Alemtuzumab-induced alopecia universalis and transient accommodation spasm in a patient with multiple sclerosis

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Abstract: Herein, we report a case of alopecia universalis and transient accommodation spasm presented after alemtuzumab administration in a patient previously treated with fingolimod. To the best of our knowledge, this is the first report of accommodation spasm as an acute adverse effect of alemtuzumab. Treatment with alemtuzumab in relapsing-remitting multiple sclerosis has been identified as a risk factor for developing secondary autoimmunity within the follow-up period (peak 18–36 months from the first infusion) such as thyroid disorders. This case highlights the need for postmarketing surveillance and the significance of reporting rare side effects related to alemtuzumab; its high efficacy should be weighted with potentially severe adverse events when making a therapeutic decision. Further studies in larger cohorts are needed to elucidate pathomechanisms of alemtuzumab.

Keywords: alemtuzumab, alopecia universalis, autoimmunity, transient accommodation spasm

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Introduction
Alemtuzumab is a humanized anti-CD52 monoclonal antibody licensed to treat highly active relapsing-remitting multiple sclerosis (RRMS). Despite its high efficacy, alemtuzumab-treated patients may develop secondary autoimmune diseases within the follow-up period, with a peak within 18–36 months from the first infusion. The most common are thyroid disorders (up to 40% of patients);1 interestingly, recently autoimmune hemolytic anemia was reported.2 Pre-treatment with fingolimod in RRMS has also been identified as a risk factor for developing secondary autoimmunity.3 Herein, we report a case of alopecia universalis and transient accommodation spasm occurring after alemtuzumab administration in a patient previously treated with fingolimod.

Case report
A 24-year-old male, with an unremarkable medical history, presented with lower limb weakness in 2004. He relapsed a year later with magnetic resonance imaging (MRI) findings fulfilling the 2005 McDonald multiple sclerosis (MS) criteria. The patient was started on interferon beta-1b for 2 years, then switched to glatiramer acetate due to MRI activity, and then to natalizumab. For 5 years, no disease activity was noted under natalizumab; however, the anti-John-Cunningham-virus-antibody-index was increasing, indicating a relatively higher risk of progressive multifocal leukoencephalopathy, and a decision was made to switch to another second-line disease-modifying therapy (DMT); fingolimod was initiated 3 months later. No relapses were reported for the next 5 years until a new clinical relapse with MRI activity occurred. After the discontinuation of fingolimod, he received intravenous methylprednisolone (IVMP) for two consecutive months (3 gr/month). However, 4 months later he relapsed again with 4 gadolinium-enhancing lesions on brain MRI [Figure 1(a) and (b)] and received IVMP again. A few days later, the first, 5-day, course of alemtuzumab was administered (EDSS score of 3) and only mild infusion-associated reactions were observed.
Eight months later, he complained of gradual loss of head hair, initially in the form of patches [Figure 1(c)], and then gradual loss of body hair was noted. A skin biopsy of the skull showed ‘scarring alopecia’; intravenous and oral corticosteroids were co-administered for a month with no response. Hair loss was exacerbated and 3 months later a complete loss of all scalp and body hair and an almost complete loss of the eyebrows and eyelashes were observed; these findings were consistent with alopecia universalis which persisted even 14 months after the first alemtuzumab-cycle [Figure 1(d)]. No activity on brain/spinal MRI (EDSS score of 1) was noted and a second alemtuzumab cycle was started. Before each infusion, the patient was premedicated with IVMP, dimetindene, paracetamol, omeprazole, ondansetron, and cetirizine; valaciclovir was initiated for herpes prophylaxis. On the third-day of the second alemtuzumab-cycle (after 12 mg X 2 days), he complained of blurred distance vision; noteworthy, he had no history of refractive errors or other visual impairment. On ophthalmological examination, uncorrected visual acuity was 20/200 in both eyes. Manifest refraction was -3.75 in the right eye (OD) and -3.75/-1.00 \( \times \) 80\( ^\circ \) in the left eye (OS), yielding best-corrected visual acuity (BCVA) of 20/20 in each eye. Color vision testing was normal. Slit-lamp examination revealed shallow and quiet anterior chambers in both eyes. Intraocular pressure was 16 mmHg in each eye, by Goldmann applanation tonometry. Optical biometry was performed by IOL Master and revealed axial length of 24.15 mm OD, and 24.00 mm OS with anterior chamber depths of 2.50 mm and 2.44 mm, respectively. Lens thickness was

