Simultaneous CMV and *Listeria* infection following alemtuzumab treatment for multiple sclerosis

Agustín Pappolla, MD*, Luciana Midaglia, MD*, Claudia P. Boix Rodríguez, MD, Adaia Albasanz Puig, MD, Maiylyi Lung, MD, PhD, Isabel Ruiz Camps, MD, PhD, Joaquín Castilló, MD, PhD, Patricia Mulero, MD, Angela Vidal-Jordana, MD, PhD, Georgina Arrambide, MD, PhD, Breogán Rodriguez-Acevedo, MD, Jaume Sastre-Garriga, MD, PhD, Jordi Río, MD, PhD, Manuel Comabella, MD, PhD, Ingrid Galán, MD, Mar Tintoré, MD, PhD, and Xavier Montalbán, MD, PhD

Correspondence
Dr. Midaglia
lmidaglia@cem-cat.org

Neurology® 2019;92:296-298. doi:10.1212/WNL.0000000000006801

Alemtuzumab, a humanized monoclonal antibody for the treatment of relapsing-remitting multiple sclerosis, produce the rapid depletion of all mature lymphocytes. For this reason, patients are at an increased risk of developing infections due to the reactivation of latent agents or acquired microorganisms. Most infections reported during the phase III trials were mild or moderate in severity, while serious infections were surprisingly uncommon.[1] However, during the postmarketing use of alemtuzumab, several opportunistic infections have been reported.[2–5] We describe a patient who presented simultaneous cytomegalovirus (CMV) reactivation and *Listeria* meningitis promptly following the first course of alemtuzumab.

Case report

We present a 32-year-old man with no relevant medical history. His first episode of neurologic dysfunction occurred at the age of 7, presenting as bilateral inferior limb pain and paraparesia that resolved spontaneously. A second event occurred 12 years later, characterized by horizontal diplopia. He underwent a brain MRI, which revealed inflammatory-demyelinating lesions in the subcortical, periventricular, and juxtacortical white matter, as well as in the splenium of the corpus callosum and brainstem. Serologic and systemic autoimmune screenings were negative, and a lumbar puncture disclosed no oligoclonal bands. A diagnosis of multiple sclerosis was made, and he started treatment with subcutaneous interferon-β-1a. Despite treatment, he presented 2 new relapses, and treatment was changed to fingolimod. During follow-up, he presented no further clinical events; however, in annual MRI, inflammatory activity was detected characterized by new lesions (4–7) and gadolinium-enhancing lesions (1–6). Given the persistent radiologic disease activity, we decided to start treatment with alemtuzumab. The patient received the first course from March 19 to 23, 2018. In the next 5 days after the last treatment infusion, he complained of persistent fever, abdominal pain, and a pulsatile headache. An initial urinalysis, a basic laboratory screening, and a chest X-ray were normal. However, during the following 24 hours, symptoms persisted, and neck stiffness and a positive Kernig sign were detected. Laboratory tests and a lumbar puncture were performed at admission, showing the following positive results: C-reactive protein 2.75 mg/dL, white blood cells 16.6 × 1,000/μL (96% neutrophils, 0.2% lymphocytes), and serum gamma-glutamyl transpeptidase 383 IU/L. CSF analysis showed 280 cells/μL (90% neutrophils and 10% mononuclear cells), glucose 36 mg/dL, and proteins 159 mg/dL. A serum CMV viral DNA PCR disclosed active replication at 1,799 IU/mL (immunoglobulin M negative, immunoglobulin G 30 mIU/mL, 3.26 log IU/10 mL). An abdominal CT scan revealed a distended bowel, without other signs of infection. Both PCR and cultures were positive for *Listeria*

*These authors contributed equally to this work.

From the Department of Neurology-Neuroimmunology, Multiple Sclerosis Centre of Catalonia (Cemcat) (A.P., L.M., J.C., P.M., A.V.-J., G.A., B.R.-A., J.S.-G., J.R., M.C., I.G., M.T., X.M.), Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain; Department of Internal Medicine (C.P.B.R.) and Center of Biomedical Research in Network on Neurodegenerative Diseases (CIBERNED) (C.P.B.R.), Sant Joan d'Alacant University Hospital, Alicante, Spain; Department of Neurology (A.P.), Hospital Italiano, Buenos Aires, Argentina; Department of Infectious Diseases (C.P.B.R., A.A.P., I.R.C.) and Microbiology Department (M.L.), Vall d'Hebron University Hospital, Barcelona, Spain; and Division of Neurology (X.M.), University of Toronto, St Michael's Hospital, Toronto, Canada.

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monocytogenes serotype 4. The patient was diagnosed with concurrent reactivation of CMV and *Listeria* meningitis. He currently receives simultaneous treatment with ganciclovir for 2 weeks and penicillin (according to the antibiogram) for 3 weeks, and his symptoms are improving to date.

