

# Tumefactive demyelination with a transient appearance of oligoclonal bands in MS under fingolimod

Kazumasa Okada, MD, PhD, Tomoyo Hashimoto, MD, PhD, Masako Kobata, MD, Shingo Kakeda, MD, PhD, Toshiyuki Takahashi, MD, PhD, and Junko Hirato, MD, PhD

## Correspondence

Dr. Okada  
gion@med.uoeh-u.ac.jp

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Fingolimod is a structural analog to sphingosine and acts as a functional antagonist for the sphingosine-1-phosphate receptor, exerting disease-modifying effects in MS by trapping lymphocytes in lymph nodes.<sup>1</sup> Patients with MS have been rarely reported to develop tumefactive demyelinating lesions (TDLs) during fingolimod therapy, especially within the early period following the initiation of treatment.<sup>1</sup> It has been speculated that alterations in the population of immune cells during fingolimod therapy may lead to TDLs.<sup>2</sup>

## Case

A 50-year-old, right-handed woman with relapsing-remitting MS (RRMS) was admitted to our hospital because of difficulty conversing and performing activities of daily living (ADLs). She first presented with a brainstem lesion at the age of 31 years, following which she was diagnosed with RRMS on the appearance of a thoracic cord lesion at the age of 40 years. Anti-aquaporin 4 (AQP4) antibody and other autoantibodies associated with collagen vascular diseases were not detected. CSF was negative for oligoclonal bands (OCBs). Interferon- $\beta$  treatment was promptly initiated following diagnosis but was ceased because of symptoms of depression. She experienced 2 independent bouts in the cervical cord and pons, following which she was referred to us at the age of 46 years. She remained free of relapses after the introduction of fingolimod in February 2013. However, she was admitted to our hospital in August 2016 because of difficulty with conversation and ADLs, which were accompanied by mild weakness in the right hand.

Neurologic examination revealed motor aphasia, ideational apraxia, and moderate right hemiparesis accompanied by mild weakness of the right facial muscles. Tendon reflexes were exaggerated in the right extremities. Babinski signs were not detected. CSF examination revealed mild elevation of protein levels (61.0 mg/dL) without pleocytosis. Typical OCBs were positive at this time. Serum AQP4 and anti-myelin oligodendrocyte glycoprotein antibodies were negative. The patient tested positive for serum anti-John Cunningham virus antibodies but not in the CSF. Contrast-enhanced MRI revealed a massive lesion in the white matter of the left hemisphere (figure). The lesion was biopsied to exclude the possibility of CNS lymphoma and progressive multifocal leukoencephalopathy (PML). Histopathologic analysis revealed inflammatory demyelination accompanied by parenchymal inflammatory infiltrates and perivascular cuffing (figure). Components of the perivascular lymphocytic cuffing were predominantly CD8-positive cytotoxic T lymphocytes and CD4-positive helper T cells, with relatively fewer B cells. Thus, both lymphoma and PML were excluded.

