Eye (2019) 33:223–229
https://doi.org/10.1038/s41433-018-0282-1

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Immune reconstitution after alemtuzumab therapy for multiple sclerosis triggering Graves' orbitopathy: a case series

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Received: 5 November 2018 / Accepted: 6 November 2018 / Published online: 29 November 2018

Abstract

Alemtuzumab—a monoclonal antibody targeting the CD52 glycoprotein expressed by most mature leucocytes—effectively decreases relapse rate and disability progression in early, relapsing–remitting multiple sclerosis (MS). However, secondary autoimmune disorders complicate therapy in nearly 50% of treated patients, with Graves' disease being the most common. Rarely, thyroid eye disease (TED) ensues; only seven such cases have been reported. Our aim was to analyse the largest series of MS patients developing thyroid eye disease after alemtuzumab treatment. We performed a retrospective chart review of MS patients treated with alemtuzumab (1995–2018) and subsequently identified by their treating physicians as having developed TED and referred to our ophthalmology service. As an original trial centre for alemtuzumab, our hospital has treated approximately 162 MS patients with this novel therapy. In total, 71 (44%) developed thyroid dysfunction, most of whom (87%) developed Graves' disease, with ten (16%) referred for ophthalmological evaluation. Two developed active orbitopathy following radioiodine treatment; one occurred after cessation of anti-thyroid drug treatment. Three developed sight-threatening disease requiring systemic immunosuppression, with one refractory to multiple immunosuppressants. The remaining patients were treated conservatively. TSH-receptor antibody (TRAb) levels were significantly raised in all cases, when ascertained. We report sight-threatening as well as mild TED in MS patients after treatment with alemtuzumab. Endocrine instability, radioiodine treatment and positive TRAb are all likely risk factors. The data support at least 6-monthly biochemical and clinical assessment with a low threshold for referral to an ophthalmologist, particularly for those with higher TRAb levels who may be at greater risk of orbitopathy.

Introduction

Alemtuzumab (Lemtrada; Campath-1H) is a humanised monoclonal antibody developed in Cambridge to target cells expressing CD52 [1]. This membrane glycoprotein is found on almost all mature leucocytes but critically not on their haematopoeitic precursor stem cells, allowing for a 'reboot' of the immune system with rapid depletion and gradual reconstitution of the immune system [2]. This has made it a helpful agent in the treatment of B-cell chronic lymphocytic leukaemia [3], organ transplantation [4, 5], vasculitides [6], uveitis [7, 8] and most recently as an effective treatment for multiple sclerosis (MS) [9]. It has been shown to decrease both the annualised relapse rate as well as reduce the overall accumulation of disability compared with interferon beta-1a treatment [10, 11].

The drug is administered intravenously over two courses: 12 mg/day for 5 consecutive days, followed by the same dose for 3 consecutive days 12 months later; additional courses may be considered. Despite a drug half-life of less than a week [12], treatment results in a rapid depletion of circulating lymphocytes which can persist for several years; median recovery of CD4+cells took 35 months [2], whilst B cells returned within 7 months but continued to rise, reaching 124% of baseline 27 months post treatment [13]. These temporal changes are likely significant for pathogenesis and will be discussed later.

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Alemtuzumab is also associated with side effects, such as infusion reactions and infections [14]. However, the principal adverse effect is the development of secondary autoimmunity during immune reconstitution, occurring in 12–48% of treated patients [15, 16]. Reported cases have included Goodpasture's syndrome and fatal idiopathic thrombocytopenic purpura, but thyroid autoimmunity is the most common by far representing up to 77% of the cases of autoimmunity [17].

The onset of Graves' disease or other thyroid dysfunction peaked at 3 years post treatment but could occur as early as 6 months after treatment or as late as 7 years thereafter [18]. More than 96% of the patients were positive for TRAb [14]. Whilst MS may confer a higher risk of developing Graves' disease, the incidence is only around 1–2% [19, 20] and therefore an order of magnitude smaller than that reported after alemtuzumab treatment. Furthermore, patients treated with interferon had a rate of only around 3%. A causative link to alemtuzumab treatment was therefore quickly established.

