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Conjunctival lymphoid hyperplasia treated with topical tacrolimus: A report of two cases

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ABSTRACT

Purpose: Conjunctival lymphoid hyperplasia is a benign condition that typically presents with irritation, conjunctival injection, and eyelid edema. Topical corticosteroid drops are often the first-line treatment when not excised, but long-term use may cause intraocular pressure spikes or cataract formation. Steroid-sparing agents could be considered to manage patients who require long-term treatment. Here we discuss the potential benefit of topical tacrolimus use for the management of these patients.

Observations: We present two cases of conjunctival lymphoid hyperplasia, one in a 74-year-old man and one in a 41-year-old woman. Both showed a positive response to topical steroid treatment, but due to intraocular pressure elevations, needed to be trialed on steroid-sparing medications. Topical tacrolimus (Protopic) at 0.03 % concentration was applied to the inferior fornix. Patients were monitored for improvement on exam and for subjective improvement of their symptoms. Topical tacrolimus produced moderate to complete resolution of the lesions in these patients and resulted in symptomatic improvement.

Conclusions and importance: Tacrolimus is an immunomodulatory medication. The ointment form is approved for use in atopic dermatitis (eczema). Although it is an off-label use, it has been used for other ocular conditions with variable success and tolerability, but we did not find any prior reports of its use in conjunctival benign lymphoid hyperplasia.

1. Introduction

Lymphoid hyperplasia (LH) is a benign condition that affects the orbit and ocular adnexa. The term "reactive" indicates a benign lesion, whereas "atypical" suggests malignant features, including monoclonality, yet does not meet the definition of lymphoma. The pathogenesis is theorized to be secondary to an antigen response, which begins the cascade of T cell immunoregulatory dysfunction resulting in B-cell proliferation.[1,2] About one-third of ocular adnexa cases are conjunctival.[3] A literature review of 235 conjunctival LH cases by Klavdianou et al. suggests the mean age of diagnosis is 35 years with a slight male predilection (54 %). In this review, 75 % of cases were unilateral, and over 80 % involve the nasal bulbar conjunctiva, caruncle, or semilunar folds while the remaining involve the fornix or tarsus.[3] Conjunctival LH presents clinically as smooth, nodular, or cystic salmon-colored lesions with normal overlying epithelium.[1,3] The differential diagnosis for these findings includes lymphoma, infection, allergic follicular conjunctivitis, sarcoidosis, nodular sclerosis, pyogenic granuloma, Sjogren syndrome, amyloid deposition, and vasculitis.

Biopsy with immunohistochemistry and flow cytometry confirms the diagnosis.[4] Histopathology reveals well-differentiated lymphocytes organized into germinal centers. Flow cytometry can aid with prognosis; patients with evidence of monoclonality have 4x increased risk of progression to lymphoma compared to those without, and there is a 20–30 % chance of recurrence after therapy.[1] In cases of orbital LH, staining for IgG4 and systemic work-up should be pursued.[1,3]

Here, we present two cases of inferior forniceal LH that showed moderate to complete resolution with topical tacrolimus use.

2. Findings

2.1. Case 1

The first patient is a 74-year-old male with relevant past medical history of anterior basement membrane dystrophy (ABMD), keratoconus, and chronic conjunctivitis of the left eye. He had several years of left

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ocular symptoms including itching, redness, and mattering. Biopsy findings from 5 months prior to presentation at our clinic were consistent with reactive LH. His symptoms were previously controlled with topical and oral steroids, which were discontinued after he developed significant intraocular pressure (IOP) elevation.

On presentation to our clinic, his visual acuity was 20/40 in the right eye, and 20/30 in the left eye with glasses. In both eyes, IOP was normal and slit lamp exam showed meibomian gland dysfunction; conjunctiva in the right eye was otherwise normal. The left inferior palpebral conjunctiva revealed injected, redundant salmon-colored forniceal conjunctiva, sporadic small cysts, and round lymphoid.

