8. Mallo S, Coto P, Caminal L, et al. Generalized pruritus as presentation of T-cell large granular lymphocyte leukaemia. *Clin Exp Dermatol* 2008;33:348–9.
9. Lamy T, Loughran TP. Large granular lymphocyte leukemia. *Cancer Control* 1998;5:25–33.
10. Dutton JJ, Gayre GS, Proia AD.Diagnostic atlas of common eyelid diseases. New York: Informa Healthcare, 2013.
11. Laurenti L, Tarnani M, Innocenti I, et al. Chronic lymphocytic leukemia with eyelid involvement responding to alemtuzumab. *J Clin Oncol* 2008;26:5299–301.

Ocular Findings in Alemtuzumab (Campath-1H)-induced Thyroid Eye Disease

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Abstract: ***Alemtuzumab*** **(Campath-1H) is a humanized anti-CD52 monoclonal antibody used in the treatment of multiple sclerosis (MS). Studies demonstrate significant reduction in relapse risk and the risk of accumulating sustained disability. Adverse events include infusion-associated reactions, infections, and secondary autoimmunity. Systemic thyroid disease is the most common secondary autoimmune event and affects up to approximately 30% of treated patients. This is the first description of the ocular findings and management in a case of thyroid eye disease (Graves' Ophthalmopathy [GO]) following alemtuzumab therapy. The ocular disease was managed conservatively while the systemic Graves' was managed with thyroidectomy.**

CASE REPORT

A previously healthy 36-year-old, nonsmoking, white woman was diagnosed with MS in 2007, commenced on alemtuzumab in 2008 (first dose being 12 mg/day for 5 days and 12 mg/day for 3 days 1 year later) diagnosed with systemic Graves' disease in 2010, requiring carbimazole.

Twelve months later, she developed bilateral injection, photophobia, proptosis, and upper eyelid retraction, consistent with GO. She was referred to ophthalmology in 2012 seeking rehabilitative eyelid surgery to improve cosmesis.

Using the Vision, Inflammation, Strabismus, Appearance/exposure (VISA) classification, she had no threat to vision. Visual acuity (6/6 right and 6/5 left), and colour vision, pupillary reflexes and visual field tests were normal. She had mild upper lid edema but no conjunctival inflammation. Intraocular pressure measurements were 19 mm·Hg right eye (RE) and 18 mm·Hg left eye (LE) in primary position, which increased to 31 mm·Hg and 27 mm·Hg in upgaze, respectively. There was no ocular motility disturbance. She had bilateral mild proptosis (exophthalmometry was RE, 21 mm; LE, 22 mm; and oculus, 110 mm). She also had significant upper lid retraction with increased palpebral apertures (RE, 17 mm and LE, 15 mm), upper marginal reflex distances (RE, 11 mm and LE, 9 mm), and scleral show (superior RE, 6 mm and LE, 4 mm, inferior 1 mm both eyes). She had full eyelid closure but lid lag was apparent in downgaze. Mild punctate corneal staining was evident on slit lamp examination due to blink lagophthalmos. A goitre was also present.

CT scans of the orbits were consistent with GO with mild proptosis and extraocular muscle enlargement of all muscles. Muscle tendons were not grossly thickened. There was circumferential optic nerve effacement and no evidence of orbital inflammation. Thyroid function control was unstable. TSH receptor antibody levels fluctuated from 17.3 IU/l to 33.9 IU/l, peaking at 88 IU/l (reference range, <1.8 IU/l). She was treated with ocular lubricants and selenium. No ophthalmic surgical intervention was recommended at this stage.

Her endocrinologist recommended a thyroidectomy to improve control of her Graves' disease. At her last review, 1 year later, she was biochemically euthyroid on replacement therapy. Her eye signs remained stable during this period; however, the patient had persistent cosmetic concerns. She remains a candidate for further treatment with periocular steroids or surgery to improve her lid retraction.

DISCUSSION

This case report highlights the ocular findings in alemtuzumab-related thyroid eye disease.

Alemtuzumab targets CD52, which is a lymphocyte cell surface marker of unknown function.[1–2] It is cytotoxic and significantly depletes circulating lymphocytes in the peripheral circulation.[2–6] Differences in T- and B-cell recovery times may contribute to the autoimmune process. It has been used to treat various diseases such as leukemia, organ transplant rejection, vasculitis, and ocular inflammatory disease.[7–12] More recently, phase I to phase III trials involving alemtuzumab in the treatment of MS demonstrate significant reduction in terms of sustained disability progression and annualized relapse rates.[7–9], 18This represents a substantial and exciting advance in the management of MS but management of its side effect profile clearly remains a challenge.

The main adverse reactions of alemtuzumab include infusion-related reactions, mild to moderate infections, immune thrombocytopaenia, and autoimmune thyroid disorders.[2–5] Secondary autoimmune disorders develop as the lymphocyte count recovers, at a frequency between 20% and 34%.[7–9,18]. Graves' disease as a result of alemtuzumab was first reported in 1999[10] and is reported to occur as high as 22% of patients on alemtuzumab, with 23% reverting spontaneously to euthyroid states.[18] The mechanism behind thyroid autoimmunity secondary to alemtuzumab is thought to be due to the loss of self-tolerance during the homeostatic proliferation of T-cells after significant lymphopaenia.[10] The development of Graves' disease is more common in smokers and those with a family history but does not appear to be influenced by treatment dose, frequency or interval of alemtuzumab.[17] The risk is greatest during the 12–36 months following the first infusion, as in our case, and the use of alemtuzumab therefore requires close monitoring of thyroid function for many years.

