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Thyroid dysfunction after Alemtuzumab treatment for multiple sclerosis: diagnostic and therapeutic modalities

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**Introduction:** Alemtuzumab is a humanized monoclonal antibody against CD52, located on the surface of the lymphocytes, used in the treatment of relapsing-remitting multiple sclerosis (RRMS), that can induce novel secondary autoimmune diseases. Autoimmunity may be related to the pattern of T- and B-cell depletion and repopulation following Alemtuzumab treatment. The most frequently reported autoimmune disorders observed with alemtuzumab involve the thyroid gland in up to a third of patients, followed by thrombocytopenia and nephropathies. We report our experience in treating these complications in five patients among 20 RRMS patients that received Alemtuzumab.

**Case reports**: A patient received Alemtuzumab in 2015 and 2016. Hashimoto thyroiditis (HT) occurred in 2017 with hypothyroidism and peroxidase antibodies (TPOAb). A second patient received Alemtuzumab in 2016 and 2017. In 2018, she suffered transient hyperthyroidism, followed by euthyroidism, and then a recurrence of subclinical hyperthyroidism, without the need for treatment. TPOAb, thyroglobulin antibodies (TGAb) and TSH receptor antibodies (TRAb) were positive. A third patient received Alemtuzumab in 2015 and 2016. Hypothyroidism occurred in 2017, and supplementation by Levothyroxine was introduced. In 2018, transient hyperthyroidism led to discontinuation of supplementation. Then, a resurgence of hypothyroidism was observed and Levothyroxine was resumed. TPOAb, TRAb and TGAb were positive. A fourth patient received Alemtuzumab in 2011 and 2012. In 2014, Graves’ disease (GD) occurred with overt hyperthyroidism, TPOAb and TRAb. He received radioiodine (RAI). A month later, hypothyroidism occurred. A fifth patient with RRMS received Alemtuzumab in 2016 and 2017. In 2019, HT appeared with hypothyroidism, TPOAb, TRAb and TGAb.

**Discussion:** As suggested by cases 2-to-5, Alemtuzumab-associated thyroiditis is more likely to be mediated by TRAb. Indeed, reconstitution autoimmunity is more frequently autoantibody-mediated rather than Th1-mediated, like HT. *Alemtuzumab-associated GD is an intriguing autoimmune paradigm*. First, conversion from hyper to hypothyroidism, and inversely, can be observed, like in case 3. The change from stimulating to blocking TRAb may be the mechanism for this switch. Second, these patients have a better remission rate, spontaneously or under treatment, as illustrated in case 2. Therefore, first-line treatment in Alemtuzumab-related GD should consist of antithyroid drugs, while RAI or surgery are less conservative, and should be second-line therapies.

**Conclusion:** Alemtuzumab-related thyroiditis is a model potentially leading to further inside into thyroid physiopathology. A TSH monitoring is recommended before starting Alemtuzumab, until 48 months after the last delivery. We suggest a longer follow-up, and to measure both TPO and TRAb.