Uveal lymphoid hyperplasia: treatment with combination antibiotics and steroids

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ABSTRACT
Background/aims Uveal lymphoid hyperplasia (formerly benign reactive hyperplasia of the choroid) spans histopathological characteristics ranging from reactive hyperplasia to low-grade lymphoid neoplasm. There is strong evidence that other low-grade lymphoid neoplasms, particularly of gastric derivations, respond to oral antibiotics. Here, we explore that response of uveal lymphoid hyperplasia to treatment with only oral antibiotics and steroids.

Methods Four eyes of three patients with clinically diagnosed uveal lymphoid hyperplasia were treated with a course of oral antibiotics and steroids. The main outcome was clinical response of choroidal infiltrate by optical coherence tomography (OCT) measurements of choroidal thickness and visual acuity. Secondary outcome measure included local and systemic recurrence. Clinical response was evaluated by clinical exam, fundus photography, ultrasound and OCT.

Results All 4 eyes displayed a clinical response at a median 2 weeks after starting oral antibiotics and steroid course. The choroidal infiltration regressed as evidenced by: decrease of choroidal thickness by a median of 421 nm, myopic shift in refractive error by a median of 0.50 Diopters, and improved vision by a median of 1.5 Snellen lines. At a median of 51-month follow-up, all four eyes had a sustained complete response and no patient has developed systemic disease to date.

Conclusions In this small cohort of patients with uveal lymphoid hyperplasia, measurable and sustained clinical responses were observed with antibiotics/steroids, without systemic recurrence. This suggests combination antibiotic/steroid therapy is a reasonable treatment for select cases of uveal lymphoid hyperplasia, and may avoid the need for systemic chemotherapy/monoclonal antibody and/or external beam irradiation.

INTRODUCTION
It is recognised that uveal lymphoid hyperplasia is composed of low-grade proliferation of lymphocytes ranging from reactive hyperplasia to low-grade lymphoid neoplasm.1 Mucosa-associated lymphoid tissue (MALT) or low-grade lymphoma is an antigenic process, whereby the immune system is stimulated by the presence of bacteria or its toxin, and tissues become infiltrated by the resulting B cell proliferation.2 Implicated bacteria include Helicobacter pylori, Chlamydia pneumoniae, Chlamydia psittaci and Campylobacter jejuni.3 Antibiotic therapy is a primary/intial treatment of choice for gastric MALT lymphoma with response rates ranging between 45% and 75% and has prompted the explorations for clinical trials in this disease.4 Eradication of the bacteria can lead to remission in approximately half of patients5; removal of the antigen may prevent continued stimulation and decrease the potential for further clonal expansion to lymphoma.

This understanding, along with successful treatment of conjunctival/orbital lymphoma with antibiotics,6 was the rationale behind our investigation to treat uveal lymphoid hyperplasia with combination oral antibiotics and steroids. We report here our clinical results, including local response and systemic recurrence over at least 3-year follow-up.

METHODS
This retrospective, single-centre study involved 5 eyes in 4 patients recruited from Memorial Sloan Kettering Cancer Center, New York, between April 2016 and June 2018. Patients were clinically diagnosed with uveal lymphoid hyperplasia (on the basis of characteristic multifocal creamy, yellow choroidal infiltrates, ultrasound demonstrating choroidal enlargement and optical coherence tomography (OCT) depiction of choroidal infiltration) with measurable choroidal disease. On ultrasound, all patients had low–medium internal reflectivity that is characteristic of uveal lymphoid hyperplasia and all patients had echographic documentation of episcleral nodules, which are ‘one of the most important diagnostic features’ of uveal lymphoid hyperplasia.7 No patient presented with anterior chamber cell, anterior chamber flare, vitritis nor vasculitis. Following discussion of their presumptive diagnosis, an explanation of management options (risks, benefits and alternatives) and rationale for each, all patients gave verbal consent and were treated with a course of oral antibiotics and steroids (table 1).

