The main adverse reactions affect the central nervous system and the cardiovascular system, due to the drug's action on the channels responsible for initiating and propagating the action potential in nerves and muscles. Its inhibition of serotonin reuptake would explain the risk of serotonin syndrome. Other reactions include hypersensitivity syndrome with pronounced skin involvement. These side effects have been observed at concentrations from 15.5 mg/L, but with no clear correlation between blood lamotrigine concentration and clinical toxicity. Furthermore, the concentrations observed seem to differ in patients ingesting the same amount of the drug[3]; some patients may not present toxic effects despite the overdose.[1]

The most frequent neurological presentations are decreased level of consciousness and ataxia, followed by vertigo, confusion, agitation, dysarthria, nystagmus, headache, seizures, and other findings associated with serotonin syndrome. Cardiac effects, which are less frequent, include sinus tachycardia and QRS and QTc widening, with the subsequent risk of arrhythmia.[1] Nausea, vomiting, and exanthema are also frequent.

In the case of our patient, altered level of consciousness and sustained spontaneous clonus may be considered part of a serotonin syndrome, fulfilling the Hunter criteria for this diagnosis,[4] in addition to lactic acidosis, slight fever with no apparent focus, and isolated leukocytosis, which normalised in the first 24 hours. He also presented other polymorphic neurological symptoms, particularly nystagmus, ataxia, and dysarthria. In terms of cardiac manifestations, he only presented self-limited sinus tachycardia. Although it was not witnessed, the tongue biting and the limited reactivity at baseline may have been associated with a seizure, which is consistent with the paroxysmal convulsive action of overdoses of certain AEDs.[1,3]

Our treatment was exclusively symptomatic due to the time elapsed. However, gastrointestinal decontamination is possible when patients are examined early, although previous protection of the airway is essential due to the risk of decreased level of consciousness and presence of seizures. Other treatments used are alkalinisation with sodium bicarbonate, intravenous lipid emulsions, and even haemodialysis, although published experience is limited.[1,3]

In conclusion, our case exemplifies the polymorphic presentation of lamotrigine intoxication. Due to the wide array of neurological symptoms and the association with serotonin syndrome, we consider it a good example to illustrate the adverse effects of a frequently used drug that, in the absence of suspicion, may be life-threatening.

References

1. Alabi A, Todd A, Husband A, Reilly J. Safety profile of lamotrigine in overdose. Ther Adv Psychopharmacol. 2016;6:369—81.
2. Wills B, Reynolds P, Chu E, Murphy C, Cumpston K, Stromberg P, et al. Clinical outcomes in newer anticonvulsant overdose: a poison center observational study. J Med Toxicol. 2014;10:254—60.
3. Alyahya B, Friesen M, Nauche B, Laliberté M. Acute lamotrigine overdose: a systematic review of published adult and pediatric cases. Clin Toxicol (Phila). 2018;56:81—9.
4. Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003;96:635—42.

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Primary cytomegalovirus infection in a patient with relapsing-remitting multiple sclerosis under treatment with alemtuzumab☆

Primoinfección por citomegalovirus en un paciente con esclerosis múltiple recurrente-remitente tratado con alemtuzumab

Dear Editor:

Alemtuzumab is a monoclonal antibody targeting the CD52 receptor, and is approved for treating active relapsing-remitting multiple sclerosis (RRMS). It depletes T and B cells by binding to the CD52 receptor.

Adverse effects of alemtuzumab include infections, with the most frequent being nasopharyngitis, urinary tract infection, upper respiratory tract infection, and herpesvirus infection.[1,2] Opportunistic infections after treatment have also been described, such as tuberculosis reactivation, listeria meningitis, and cerebral nocardiosis.[3] Recent studies report 2 cases of cytomegalovirus (CMV) reactivation[4] and a case of coinfection with CMV and *Pneumocystis jirovecii*.[5] Another case of CMV infection was reported in the group receiving high-dose alemtuzumab (24 mg/kg) in a phase III clinical trial.[6]

We report the case of a patient with pneumonia due to coinfection with CMV and *P. jirovecii* after the first cycle of alemtuzumab.

