


CASE REPORT

Graves' orbitopathy after allogeneic bone marrow transplantation in a patient with Fanconi anemia – side effect of alemtuzumab therapy?

Luminita Nicoleta Cima¹ , Ioana Maria Lambrescu^{1,2}, Lavinia Stejereanu^{1,2}, Anca Colita^{3,4}, Reuven Or^{5,6} & Simona Fica^{1,7}

¹Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

²Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

³Department of Pediatric Bone Marrow Transplantation, Fundeni Hospital, Bucharest, Romania

⁴Pediatrics, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

⁵Department of Bone Marrow Transplantation, Cancer Immunotherapy & Immunobiology Research Center, Hadassah University Hospital, Jerusalem, Israel

⁶Hematology, Hadassah Hebrew University Medical Center, Jerusalem, Israel

⁷Department of Endocrinology, Diabetes and Metabolic Disorders, Elias University Hospital, Bucharest, Romania

Correspondence

Luminita N. Cima, Assistant Professor in Endocrinology Carol Davila University of Medicine and Pharmacy, Endocrinology Department Elias Hospital Address: Marasti Avenue 17, 011461, Bucharest, Romania. Phone/Fax: +40 213161614; E-mails: luminita.cima@gmail.com; luminitasapera82@yahoo.com

Key Clinical Message

A few cases of thyroid eye disease following alemtuzumab therapy have been described in patients with multiple sclerosis. Our patient is the first case of Graves' orbitopathy after alemtuzumab conditioning for hematopoietic stem cell transplantation.

Keywords

alemtuzumab therapy, bone marrow transplantation, Graves' orbitopathy.

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Introduction

Fanconi anemia (FA) is a rare autosomal recessive or X-linked syndrome that is characterized by bone marrow failure and congenital abnormalities. Allogeneic bone marrow transplantation (BMT) is currently the only cure for the hematological complications associated with FA [1, 2]. Alemtuzumab is a monoclonal antibody directed against CD52-positive cells used in some of the pre-BMT conditioning regimens. This drug has been associated with autoimmune thyroid disease (ATD) in approximately a third of treated patients with multiple

sclerosis (MS) [3–5]. Three cases of new onset ATD have been reported after the use of alemtuzumab in pediatric patients following allogeneic BMT for sickle cell disease [6]. Less than ten cases of thyroid eye disease following alemtuzumab therapy have been reported in patients with MS [7–9], but none in patients with BMT.

In this article, we report a case of a patient who developed both Graves' disease (GD) and Graves' orbitopathy (GO) 3 years after BMT for FA. To the best of our knowledge, our patient is the first case in which GO is documented in the post-BMT period in a patient who received conditioning regimen with alemtuzumab.

Case Report

The patient was diagnosed with FA at 7 years of age (2009) and an allogeneic BMT from a HLA partially matched unrelated female donor (mismatched allele at B and at DR loci) was performed at the age of 10 (2012). Personal and family history of the donor and recipient were unremarkable for thyroid autoimmunity.

Pre-BMT conditioning consisted of fludarabine 30 mg/m² per day X 6 days 30 mg/m²/day X-6 days, endoxan 10 mg/kg X 4, iv Thymoglobulin 2.5 mg/kg once (treatment was stopped following severe allergic reaction) and Campath (alemtuzumab) 15 mg S.C. injection X 1. The patient received peripheral blood stem cells from an unrelated donor (TNC- 22 × 10⁸/kg; CD34 = 7 × 10⁶/kg). After the BMT, he started immunosuppressive treatment with CSA and mycophenolate mofetil (Cellcept) for the prophylaxis of graft-versus-host-disease (GVHD). At day 15 after engraftment, the patient suffered from severe acute GVHD that was treated with steroids and low dose methotrexate with good response.

In May 2015, 3 years after BMT, he was first referred to our clinic for endocrine evaluation presenting diffuse goiter. The laboratory evaluation revealed hyperthyroidism: free thyroxine (FT4), 4.4 ng/dL (reference range: 0.89–1.76 ng/dL); thyroid-stimulating hormone (TSH), <0.004 µIU/mL (reference range: 0.4–4.4 µIU/mL); and the thyroid ultrasound showed a diffused enlarged, hypervascular thyroid gland with heterogeneous thyroid echotexture. Both antiperoxidase antibodies (ATPO) and TSH receptor antibodies (TRAb) were highly elevated at the time of diagnosis: ATPO = 324 IU/mL (reference range: 5–35 IU/mL), TRAb = 28 U/L (reference range < 1.5 U/L). In this context, he was diagnosed with GD and received treatment with antithyroid drugs.

In November 2015, he was reevaluated in our clinic due to the appearance of ophthalmologic abnormalities (upper eyelids swelling, retraction of the lower eyelids, discrete eyelids erythema, mild exophthalmia, especially at his right eye). The ophthalmological examination diagnosed evolutive orbitopathy. Magnetic resonance of the orbits showed enlargement of both the orbital fat compartments and the extraocular muscles (Fig. 1A and B). He started a 6-month course of selenium supplementation and pulse therapy with methylprednisolone with a good clinical outcome.

Discussion

Disorders of the thyroid are common in FA [1, 2]; 60% of individuals with FA have primary hypothyroidism [2]. The mechanism of hypothyroidism in FA is usually not autoimmune; thyroid cell apoptosis as a consequence of unrepaired

DNA damage from oxidative injury or central hypothyroidism due to hypothalamic dysfunction is probably the underlying mechanisms [2]. In spite of being a phenotypically heterogeneous disease, FA is not linked to autoimmune hyperthyroidism to the best of our knowledge.