Development of thyroid eye disease is less common, occurring in less than 2% of alemtuzumab-treated MS patients [21]. Consequently, only a handful of cases have been reported in the literature (see Table 2) [22–24]. These have ranged from the mild, requiring no treatment, to more serious disease manifestations requiring orbital wall decompression.

Until recently, no associations had been found between the risk of developing autoimmunity and the severity of MS, treatment response, total dosage or intervals between treatment, immune status or reconstitution speed [15, 22]. Neither increasing age nor sex played a role; however, as is the case for non-alemtuzumab-associated TED, smoking was found to predispose (threefold greater risk), as was family history (sevenfold greater risk) [13, 25].

As part of its development, alemtuzumab has been administered at our hospital since 1991 [26] and thereafter in the many phase II and III studies which have helped to confirm a sustained lower annualised relapse rate and reduced accumulation of disability compared to other treatments [10, 11]. As the local dedicated thyroid eye disease service, we therefore are able to present the largest case series of alemtuzumab-induced thyroid orbitopathy and to provide an update on recommendations for monitoring and treatment.

Methods

We searched our bespoke electronic medical ophthalmology database for all patients with MS treated with alemtuzumab (Campath-1H) who were referred to the ophthalmology department for evaluation for thyroid eye disease between 1991 and 2018. Serum-free T4 (FT4), free T3 (FT3) and TSH were measured using the ADVIA Centaur (Siemens, Munich, Germany) standard automated immunoassay systems. Over the three decades of this study, TRAb levels were first assayed using a first-generation ELISA assay, and later replaced by the LUMItest TRAK assay from 2002 onwards. It has an upper accurately quantifiable limit of 40 IU/L (with levels greater than this being reported as > 40 IU/L). Anti-TPO antibody was measured using a variety of standard commercially available assays over the study period.

Cases

Out of 162 patients with MS who had been treated with alemtuzumab in Cambridge, 71 developed thyroid dysfunction [27]. Of these, we identified ten patients who were subsequently found to have developed thyroid eye disease (14%). Of these, only six were felt to require review by our ophthalmology department as the other four were patients from outside our region who only attended our hospital for the clinical trials. They had only a very mild eye disease and were instead offered a review by their local units.

The six patients seen in our clinic are summarised in Table 1. None of them had a family history of endocrine disease. Three were non-smokers at the time of developing ocular signs and symptoms. Five had significantly raised TRAb (> 20 IU/L, reference range < 1 IU/L throughout) at presentation with eye disease—the sixth presented at a time prior to this test being routinely available in the hospital. Unusually, there was a 2:1 ratio of males to females. Two developed active orbitopathy following radioiodine (^{131}I) ablation of the thyroid gland—without steroid cover—for their Graves' disease. One case occurred with relapse of Graves' after cessation of anti-thyroid drug treatment and the resulting endocrine instability as the likely trigger. Three patients required systemic immunosuppression for sight-threatening disease, with the other three being managed conservatively. Their disease courses are summarised briefly below (Table 1).

Case 1: This 36-year-old man developed TED 26 months after his last alemtuzumab infusion and 10 years after his MS diagnosis. At presentation, he had pain on eye movement but only mild TED which did not require immunosuppression. TRAb was very elevated (> 40 IU/L). Endocrine control was achieved with a combination of carbimazole and thyroxine medication, with slight reduction of his TRAb, 24 months after disease onset.

