# Clinical/Scientific Notes

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## TUMEFACTIVE MULTIPLE SCLEROSIS LESIONS UNDER FINGOLIMOD TREATMENT

Fingolimod is an oral sphingosine 1-phosphate receptor modulator that prevents recirculation of lymphocyte subsets from lymph nodes. It decreases the number of relapses, slows the progression of disability, and improves MRI endpoints in patients with relapsing-remitting multiple sclerosis (RRMS).[1] Infrequent but specific side effects are bradycardia, leukopenia, and macular edema.

**Case report.** In November 2010, a 23-year-old woman with RRMS since September 2007 started fingolimod 0.5 mg per day in the setting of the open-label FTY720D2316 trial. Interferon-$\beta$ treatment was initiated in 2008, but discontinued mid-2010 because of side effects. Her disease course was relatively mild with low frequency and complete recovery of relapses. In March 2011, she presented with a left-sided hemiparesis, headache, and nausea that had gradually developed over 2 weeks. Because she had no clinical signs of infection, an exacerbation of multiple sclerosis (MS) was considered initially and she was admitted for IV methylprednisolone treatment. During the administration of the first dosage, the hemiparesis progressed and she had 2 partial epileptic seizures with jerks of the left leg, 1 of which generalized. We discontinued methylprednisolone and fingolimod and started valproic acid and acyclovir. New demyelinating lesions, infection (herpes or varicella encephalitis, toxoplasmosis, or brain abscess), and neoplasm (lymphoma, glioma) were considered to be possible causes of her symptoms.

Cranial MRI showed 2 large white matter lesions in the right hemisphere with surrounding vasogenic edema, mass effect, and open ring enhancement after gadolinium administration (figure, A). This suggested multifocal tumefactive demyelination, which was supported by magnetic resonance spectroscopy (figure, B–D). A pyogenic abscess was unlikely because of absence of diffusion restriction.

Serologic studies were negative for syphilis, Borrelia, HIV, and toxoplasmosis; and cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) were all immunoglobulin G positive and immunoglobulin M negative. In the CSF we found 7 leukocytes/$\mu$L (0–4), glucose 3.5 mmol/L (serum glucose 6.4 mmol/L), protein 1,065 mg/L (0–500). No pathologic cells were found in the CSF. CSF cultures for bacteria, mycobacteria, yeast, and fungus were negative. CSF PCR for mycobacteria, CMV, EBV, HSV-1, HSV-2, VZV, and JCV was negative.

We discontinued treatment with acyclovir after viral PCRs returned negative. The patient recovered within 1 week and was discharged with a slight residual left-sided hemiparesis.

In the weeks after discharge she recovered completely. We performed serial follow-up MRI, showing gradual regression and remyelination of the lesions. Discrete areas of focal demyelination remained. One month after discharge, small new gadolinium-enhancing lesions were seen, indicating new inflammatory MS activity (figure, A). This led us to start glatiramer acetate.

**Discussion.** Tumefactive demyelination refers to demyelinating brain lesions mimicking brain neoplasm clinically and radiographically. These lesions are larger than 2 cm, and show vasogenic edema, mass effect, and variable, typical open ring enhancement after gadolinium administration on MRI.[2] Tumefactive demyelination is a rare phenomenon. If present, it is as the presenting demyelinating event in 61% of cases. Only 5% of tumefactive lesions occur in established MS.[2]

Although a causative role of fingolimod on the basis of one case report is uncertain, the concomitant occurrence is noteworthy. First, the time course is suggestive, as our patient developed tumefactive lesions only a few months after starting fingolimod, whereas her disease course had been unexceptional before the start and after the cessation of fingolimod treatment. Secondly, tumefactive lesions—particularly if multifocal—in established MS are very rare.[2]

An association between fingolimod and tumefactive demyelination is further supported by reports of similar cases of patients with MS on fingolimod with tumefactive lesions,[3,4] in one case requiring craniectomy.[4] Possibly related are reports concerning a young woman with a severe MS relapse[5] and a man with neuromyelitis optica spectrum disorder with ex-

