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Case report

Cytomegalovirus primary infection in a patient with multiple sclerosis treated with alemtuzumab

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ABSTRACT

Alemtuzumab is an anti-CD52 monoclonal antibody approved for the treatment of multiple sclerosis (MS). It produces rapid depletion of T and B lymphocytes, which could predispose to opportunistic infections. We report one patient with MS who develops cytomegalovirus (CMV) primary infection after a third cycle of alemtuzumab, with spontaneous recovery associated with rapid lymphocyte reconstitution.

1. Introduction

Alemtuzumab is an anti-CD52 humanized monoclonal antibody. First approved for the treatment of B cell chronic lymphocytic leukemia (CLL), (Moreton et al., 2005) alemtuzumab is approved for the treatment of relapsing-remitting MS since 2013 (Artung et al., 2015).

CD52 antigen is expressed mainly in T and B lymphocytes. Each course of alemtuzumab produces a rapid depletion of these cells, increasing the risk of opportunistic infections in the first weeks after treatment. In patients treated with alemtuzumab for CLL, the incidence of symptomatic CMV infection has ranged from 5 to 30% (Moreton et al., 2005). Its prompt diagnosis is mandatory in order to start specific treatment. As far as we are aware, 6 cases of CMV reactivation after alemtuzumab treatment for MS have been reported (Clerico et al., 2017; Barone et al., 2018; Pappola et al., 2019; Yann et al., 2017; Buonomo et al., 2019), some of them with severe respiratory infection, none with spontaneous recovery.

We report one patient with MS who develops CMV primary infection after third cycle of alemtuzumab, with spontaneous recovery associated with rapid lymphopenia recuperation.

2. Case report

A 36-year-old woman, with no relevant medical history, presented in 2001 with right optic neuritis. She was diagnosed with MS in 2005 after a second relapse. She was treated with subcutaneous interferon beta-1a between 2006 and 2008, then switched to glatiramer acetate due to inefficacy. In 2009, she started alemtuzumab because of clinical and radiological disease activity. She received a 5-dose cycle in 2009 and a 3-dose cycle in 2010, without complications (12 mg/day each dose). She had two term pregnancies, in 2013 and 2016, with no obstetric or neurological incidences. In 2017, she developed new symptoms and 3 new gadolinium-enhancing lesions in brain MRI. Because of that, she received a third cycle of alemtuzumab (3 doses). CMV IgG was negative prior to treatment. She consumed a diet free of undercooked meats, soft cheeses, and unpasteurized dairy products one month prior to treatment and prophylaxis with acyclovir and cotrimoxazole since the first day of alemtuzumab. Ten days later, she presented with asthenia and persistent fever despite having received antibiotics for a urinary tract infection (ciprofloxacin 500 mg every 12 h during 7 days). Chest X-ray, blood tests and lumbar puncture showed no abnormalities, apart from grade 2 lymphopenia (0.59×10^9/l) that resolved in 5 days. 15 days later, blood tests were consistent with a mononucleosis-like disorder (polymorphic lymphocytes with predominance of atypical large lymphocytes), positive CMV IgM and CMV viral DNA PCR in serum (665 UI/ml). Slight liver function abnormality (alanine aminotransferase (ALT) 47 UI/l, aspartate aminotransferase (AST) 34 UI/l) was also found. Abdominal echography was normal. The patient recovered completely in a couple of days, and CMV PCR was negative within a month, so we decided to continue on acyclovir instead to switch to valganciclovir. No other infectious events have been noted to date.

3. Discussion

Alemtuzumab is a highly effective treatment for relapsing-remitting MS. Nevertheless, due to its mechanism of action, it may be associated with opportunistic infections. To prevent them, diet recommendations to avoid Listeria infection and use of acyclovir 200 mg twice a day at least one month after treatment should be recommended to all patients. (Genzyme, 2016) However, acyclovir is not effective in preventing CMV reactivation. Change to valganciclovir should be considered in these

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cases (Clerico et al., 2017; Barone et al., 2018; Martin-Gandul et al., 2017).

To our knowledge, only 6 cases of CMV reactivation after alemtuzumab treatment for MS have been reported (Clerico et al., 2017; Barone et al., 2018; Pappola et al., 2019; Yann et al., 2017; Buonomo et al., 2019). All of the patients described developed the infection within the first month after first cycle of alemtuzumab, with symptoms from fever and abdominal pain to severe respiratory infections as pneumonia (Buonomo et al., 2019) or acute respiratory distress syndrome (Yann et al., 2017). None of them presented spontaneous recovery as with our patient.

In patients who develop fever the first month after alemtuzumab treatment, especially if they also have liver function abnormality or mononucleosis-like syndrome, CMV infection must be considered. Guidelines recommend treatment of all symptomatic patients with positive CMV DNA using valganciclovir or ganciclovir (O´Brien et al., 2019). The performance of liver ultrasound could be considered to rule out the existence of hepatic cysts associated with CMV reactivation.

As far as we are aware, this is the first case reported of CMV primary infection after alemtuzumab. It raises the question of the possible need for pre-treatment in patients with negative CMV IgG prior to alemtuzumab (O´Brien et al., 2019).

Moreover, this is the first case reported of CMV infection after the third cycle of treatment, which emphasizes the need for constant vigilance on this immunotherapy beyond the first cycles.

In addition, unlike other cases described, this case has the peculiarity of spontaneous recovery, probably related to the rapid lymphopenia recuperation of our patient.

Declaration of Competing Interest

The authors of the work “Cytomegalovirus primary infection in a patient with multiple sclerosis treated with alemtuzumab” declare that they have no conflict of interests. Clara Aguirre on behalf of the authors.

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