Kazuhiro Ikumi, MD
Tetsuo Ando, MD
Harutaka Katano, DDS,
PhD
Masahisa Katsuno, MD,
PhD
Yu Sakai, MD, PhD
Mari Yoshida, MD, PhD
Takahiko Saida, MD,
PhD
Hiroshi Kimura, MD,
PhD
Gen Sobue, MD, PhD

*Neurol Neuroimmunol
Neuroinflamm*
2016;3:e247; doi: 10.1212/
NXL.0000000000000247

HSV-2-RELATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A FINGOLIMOD-TREATED PATIENT WITH MS

OPEN

Fingolimod is an oral, disease-modifying therapy used to treat multiple sclerosis (MS).¹ However, severe viral infections, including disseminated varicella-zoster virus infection,¹ herpes simplex encephalitis,^{1,2} varicella-zoster virus encephalitis and vasculopathy,³ or progressive multifocal leukoencephalopathy,⁴ have been reported during fingolimod therapy. Hemophagocytic lymphohistiocytosis (HLH), often triggered by certain viral infections, is a fatal disease characterized by fever, pancytopenia, elevated liver enzymes, hyperferritinemia, hepatosplenomegaly, and hemophagocytosis.⁵ A triggering infection causes persistent activation of lymphocytes and histiocytes, resulting in exaggerated immune responses and hemophagocytosis. We describe an autopsied case of disseminated herpes simplex virus type 2 (HSV-2) infection presenting with HLH, following 0.5 mg fingolimod and corticosteroid therapies.

Case report. A 56-year-old man had relapsing-remitting MS for 4 years, since 2008 (figure 1, A and B; table e-1 at Neurology.org/nn). He was not sexually active and did not have past or current oral/genital herpes infections. Fingolimod 0.5 mg was begun 10 months before admission, when the Expanded Disability Status Scale score was 5.0. Anti-varicella-zoster virus immunoglobulin G (enzyme immunoassay) was positive, although anti-herpes simplex virus immunoglobulin G was not obtained. His white cell and lymphocyte counts decreased during the fingolimod therapy (table e-2). He was admitted on the fourth relapse (table e-1), presenting with muscle weakness in both legs. Two courses of methylprednisolone pulse therapy at 1 g/d for 3 days temporarily enabled him to walk. However, it was followed by fever, sore throat, and jaundice. A laboratory test showed marked pancytopenia, elevated liver enzymes, and hyperferritinemia (table e-2). CT showed hepatosplenomegaly, and bone marrow aspiration revealed hemophagocytosis. These findings were consistent with HLH.⁵ Antiviral drugs could not be used because of lack of proof indicating a certain viral infection. The patient died 18 days after admission

(figure e-1). An autopsy was performed with the consent of his family. This adverse event was reported to the Food and Drug Administration via Novartis Pharmaceuticals.

The autopsy was performed 2 hours and 20 minutes post mortem. On gross inspection, the liver showed massive hemorrhagic necrosis (figure 1C), with degenerative hepatocytes that contained large, pink to purple intranuclear inclusion bodies (Cowdry type A) on hematoxylin & eosin staining, suggesting herpes infection (figure 1D). To identify the viruses potentially causing HLH, multivirus real-time PCR, which can detect more than 160 human pathogenic viruses in pathologic samples, was performed as previously described.⁶ The HSV-2 DNA was detected in the liver and most of the other pathologic samples (appendix e-1, tables e-3 and e-4). Viral copies per cell (organ) were as follows in descending order: 3.946 (liver), 1.439 (rectum), 1.427 (adrenal gland), 0.936 (esophagus), 0.416 (tongue), 0.160 (spleen), 0.041 (bone marrow), 0.015 (kidney), and 0.011 (bladder). Retrospective analysis of serum taken at the diagnosis of HLH (after methylprednisolone pulse therapy) revealed an elevated HSV-2 DNA concentration of 331,650 copies/ μ L (appendix e-2, table e-2). Immunohistochemistry using an anti-HSV-2 monoclonal antibody also identified HSV-2 antigen at multiple sites (figure 1, E and F, table e-4). Remarkable hemophagocytosis was observed within the bone marrow (figure 1G), liver, and spleen. Neuropathologic findings were consistent with MS.