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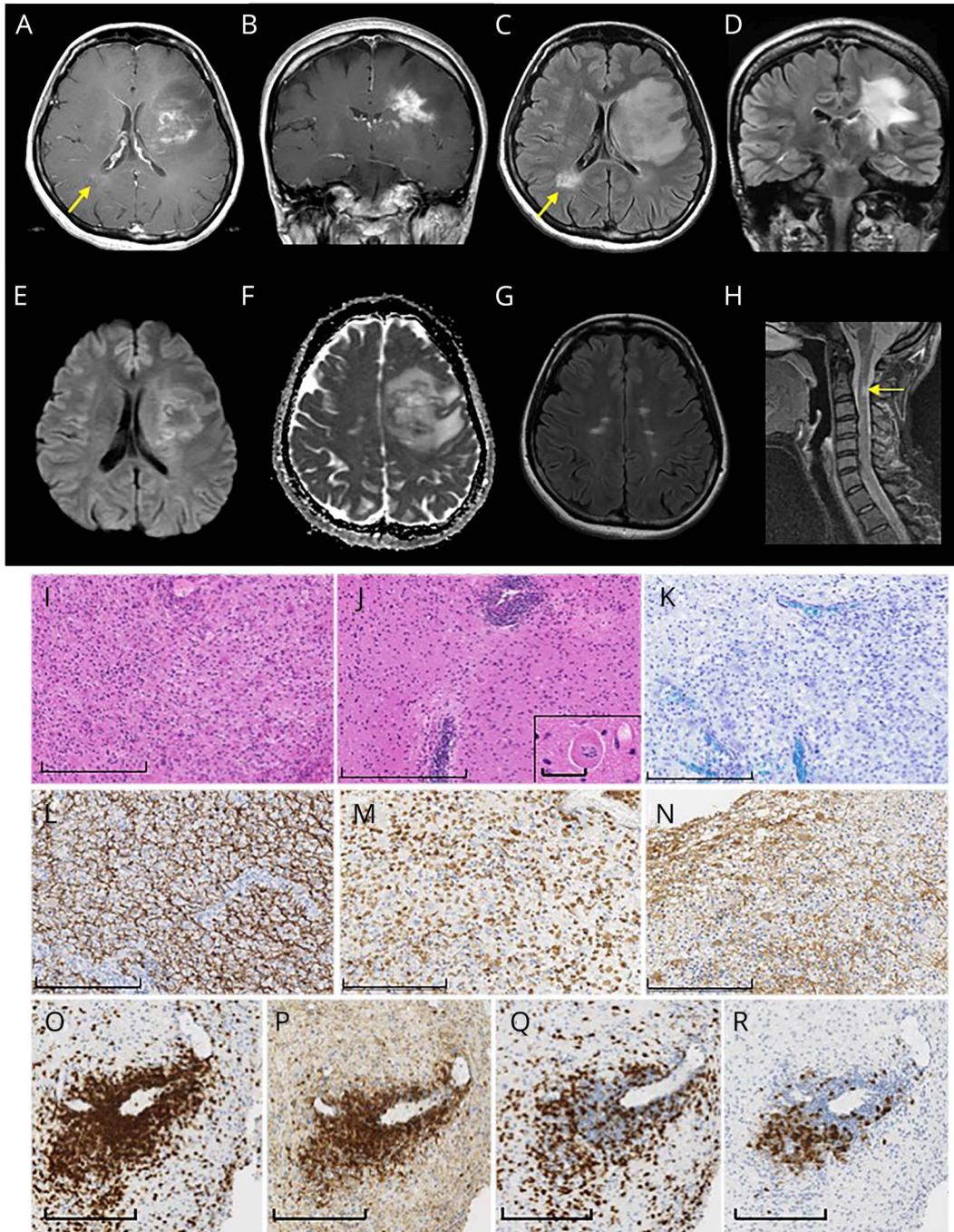
From the Department of Neurology (K.O., T.H., M.K.), and the Department of Radiology (S.K.), University of Occupational and Environmental Health School of Medicine, Kitakyushu, Japan; the Department of Neurology (T.T.), Tohoku University Graduate School of Medicine, Sendai, Japan; the Department of Neurology (T.T.), Yonezawa National Hospital, Yamagata, Japan; and the Department of Pathology (J.H.), Gunma University Hospital, Maebashi, Maebashi, Japan.

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**Figure** MRI and neuropathologic characteristics of the tumefactive demyelinating lesion in our patient



