Autoimmune thyroid disease following treatment with alemtuzumab for multiple sclerosis

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Abstract
Alemtuzumab, an anti-CD52 monoclonal antibody, is effective in the treatment of relapsing–remitting multiple sclerosis (RRMS). Common adverse effects include the development of autoimmune diseases, and Graves' disease is one of the most frequent presentations. We report here a case of alemtuzumab-induced thyroid disease in a female patient who showed a phase of thyrotoxicosis with positive anti-thyroglobulin (anti-Tg) and anti–thyroid peroxidase (TPO) antibodies, but a negative TSH receptor antibody, spontaneously followed by hypothyroidism. The aim is to illustrate the clinical presentation, evaluation over time, and the possibility to consider a conservative management up to the spontaneous resolution of the thyrotoxicosis. All these are intended to emphasize the importance of pretreatment screening and follow-up in the management of treatment with alemtuzumab.

Keywords
alemtuzumab, autoimmunity, monoclonal antibody, multiple sclerosis, thyroid disease

Date received: 23 October 2018; accepted: 21 February 2019

Introduction
Multiple sclerosis (MS) is a debilitating chronic immune-mediated disease of the central nervous system. The prevalence of autoimmune thyroid diseases in patients has been examined in several studies with conflicting results. Some authors report rates consistent with the prevalence in the general population.

Alemtuzumab is a monoclonal antibody directed against CD52, a cell surface marker found on mature lymphocytes, which is approved for the treatment of active relapsing–remitting multiple sclerosis (RRMS). MS pathogenesis is believed to begin with activation and proliferation of autoreactive lymphocytes that recognize as-yet-unidentified autoantigens and initiate inflammation via production of pro-inflammatory cytokines. Alemtuzumab effectively decreases the relapse rate and the disability progression in RRMS also in patients resistant to basic immunomodulatory drugs. Alemtuzumab acts altering the circulating lymphocyte pool, and autoimmunity is the most important adverse event associated with its administration.

Thyroid autoimmune dysfunction may occur in approximately 20%–30% of the patients who receive alemtuzumab for MS, and Graves' disease is the most common presentation (60%–70%). The annual incidence of the first episode of thyroid dysfunction increases each year for 3 years, and
International Journal of Immunopathology and Pharmacology

during follow-up, the prevalence of thyroid dysfunction increased to 30%, with the onset ranging from 6 to 61 months after first administration. For these reasons, many authors recommend thyroid evaluation prior to alemtuzumab and quarterly during its administration for 48 months. Daniels and colleagues proposed to prolong the surveillance period of these patients up to a median time of 57.3 months and a maximum of 80.6 months.

Nevertheless, the pathogenesis of alemtuzumab-associated autoimmune disorders has not yet been fully established; few clinical cases have been reported, and the most frequent cases are patients with Graves' disease. We describe here a patient with alemtuzumab-induced thyroid disease who showed a phase of thyrotoxicosis that underwent to spontaneous resolution.

Case presentation

A 37-year-old female, weight 56.5 kg and height 1.67 m, with RRMS resistant to interferon administration and a family history positive for hypothyroidism pathology received alemtuzumab in April 2016 for 6 days. In October 2017 (18 months after the second alemtuzumab administration), the patient had tachycardia, and the ultrasound scan showed a volume-increased thyroid gland and a markedly inhomogeneous parenchyma suggesting the presence of thyroiditis. The blood test revealed a suppressed thyroid-stimulating hormone (TSH; 0.02 mIU/L) and low levels of FT4 (4.8 ng/dL), but normal values of FT3 (4.1 ng/dL; Figure 1). As a result of persistence of hypothyroidism, the patient was given LT4 replacement therapy at the dose of 50 µg once daily.

In May 2018, the patient must increase the dosage of LT4 replacement therapy at 75 µg once daily to achieve good hormonal compensation. In effect, the patient takes LT4 replacement therapy at the dose of 87.5 µg once daily.

Discussion

Alemtuzumab treatment is effective in patients with RRMS. It is a monoclonal antibody that acts by inducing rapid and prolonged depletion of lymphocytes with a consequent immunosuppression. This effect is followed by a phase of immune reconstruction with restoration of lymphocyte networks. Therefore, this monoclonal antibody aims to remove the cause of inflammation in MS.