On review, the outside pathology and flow cytometry was consistent with stromal lymphoid aggregate with a germinal center. Immunohistochemistry staining was positive for CD3, CD5, CD10, CD20, and BCL-2 positive cells, and flow cytometry showed 73 % B-cells, 23.6 % T-cells (CD4:CD8 6:1), and 1.9 % NK cells, without monoclonality. Given his IOP elevations and lack of interest in other offered treatments he was started on 0.03 % tacrolimus (Protopic) in his left eye daily. At his 6-week follow-up he reported 50 % subjective improvement in symptoms, and examination showed decreased lesion size and reduced conjunctival injection (Fig. 1). His 6-month follow-up did not show any additional improvement beyond the initial response. After 6 months of use the patient discontinued use of tacrolimus and at his follow up 10 months following discontinuation of tacrolimus, he had a normal conjunctival exam and has only occasional pruritis in the left eye.

2.2. Case 2

The second patient is a 41-year-old female with relevant past medical history of Raynaud's (anti-SSA/Ro antibody positive) and arthralgias who presented to clinic due to recurrent erosions and chronic conjunctivitis of the left eye. Her symptoms began after being kicked in the eye 7 years prior to presentation. Since the injury, she experienced intermittent eyelid swelling and mild itching. Her symptoms improved on topical prednisone but flared again upon stopping the medication.

Follicles in the inferior palpebral conjunctiva were noted and biopsied during a significant flare 3 years prior to presentation. Immunohistochemistry staining showed mature lymphocyte stromal infiltration in a follicular pattern with immunohistochemistry staining for CD3, CD20, and BCL-2 confirming a normal follicular staining pattern. Flow cytometry confirmed polyclonality with 20 % mature B-cells, 17 % T-cells (CD4:CD8 5:1), and 0.4 % NK cells with the remaining population being granulocytes, monocytes, connective tissue, and debris. She tried several medications without relief: oral Valtrex, topical azithromycin, topical tobramycin, oral doxycycline, Muro ointment, and Genteal ointment. She was then referred to our clinic for further evaluation.

Her visual acuity on presentation was 20/15 in both eyes without correction, and IOP was normal bilaterally. Slit lamp exam showed bilateral Meibomian gland dysfunction, and medium-large follicles in the superior and inferior palpebral conjunctiva of the left eye. The right eye slit lamp exam was normal. She expressed concern about using topical steroids long-term, so was started on 0.03 % tacrolimus (Protopic) in the left eye daily. At 2-month follow-up she reported 100 % subjective resolution of symptoms, and examination showed complete resolution of the conjunctival lesions (Fig. 1). After 1 year of use, she discontinued tacrolimus and after 2 weeks after discontinuation, subjectively felt that her symptoms returned and therefore resumed its use once daily.

3. Discussion

Both cases had marked improvement in symptoms and appearance after beginning treatment with topical tacrolimus. Neither of the presented cases had a history of contact dermatitis or atopy, suggesting that the presenting symptoms were likely secondary to the lymphoid hyperplasia and not a confounding element. Given that one patient was able to stop the medication entirely, while the other was not, demonstrates, like many medications, variable response and lasting impact.

The pathology from both cases demonstrates normal germinal centers and flow cytometry and lack of monoclonality, which is consistent