Discussion. Herein, we describe disseminated HSV-2 infection in a patient with MS treated with fingolimod and corticosteroids. HSV is one of the most common viruses that develop HLH, which results from T cell/NK cell dysregulation and eventual cytokine overproduction.⁵ The pronounced viremia of HSV-2 in our case suggests that this virus potentially had a causative role in the emergence of HLH.⁷

Fingolimod may be associated with HLH, considering that a similar HLH case has been reported.⁸ A 39-year-old man with MS who had received 0.5 mg fingolimod for 15 months without adjunctive corticosteroids presented with fever, jaundice, and night sweats, but an autopsy was not performed and the causative virus was not determined. Our report, however,

Supplemental data
at Neurology.org/nn

(A) Axial T2-weighted image of the spinal cord. (B) Fluid-attenuated inversion recovery image of the brain. (C) The liver was dark red in color reflecting massive hemorrhagic necrosis. (D) H&E staining showed degenerative hepatocytes containing large, pink to purple intranuclear inclusion bodies (Cowdry type A) that push the cell chromatin out to the edges of the nucleus (arrows). This finding suggested herpes infection. Single hepatic cell necrosis is also shown (arrowhead). (E, F) Immunohistochemistry for herpes simplex virus type 2. Viral antigens were identified in the liver (E) and bone marrow (F). (G) H&E staining showed remarkable hemophagocytosis (arrows) within the bone marrow. Scale bars: 3 cm (C), 20 μ m (D–G). H&E = hematoxylin & eosin.

demonstrated HSV-2 as a potential virus for HLH in fingolimod-treated patients.

Fingolimod prevents MS relapses through inhibition of sphingosine-1-phosphate signaling that is essential for lymphocyte migration from lymphoid tissues. Since fingolimod decreases the numbers of naive and central memory T cells in the peripheral blood that are protective against novel or recurrent viral infection,⁹ fingolimod-treated patients are likely vulnerable to herpes infections. Thus, in our case, fingolimod might be associated with massive HSV-2 dissemination, which was possibly augmented by adjunctive corticosteroids.^{1,2,9}

Our case suggests that careful monitoring of herpes infection is needed, particularly if corticosteroids are added on fingolimod therapy.

From the Departments of Neurology (K.I., M.K., G.S.) and Virology (H. Kimura), and Center for Brain & Mind Research Promotion (G.S.), Nagoya University Graduate School of Medicine; Departments of Neurology (K.I., T.A.) and Pathology (Y.S.), Anjo Kosei Hospital; Department of Pathology (H. Katano), National Institute of Infectious Diseases, Tokyo; Department of Neuropathology (M.Y.), Institute of Medical Science of Aging, Aichi Medical University, Nagakute; and Department of Neurology (T.S.), Kyoto-Min-Iren-Central Hospital, Kyoto, Japan.

Author contributions: Dr. Ikumi and Dr. Ando had a major role in the conception of this work. Dr. Ikumi, Dr. Ando, and Dr. Saida were responsible for the clinical management of the patient, acquisition and interpretation of the patient's clinical information.

Dr. Katano contributed to the experimental analyses and interpretation of viral infection in this patient. Dr. Sakai and Dr. Yoshida contributed to the detailed pathologic analyses of visceral organs and the central nervous system, respectively. Dr. Katsuno, Dr. Kimura, and Dr. Sobue provided substantial contributions to supervision and revision of this work.

Acknowledgment: The authors thank the patient and his family for their cooperation regarding this report. This case report was approved by the ethical committee of Anjo Kosei Hospital. The authors obtained written informed consent from the patient's family for this publication.

