

CASE REPORT

Graves' orbitopathy in a patient with adrenoleukodystrophy after bone marrow transplantation

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Abstract

Objective: For many years, the treatment of X-linked childhood cerebral adrenoleukodystrophy (XALD) consisted of hydrocortisone replacement and a mixture of short chain-fatty acids, known as 'Lorenzo's oil'. Recently, bone marrow transplantation (BMT) has also been used.

Case report: We report the case of a patient affected by XALD who developed Graves' hyperthyroidism (GH) and Graves' orbitopathy (GO) after BMT and who we could follow-up for 6.5 years afterwards.

Evidence synthesis: A boy affected by XALD was treated at the age of 6 years, with a whole BMT from his sister. One year after BMT, the transplanted patient presented TSH at the lower normal value and 3 years later he developed thyrotoxicosis. After a further 2 years, the patient developed GO, which showed clinical evidence of reactivation 5 years after its onset as a consequence of an attempt to treat thyrotoxicosis by means of I¹³¹ (300 MBq). Seven years after BMT, the donor showed alterations of thyroid autoimmunity and 1 year thereafter she developed GH. She never presented GO during a subsequent 5 year follow-up.

Conclusions: This case illustrates that autoimmunity originating from a pre-symptomatic donor can be transferred into the host during allogeneic stem cell transplantation. In cases where autoimmune phenomena are recognized in the donor prior to donation, alternative donors or T-cell manipulation of the graft might be considered.

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Introduction

X-linked childhood cerebral adrenoleukodystrophy (XALD) is a peroxisomal disorder involving defective β -oxidation of very long-chain fatty acids that accumulate in plasma, brain, and adrenal cortex (1). Clinical symptoms include adrenal insufficiency and motor-mental deterioration accompanied by visual and hearing impairment due to intracranial demyelination (1, 2).

For many years treatment consisted of hydrocortisone replacement and administration of a mixture of short-chain fatty acids, known as 'Lorenzo's oil' (1). Recently, bone marrow transplantation (BMT) has been reported to decrease the elevated blood levels of very long-chain fatty acids, to reduce the intracranial demyelination, and in turn to ameliorate the neurologic symptoms of the disease (2–5).

BMT can be regarded as an *in vivo* model of inducing autoimmune reactions, as in this procedure human leukocyte antigen (HLA) matched bone marrow cells

are exposed to a new set of pre-existing antigens. Occasionally, BMT has been related to both transmission (6–9) and cure (10, 11) of autoimmune diseases, and relapse of Graves' disease after BMT has also been described (12). Considering that only 30% of the patients with Graves' hyperthyroidism (GH) may develop Graves' orbitopathy (GO) (13), it is not surprising that publications that link BMT to GO are scarce. We are aware of only one publication reporting concordant GH and GO after BMT (14), and could not find any other by means of a computerized search using MEDLINE.

In this article, we present and discuss the case of a patient affected by XALD, who developed GH 4 years, and GO 6 years after BMT from his sister. Seven years after BMT, the donor also showed alteration of thyroid autoimmunity and 1 year thereafter she developed GH. Both patient and donor were followed up for 12 years after BMT.

Case report

A 12-year-old boy affected by XALD was referred to the Orbital Center, Department of Ophthalmology, University of Amsterdam with a 3 month history of bilateral signs and symptoms compatible with GO. The boy had been treated with supplementary 'Lorenzo's oil' and hydrocortisone replacement therapy since when, 6 years prior to our observation, his neurological deterioration imposed a whole BMT from his sister, which resulted in successful control of XALD. The transplant was HLA identical and at 2 years post-BMT full-donor chimerism was found. There was no evidence of acute or chronic graft-versus-host disease (GVHD). BMT was preceded by cytoreductive conditioning protocol with chemotherapy (busulfan 4 mg/kg in four daily doses from day 9 till day 5 and cyclophosphamide 50 mg/kg in a single daily dose from day 5 till day 2 before BMT). After the transplant, standard cyclosporin A and a short-course methotrexate (10 mg/m² i.v. at days +1, +3, and +6) were administered to prevent acute GVHD. At the moment of BMT, the donor was 7 years old and free from thyroid diseases, but at the age of 14, 7 years after the BMT, she showed alterations of thyroid autoimmunity with raised anti-thyroperoxidase autoantibodies (TPO-Ab; 80 kU/l), and 1 year thereafter she developed GH (TPO-Ab 280 kU/l, thyroxine (T₄) 200 nmol/l, and tri-iodothyronine (T₃) 295 nmol/l).

Before BMT, the transplanted patient had never presented hypo- or hyperthyroidism, and TSH had always been normal, as documented by several blood tests performed at our hospital, during the 3 years preceding BMT. Starting from the year following the BMT, TSH was found to be at the lower normal value and 2 years prior to our examination the transplanted patient had developed thyrotoxicosis (Table 1) that was corrected with block and replacement therapy (methimazole 30 mg/die and L-T₄ 25 µg/die).