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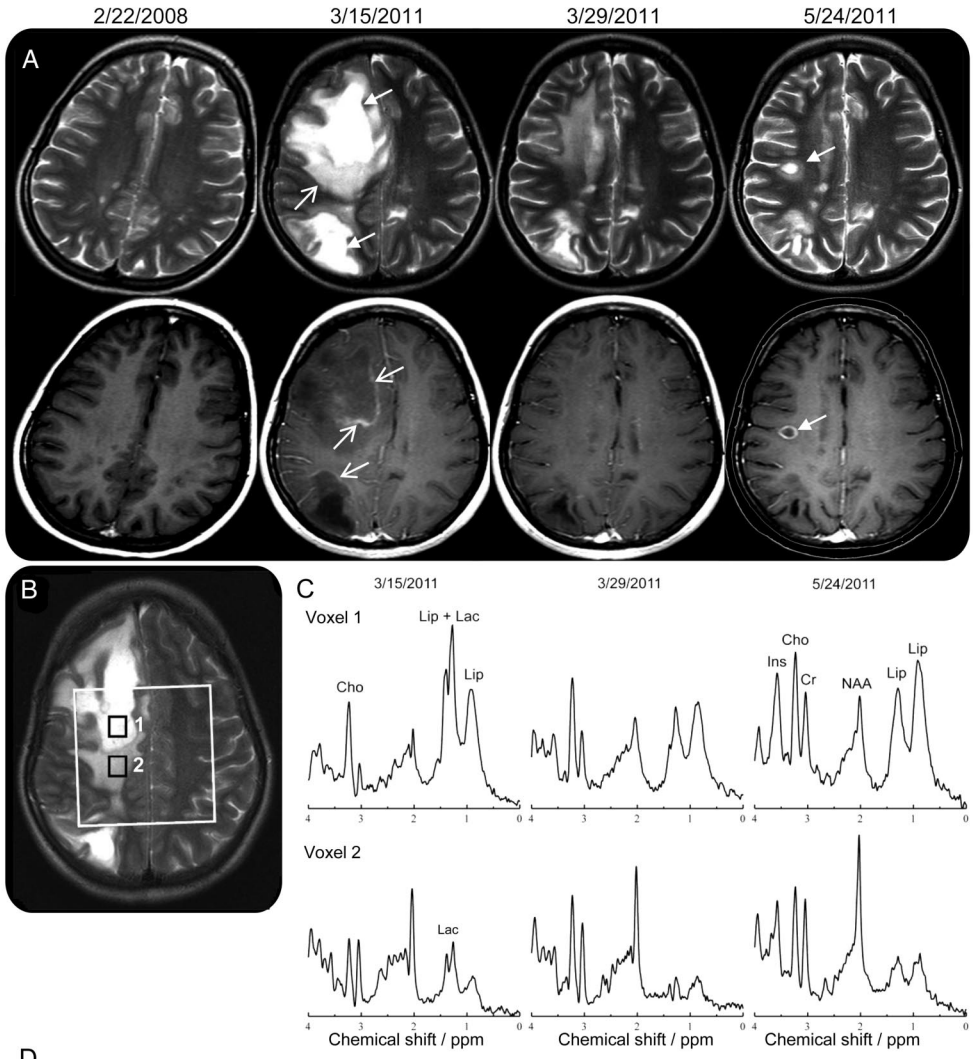
**Figure** MRI and magnetic resonance spectroscopy show evolution of multifocal tumefactive demyelination

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| | 3/15/2011 Voxel 1 | 3/29/2011 Voxel 1 | 5/24/2011 Voxel 1 | 3/15/2011 Voxel 2 | 3/29/2011 Voxel 2 | 5/24/2011 Voxel 2 | Contralateral WM Mean ± SD |
|---|---|---|---|---|---|---|---|
| Cr | 1.6 | 3.9 | 6.4 | 2.7 | 3.6 | 4.9 | 4.9 ± 0.7 |
| NAA | 1.1 | 2.1 | 3.3 | 3.4 | 4.3 | 5.8 | 7.9 ± 1.0 |
| Cho | 2.0 | 2.7 | 3.2 | 0.9 | 1.7 | 2.1 | 1.5 ± 0.2 |
| Ins | 1.1 | 3.5 | 9.0 | 1.8 | 2.6 | 5.0 | 3.7 ± 0.5 |
| Lac | 9.5 | 2.1 | 0.5 | 2.0 | 1.2 | 0.4 | 0.2 ± 0.2 |
| Lip (a.u.) | 49 | 44 | 57 | 15 | 7 | 16 | 1 ± 1 |

