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Case report

Fingolimod-induced leukoencephalopathy in a patient with neuromyelitis optica spectrum disorder

Fumihito Yoshii*, Yusuke Moriya, Tomohide Ohnuki, Masafuchi Ryo, Wakoh Takahashi

Department of Neurology, Tokai University Oiso Hospital, 21-1 Gakkyou, Oiso, Naka-gun, Kanagawa 259-0198, Japan

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ABSTRACT

Fingolimod (FTY720) is used for reducing the annualized relapse rate and slowing progression of neurological disability in relapsing-remitting forms of multiple sclerosis (MS). However, its safety is not confirmed in patients with neuromyelitis optica spectrum disorder (NMOSD), who characteristically have positive aquaporin-4 (AQP-4) antibody.

A 54-year-old female with a relapsing-remitting course of optic neuritis and myelitis for six years, diagnosed initially as MS, had been treated with interferon beta-1b and oral corticosteroid. Magnetic resonance imaging (MRI) consistently revealed lesions on the optic nerve and spinal cord, but never on the brainstem or cerebral white matter during acute exacerbation. After treatment was switched to fingolimod from interferon beta-1b, multiple new lesions appeared at the brainstem and cerebral white matter. Following discontinuation of fingolimod, these lesions completely cleared, concomitantly with clinical improvement. During fingolimod treatment, she was recognized to be positive for AQP-4 antibody.

Fingolimod may be contraindicated in patients with NMOSD.

1. . Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory demyelinating disease, associated with recurrent optic neuritis, transverse myelitis and sometimes encephalitic/brainstem presentations. Other features of NMOSD include female preponderance, higher age of onset, severe functional disability, and increased cell counts and total protein content without IgG oligoclonal bands in the CSF. Unlike multiple sclerosis (MS), NMOSD is characterized by antibodies against aquaporin-4 (AQP-4), a water channel mainly expressed on foot processes of astrocytes, in up to 80% of the cases. Unique magnetic resonance imaging (MRI) findings have also been identified in NMOSD.

Immunosuppression is the mainstay of NMOSD management. High-dose intravenous methylprednisolone and plasma exchange are employed during acute exacerbation, and corticosteroids and immunosuppressants are efficacious in reducing NMOSD relapse. Importantly, interferon-beta, a first-line disease-modifying drug of MS, is not effective in NMOSD or even causes exacerbation. Therefore, early differentiation between NMOSD and MS is important in selecting an appropriate treatment strategy.

We present a NMOSD patient with positive anti-AQP4 antibody who developed multiple extensive brainstem and cerebral white matter lesions during treatment with fingolimod. This case report describes the detailed clinical presentation, with MRI findings, of one of the anti-AQP4 antibody-positive patients who participated in the fingolimod phase 2 observational extension trial for Japanese MS patients (Kira et al., 2014).

2. Case history

The patient is a 54-year-old woman with a 6-year history of suspected multiple sclerosis (MS). Relapses had been relatively frequent (7 times in six years), with optic neuritis and transverse myelitis that were well controlled with short-term courses of steroid pulse therapy (intravenous high-dose methylprednisolone) during relapses. Interferon beta-1b and oral corticosteroid had been continued during remission (Fig. 1). Routine surveillance brain MRI had been performed every 6 months, revealing no abnormal signals in the periventricular, pericallosal or subcortical white matter. Spinal cord MRI had not identified any longitudinally extensive spinal cord lesions. Her past medical history was otherwise unremarkable and laboratory tests such as antinuclear antibody, anti-phospholipid antibody or viral antibodies were negative.

During her most recent relapse, she experienced left chest and back pain, and numbness of her arm and leg, but her physical

* Corresponding author.
E-mail address: yoshii@is.icc.u-tokai.ac.jp (F. Yoshii).

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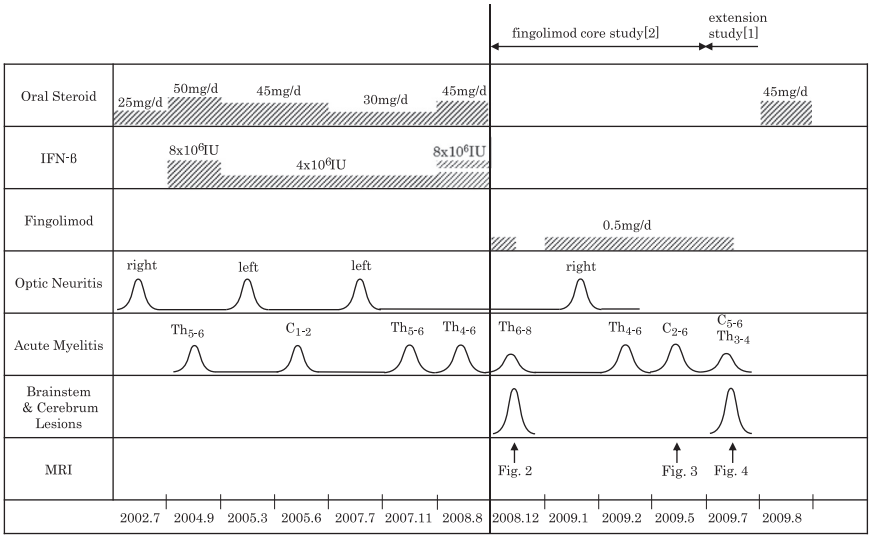

Fig. 1. Clinical course of the patient.