At his ophthalmic baseline examination, in September 2002, the patient presented an eyelid aperture of 12 mm right and 15 mm left with respectively a 2 mm lower lid retraction right, a 2 mm upper, and 1 mm lower lid retraction left. Hertel values were bilaterally 17 mm, and a mild eyeball dystopia of 2 mm with left eye over right was present (Fig. 1). The orbitopathy was not active and according with NOSPECS classification (15) its severity was 2a, 30, 40, 50, and 60. Anterior segment, intraocular pressure, and fundus were normal. Natural visual acuity was bilaterally 20/20.

Direct and indirect pupil reflexes were normal and the patient could read all the Ishihara tables either with the left or the right eye. Orthoptic evaluation was unremarkable and computer tomography of the orbit showed a mild enlargement of the extraocular muscles. The diagnosis of inactive, mild GO was made.

Table 1 Laboratory findings in a patient with adrenoleukodystrophy, before and after bone marrow transplantation that took place in 1996.

Date	09-1993	04-1994	04-1994	09-1997	03-1999	12-2000	04-2001	04-2001	04-2002	07-2003	08-2004	06-2005	06-2006	01-2007	03-2007	07-2007	11-2007	06-2008
T ₄ (nmol/l)	135	155					130	95	80	125	90	95	100	190	180	60		
T ₃ (nmol/l)	2.05	1.85					2.60	2.15	2.40	1.10	2.15	1.95	2.80	7.00	4.50	1.05		
TSH (mE/l)	2.00	2.40		0.49	0.71	<0.005	0.04	12.20	4.20	4.10	4.90	0.35	<0.01	<0.01	<0.01	<0.01		
TBG (nmol/l)	380			18.00	13.1	52.8	290	370	300	250	290	260	280	240	240	57.5	10.1	
T ₄ -free (pmol/l)	16.2	23.3					19.3	13.1	15.2	18.2	15.0	17.5	>70.0	>70.0	55.8			
Tireoglobulin (pmol/l)							32							2	<1			
TPO-Ab (kU/l)						Positive	520	220	110	280	90	90	>3000	>3000	>3000	>3000	>3000	
TBII (E/l)							2.9	2.9	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	56.0	31.2	10.6	4.1
TSI (E/l)							46											

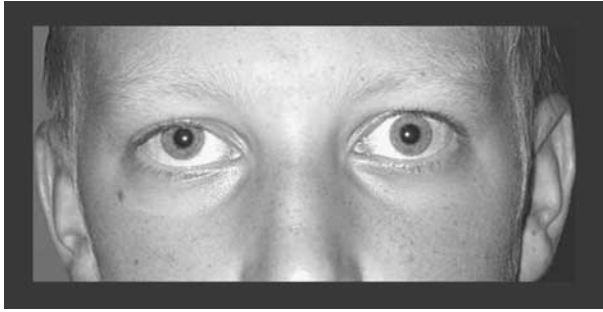


Figure 1 The patient affected by adrenoleukodystrophy, aged 12 years, at his baseline ophthalmic examination 6 years after bone marrow transplantation.

After block and replacement therapy had been suspended for a few months, the patient developed recurrent thyrotoxicosis. For this I^{131} (300 MBq) was administered in February 2007. About 6 weeks later, the patient, aged 17 years, presented a reactivation of the orbitopathy. The reactivation included worsening of the soft tissue signs, increasing of the exophthalmos up to 23 mm both sides, with rising of the clinical activity score (16) from 0+/10 to 5+/10 (retroocular tension, conjunctival hyperemia, redness of the skin, periorbital edema, and increased exophthalmos). Visual function and extraocular eye motility remained normal. The symptoms could be controlled with oral glucocorticoids, and in a few months, by the end of the summer, the orbitopathy became inactive, all the soft tissue signs disappeared, while the increased exophthalmos persisted.

The ophthalmic picture remained stable up to the end of the summer 2008, despite a further treatment with I^{131} (350 MBq) that took place in April 2008. A few months after this further treatment with I^{131} the patient became euthyroid under $L-T_4$ replacement therapy, thyrotropin-binding inhibitor immunoglobulin (TBII), and TPO-Ab remained elevated (4.1 E/I and > 3000 kU/l respectively).

The patient's sister never showed clinical evidence of GO during the entire follow-up period, which lasted 5 years from her first alterations of thyroid autoimmunity.

Discussion

We report the case of a boy who was treated with whole BMT for XALD. This X-linked disorder has stabilized following treatment, but the patient developed GH and GO thereafter. Although the temporal relation among these events supports the role of BMT in inducing GH and GO, other etiopathogenetic hypothesis cannot be neglected and should therefore be included into the possible case scenario.

