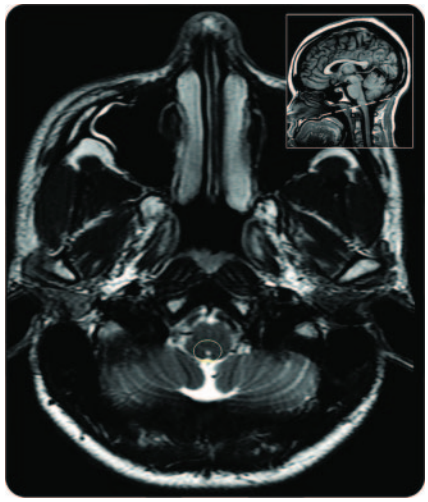
WriteClick: Editor's Choice

Editors' Note: In reference to a NeuroImage submitted by Drs. Schlaeger and Sollberger, Dr. Wang et al. clarify the anatomic location of the area postrema and explain its possible significance to radiation therapy. Other correspondents this week react to 2 articles on progressive multifocal leukoencephalopathy (PML). Dr. Phan-Ba et al. disagree with the definition of Dr. Tan et al. of early PML–immune reconstitution inflammatory syndrome (IRIS), arguing that the inflammatory MRI signs in the study's early PML-IRIS patients occurred while natalizumab was still inhibiting the requisite immunologic response. They offer alternative nomenclature. The authors defend their terminology, countering that any inflammation in these patients is a sign of immune reconstitution. Drs. Sethi and Torgovnick suggest that, in the case report of Tan et al. of a man with PML without immunodeficiency, the patient's unusual presentation may have been due to a primary JC virus infection rather than reactivation. The authors reply that the immune response suggests previous exposure to the virus.

Megan Alcauskas, MD, and Robert C. Griggs, MD

Figure **Axial T2-weighted image shows the approximate location of the circumventricular area postrema (yellow circle) in the dorsal medulla adjacent to the obex of the fourth ventricle**



The inset sagittal T1-weighted image indicates the level as the inferior medulla.

AN UNUSUAL CAUSE OF ISOLATED VOMITING

Tony J. Wang, Nancy Y. Lee, Robert J. Young, New York: We seek to clarify the anatomy of the area postrema in response to this NeuroImage by Drs. Schlaeger and Sollberger.[1] They described a diffusion-restricted lesion in the medial brachium pontis as the area postrema. A subsequent correction states that the lesion is a "few millimeters above" the area postrema. In fact, the area postrema is a circumventricular organ in the inferior dorsal medulla adjacent to the obex of the fourth ventricle (figure), and probably greater than 2 cm away from the brachium pontis. Despite this, we acknowledge that it is possible that the lesion induced therapy-refractory vomiting through a still undefined neural network. We remind *Neurology*® readers that Misu et al.[2] presented superb radiologic and schematic illustrations of the area postrema, and that Popescu et al.[3] presented excellent neuropathologic correlations.

There has been renewed interest in the area postrema in radiotherapy for head and neck cancers, in order to improve radiation-induced nausea and vomiting.[4,5] These patients may benefit from intensity-modulated radiotherapy that increases tumor dose while reducing normal tissue dose including the area postrema. Understanding anatomic and functional significance of the area postrema is necessary to accurately develop radiation contours and dosimetry, and maximize patient quality of life.

1. Schlaeger R, Sollberger M. An unusual cause of isolated vomiting. Neurology 2010;75:1303.
2. Misu T, Fujihara K, Nakashima I, Sato S, Itoyama Y. Intractable hiccup and nausea with periaqueductal lesions in neuromyelitis optica. Neurology 2005;65:1479–1482.
3. Popescu BF, Lennon VA, Parisi JE, et al. Neuromyelitis optica unique area postrema lesions: nausea, vomiting, and pathogenic implications. Neurology 2011;76:1229–1237.
4. Ciura K, McBurney M, Nguyen B, et al. Effect of brain stem and dorsal vagus complex dosimetry on nausea and vomiting

in head and neck intensity-modulated radiation therapy. Med Dosim 2011;36:41–45.
5. Monroe AT, Reddy SC, Gibbs GL, White GA, Peddada AV. Factors associated with radiation-induced nausea and vomiting in head and neck cancer patients treated with intensity modulated radiation therapy. Radiother Oncol 2008;87:188–194.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN NATALIZUMAB-ASSOCIATED PML

Remy Phan-Ba, Emile Lommers, Gustave Moonen, Shibeshih Belachew, Liege, Belgium: Tan et al.[1] dichotomized early vs late types of the immune reconstitution inflammatory syndrome (IRIS), which appears to be universal in patients with multiple sclerosis (MS) who develop progressive multifocal leukoencephalopathy (PML) in the setting of natalizumab therapy.

