles for multiple sclerosis differentially regulate anti-JC virus antibody serostatus along with fingolimod. *J Neuroinflammation*. 2020;17(1):206. doi:10.1186/s12974-020-01865-7