(A) Axial T2 (top row) and gadolinium-enhanced T1-weighted MRI (bottom row) illustrate the lesion evolution at baseline (February 22, 2008), at the time of the admission to our hospital (March 15, 2011), and during follow-up (March 29, 2011, May 24, 2011). On March 15, 2011, the patient presented with multifocal tumefactive lesions in both hemispheres particularly on the right side. One part of the lesion showed a necrotic and cystic appearance on the T2-weighted images (closed head arrows) and other parts showed signs of active demyelination with disruption of the blood-brain barrier leading to contrast enhancement (open head arrows). After cessation of immune-modulating treatment, the volume of the demyelinating areas decreased, suggesting remyelination, and the contrast enhancement disappeared (see MRI of March 29, 2011). However, during follow-up new multiple sclerosis lesions with active inflammation in terms of contrast enhancement occurred (closed head arrows in the MRI of May 24, 2011). (B) Quantitative chemical shift imaging (CSI) was performed with PRESS localization (repetition time/echo time 3,000/30 msec), as indicated with large white volume of interest. (C) Top row: longitudinal spectra from voxel 1 in the cystic/necrotic area. The initial spectrum (March 15, 2011) shows an almost complete absence of all metabolites except choline-containing compounds (Cho) due to membrane degradation. It also shows a huge elevation of lactate (Lac) due to inflammatory components, and of lipids (Lip) consistent with the presence of macrophages. Over time (March 29, 2011, and May 24, 2011), NAA slightly improves but remains low, due to neuro-axonal loss or damage, whereas creatine (Cr), myo-inositol (Ins), and Cho strongly increase due to glial proliferation. Lac has diminished, but Lip remains very prominent. Bottom row: longitudinal spectra from the surrounding border (voxel 2) are initially characterized by a reduced concentration of all metabolites, probably due to the diluting effect of edema, and the presence of Lac. Over time, the spectra almost normalize, although NAA remains slightly reduced and some lipid signals remain visible. (D) Metabolite concentrations (in mmol/L) corresponding to these spectra were quantified with LCModel, and compared to concentrations in contralateral white matter (WM).

tensive brain lesions and vasogenic edema after starting fingolimod.[6] The origin of tumefactive lesions in patients with MS during fingolimod treatment remains speculative. As fingolimod only prevents the lymph node egress of subsets of lymphocytes, one can imagine that in a minority of patients this will preferentially affect inhibitory immune cells. Fingolimod also has largely unknown effects on astrocytes, neurons, oligodendrocytes, and microglial cells in the CNS, which might have unpredictable side effects in certain individuals.[7]

A relationship between tumefactive MS lesions and fingolimod treatment remains uncertain. Although fingolimod is a promising and generally safe treatment of RRMS, doctors should be alert for unknown side effects. Precise registration and publication of these complications during fingolimod treatment is important.

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## VARICELLA-ZOSTER VIRUS ENCEPHALITIS AND VASCULOPATHY IN A PATIENT TREATED WITH FINGOLIMOD

A 50-year-old man with multiple sclerosis (MS) was admitted with a seizure and coma in the setting of herpes zoster. The patient developed MS in 2003 and was switched to fingolimod in 2011, 4 months after discontinuing natalizumab (54 doses). He was clinically stable, but mostly wheelchair-bound with relatively preserved upper extremity function. Brain MRI obtained before starting fingolimod was stable. He had a history of chicken pox, and he had not received the herpes zoster (shingles) vaccine. Three months after starting fingolimod he developed herpes zoster. Oral valacyclovir was started 4 days after onset of the rash. Four days after initiating valacyclovir, the patient had a generalized seizure and was hospitalized. He was deeply comatose and required intubation. CSF analysis showed 27 leukocytes (84% lymphocytes, 9% neutrophils, 7% monocytes), 217 erythrocytes, glucose 61 mg/dL (normal 50–75), and protein 201 mg/dL (normal 15–45). CSF varicella-zoster virus (VZV) PCR was positive, and CSF showed a low-level positive JC virus PCR in the hospital laboratory. PCR tests for herpes simplex virus (HSV), cytomegalovirus, Epstein-Barr virus, and enteroviruses were negative. Absolute lymphocyte count was 190 cells/μL (normal 1,100–4,800). MRI of the brain revealed 2 new punctate areas of restricted diffusion in the posterolateral medulla, most consistent with focal infarcts (figure). His MS lesions were unchanged. Gadolinium was not administered due to acute renal failure. Magnetic resonance angiography of the head was normal. He was diagnosed with VZV encephalitis, seizures, and a brainstem infarct believed to be a result of VZV vasculitis. There was no clinical evidence of PML. He was treated with levetiracetam, IV acyclovir for 21 days, and prednisone 1 mg/kg daily for 7 days for VZV vasculitis. During a complex hospitalization he slowly improved, and 1 month later he was awake and oriented with significant psychomotor slowing and persistent quadriparesis in this patient who was wheelchair-bound at baseline. He was transferred to a rehabilitation hospital for continued ventilator weaning. The case was reported to the Food and Drug Administration (via MedWatch) and to Novartis.

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**Discussion.** This patient developed herpes zoster in the setting of fingolimod-related lymphopenia, which progressed to VZV encephalitis and multifo-