Patients underwent systemic work up for lymphoproliferative, inflammatory or infectious aetiology, including blood tests (complete blood count, rapid plasma regain, Borrelia burgdorferi antibodies, ACE, antineutrophil cytoplasmic antibodies, anti-nuclear antibody, hepatitis serologies, protein electrophoresis, lactate dehydrogenase and uric acid), urinalysis and whole-body (neck to thigh) positron emission tomography CT. These tests were within normal range/negative in all patients.

Antibiotics consisted of either doxycycline 100 mg two times per day and steroids consisted of 6-day taper of 24 mg methylprednisolone (3 eyes) or subtenon triamcinolone (1 eye).
Table 1  Patient demographics and treatment details

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>gender</th>
<th>Eye</th>
<th>Wt (kg)</th>
<th>Clinical pres*</th>
<th>Clinical site</th>
<th>Treatment</th>
<th>Rpns interval (months)</th>
<th>Choroidal thickness (μm)</th>
<th>Rpns by OCT/US</th>
<th>BCVA response</th>
<th>Refractive shift response</th>
<th>Last Flu (months)</th>
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<tbody>
<tr>
<td>1</td>
<td>30 F</td>
<td>OD</td>
<td>75</td>
<td>None</td>
<td>None</td>
<td>Methylypred 24 mg 6 day taper; Doxy 100 two times per day×1 month</td>
<td>0.5</td>
<td>711–343 nm</td>
<td>Gain one line (20/25 to 20/20)</td>
<td>0.50 D myopic (−6.75 to −2.75)</td>
<td>36.1</td>
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<tr>
<td>1</td>
<td>30 F</td>
<td>OS</td>
<td>75</td>
<td>None</td>
<td>None</td>
<td>Methylypred 24 mg 6 day taper; Doxy 100 two times per day×1 month</td>
<td>0.5</td>
<td>917–286 nm</td>
<td>Gain two lines (20/10 to 20/20)</td>
<td>0.75 D myopic (−6.25 to −7.00)</td>
<td>38.1</td>
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<tr>
<td>2</td>
<td>50 M</td>
<td>OD</td>
<td>72</td>
<td>None</td>
<td>None</td>
<td>Subtenon triamcinolone; ComboAbx* for 14 days</td>
<td>1.1</td>
<td>408–289 nm</td>
<td>Gain two lines (20/100 to 20/25)</td>
<td>0.75 D hyperopic (−1.25 to −0.750)</td>
<td>53.7</td>
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<tr>
<td>3</td>
<td>60 M</td>
<td>OD</td>
<td>109</td>
<td>Blurry vision and retinal folds</td>
<td>Orbit</td>
<td>Methylypred 24 mg 6 day taper; Doxy 100 mg twice daily</td>
<td>0.4</td>
<td>6.54–1.80 mm Gain one line (20/25 to 20/20)</td>
<td>0.50 D myopic (−0.75 to −1.25)</td>
<td>50.8</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Median</td>
<td></td>
<td></td>
<td>0.5</td>
<td>Decrease: 421 nm Gain 1.5 lines</td>
<td>0.50 D myopic</td>
<td>50.8</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
<td>0.6</td>
<td>Decrease: 398 nm Gain 2.8 lines</td>
<td>0.50 D myopic</td>
<td>46.9</td>
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</table>

Methylpred 24 mg 6 day taper means 24 mg, 10 mg, 16 mg, 12 mg, 8 mg and 4 mg daily over 6 days.
*Clinical presentation in addition to the multifocal creamy, yellow choroidal infiltrates.
†Spherical equivalence.

Clinical presentation in addition to the multifocal creamy, yellow choroidal infiltrates.