Case 2: A 47-year-old man presented with sight-threatening disease 20 months after alemtuzumab treatment and 6 years after his MS diagnosis. He had marked proptosis with corneal exposure and compressive optic neuropathy with red desaturation. With a clinical activity

Table 1 Patients treated with alemtuzumab for multiple sclerosis and managed in the Thyroid Eye Disease Service

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex and age at the first symptom of MS	M, 26	M, 41	M, 14	M, 46	F, 43	F, 46
Age at the start of alemtuzumab	34	45	30	46	52	49
Treatments prior to alemtuzumab for MS	Interferon beta 1a	Interferon beta 1a, glatiramer acetate	Interferon beta 1a	Steroid only	Steroid only	Interferon beta 1a
Smoker	No	Yes, stopped after TED diagnosis	Yes, stopped after radioiodine	Yes, stopped after TED diagnosis	No	No
Past medical history	No FHx or PMHx	No FHx or PMHx	No FHx or PMHx	No FHx or PMHx	No FHx or PMHx	No FHx or PMHx
Alemtuzumab therapy first started, stopped (number of courses)	2009–2014 (4)	2015–2016 (2)	2006–2011 (3)	2017–2018 (2)	1995 (1)	2007–2008 (2)
Time to diagnosis of Graves' disease post alemtuzumab	2015, 12 months	2016, 7 months	2007, 1 year	2017, 10 months subclinical low TFT, then Hashimoto's	1997, 2 years	2009, 2 years
Time to diagnosis of TED from Graves' disease (autoimmune thyroid disease) diagnosis	2015, 14 months	2017, 13 months	2015, 8 years, 1 year post radioiodine	Concurrent	2001, 4 years, 2 years post last radioiodine	2012, 3 years
Severity of TED at presentation	Mild	Severe (neuropathy and exposure)	Mild	Mild	Severe (exposure)	Moderate, but became severe over 12 months (exposure, globe prolapse)
Imaging findings	No STIR hyperintensity	STIR hyperintensity BE and muscle enlargement	Mild enlargement of muscles with T2 hyperintensity	Bilateral proptosis but not STIR hyperintensity or abnormal signal	Muscle enlargement and signal increase on T2	Enlargement of all muscles with increased T2 signal
Nasal staph cultured	Negative	Positive	Negative	Negative	Negative	Negative
Thyroid function at diagnosis of TED	TSH < 0.03 mU/L FT4 63 pmol/L TPO 54 IU/L	TSH < 0.03 mU/L FT4 78.9 pmol/L T3 30.8 pmol/L TPO > 1300 IU/L	TSH 0.19 mU/L FT4 21.9 pmol/L T3 5.6 pmol/L TPO > 1300 IU/L	TSH 12.4 mU/L FT4 14.7 pmol/L TPO > 1300 IU/L	TSH 6.3 mU/L FT4 18.8 pmol/L TPO 1378 IU/L	TSH < 0.03 mU/L FT4 33.7 pmol/L TPO < 5 IU/L
Treatment modality for GD and TED	Block and replace lubricants only	Block and replace cyclosporine and prednisolone	Radioiodine 2014 thyroxine lubricants only	Thyroxine lubricants only	Radioiodine 1999, thyroxine. Cyclosporine and prednisolone. Right two-wall decompression surgery	Cyclosporine (not tolerated) and prednisolone. Tacrolimus and mycophenolate
Mode of definitive treatment for endocrine control	Awaiting thyroidectomy	Awaiting thyroidectomy	Awaiting thyroidectomy	None required	Radioiodine thrice (1997, 1998 and 1999)	Total thyroidectomy 2018
Visual acuity at diagnosis and after treatment	6/5 OD, 6/5 OS unchanged	6/5OD; 6/5 OS 6/4 OD; 6/6 OS	6/4 OD; 6/4 OS 6/5 OD; 6/5 OS	6/5 OD; 6/5 OS	6/6 OD; 6/9 OS 6/6 OD; 6/6 OS	6/5 OD; 6/6 OS 6/5 OD; 6/5 OS
TRAb at diagnosis and after treatment	>40 IU/L; 17 IU/L (persistent)	29.2 IU/L; 1.2 IU/L	22.5 IU/L 19.1 IU/L (persistent)	15.9 IU/L	Not available < 0.4 IU/L	>40 IU/L 2.6 IU/L
CAS at diagnosis; and after treatments	3; 3	8; 0	2; 0	< 3;	7;0	7;3
Proptosis at diagnosis OD/OS and after treatment OD/OS	21 mm, 21 mm; 21 mm, 21 mm	28 mm, 25 mm; 24 mm, 26 mm	21 mm, 22 mm 22 mm, 20 mm	24 mm, 25 mm	27 mm, 26 mm 28 mm, 26 mm	29 mm; 28 mm 28 mm; 28.5 mm