Study funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure: K. Ikumi and T. Ando report no disclosures. H. Katano is on the editorial board for the Japanese Journal of Infectious Diseases, received research support from the Ministry of Health, Labor and Welfare, The Agency for Medical Research and Development, Japan, Ministry of Education, Culture, Sports, Science and Technology of Japan. M. Katsuno is on the scientific advisory board for Pharmaceuticals and Medical Devices Agency, Japan, received travel and speaker's fees from Pfizer, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, holds a patent for nonhuman animal reproducing pathogenic conditions of spinal and bulbar muscular atrophy and remedy for spinal and bulbar muscular atrophy, anto-spinal and bulbar muscular atrophy therapy, received research support from the Ministry of Education, Culture, Sports, Science and Technology of Japan. Y. Sakai, M. Yoshida, T. Saida, and H. Kimura report no disclosures. G. Sobue served on the scientific advisory board for Kanoe Science Foundation for the Promotion of Medical Science, Naito Science Foundation, Takeda Foundation, is on the editorial board for Brain, Degenerative Neurological and Neuromuscular Disease, Journal of Neurology, Amyotrophic Lateral Sclerosis, received research support from the Ministry of Education, Culture, Sports, Science and Technology of Japan, Ministry of Welfare, Health

and Labor of Japan, the Japan Science and Technology Agency, Core Research for Evolutional Science and Technology. Go to Neurology.org/nn for full disclosure forms. The Article Processing charge was paid by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Received December 10, 2015. Accepted in final form April 26, 2016.

Correspondence to Dr. Ikumi: ikumi.kazuhiro@a.mbox.nagoya-u.ac.jp

1. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362:402–415.
2. Pfender N, Jelcic I, Linnebank M, Schwarz U, Martin R. Reactivation of herpesvirus under fingolimod: a case of severe herpes simplex encephalitis. *Neurology* 2015;84:2377–2378.
3. Ratchford JN, Costello K, Reich DS, Calabresi PA. Varicella-zoster virus encephalitis and vasculopathy in a patient treated with fingolimod. *Neurology* 2012;79:2002–2004.
4. Fitzgerald S. Third PML case associated with fingolimod: how to distinguish PML from MS relapse. *Neurol Today* 2015;15:10–11.
5. Roupheal NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. *Lancet Infect Dis* 2007;7:814–822.
6. Katano H, Kano M, Nakamura T, Kanno T, Asanuma H, Sata T. A novel real-time PCR system for simultaneous detection of human viruses in clinical samples from patients with uncertain diagnoses. *J Med Virol* 2011;83:322–330.
7. Kimura H, Nishikawa K, Hoshino Y, Sofue A, Nishiyama Y, Morishima T. Monitoring of cell-free viral DNA in primary Epstein-Barr virus infection. *Med Microbiol Immunol* 2000;188:197–202.
8. Abreu P, Peixoto C, Carvalho C, et al. A case of hemophagocytic lymphohistiocytosis syndrome in a patient with multiple sclerosis on fingolimod therapy. *Neurology* 2014;82:P2.206. Abstract.
9. Alvin AM, Wolinsky J, Kappos L, et al. Varicella-zoster virus infections in patients treated with fingolimod: risk assessment and consensus recommendations for management. *JAMA Neurol* 2015;72:31–39.

Neurology[®] Neuroimmunology & Neuroinflammation

HSV-2–related hemophagocytic lymphohistiocytosis in a fingolimod-treated patient with MS

Kazuhiro Ikumi, Tetsuo Ando, Harutaka Katano, et al.
Neurol Neuroimmunol Neuroinflamm 2016;3;
DOI 10.1212/NXI.0000000000000247

This information is current as of June 7, 2016

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright © 2016 American Academy of Neurology. All rights reserved. Online ISSN: 2332-7812.

Updated Information & Services	including high resolution figures, can be found at: http://nn.neurology.org/content/3/4/e247.full.html
Supplementary Material	Supplementary material can be found at: http://nn.neurology.org/content/suppl/2016/06/07/3.4.e247.DC1
References	This article cites 9 articles, 0 of which you can access for free at: http://nn.neurology.org/content/3/4/e247.full.html##ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://nn.neurology.org/content/3/4/e247.full.html##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://nn.neurology.org/cgi/collection/all_clinical_neurology Autoimmune diseases http://nn.neurology.org/cgi/collection/autoimmune_diseases Class IV http://nn.neurology.org/cgi/collection/class_iv Multiple sclerosis http://nn.neurology.org/cgi/collection/multiple_sclerosis Viral infections http://nn.neurology.org/cgi/collection/viral_infections
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://nn.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://nn.neurology.org/misc/addir.xhtml#reprintsus

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright © 2016 American Academy of Neurology. All rights reserved. Online ISSN: 2332-7812.