The patient was a 39-year-old woman who was diagnosed with RRMS in 2009. She was initially treated with interferon beta 1b, which was switched to fingolimod after 9 months due to ineffectiveness. In 2014, the patient started treatment with natalizumab due to persistent disease activity. In 2016, she presented John Cunningham virus seroconver-

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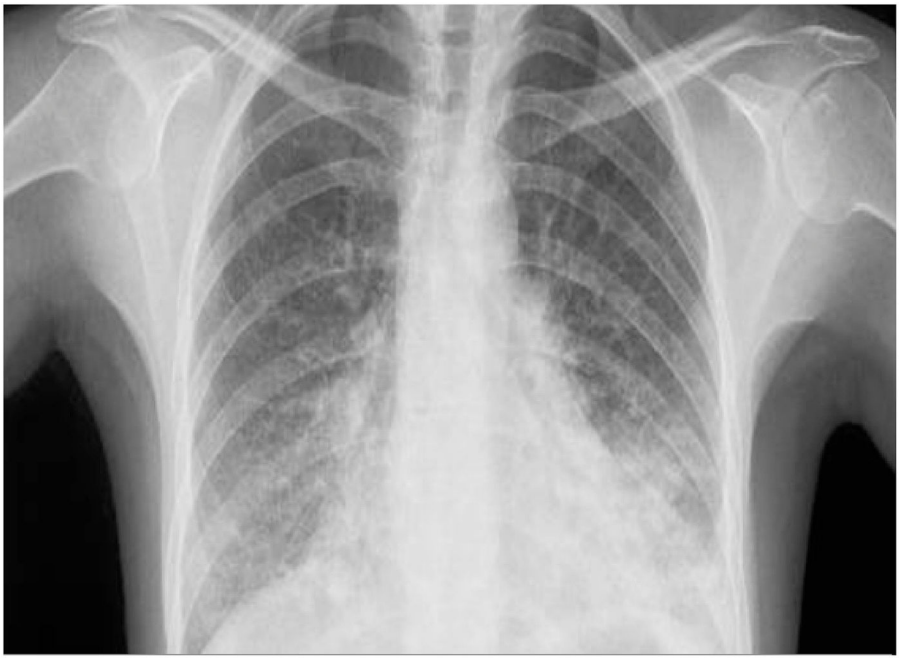

Figure 1 Chest radiography: bilateral ground-glass opacities, predominantly affecting the lung bases.

sion, and treatment was changed to alemtuzumab for safety reasons.

Eight weeks before starting treatment with alemtuzumab, a complete blood count and a serology test including HIV, hepatitis, and varicella zoster viruses yielded normal results. A CMV IgG and IgM test showed negative results.

After a wash-out period of 7 weeks, a first cycle of alemtuzumab was administered over 5 consecutive days without event. Aciclovir at 200 mg/12 hours was started for prophylactic treatment of herpesvirus infection, and maintained for one month. Dietary recommendations to avoid listeriosis were given. A one-month follow-up blood analysis showed 3370 leukocytes/mm^3, with 540 lymphocytes/mm^3 and 6 CD4 + T cells/mm^3. The remaining parameters, including platelets, biochemistry, thyroid hormones, and urine test results, were within normal ranges.

Five weeks after starting treatment with alemtuzumab, the patient attended the emergency department due to fever of up to 38 °C occurring in the evenings since the previous week, and dyspnoea, with a blood oxygen saturation of 93%. Physical examination revealed hypoventilation. A blood analysis revealed elevated transaminase and acute-phase reactant levels (aspartate transaminase 169 IU/L, alanine aminotransferase 163 IU/L, alkaline phosphatase 281 IU/L, gamma-glutamyl transpeptidase 513 IU/L, C-reactive protein 46 mg/dL). Leukocyte count was normal (1310 lymphocytes/mm^3). A chest radiography revealed bilateral ground-glass opacification in the lungs (Fig. 1), which was subsequently confirmed by a chest computed tomography scan that also revealed left basal pneumonia (Fig. 2). Results from blood and urine cultures and an abdominal ultrasound were normal. A serology study returned positive results for CMV IgG and IgM antibodies, with the remaining values being normal.

Polymerase chain reaction (PCR) quantification of CMV DNA revealed 3893 copies/mL; the patient was admitted and started on treatment with valganciclovir dosed at 900 mg/12 hours and intravenous piperacillin/tazobactam dosed at 4/0.5 g/8 hours.

A culture of bronchoalveolar lavage was positive for *P. jirovecii*, and trimethoprim-sulfamethoxazole (TMP-SMX) dosed at 160/800 mg was added. Symptoms resolved after 10 days of treatment, but secondary prophylactic treatment with valganciclovir and TMP-SMX was maintained until the level of CD4 + T cells increased above 200/mm^3. Quantification of CMV DNA was performed weekly, with positive results persisting for 7 weeks.

The patient currently presents no respiratory symptoms and is neurologically stable. The second cycle of alemtuzumab was also administered without event.