In contrast, after the BMT, both occurrence [10] and remissions [11] of GD have been reported. According to Weetman, most cases of GD which follow BMT are probably the result of adoptive immunity [12], in which clones of autoreactive T cells from a donor with G expand in the recipient [11, 12], but there is also some evidence that link disordered immunoregulation due to chronic GVHD with expansion of clinically silent autoreactive donor lymphocytes to produce autoimmune disease in the recipient [12]. Our patient presented with acute GVHD that was successfully treated with glucocorticoids and methotrexate, making this an unlikely etiology.

Arguing against the possibility of transmission of alloreactive lymphocyte clone from the donor is the possibility of spontaneous development of GD in a patient at high risk of ATD on a genetic basis. However, this is probably not the case given the family history of our patient. In addition, the extended interval between the BMT and the onset of the symptoms makes this pathogenesis unlikely.

We were not able to assess if the immune clone that led to the appearance of hyperthyroidism in this patient was transmitted from the donor graft—or had its origin in the recipient's bone marrow, but giving the fact that there is no family/personal history of thyroid autoimmunity and the fact that the patient is 100% donor chimera we speculated that the clone was of donor origin.

Furthermore, alemtuzumab therapy that was used in the pre-BMT conditioning in our patient has been linked to the appearance of autoimmune diseases in adult patients with MS [4, 5]. This drug was associated with ATD in approximately a third of treated MS patients and overt Graves' hyperthyroidism represented approximately half of these cases [5]. A study performed by Cossburn et al. showed that the ATD following alemtuzumab occurred most frequent after 12–18 months after the first dose, the risk of ATD was independent of total alemtuzumab dose [3] and immune reconstitution has been implicated in the pathogenesis of ATD after the use of this monoclonal antibody [13]. Daniels et al. observed that the alemtuzumab-treated patients with MS developed GD mainly in the third year after first administration (16.1%) [8] and four of the 39 hyperthyroid patients developed GO [8]. The authors remarked the high incidence of GD in alemtuzumab-treated patients with MS in spite of the fact that thyroid dysfunction is not commonly observed in patients with chronic B-cell leukemia treated with a much higher total dose of alemtuzumab than used

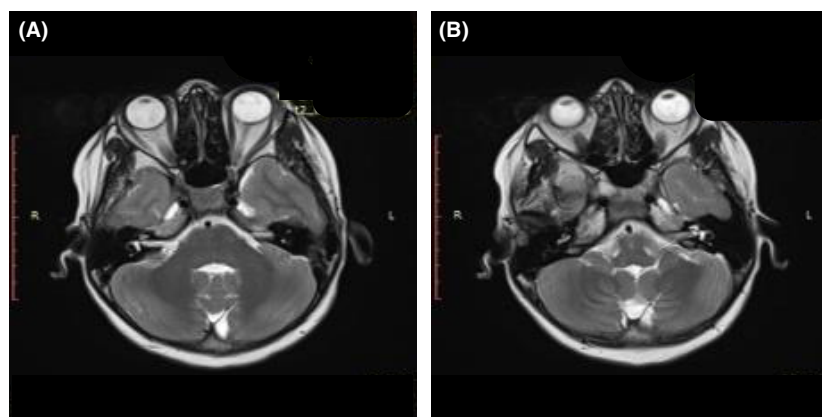


Figure 1. (A and B) The native MRI scan of the orbits, without contrast, showing enlargement of extraocular muscles and orbital fat.

for MS. However, GD has been described in patients receiving alemtuzumab after renal transplantation [8] and three cases of new onset ATD have been reported after the use of alemtuzumab in pediatric patients following allogeneic BMT for sickle cell disease [12].

The mechanisms behind it are still uncertain, but it seems that thyroid dysfunction occurring after alemtuzumab therapy is an example of acquired autoimmunity [6, 12]. The study of Cox *et al.* showed that after an initial depletion of lymphocytes, the B lymphocytes recovered earlier than T lymphocytes [14], making the patients more susceptible to autoimmunity [4, 9]. Also, the level of IL-21 was elevated in patients who developed ATD following alemtuzumab administration [5, 15] and it has been shown that this molecule promotes proliferation of CD4⁺ and CD8⁺ cells *in vitro*, enhancing cell cycling and potentially the risk for autoimmune complications [5].

The conditioning regimen for allo-BMT in the three patients with sickle cell disease who developed GD included busulfan [6], which is known to be involved in thyroid damage, but all of these patients presented high titers of thyroid antibodies as well that could have been related to alemtuzumab-induced auto/allo-immunity [6].

A few cases of thyroid eye disease following alemtuzumab therapy have been described in patients with MS [7–9], but we found no report of GO in the post-BMT period in a patient that received conditioning regimen with alemtuzumab. We found one case of GO in the literature in a patient with GD following BMT that appeared to be a consequence of radioiodine treatment (I131–300 MBq) for GD. The patient was treated with oral glucocorticoids; in a few months, the orbitopathy became inactive, all the soft tissue signs disappeared, while the increased exophthalmos persisted [10]. However, this case was not related to alemtuzumab administration.

Conclusion

To the best of our knowledge, our patient is the first case of GO following allo-BMT after performing conditioning with alemtuzumab. GO is a rare complication in transplanted patients and was not present in our patient from the start. It may be a side effect of alemtuzumab therapy, but also it can be a result of allo-immunity adopted from the donor or a subclinical manifestation of chronic GVHD.

In conclusion, transplanted patients need lifelong endocrine follow-up because of the possible endocrine complications that can occur as a result of pathological clones either transmitted or self-originated even a few years after BMT.

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Conflict of Interest

There is no conflict of interest to declare.

Authorship

CL: performed the literature review for documentation, designed the article, collected and assembled data from patient's sheet, interpreted results, and drafted the manuscript. LI and SL: contributed with patient care and reviewed the manuscript. CA, RO, and FS: contributed with patient care and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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