The authors identified early PML-IRIS based on gadolinium enhancement in the lesions on brain MRI at the time of PML diagnosis, before natalizumab withdrawal. Early PML-IRIS occurred approximately 19 days after the last natalizumab infusion when natalizumab effect on alpha4-integrin binding remained optimal.[2] Hence, inflammatory MRI signs of this early PML-IRIS take place in the absence of ongoing restoration of the immune competence within the brain. This is different from what is seen in HIV-related PML where IRIS occurs only after inducing the immune reconstitution through the initiation of anti-retroviral therapy.[3]

Early PML-IRIS in natalizumab-associated PML may only represent radiologic signs of blood–brain barrier alteration due to JC virus infection in this specific context. The operational definition of early PML-IRIS should be early infection-related or idiopathic radiologic inflammatory syndrome vs delayed IRIS, which truly reflects an immune reconstitution. The prognostic factors, responsiveness to steroid administration and to plasma exchanges, should then be evaluated separately for these 2 distinct conditions.

Author Response: Avinda Nath, Bethesda, MD: We thank Phan-Ba et al. for their suggestions on how to better define the 2 different forms of PML-IRIS. We attempted to develop terminology that could be used not only for patients with MS who develop PML but other immune-compromised states such as HIV infection or organ transplants. Typically, in immune-suppressed individuals who develop PML, there is no evidence of inflammation so any inflammation in the early or late stage is a form of immune reconstitution. Furthermore, PML-IRIS is not always a radiologic diagnosis. The enhancement associated with PML-IRIS on MRI can be very subtle or not noticeable to the naked eye particularly in HIV-infected and organ transplant patients.[4] We prefer the term "early PML-IRIS" to define individuals who have evidence of IRIS at the time of diagnosis of PML and "delayed PML-IRIS" to define individuals who were known to have PML but develop IRIS later in the course of the illness usually associated with an improvement of the underlying immune dysfunction.

1. Tan IL, McArthur JC, Clifford DB, Major EO, Nath A. Immune reconstitution inflammatory syndrome in natalizumab-associated PML. Neurology 2011;77:1061–1067.
2. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. Neurology 2009;72:402–409.
3. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. Neurology 2009;72:1458–1464.
4. Harrison DM, Newsome SD, Skolasky RL, McArthur JC, Nath A. Immune reconstitution is not a prognostic factor in progressive multifocal leukoencephalopathy. J Neuroimmunol 2011;238:81–86.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN A PATIENT WITHOUT IMMUNODEFICIENCY

Nitin K. Sethi, Josh Torgovnick, New York: The case report by Tan et al.[1] of a 62-year-old man with progressive multifocal leukoencephalopathy (PML) without immunodeficiency was interesting given our experience with AIDS-related PML and current literature.[2] The authors assume that their patient's disease was due to reactivation of latent JC virus infection caused by a transient dysfunction of cellular immunity triggered by another subclinical viral infection such as parvovirus B19. A 60-year-old colleague of ours recently had acute mononucleosis and her comment was that she had not kissed enough boys when she was younger. Little is still known about what triggers JC virus activation and its primary manifestation varies in the immunosuppressed, minimally immunosuppressed, and the immunocompetent patient. Is it possible that this case reflects the manifestation of disease in a 60-year-old man contracting the virus acutely? This might explain the unusual protracted course of his illness. We suspect that mefloquine played no role in his recovery, which was likely spontaneous.[3,4]

Author Response: Justin C. McArthur, I.L. Tan, Baltimore; I.J. Koralnik, Boston: PML is classically caused by reactivation of JC virus in the context of immunosuppression, although the exact mechanism of reactivation remains unclear. We agree with Drs. Sethi and Torgovnick that little is known about the manifestations of JC virus in acute infection. However, it is unlikely that PML in our patient was

caused by an acute infection given the presence of a robust immune response against JC virus VP1 protein that was mediated by CD4+ and CD8+ T cells. This was part of the acquired immune response suggesting a previous exposure to the JC virus. The exact role of mefloquine in our patient's favorable recovery is difficult to define. A recent mefloquine clinical trial (ClinicalTrials.gov identifier: NCT00746941) in patients with PML was well-tolerated, but was terminated early as it did not achieve the primary endpoint of showing a reduction of JC viral DNA in the CSF.[5] The favorable clinical outcome in our patient was likely associated with the strong cellular immune response to JC virus.[6]

1. Tan IL, Koralnik IJ, Rumbaugh JA, Burger PC, King-Rennie A, McArthur JC. Progressive multifocal leukoencephalopathy in a patient without immunodeficiency. Neurology 2011;77:297–299.
2. Torgovnick J, Sethi N, Karter D, Arsura E. Remission of AIDS-associated progressive multifocal leukoencephalopathy with combined cidofovir and radiotherapy: a case report. AIDS 2006;20:1569–1570.
3. Study to explore the effect of mefloquine in subjects with progressive multifocal leukoencephalopathy (PML). Available at: http://clinicaltrials.gov/ct2/show/NCT00746941.
4. News from the AAN annual meeting: malaria drug fails to fulfill promise in PML. Available at: www.aan.com/elibrary/neurologytoday/?event=home.showArticle&id=ovid.com:/bib/ovftdb/00132985-201104210-00004.
5. Friedman R. News from the AAN annual meeting: malaria drug fails to fulfill promise in PML. Neurol Today 2011;11:8.
6. Gheuens S, Bord E, Kesari S, et al. Role of CD4+ and CD8+ T-cell responses against JC virus in the outcome of patients with progressive multifocal leukoencephalopathy (PML) and PML with immune reconstitution inflammatory syndrome. J Virol 2011;85:7256–7263.

Author disclosures are available upon request (journal@neurology.org).

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