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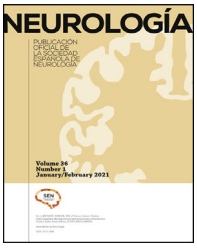

LETTER TO THE EDITOR

Alemtuzumab and autoimmune polyglandular syndrome with type 1 diabetes mellitus

Alemtuzumab y síndrome poliglandular autoinmune con diabetes mellitus tipo 1

Dear Editor,

Alemtuzumab is an anti-CD20 monoclonal antibody used to treat multiple sclerosis (MS) with high clinical and/or radiological activity.[1] This immune reconstitution therapy is known to be associated with adverse autoimmune effects, with autoimmune thyroid diseases (AITD) such as Hashimoto thyroiditis and Graves-Basedow disease being the most frequent.[2,3] Other autoimmune alterations associated with treatment with alemtuzumab for MS, although less prevalent, are glomerulonephritis, immune thrombocytopenic purpura, and vitiligo. In recent years, such other autoimmune diseases as Lambert-Eaton syndrome[4] and type 1 diabetes mellitus (DM1) have also been reported in association with alemtuzumab treatment.[5,6]

We present the case of a patient with MS who, while receiving treatment with alemtuzumab, developed autoimmune diabetes, with autoimmunity defined by positive results in tests for different pancreatic antibodies.

Our patient is a 42-year-old man who was diagnosed with MS in 2007, after presenting neuritis optica. He had no personal or family history of other autoimmune diseases. Due to the high risk of progressive multifocal leukoencephalopathy, treatment with natalizumab was switched for alemtuzumab. At 11 months after receiving the first course of alemtuzumab, he presented hyperthyroidism, with positive test results for antithyroid antibodies (anti—thyroid peroxidase and anti—thyroid stimulating hormone). After the thyroid dysfunction was controlled, he received a second cycle of alemtuzumab, 17 months after the first course. Subsequently, in the light of clinical progression of pyramidal and cognitive symptoms, a third cycle of alemtuzumab was administered at 13 months after the second cycle. Finally, at 25 months after the last cycle, he was diagnosed with DM1, and presence of pancreatic antibodies (ICA, anti-GAD64/65K, anti-IA-2) was detected.

AITD is the most frequent autoimmune complication in patients with MS receiving alemtuzumab,[2,3] whereas autoimmune DM is exceptional.[5,6] In fact, autoimmune DM is not included as an adverse autoimmune effect in alemtuzumab follow-up studies.[3] Despite the possibility that a new autoimmunity may be generated after immune reconstitution treatment, there is always uncertainty as to whether alemtuzumab is the cause or whether the association is coincidental, with different autoimmune diseases occurring in a patient with a certain genetic predisposition. The presence of DM1 is a frequent adverse immune reaction in patients under oncological treatment with monoclonal antibodies acting as immune checkpoint inhibitors; these patients also show presence of pancreatic antibodies and a genetic predisposition through HLA-DR4.[7]

An epidemiological study performed in Sardinia, a Mediterranean region with a high risk of developing MS and DM1, revealed that patients with MS present a high risk of developing DM1, with greater risk among patients with MS who had family members also affected by the disease.[8] Another epidemiological study conducted in the United States reported that DM1 presents a prevalence of 0.92% among patients with MS and that this percentage did not significantly differ from that observed in the general population. It also reported that diabetes usually manifests before diagnosis of MS, with a mean duration of diabetes of 17 years, with family history of the disease in 36% of cases.[9] Between 3.9% and 24% of patients with DM1 also present AITD, and 24% of adult patients with latent autoimmune DM present thyroid antibodies. However, between 1% and 10% of patients with AITD but not DM1 present pancreatic antibodies.[10]

From an endocrine viewpoint, our patient presents autoimmune polyglandular syndrome type 3 (APS-3). Specifically, he presents 3 autoimmune diseases that correspond with 2 types of APS-3: type 3, with AITD associated with DM1, and type 3C, in which AITD is associated with MS.[10]

Given the strong association between AITD and autoimmune diabetes, and the fact that risk of DM1 in patients with AITD is proportionate to the number of positive pancreatic antibodies,[10] we consider it potentially beneficial to determine these pancreatic antibodies early in patients with MS and AITD treated with alemtuzumab to monitor for the development of diabetes mellitus. Further-

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more, our clinical case supports previous reports of DM1 as a new adverse autoimmune reaction to treatment with alemtuzumab.[5,6]

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