T1-weighted imaging revealed a nodular and linear enhancement with gadolinium in the center of the lesion (A and B). FLAIR imaging revealed an extensive hemispheric white matter lesion with a mass effect in the left fronto-parieto-temporal lobe (C and D). The high-intensity lesion observed on FLAIR images appeared as a lesion of slightly lower signal intensity on diffusion-weighted images (E) and exhibited an increased apparent diffusion coefficient value (F), suggestive of vasogenic edema. An existing periventricular lesion was detected in the right posterior ventricular horn without gadolinium enhancement (A, C, arrow). FLAIR imaging of the brain (G) and T2-weighted imaging of the cervical cord (H) before TDL development showed typical MS lesions (arrow indicates a cervical lesion). We performed a biopsy of the enhanced lesion. Parenchymal inflammatory infiltrates were invariably present and were accompanied by foamy macrophages and reactive astrocytes (I). Perivascular lymphocytic cuffing and Creutzfeldt-Peters cells (inset) were also observed (hematoxylin and eosin stain, scale bar = 300  $\mu$ m, inset scale bar = 25  $\mu$ m) (J). Demyelination was observed as a loss of Luxol fast blue staining (Klüver-Barrera stain, scale bar = 200  $\mu$ m) (K). Relative axonal preservation (IHC stain for neurofilaments, scale bar = 200  $\mu$ m) (L). Extensive macrophage infiltration presenting with lipid-laden foamy macrophages (IHC for CD68, scale bar = 200  $\mu$ m) (M). Relative glial fibrillary acidic protein preservation within the TDL (IHC for GFAP scale bar = 200  $\mu$ m) (N). Continuous sections of the perivascular lymphocytic cuffing lesion (O: IHC for CD3; P: IHC for CD8; Q: IHC for CD4; R: IHC for CD20, scale bar = 200  $\mu$ m). Inflammatory infiltrates were composed of lymphocytes (O), most of which were CD8-positive cytotoxic T lymphocytes (P). Scattered CD4-positive helper T cells (Q) and relatively fewer B cells were observed (R). CD4-positive T lymphocytes tended to accumulate predominantly in the parenchymal tissue (Q). FLAIR = fluid-attenuated inversion recovery; IHC = immunohistochemical; TDL = tumefactive demyelinating lesion.

Two months after IV methylprednisolone and plasma exchange therapy, her symptoms gradually improved such that she was able to speak fluently and perform ADLs with little trouble, although she exhibited mild difficulty with word recall. Non-contrast-enhanced MRI revealed that the lesion had shrunk, and CSF analysis was normal. The patient again exhibited negative OCB findings.

## Discussion

The precise mechanisms underlying the development of fingolimod-induced TDLs in patients with MS remain to be elucidated. Recent reports have suggested that fingolimod alters the population of immune cells and may cause paradoxical augmentation of disease activity in some patients with MS.<sup>3–5</sup> Pilz et al.<sup>2</sup> reported that effector CD8<sup>+</sup> T cells were enriched in the CSF of a patient with MS who developed a TDL, speculating that effector CD8<sup>+</sup> T cells had an increased propensity to migrate into the CNS.

Of interest, in our patient, OCB findings transitioned from negative to positive following the development of the TDL, again returning to negative after TDL resolution and the withdrawal of fingolimod. This finding suggests that, in our patient, the TDL was associated with the activation of antibody-producing cells, such as plasmablasts. Our patient's case was consistent with a previous case involving TDL with positive OCB conversion and upregulation of the B-cell population in CSF.<sup>6</sup> A recent study demonstrated that fingolimod increases serum levels of B cell-activating factor of the tumor necrosis factor family, which aids in the development of mature B cells and maintains antibody-producing cells.<sup>5</sup> Additional studies have revealed that the proportion of activated plasmablasts is increased in the peripheral blood of the patients with MS undergoing fingolimod therapy.<sup>7</sup> These studies suggest the possibility that fingolimod activates and maintains antibody-producing cells under particular circumstances.

Although there is much debate surrounding the underlying immunologic mechanisms, we speculate that fingolimod-induced TDL was associated with B-cell activation in our patient. Because TDLs more often develop in MS without OCBs, negative OCBs possibly indicate a propensity to develop TDLs with fingolimod therapy.<sup>1</sup> Further studies are

required to determine whether B-cell lineage plays a role in the induction of TDLs, or whether patients at risk for TDLs exhibit unique B-cell characteristics. Finally, patients should be closely monitored for TDLs when fingolimod is used.

## Author contributions

Dr. K. Okada: conceptualization and design of the study, analysis and interpretation, study supervision, and manuscript drafting. Dr. T. Hashimoto: acquisition of data, pathologic analysis, and revision of the manuscript for important intellectual content. Dr. M. Kobata: acquisition and analysis of clinical data and preparation of the manuscript. Dr. S. Kakeda: acquisition and analysis of the MRI study and revision of the manuscript for important intellectual content. Dr. T. Takahashi: laboratory assay and data analysis and revision of the manuscript for important intellectual content. Dr. J. Hirato: pathologic analysis and revision of the manuscript for important intellectual content.

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