Autoimmunity is the most important adverse event associated with alemtuzumab treatment; however, the cause of this event is not clear. A single administration of alemtuzumab can lead to a rapid, profound, and prolonged lymphopenia. However, lymphopenia alone does not induce autoimmunity. Two important factors that play a role in this mechanism are the depletion of the regulatory T cells (Tregs) and the overproduction of interleukin (IL)-21. Lympocyte depletion is driven by levels of IL-21 that are genetically higher in patients who develop autoimmunity even before starting treatment. Therefore, this genetic asset had also positive anti-thyroglobulin (TG; 196 IU/mL, normal values <4) and anti–thyroid peroxidase (TPO) antibodies (482 IU/mL, normal values <9), but negative TSH receptor antibody. The patient was prescribed propranolol (40 mg, once daily) up to the remission of symptoms.

In November 2017, the patient was already asymptomatic. The blood test revealed TSH (0.02 mIU/L) and low levels of FT4 (0.67 ng/dL) and FT3 (2.32 ng/dL). TSH receptor antibody continued to be negative. The patient begins a tight control without therapeutic prescription.

In December 2017, the ultrasound scan showed a thyroid parenchyma with a leopard patch appearance as a flogistic insult and vascularization of both lobes increased widely. The blood test revealed a strong spontaneous increase in TSH (43.97 mIU/L) and persisting low FT4 (4.8 ng/dL), but normal values of FT3 (4.1 ng/dL; Figure 1). As a result of persistence of hypothyroidism, the patient was given LT4 replacement therapy at the dose of 50 µg once daily.

In May 2018, the patient takes LT4 replacement therapy at 75 µg once daily to achieve good hormonal compensation. In effect, the patient takes LT4 replacement therapy at the dose of 87.5 µg once daily.

Figure 1. Serum TSH, FT4, and FT3 values in the patient with relapsing–remitting multiple sclerosis.
increases the probability of encountering specific self-antigens and generating self-reactive T-cells.\textsuperscript{10} Autoimmune thyroid dysfunction seems to occur in approximately 20\%-30\% of patients who receive alemtuzumab for RRMS, and all these factors together have been called into play to trigger thyroid autoimmunity. In addition, Tregs have immunomodulatory properties; therefore, a dysbalance of Tregs can trigger the production of autoantibodies against the thyroid gland.\textsuperscript{6}

Graves’ disease is the most common alemtuzumab-associated thyroid dysfunction (60\%-70\%).\textsuperscript{7} There is a specific susceptibility to develop Graves’ disease.\textsuperscript{9}

In a phase 2 trial of patients with RRMS treated with alemtuzumab, positive antibodies were found in 84.7\% of episodes of overt or subclinical hyperthyroidism. The presence of TRAb is usually specific for Graves’ syndrome, despite this can turn to Hashimoto’s thyroiditis and hypothyroidism and vice versa. The probability that an individual will develop TRAb positive and Graves’ disease depends on sex, human leukocyte antigen (HLA) genotype, and family history,\textsuperscript{11} and positivity to the TRAb indicates a probable relapse of the disease.

We reported here the case of a patient with RRMS who developed thyroid disease after treatment with alemtuzumab. The patient showed a phase of thyrotoxicosis with positive anti-TG and anti-TPO antibodies, but a negative TSH receptor antibody, followed by a spontaneous phase of hypothyroidism, and she achieved euthyroidism only after LT4 administration.

This case report aims to remember the hypothesis that although Graves’ disease is the most common thyroid autoimmune disease that develops during treatment with alemtuzumab, it must be considered that destructive thyroiditis with thyrotoxicosis may be found and that spontaneous remission of overt thyrotoxicosis may occur in some patients. Indeed, Daniels and colleagues have reported that this disease may be found in about 4\% of the patients.\textsuperscript{5} In our case, it is interesting to note the rapid spontaneous resolution of thyrotoxicosis to emphasize that the normalization of thyroid dysfunction can be achieved. In light of all these, we suggest pretreatment screening and continued follow-up for thyroid function and autoimmune assessment in patients with RRMS undergoing treatment with alemtuzumab.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent
The patient has signed an informed consent for the use of her sensitive data.

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