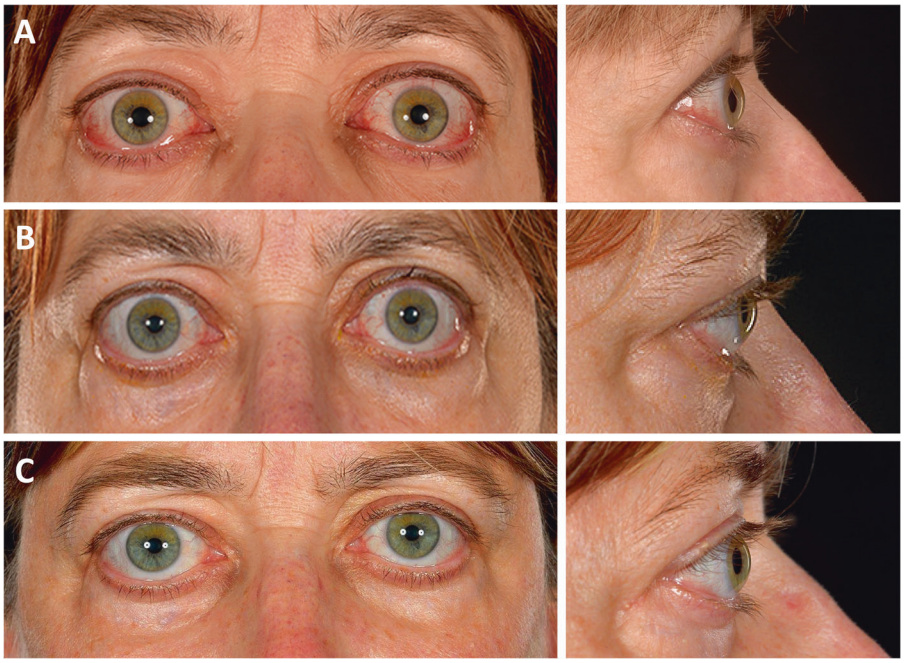

Fig. 1 Patient #6 shown at presentation (**a**) with a CAS of 7 and active orbitopathy, lid retraction, firm orbits, mild proptosis, chemosis, bilateral upgaze restriction, reduced binocular field, and early optic neuropathy (with reduced colour by four Ishihara plates and reduced vision to 6/12). The TRAb level was > 40 IU/L. Three years later (panel **b**) and following systemic immunosuppression with i.v. methylprednisolone, oral prednisolone and cyclosporine she had a CAS of 3 and TRAb of 0.4 IU/L. Acuity was restored to 6/6 with a full Ishihara and reduction in proptosis. Ciclosporin was substituted for tacrolimus and mycophenolate mofetil due to side effects. Following thyroidectomy (**c**) the patient remained well; CAS of 0 and no lagophthalmos. Proptosis persisted at 28 mm

score (CAS) [28] of 10 he was started on treatment with ciclosporin, i.v. methylprednisolone and prednisolone according to the Cambridge regimen [29]. At presentation his TRAb was significantly elevated at 29 IU/L but normalised by 9 months at which time his CAS was zero. He is now awaiting definitive treatment of Graves' thyrotoxicosis.

Case 3: A 39-year-old male ex-smoker presented with mild TED associated with high TRAb post ^{131}I radioiodine ablation. This was 4 years after his last alemtuzumab treatment. His TED settled with lubricants only.

Case 4: A 46-year-old male smoker presented with mild TED in the context of high TRAb 10 months after treatment with alemtuzumab. Since he was hypothyroid [TSH 12.4 mU/L (0.35–5.5 mU/L), FT4 14.7 pmol/L (10–19.8 pmol/L)] it was felt that the TRAb was most likely blocking in nature. He was managed with lubricants and thyroxine and remains under follow up.