In addition to the case described above, a further 4 cases of patients presenting CMV infection after alemtuzumab treatment have been published.[4,5,7] To our knowledge, this is the first case of primary infection with CMV, with positive results for CMV IgG and IgM antibodies approximately one month after onset of treatment with alemtuzumab. This is unusual since the prevalence of CMV seropositivity is approximately 60% in immunocompetent adults from developed countries.[8,9]

Coinfection with *Pneumocystis* spp. is frequent in these patients, since CMV infection enhances the adhesion and replication of other microorganisms.[10]

Cases have previously been reported of CMV reactivation in patients under treatment with alemtuzumab due to chronic lymphocytic leukaemia (CLL), with 4% to 29% of

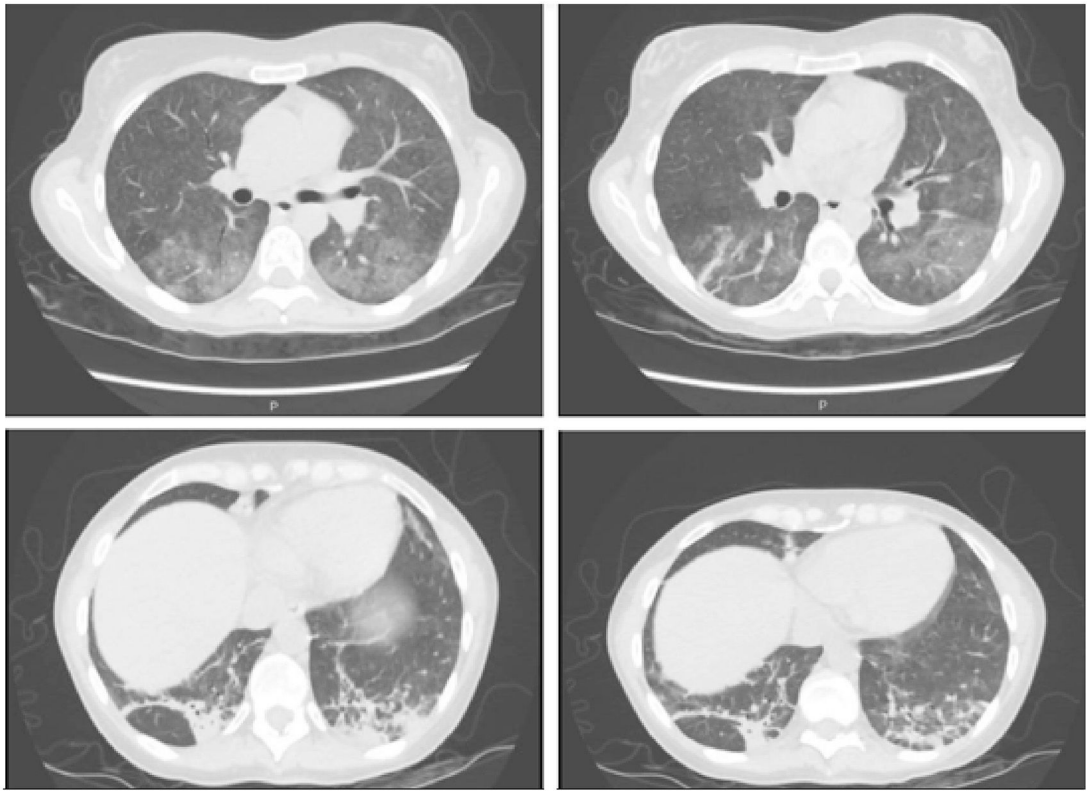

Figure 2 Pulmonary high-resolution computed tomography: infiltrate predominating in both lung bases and left basal pneumonia.

these patients being affected.[11] Guidelines for the management of CMV infection in patients with CLL recommend that a serology test and PCR for CMV be performed before treatment with alemtuzumab is started, and weekly after treatment. In these patients, if PCR results for CMV are positive for 2 consecutive weeks, or if a single assessment with positive results is associated with clinical symptoms, it is recommended to start treatment with valganciclovir for 14 to 21 days (in symptomatic patients) or 7 to 14 days (asymptomatic patients), or until 2 CMV PCR tests return negative results.[11]

CMV infection is a potentially severe complication of treatment with alemtuzumab. With a view to its prevention or early diagnosis, we suggest quantifying CMV IgG and IgM antibodies before administering the treatment and subsequently in patients developing symptoms compatible with the infection. In our opinion, seronegativity for CMV should not rule out the administration of alemtuzumab if the risk/benefit ratio favours treatment; however, clinical vigilance should be increased to detect possible symptoms of primary infection, and serology tests should be performed in case of suspicion. PCR quantification of CMV DNA should be conducted in patients with seroconversion. As recommended by Clerico et al.,[4] patients with positive PCR results should switch from aciclovir to ganciclovir or valganciclovir, as both of these treatments are effective against CMV. In these cases, the addition of prophylactic treatment with TMP-SMX should be considered to prevent coinfection with pneumocystis.