In the original trials, 4 cases of GO were reportedly induced by alemtuzumab, but the ophthalmic management has not been detailed.[4,14,16] One case developed after radioactive iodine treatment and no patients required ophthalmic surgical intervention.

The management and course of the systemic Graves' disease for this case has previously been reported.[9] It is interesting to note that the disease course is similar to that of idiopathic Graves' disease, and that conventional treatment is often

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all that is warranted.[19] However, the objective of our study was to outline the ocular findings, course, and management of the alemtuzumab-related GO for this patient.

The management and course of the GO in this case did not differ significantly from nonalemtuzumab-related GO. At the time of presentation she had mild eye disease. The lubricants provided symptomatic relief and oral selenium was recommended at a dose of 100 mcg twice daily in line with current evidence.[8] Our approach was cautious to ensure stability, particularly in view of the ongoing systemic thyroid treatment, prior to recommending treatment for the upper eyelid retraction which was her main concern.

This case demonstrates that physicians treating patients with alemtuzumab should be aware of the signs and symptoms of Graves' ophthalmopathy. Should these develop, then concurrent monitoring between ophthalmologists, neurologists, and endocrinologists is vital to ensure that patients undergo timely and appropriate surgery while simultaneously ensuring the continued success of alemtuzumab in the management of MS.

REFERENCES

1. Compston A, Coles A. Multiple sclerosis. *Lancet* 2008; 372:1502–1517.
2. Hale G. The CD52 antigen and development of the CAMPATH antibodies. *Cytotherapy* 2001;3:137–143.
3. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012;78:1069–1078.
4. Coles AJ, Compston AS, et al Alemtuzumab vs interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008;359:1786–1801.
5. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab versus interferon β-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. *Lancet Neurol* 2011;10:338–348.
6. Jones JL, Coles AJ. Campath-1H treatment of multiple sclerosis. *Neurodegener Dis* 2008;5:27–31.
7. Cossburn M, Pace AA, Jones J, et al. Autoimmune disease after alemtuzumab treatment for multiple sclerosis in a multicenter cohort. *Neurology* 2011;77:573–579.
8. Costelloe L, Jones J, Coles A. Secondary autoimmune diseases following alemtuzumab therapy for multiple sclerosis. *Expert Rev Neurother* 2012;12:335–341.
9. Osterborg A, Dyer MJ, Bunjes D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. European Study Group of CAMPATH-1H Treatment in Chronic Lymphocytic Leukemia. *J Clin Oncol* 1997;15:1567–1574.
10. Dick AD, Meyer P, James T, et al. Campath-1H therapy in refractive ocular inflammatory disease. *Br J Ophthalmol* 2000;84:107–109.
11. Walsh M, Chaudhry A, Jayne D. Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). *Ann Rheum Dis* 2008;67:1322–1327.
12. Coles AJ, Wing MG, Molyneux P, et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol* 1999;46:296–304.
13. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012;380:1819–1828.
14. Coles AJ, Twyman CL, Arnold DL, et al; CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012;380:1829–1839.
15. Aranha AA, Amer S, Reda ES, et al. Autoimmune thyroid disease in the use of alemtuzumab for multiple sclerosis: a review. *Endocr Pract* 2013;19:821–828.
16. Gilbert D, Vladic A, et al. Alemtuzumab-related thyroid dysfunction in a phase 2 trial of patients with relapsing-remitting multiples sclerosis. *J Clin Endocrinol Metab* 2014;99:80–89.
17. Coles AJ, Wing M, Smith S, et al. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. *Lancet* 1999;354:1691–1695.
18. Weetman AP. Graves' disease following immune reconstitution or immunomodulatory treatment: should we manage it any differently? *Clin Endocrinol (Oxf)* 2014;80:629–632.
19. Marcocci C, Kahaly GJ, Krassas GE, et al; European Group on Graves' Orbitopathy. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med* 2011;364:1920–1931.

Conjunctival Pigmentation Following Minocycline Therapy

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Abstract: **Minocycline is a tetracycline antibiotic commonly used to treat acne and rosacea. Although pigmentation of the skin, nails, teeth, oral mucosa, and sclera is a well-recognized adverse outcome associated with minocycline, ocular pigmentation may be missed on routine examination. The authors present a case of a 43-year-old white woman who demonstrated bilateral pigmented palpebral conjunctival cysts after 12 months of minocycline therapy for cystic acne. To date, only 5 cases of minocycline-induced conjunctival pigmentation have been reported. After drug discontinuation, the patient's examination remained stable and no new ocular lesions were noted.**

Minocycline is a semisynthetic tetracycline antibiotic commonly used for the treatment of rosacea and acne. As a highly lipophilic drug, minocycline readily achieves peak serum concentration by virtue of its increased tissue penetration. Compared with other drugs within the tetracycline family, minocycline offers greater broad-spectrum antimicrobial activity and lower rates of drug resistance. Conversely, minocycline is also most closely associated with cutaneous and visceral pigmentation.[1] Conjunctival pigmentation linked to minocycline use, however, has rarely been reported.

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CASE REPORT

A 43-year-old white woman was referred for evaluation of a 3-month history of bilateral conjunctival pigmentation. As per the patient's report, the lesions had increased in number and progressively darkened. An examination revealed several flat, well-demarcated, pigmented cysts on bilateral upper and lower palpebral conjunctivae, including a larger pigmented cyst in the OS caruncle (Fig.). Of note, no other pigmented lesions were discovered elsewhere on the patient.

The patient's past medical history was significant for cystic acne and recent gastric bypass surgery. She had been on minocycline for the last 12 months to treat her acne.

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