Case 5: A 54-year-old woman developed severe sight-threatening TED two years after her third radioiodine treatment for Graves' disease and 4 years post alemtuzumab. She had severe corneal exposure and was treated with the Cambridge regimen detailed above as well as requiring right two-wall decompression. There were no TRAb measurements in use clinically at the time of her presentation but subsequent assays shows that it has remained undetectable for years.

Case 6: A 54-year-old woman presented 48 months after alemtuzumab treatment with moderately severe TED (CAS 7), which became increasingly severe over the next 12 months with sight-threatening exposure and globe prolapse (Fig. 1). TRAb at diagnosis was very elevated (> 40 IU/L). She was immunosuppressed on the Cambridge regimen but her pain worsened, so tacrolimus and mycophenolate mofetil replaced the ciclosporin. Her TED proved difficult to control—in fact she has been one of the most challenging patients treated in Cambridge to date. Her TRAb improved over a year but reduction in disease activity on imaging only occurred 3 years later (Fig. 2). Now, 5 years after presentation, her CAS is 3 and she has opted for elective thyroidectomy with steroid cover as a definitive treatment of Graves' thyrotoxicosis.

Discussion

Alemtuzumab-related Graves' disease has been characterized as having an "indolent" course [27] and most cases of the associated TED had been thought of as equally mild. However, our data confirms that immune reconstitution post alemtuzumab can trigger sight-threatening disease in two out of ten patients. Our patients exhibited the full spectrum of TED severity ranging from mild to severe disease

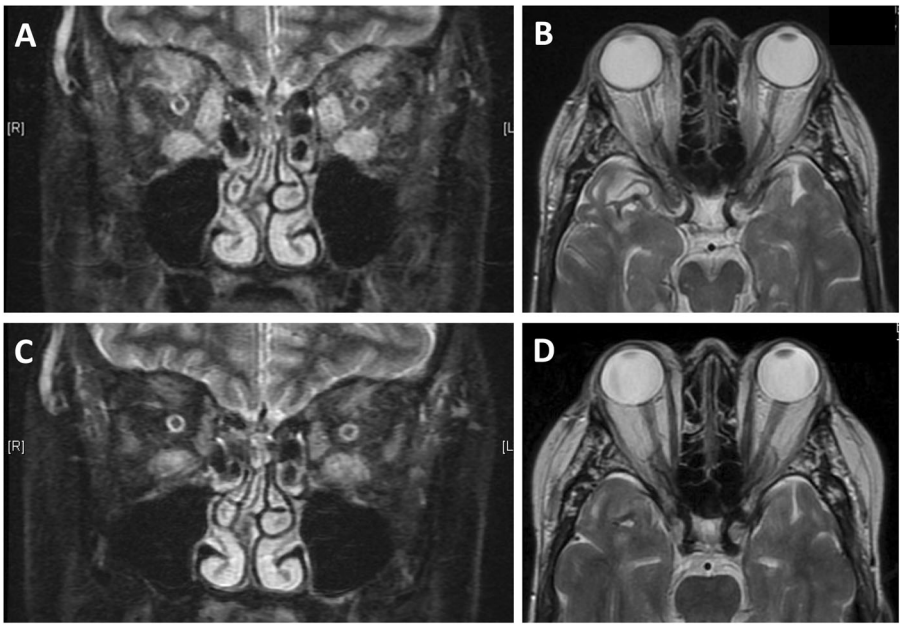

Fig. 2 Coronal MRI STIR sequence of patient #6 at presentation (**a**), exhibiting enlarged and hyper-intense signal in all extraocular muscles coupled with orbital fat oedema. This has caused proptosis, optic nerve stretch and orbital apex crowding as shown in the axial MRI with T2 weighting (**b**). Following immunomodulatory therapy, muscle size and signal intensity are improved (**c**; STIR sequence) and there is reduced crowding and nerve stretch (**d**; axial T2 MRI)

refractory to even powerful immunosuppressive regimens. We found a fluctuating and unpredictable course in these patients and a high frequency of TRAb-positive hypothyroidism following the hyperthyroidism. One can speculate that this may represent the underlying flux of the immune system during reconstitution.