References

1. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380:1829—39.
2. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380:1819—28.
3. Penkert H, Delbridge C, Wantia N, Wiestler B, Korn T. Fulminant central nervous system nocardiosis in a patient treated with alemtuzumab for relapsing-remitting multiple sclerosis. JAMA Neurol. 2016;73:757—9.
4. Clerico M, De Mercanti S, Artusi CA, Durelli L, Naismith RT. Active CMV infection in two patients with multiple sclerosis treated with alemtuzumab. Mult Scler. 2017;23(6):874—6.
5. Yann K, Jackson F, Sharaf N, Mihalova T, Talbot P, Rog D, et al. Acute respiratory distress syndrome following alemtuzumab therapy for relapsing multiple sclerosis. Mult Scler Relat Disord. 2017;14:1—3.
6. S. Wray, D.L. Arnold, J. Cohen, A.J. Coles, C. Confavreux, E.J. Fox, et al. Herpes infection risk reduced with acyclovir pro-

phylaxis after alemtuzumab. In: Presented as poster at the annual meeting of the consortium for multiple sclerosis centers, Orlando, FL, 29 May—1 June 2013.
7. Brownlee WJ, Chatawa J. Opportunistic infections after alemtuzumab: New cases of nocardial infection and cytomegalovirus syndrome. Mult Scler. 2017;23(6):876—7.
8. Gkrania-Klotsas E, Langenberg C, Sharp SJ, Luben R, Khaw K-T, Wareham NJ. Seropositivity and higher immunoglobulin g antibody levels against cytomegalovirus are associated with mortality in the population-based European prospective investigation of cancer-norfolk cohort. Clin Infect Dis. 2013;56:1421—7.
9. Gámez SS, Ruiz MP, Marí JMN. Infección por citomegalovirus humano. Enfermedades Infecciosas y Microbiología Clínica. 2014;32:15—22.
10. Fishman JA. Pneumocystis carinii and parasitic infections in the immunocompromised host. In: Rubin RH, Lowell SY, editors. (ed.) Clinical approach to infection in the compromised host. New York, N.Y.: Kluwer Academic/Plenum Publishers; 2002. p. 265—334.
11. O'Brien SM, Keating MJ, Mocarski ES. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. Clin Lymphoma Myeloma. 2006;7:125—30.

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Cerebellar alterations: an infrequent presentation of neurosyphilis☆

Cerebelopatía por sífilis: una presentación infrecuente de neurolúes

Dear Editor:

With the era of antibiotics, the prevalence of syphilis decreased; however, it has increased in the past 10 years, with an estimated 18 million cases among people aged between 15 and 49 years.[1] Global incidence is 1.5 cases per 1000 population, with higher risk in homosexual men.[2] Neurosyphilis is the term used to refer to central nervous system involvement, which may develop at any stage, even in the early phase. Its manifestations include asymptomatic neurosyphilis, meningitis, meningovascular syphilis, general paresis, and tabes dorsalis, although there are also ''atypical'' forms, which do not meet clinical criteria for classic forms.[3]

We present the case of a 52-year-old homosexual man with a history of secondary syphilis 7 years before. Diagnosis was clinical and results from the non-treponemal (rapid plasma reagin [RPR] of 1:138) and treponemal tests were positive. We administered 2.4 million units of benzathine penicillin, and improvements were observed, with RPR titres decreasing to 1:2; however, at 3 years of follow-up, the same titre persisted and he voluntarily stopped attending his periodic follow-up consultations. The patient attended the emergency department due to a 3-month history of instability and gait disorder, which had worsened in the previous week, when he also developed language impairment. Physical examination revealed mild bulbar dysarthria and dysmetria in all 4 limbs (predominantly in the right side), as well as gait ataxia with tendency to drift, increased base of support, and Romberg sign, and even falls. Ocular motility showed no alterations, muscle balance was preserved in all 4 limbs, superficial and proprioceptive sensitivity were normal, and deep tendon reflexes were present and symmetrical in all 4 limbs. In the targeted medical history interview, the patient reported that he had not presented associated sphincter alterations or neuropathic pain. A cranial and spinal cord magnetic resonance imaging study revealed chronic small vessel disease in both brain hemispheres, without involvement of the cerebellar parenchyma or spinal cord or pathological contrast uptake. A subsequent spinal cord study with somatosensory evoked potentials yielded normal results. A basic blood analysis (blood count, biochemistry, vitamin B_{12} and copper levels) revealed no alterations; in the syphilis serological test, RPR titre was 1:128 and VDRL titre was 1:64; the HIV serology test was negative. A lumbar puncture revealed predominantly lymphocytic pleocytosis (157 cells/mm^3), high protein levels (57 mg/dL), positive VDRL of 1:4, and positive PCR findings for *Treponema pallidum*. Differential diagnosis of rapidly progressive cerebellar syndrome should include structural cerebellar lesions (ischaemic, inflammatory, or tumour), infectious causes (HIV, Epstein-Barr virus, or cytomegalovirus), autoimmune

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