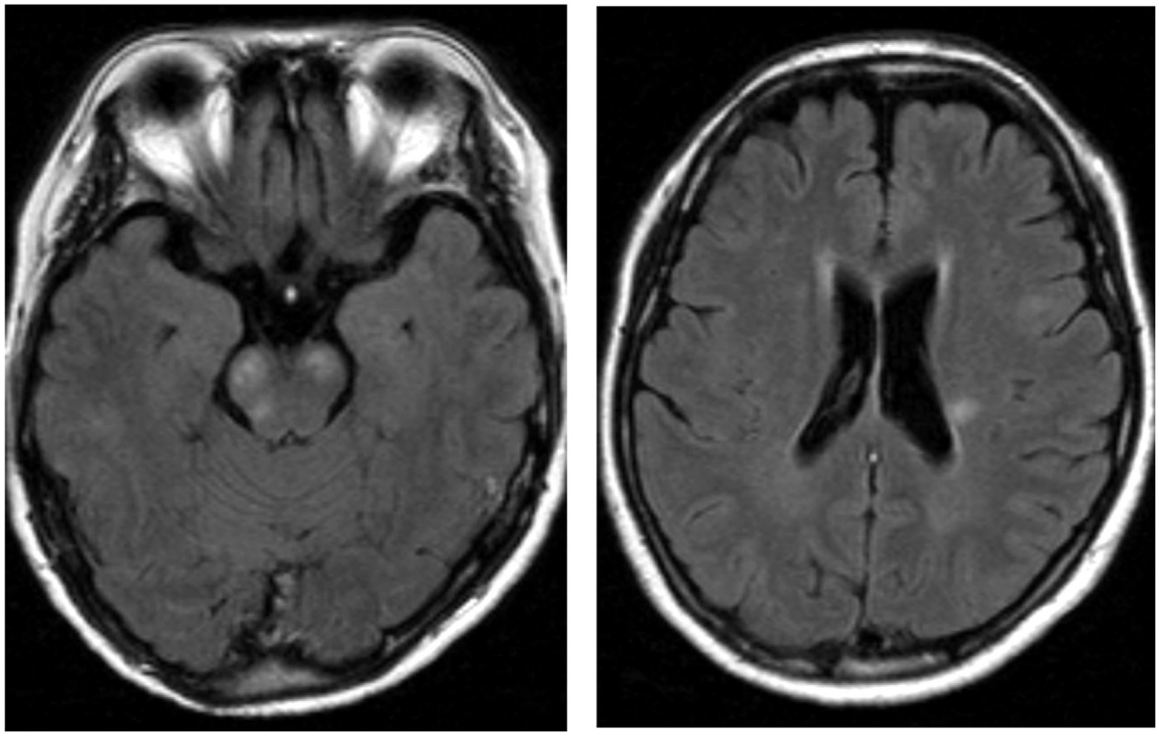

Fig. 2. MRI (FLAIR image) at ten days after the start of administration of fingolimod, showing scattered lesions at the brainstem and periventricular white matter.

examination was unremarkable. Spinal cord MRI showed high intensity signals at the Th_{4-6} levels. She almost completely recovered after a course of steroid pulse therapy. The disease-modifying drug was switched to fingolimod (0.5 mg/day) from interferon beta-1b after this exacerbation, because the relapse-preventing effect of interferon beta-1b was judged insufficient, and she was enrolled in a clinical study of fingolimod (core study: ClinicalTrials.gov, NCT00537082 (Saida et al., 2012) and extension study: ClinicalTrials.gov, NCT00670449 (Kira et al., 2014)), which had just started at that time. Five days after administration of fingolimod, she complained of chest discomfort, right chest paresthesia and double vision. Pulse rate was 44/min and lymphocyte count was decreased (640/mm^3). Spinal cord MRI revealed enlargement of the pre-existing spinal cord lesions at the Th_{6-8} levels. Brain MRI (FLAIR image) showed new, scattered lesions at the bilateral basilar part of the pons, right cerebral peduncle of the midbrain and periventricular white matter (Fig. 2). Fingolimod was discontinued for one month and then administered again after her symptoms disappeared and abnormalities of MRI and laboratory tests were normalized. However, she subsequently relapsed three times, and longitudinally extensive spinal cord lesions (LESCLs) on MRI appeared for the first time (Fig. 3). She again complained of diplopia, and left muscle weakness of her face and upper extremities after 6 months of fingolimod therapy. Brain MRI (FLAIR) disclosed new multifocal extensive hyper-intense lesions, especially involving the brainstem, cerebellum and subcortical cerebral white matter; the lesions were slightly enhanced with gadolinium (Fig. 4). Spinal cord MRI also showed lesions at C_{5-6} and Th_{3-4}. Intravenous corticosteroid pulse therapy was carried out and her neurological symptoms improved. Brain MRI