Although Laureti *et al.* (17) reported that two out of five patients with adult onset of XALD presented elevated titers of thyroid microsomal autoantibodies

and one of them developed clinical hypothyroidism, GO has never been described as part of XALD, and at present there is no evidence that GH or GO and XALD are connected in one way or another. Nevertheless, immunomodulation might play a role in the pathomechanism of demyelination as well as in the development of GH or GO. The positive familiar history for alteration of thyroid autoimmunity presented by the transplanted patient that we report may itself be a factor connected with a higher risk for developing other autoimmune disorders such as autoimmune thyroid disease (ATD) or GO (14, 18), although he had never presented hypo- or hyperthyroidism or alterations of thyroid autoimmunity before BMT as is documented by several blood tests performed in the years preceding such a procedure (Table 1).

Occurrence and remission of GH after BMT have been reported (11, 12). Although thyroid dysfunction is a common long-term complication associated with total body irradiation given in the pre-BMT conditioning protocol, Slatter *et al.* (9) reported thyroid dysfunction also in patients who were given cytoreductive conditioning with chemotherapy, but without total body irradiation as was the case for the patient we report. They found that 10.8% of their patients had clinical and/or biochemical thyroid dysfunction at 4 months to 4.5 years post-BMT, and 33% of these patients had positive antithyroid microsomal antibodies.

Both thyroid stimulating and blocking autoantibodies were detected after BMT (10).

According to Sherer's and Shoefeld's hypothesis, the induction of autoimmune diseases post-BMT lays its foundations into the current understanding of GVHD (19), and it could fit to the case that we report, although the patient did not show typical evidences of GVHD. Graves' disease is a multisystemic autoimmune disorder characterized in its complete form by alteration of thyroid metabolism, orbitopathy, dermatopathy, and acropachy. It involves autoantigens common to the thyroid and other affected body districts. The autoimmune attack on the thyroid leads, in the majority of cases, to alteration of thyroid hormones homeostasis, and the autoimmune attack on the orbit causes the typical constellation of signs and symptoms that characterize the clinical picture of GO.

It has been shown that orbital tissue from patients with GO is infiltrated with B and T cells, and it has been reported that orbital fibroblasts from Graves' patients can stimulate proliferation of autologous T cells (20) and that autologous T cells from patients with GO can stimulate proliferation of orbital fibroblasts, thus providing a mechanism by which infiltration of orbital tissue by autoimmune lymphocytes can drive the pathogenic features of GO (21). Another evidence of the involvement of T lymphocytes in the pathogenesis of GO derives from the observation that newborns from mothers with GO can be hyperthyroid as a result of possible passage of thyroid-stimulating IgG through the

placental barrier, but they never show GO at birth due to the placental barrier to T lymphocytes (22, 23).

Here, we show that whole BMT, from a donor who was free from thyroid diseases at the time of BMT, but who developed GH thereafter, may be involved in the induction of GO 6 years later in the transplanted patient. It is likely that the disease process is primarily dependent upon altered function of the T lymphocyte. Although the immune mechanisms underlying the orbitopathy as well as the primary autoantigens involved in the disease are poorly characterized, it can be hypothesized that dormant autoreactive T cells once transplanted could have been activated by non-professional antigen-presenting cells, such as orbital fibroblasts.

Afterwards, T-cell-driven stimulation of orbital fibroblasts to upregulate expression of MHC class II and the presentation of autoantigens could have occurred. This in turn could have further activated T cells to produce surface and/or diffusible factors that drive activation and proliferation of orbital fibroblasts, leading to expression of fibroblast-based diseases, i.e. proliferation of fibroblasts and excess connective tissue, deposition of matrix glycosaminoglycans, intramuscular fibrosis, and differentiation and proliferation of adipocytes.

Another interesting issue regards the time between BMT and the onset of GH and GO. A delay due to immune reconstitution of the recipient should be expected, but it can also be hypothesized that an additional stimulus like an infection, even subclinical, or an inflammation could have played a role in triggering the process. Indeed, orbital fibroblasts, upon stimulation with IFN- γ produced during infections/inflammations, are able to overexpress MHC class II molecules on their surfaces (24) and to produce proinflammatory cytokines, such as IL-8 and IL-6. This suggests that orbital fibroblasts may be crucial in the trafficking of bone marrow-derived immune cells to the orbit in states of infection/inflammation.

Here, we propose that the recipient passively acquired dormant autoreactive T cells from his sister, although she was apparently healthy. This case report suggests to consider, if available, the use of a matched unrelated donor when a potential HLA-identical sibling donor presents relevant immune-mediated diseases. In the case where a matched unrelated donor is not available, a T-cell depleted rather than whole BMT might be an alternative when the donor is affected by ATDs or other T-cell-driven autoimmune disorders, although the role of bone marrow graft engineering is still under study. T-cell depletion of the graft might in theory change/prevent the occurrence of autoimmunity; however, we acknowledge that the evidence is very limited to make this statement, and we are aware that T-cell-depleted bone marrow has major drawbacks, such as an enhanced risk of graft rejection as well as delayed immune reconstitution, with a consequent increased risk of viral and fungal infections.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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