**Clinical science**

Examination

Patients received a complete ophthalmic examination along with best-corrected visual acuity (BCVA), fundus photography and B-scan ultrasonography (Ellex, Adelaide, Australia) where indicated. Enhanced depth imaging OCT (EDI-OCT) images were obtained with the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering). A 9-millimetre scan and a 32-line cross scan pattern (in the horizontal direction, each consisting of a maximum of 50 averaged scans) were used. Choroidal thickness was measured on EDI-OCT imaging with the calliper tool, spanning the vertical distance from the hyperreflective line (corresponding to Bruch’s membrane) to the choriocapillaris border. Two independent observers (JPW and JHF) measured choroidal thickness and the mean was recorded. Non-cycloplegic autorefraction was measured (Marco Tonoref II ARK).

Data collection

Demographic data were collected on each patient, including gender, age and other comorbidities. Treatment data included the drugs and dosage. Clinical data included response type (complete response versus partial response), time to response, BCVA (in Snellen and logMAR), spherical equivalence obtained by autorefractor, choroidal thickness in the location of lymphoid infiltration and occurrence of systemic recurrence. Follow-up period was defined from the initial treatment date through the date of last follow-up.

Choroidal thickness was measured on EDI-OCT imaging with the calliper tool, as the vertical distance from the hyperreflective line (corresponding to Bruch’s membrane) to the choriocapillaris border.

RESULTS

Patient demographics and treatment details are outlined in table 1.

Mean and median age were 58 years and 53 years, respectively. One patient (patient number 3) had a history of cutaneous melanoma, basal cell carcinoma and squamous cell carcinoma. No patient had comorbidities associated with abnormal choroidal thickness. All patients presented with blurry vision in the affected eye and a dull pain was reported in three eyes. Systemic evaluation included radiographic imaging (either whole-body positron emission tomography or CT of the chest, the abdomen and the pelvis) and blood testing (hepatitis serologies, blood count, complete metabolic panel, uric acid, protein electrophoresis and lactate dehydrogenase); these were negative for systemic lymphoma in all patients.

At a median of 2 weeks after starting oral antibiotics and steroids, all 4 eyes displayed a clinical response (figure 1). Choroidal infiltration regressed such that the choroidal thickness decreased by a median of 421 μm (range: 119–631 μm). Consistent with this, the refractive error underwent a myopic shift by a median 0.50 Dipters (range: +0.75 Dipters to −0.75 Dipters); and patients gained a median of 1.5 Snellen lines of BCVA (range: 1–7 Snellen lines). At a median of 51-month follow-up, all 4 eyes had a sustained complete response. No patient has developed systemic disease to date.

DISCUSSION

We present a cohort of four eyes with uveal lymphoid hyperplasia diagnosed clinically with confirmation with ultrasound and OCT, which exhibited responses to oral antibiotics and steroids. All cases had measurable clinical responses with a striking reduction in choroidal infiltration and thickness, in association with improved vision. In all eyes, the choroid exhibited a complete response; in the one eye with locoregional orbital disease, the orbit responded completely. Over 4-year median follow-up, no patient developed systemic recurrence.

The rationale for this treatment approach is supported by the large body of evidence in the management of gastric MALT lymphoma. Both gastric lymphoma and uveal lymphoid hyperplasia are believed to predominantly be the result of clonal B cell expansion (propagated by an antigenic reaction) and while typically low grade, it has the potential to transform.1-3 Given these similarities and the encouraging knowledge that 45%–75% of gastric cancers respond to antibiotics,3 we attempted a similar treatment strategy in a small cohort of uveal lymphoid hyperplasia patients. The selected antibiotics (combination doxycycline or amoxicillin/clarithromycin) mirror those used in gastric MALT lymphoma and were chosen for their activity against the pathogens identified and proposed as the antigenic stimuli that initiate the disease.2

The rationale for antibiotic treatment is further supported by evidence of an antigenic trigger and antibiotic responses in ocular adnexal lymphoma.4 Ferreri et al found 32 of 40 (80%) of ocular adnexa lymphomas were positive for C. psittaci by PCR; and in evaluable cases, 50% had objective response and 78% had chlamydial DNA that was no longer detectable after doxycycline treatment.4 Contrary to these findings, an Austrian cohort found no responses in ocular adnexa lymphoma following doxycycline.5 The authors offer a number of explanations for the disparity in response, including the heavy prevalence of autoimmune status in their cohort negatively affecting the impact
of antibiotics or geographic differences in *C. psittaci* status (although chlamydial status was not available for their patients). In support of this latter point, Ruiz *et al.* determined their series of 30 ocular adnexal lymphoma were all negative for *C. psittaci* by PCR.