Secondary thyroid autoimmunity and orbitopathy has also been described in other situations of immune reconstitution such as in HIV patients on highly active antiretroviral therapy [30–32] or following bone marrow transplantation [33]. Nevertheless alemtuzumab appears particularly prone to triggering this phenomenon. This is likely due to homoeostatic T-cell proliferation generating constantly activated and highly proliferative CD4+ and CD8+ populations which promote further inflammation [34]. IL-21 is a cytokine that has been strongly linked to a host of autoimmune diseases and is known to drive CD4+ and CD8+ T-cell proliferation as well as promoting B-cell survival and class-switching [35]. Studies have shown that higher circulating levels of IL-21 correlate with thyroid disease severity and increased risk of developing autoimmunity after alemtuzumab treatment [36]. The timing is also important: as alluded to earlier, median recovery of CD4+ cells took 35 months [2] whilst B-cells returned within 7 months and then rising to 124% of baseline 27 months post treatment [13].

The time course informs monitoring and management. Our six patients fit previous studies which report the onset of Graves' disease ranging from 6 months to 7 years but with a peak at around 18–36 months [15, 21] which coincides with when the B-cells are reconstituted and later peak. It is likely sufficient, and also supported by the accumulated literature shown in Table 2, to discontinue monitoring for secondary autoimmunity after 5 years.

Taken together, we recommend at least six-monthly clinical reviews for alemtuzumab-treated patients coupled with serial measurements of TRAb for a period of up to 5 years post treatment. Clinicians should have a low threshold for ophthalmological assessment in patients with high TRAb levels [37], and particularly prior to considering definitive endocrine treatment with radioiodine. Two of our patients developed TED following ^{131}I treatment—a known risk factor for progression and new TED [38]; our group has shown rise in TRAb following radioiodine ablation of the thyroid gland [39].

In this study, 14% of patients with alemtuzumab-induced Graves' disease subsequently developed thyroid eye disease. However, this is likely an underestimate as the patients did not undergo routine ophthalmological assessment and only those with obvious ophthalmic symptoms were referred to the TED service. As a result, subclinical and very mild TED may not have been recorded. As alemtuzumab is superior to conventional MS treatments it will be used widely. Ophthalmologists will benefit from being aware of the link with thyroid eye disease and how best to manage and monitor patients.

Acknowledgements The authors would like to thank Mr Cornelius Rene and Dr Paul Meyer for helpful discussions and insights into the management of thyroid eye disease over many years.

Funding There was no funding sought or obtained for this research. JJ is funded by the Wellcome Trust.

Table 2 Cases of alemtuzumab-related thyroid eye disease reported in the literature

Number of cases	Severity	Time of onset post alemtuzumab	Treatment	Underlying disease	Reference
4 patients	3 severe 1 moderate	Not recorded	Of severe cases—one received radioiodine and one required orbital decompression. No further information available	All MS	Daniels et al. [22]
2	(a) moderate (b) mild	(a) 38 months (b) 23 months	(a) iv methylprednisolone & endocrine control (b) lubricants & endocrine control with subsequent thyroidectomy	All MS	Tsourdi et al. [23]
1	Mild	2 years	Endocrine control, lubricants, selenium, thyroidectomy	MS	Trinh et al. [24]
1	Moderate	3 years	Endocrine control selenium iv methylprednisolone	Bone Marrow Transplantation for fanconi anaemia	Cima et al. [33]
10 patients	Ranging from mild to severe	Range of 10 months to 4 years	Lubricants to systemic immunosuppression and surgery	All MS	This series

Author contributions All authors have contributed to the data collection and writing.

Compliance with ethical standards

Conflict of interest All authors are doctors who manage patients with thyroid disease, thyroid eye disease or multiple sclerosis. AJC received honoraria and speakers' fees from Sanofi, up until September 2017. JJ reports receiving speaker honoraria and consulting fees from Sanofi.

Ethics statement As an anonymised retrospective chart review no institutional review board authorisation was necessary.

Guarantor Dr Murthy serves as guarantor of this work. It is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

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