Figure 1. Multiple typical MS lesions are shown in the cerebral hemispheres on FLAIR-images [(a) sagittal] and 2 gadolinium-enhancing lesions at T1-weighted images post-contrast [arrows (b) axial]; MRI was acquired before alemtuzumab initiation. Alopecia at onset [month 8] with hair loss in the form of patches [(c)]; month 14 (d) after alopecia universalis diagnosis; month 20 (e) after the first alemtuzumab course when only partial recovery of hair loss was noted. Anterior segment OCT of the right eye, at the onset of blurred distance vision [third day of the second alemtuzumab-cycle], reveals a narrow iridocorneal angle [(f)-i]; 2 days later, deepening of the angle is observed with reduction of iris convexity [(f)-ii]; resolution of angle closure 5 days following the initial event with horizontal iris, no iridocorneal apposition, or anterior lens vault [(f)-iii]. FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCT, optical coherence tomography.
measured 4.60 mm OD and 4.47 mm OS. Anterior segment optical coherence tomography (OCT) confirmed the anterior displacement of iris [Figure 1(f)-i]. The provisional diagnosis of accommodation spasm was established and topical administration of cyclopentolate 1% was commenced 3 times per day in each eye. The patient was re-examined 2 days later, reporting stable symptoms. BCVA was 20/20 in both eyes with manifest refraction of -3.25 OD and -3.25/-1.00 x 80° OS. Anterior chamber depth was measured 2.88 mm OD and 2.95 mm OS with mild deepening of the angle [Figure 1(f)-ii]. Lens thickness was 4.46 mm OD and 4.37 mm OS. Topical administration of atropine 1% was given 2 times per day for each eye. Three days later, his vision returned to normal with unaided visual acuity of 20/16 OD and 20/20 OS. Slit-lamp examination revealed deepening of the anterior chambers, which were measured 3.48 mm OD and 3.56 mm OS, with normalization of corneal angle [Figure 1(f)-iii]. Lens thickness was 4.33 mm OD and 4.19 mm OS. The ophthalmological findings in chronological order are indicated in Table 1.

At the last follow-up 6 months after the second course, there was a partial hair regrowth [Figure 1(e)], the ophthalmologic examination had no abnormal findings and there was complete resolution of symptoms for distance, and the EDSS score was 1. Until September 2021, no disease (MS) activity was observed and our patient has not received a third dose of alemtuzumab or any other treatment for MS.

**Discussion**

We report here two rare adverse events following alemtuzumab administration: (1) alopecia universalis and (2) transient accommodation spasm. Autoimmune conditions post-alemtuzumab are frequent compared to other therapies for RRMS and although alemtuzumab-induced alopecia universalis is rare but well-reported we found no previous report of an accommodation spasm associated with alemtuzumab. In addition, a recent analysis showed an increased risk of secondary autoimmunity following alemtuzumab in previously treated patients with fingolimod.3 Regarding the response to DMTs in our case, MS reactivation was noted after switching from natalizumab to fingolimod, and followingly, alemtuzumab was administered as an escalation therapeutic choice; even though the two above-mentioned adverse events occurred post-alemtuzumab, it also resulted in no disease activity thereafter.

Given our patient’s onset of symptoms, within a few hours after the second daily dose of alemtuzumab, and observing a rapid improvement following cessation of treatment and administration of cycloplegics, we speculate that alemtuzumab administration could explain the accommodative spasm we describe in this patient. Drug-induced accommodative spasm has been reported following miscellaneous drugs, for example, sulphonamide-derivatives;4 however, none of the premedications of our protocol have been reported to date to cause this condition. Of note, our patient had previously developed a rare but well-reported autoimmune adverse event following the first course of alemtuzumab; alopecia universalis. This could further indicate an acquired immunological imbalance following alemtuzumab.

To the best of our knowledge, this is the first report of transient accommodation spasm as an acute adverse effect of alemtuzumab. Its resolution with cycloplegics suggests that the accommodative spasm might have been the primary mechanism for the myopic shift. The mechanisms of acute accommodation spasm typically include

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**Table 1.** Ophthalmological findings in our patient are indicated in chronological order.

|                      | Refraction (OD/OS) | Anterior depth (OD-OS) | Lens thickness (OD-OS) |
|----------------------|-------------------|------------------------|-----------------------|
| Initial findings     | -3.75 / -3.75 -1.00 x 80° | 2.50 mm - 2.44mm | 4.60mm - 4.47mm |
| Two days following cycloplegia | -3.25 / -3.25 -1.00 x 80° | 4.46 mm - 4.37mm | 4.46 mm - 4.37mm |
| Five days following cycloplegia | 0 / -1.00 x 80° | 3.48 mm - 3.56mm | 4.33mm - 4.19mm |

OD, right eye; OS, left eye.
pupillary block following pupil constriction and idiosyncratic drug reactions that change the irido-
corneal angle by ciliochoroidal effusion.\textsuperscript{3}

The underlying pathology of transient myopia is not completely understood. Several theories have
been proposed including functional changes triggered by emotional stress\textsuperscript{6,7} as well as organic
causes due to ocular inflammation, tumors, cere-
bellar lesions, acute stroke, idiopathic intracranial
hypertension or as an uncommon manifestation
of MS.\textsuperscript{8,9} It is not known whether an inflam-
matory process was triggered, in the presented
patient, due to his underlying condition or medi-
cation-related disruption of the blood-aqueous
barrier along with the liberation of free radicals
and arachidonic acid derivatives. This case high-
lights the need for postmarketing surveillance and
the significance of reporting rare side effects
related to alemtuzumab; its high efficacy should
be weighted with potentially severe adverse events
when making a therapeutic decision. Further
studies in larger cohorts are needed to provide a
better understanding of the pathomechanisms of
alemtuzumab.

**Declarations**

**Ethics approval and consent to participate**
The study was approved by the Eginition Hospital
Institutional Review Board (12360/2.12.2019).

**Consent for publication**
The patient has provided written informed con-
sent for publication of the images/photos and
clinical information related to this case.

**Author contributions**

**Dimitrios Tzanetakos**: Conceptualization and
design; Investigation; Data curation; Formal
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