The present study borrows knowledge regarding ocular adnexal lymphoma and applies it to choroidal lymphoma, with the assumption that the two are similar. Histopathology would suggest that the intraocular choroidal lymphoma and its extraocular extension are the same lesion as evidenced by stromal infiltration and uninvolved of the grenz zone (an area between the infiltrate and the epithelium) suggesting an intraocular origin of the lymphoid infiltrate. Thus, pathology would argue against the choroidal and overlying episcleral nodule being colliding and

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**Figure 1** Representative images of uveal lymphoid hyperplasia and response to combination antibiotics/steroids. Right eye (A) and left eye (D) fundus photograph of patient 1 demonstrating choroidal/scleral infiltration on OCT (B and E), which dramatically regresses 2 weeks after oral methylprednisolone and doxycycline (C and F). Fundus photography (G) and ultrasound (H) of right eye of patient 2 demonstrating choroidal thickening from uveal lymphoid hyperplasia, which regresses 1 month after amoxicillin, clarithromycin and a subtenon steroid injection (I). Fundus photography (J) and ultrasound (K) of right eye of patient 3 demonstrating choroidal thickening and locoregional orbital extension from lymphoid hyperplasia, which regresses 2 weeks after oral methylprednisolone and doxycycline (L). OCT, optical coherence tomography.
separate lesions. Rather puzzling is the observation that episcleral and choroidal components are not always congruent in their clonality as established by immunohistochemistry or PCR.9 Perhaps, these differences are driven by the distinct microenvironment inherent to the choroid and episclera.

Since all patients in the present cohort received concomitant steroids, sceptics may argue clinical responses were due to steroids and question whether antibiotics had an additive impact. There are published cases of uveal lymphoid hyperplasia responding adequately to steroids.5 10 11 However, in our experience, monotherapy with steroids yields subpar clinical responses. In support of this, Harris et al describe seven eyes with uveal lymphoid hyperplasia all of which failed oral steroids.12 Furthermore, 39% of the Philadelphia cohort, comprised of 59 patients, had failed steroids prior to referral to their centre.13 For this reason, we have abandoned treatment of uveal lymphoid hyperplasia by steroids alone, and opt for combination antibiotics and steroids if clinically indicated. While this present series does not formally compare treatment subgroups of steroids alone, antibiotics alone or steroids and antibiotics, we are hopeful that future studies will address this question.

Established treatments for choroidal lymphoma include systemic chemotherapy or monoclonal antibodies, external beam radiation, observation, oral steroids and occasionally encapsulation.13 14 While oral antibiotics have been sparsely mentioned in a handful of patients with choroidal lymphoma, there are no details on the drug or dosage used, documentation of regression by OCT, short-term and long-term response, or need for additional therapies.14 In our search of the literature, there were no reports dedicated to the discussion of choroidal lymphoma eyes that were exclusively managed by oral antibiotics and steroids.

Our promising results demonstrate measurable and sustained responses in this small cohort of patients with uveal lymphoid hyperplasia, without systemic recurrence over 4-year follow-up. Combination antibiotic/steroid therapy for uveal lymphoid hyperplasia, including MALT/low-grade lymphomas,15 may obviate the need for systemic chemotherapy/ monoclonal antibody and/or external beam irradiation in select cases. Cohort expansion of this relatively rare condition would further support these findings.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by institutional review board of Memorial Sloan Kettering Cancer Center (IRB#: 16-1366: Characterization of Ocular Tumors Participants) gave informed consent to participate in the study before taking part. The study adhered to the tenets of the Declaration of Helsinki.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

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**REFERENCES**