Discussion

To our knowledge, 4 cases of CMV reactivation[2,3] and 17 cases of *Listeria* infection (3 reported cases[4,5] and 14 patients in VigiBase) have been reported in patients with multiple sclerosis treated with alemtuzumab. However, we found no reports of confections with both agents.

Usually, neither *Listeria* nor CMV develops into severe infections in immunocompetent hosts; however, in patients with defective cellular immunity, *Listeria spp.* may cause septicemia, meningitis, or encephalitis, and CMV may lead to a disseminated infection with the involvement of multiple organs, causing encephalitis, retinitis, hepatitis, or colitis. As both pathogens are intracellular, the cellular immune response, mediated by CD4 and CD8 cells, is primarily involved in their elimination. In addition, the humoral immune response may play a significant role in preventing CMV dissemination.[6,7]

To prevent *Listeria* infections, the Summary of Products Characteristics (SPC) for Lemtrada recommends that patients should avoid the ingestion of undercooked meats, soft cheeses, and unpasteurized dairy products 2 weeks prior to, during, and for at least 1 month after alemtuzumab treatment.[8] However, asymptomatic human carriers are not protected by these recommendations. For the avoidance of viral infections, acyclovir prophylaxis is partially effective against herpes simplex virus reactivation but is ineffective at preventing CMV reactivation.[7]

The present case highlights that every patient who develops fever soon after alemtuzumab treatment should undergo an extensive study for opportunistic infections. If headache is associated, a lumbar puncture should be performed to rule out meningitis due to *L monocytogenes*. In addition to the SPC recommendations, to prevent infection with both agents, we suggest (1) administering trimethoprim-sulfamethoxazole 3 times a week, as long as the lymphocyte count remains under 1.0 × 1,000/μL, and (2) performing a monthly serum CMV PCR assay in patients with positive CMV immunoglobulin G and in all patients presenting with fever or an increase in liver enzymes during alemtuzumab treatment, regardless of the serostatus.

Author contributions

A. Pappolla contributed to the concept and design of the work and acquisition, analysis, and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. L. Midaglia contributed to the concept and design of the work and acquisition, analysis, and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. C.P. Boix Rodriguez contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. A.A Puig contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. M. Lung contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. I.R. Camps contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. J. Castilló contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. P. Mulero contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. A. Vidal-Jordana contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. G. Arrambide contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. Breogán Rodriguez-Acevedo contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. J. Sastre-Garriga contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. J. Río contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. M. Comabella contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. I. Galán contributed to the acquisition and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. M. Tintore contributed to the concept and design of the work and acquisition, analysis, and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. X. Montalban

contributed to the concept and design of the work and analysis and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published.

Study funding

No targeted funding reported.

Disclosure

A. Pappolla, L. Midaglia, C. Boix Rodriguez, A. Albasanz Puig, M. Lung, I. Ruiz Camps, J. Castilló, and P. Mulero report no disclosures relevant to the manuscript. A. Vidal-Jordana receives support for contracts Juan Rodes (JR16/00024) from Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III, Spain; and has received compensation for consulting services from Roche and speaking honoraria from Novartis, Stendhal, Roche, and Sanofi-Aventis. G. Arrambide has received compensation for consulting services from Biogen-Idec, research support from Novartis, travel expenses for scientific meetings from Novartis, Roche, and Stendhal, and speaking honoraria from Sanofi-Aventis and Stendhal. B. Rodriguez-Acevedo reports no disclosures relevant to the manuscript. J. Sastre-Garriga has received compensation for participating on advisory boards, speaking honoraria, and travel expenses for scientific meetings, consulting services, or research support from Celgene, Novartis, Biogen, Teva, Merck, Almirall, and Genzyme. J. Río has received speaking honoraria and personal compensation for participating on advisory boards from Almirall, Bayer-Schering Healthcare, Biogen-Idec, Genzyme, Merck-Serono, Novartis, Teva, and Sanofi-Aventis. M. Comabella has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma, Merck Serono, Biogen-Idec, Teva Pharmaceuticals, Sanofi-Aventis, and Novartis. I. Galán reports no disclosures relevant to the manuscript. M. Tintore has received compensation for consulting services and speaking honoraria from Almirall, Bayer Schering Pharma, Biogen-Idec, Genzyme, Merck-Serono, Novartis, Roche, Sanofi-Aventis, and Teva Pharmaceuticals. MT is co-editor of *Multiple Sclerosis Journal*-ETC. X. Montalban has received speaking honoraria and travel expenses for participation in scientific meetings and has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Actelion, Amirall, Bayer, Biogen, Celgene, Genzyme, Hoffmann-La Roche, Novartis, Oryzon Genomics, Sanofi-Genzyme, and Teva Pharmaceutical. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* June 8, 2018. Accepted in final form October 23, 2018.

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