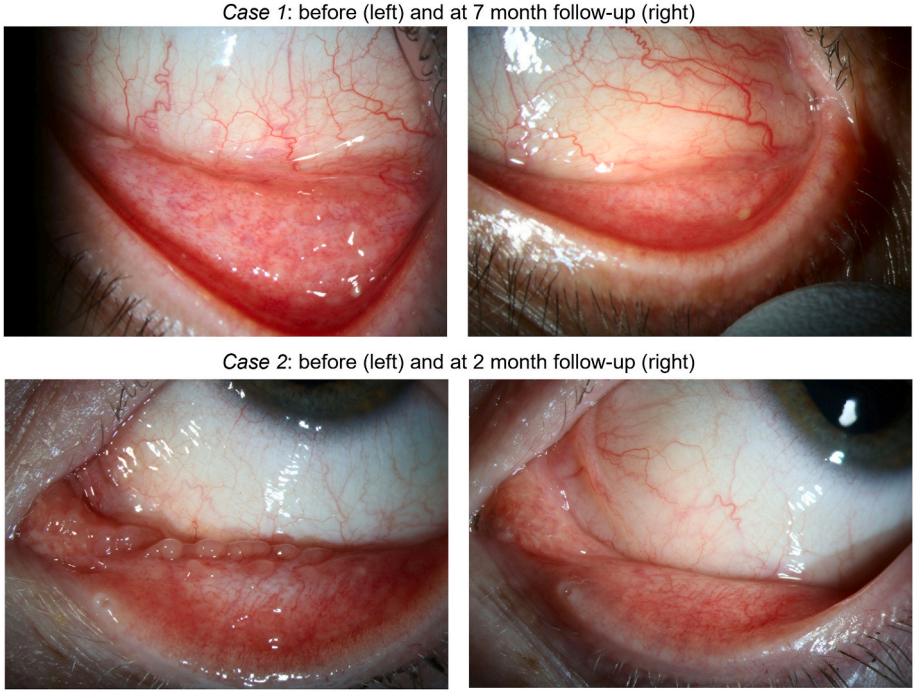

Fig. 1. Clinical photos before and after treatment
Images from before and after treatment with topical tacrolimus. In both cases, the salmon-colored patches characteristic of benign lymphoid hyperplasia can be seen on the inferior bulbar conjunctiva. Case 1 showed moderate resolution at their 7-month follow-up. The majority of the patches have resolved and the conjunctival injection has improved. Case 2 showed near-complete resolution of the lesions at 2 months.

with the pathology of orbital and ocular benign lymphoid hyperplasia. What is potentially unusual, is that both cases had a B-cell predominance. While a recent review suggests that a more typical presentation is a T-cell predominance, this is based other manuscripts that report a small number of benign lyphoproliferative cases compared to malignancy as well as two other publications that do not differentiate cutaneous from orbital or ocular location.[1] It would be benificial to see a histopathology review of benign lyphoproliferative disease specific to the conjunctiva.

There is no expert consensus or guidelines on conjunctival LH management. Observation is appropriate if the lesions are asymptomatic. In the review by Klavdianou, the most common treatment was excision (65.9 %) followed by topical or oral corticosteroids (12.7 %); however, 13/17 of the excised lesions were bulbar, which may be easier to delineate. In our cases, the lesions had indistinct borders, therefore excision was not feasible.

External beam radiation is typically reserved for orbital lesions, though has been reported in conjunctival LH.[1,3] Other therapies previously used in the treatment of conjunctival lesions include subconjunctival steroid injections, cryotherapy, oral doxycycline, topical cyclosporine,[5] and topical INF-a.[6] These reports, like ours, presented 1–3 cases with variable results. IV rituximab has only been used in orbital cases.[7]

Long-term topical steroid eye drop use is associated with potentially serious side effects including accelerated cataract formation, increased risk of opportunistic infections, slowed corneal epithelial healing, and increased intraocular pressure, which increases the risk of glaucoma.[8] Both patients had concerns about topical steroids and did not want to trial systemic medications or the other treatment modalities discussed.

Tacrolimus works by inhibiting calcineurin phosphatase, which decreases T-cell proliferation and suppresses immunity. Although cyclosporine also inhibitions calcineurin, tacrolimus uniquely works via additional pathways of immune suppresion. For example, tacrolimus can also reduce B-cell proliferation via suppresion of various interluekins, something that cyclosporone does not do.[9] In addition, tacroliums is somewhere between 20- and 100-fold potency compared to cyclosporine. Despite this, it would have been reasonable to trial these patients on topical cyclosporine (0.09–0.1 %), but given their history of treatment failure, they were eager to try something with high potency. The topical ointment formulation of tacrolimus (brand name Protopic) comes in two strengths, 0.03 % and 0.1 %, and is FDA approved for treatment of atopic dermatitis (eczema).[10] It has been used off-label for treatment of allergic contact dermatitis, oral lichen planus, psoriasis, pyoderma gangrenosum, and vitiligo.[11] Protopic has also been used off-label to treat several ocular conditions including allergic eye disease, anterior uveitis, scleritis, graft-versus-host disease, ocular cicatricial pemphigoid, and post-corneal transplantation.[12] It is generally well-tolerated despite not being formulated for ocular use.[12] Though we did not find any prior reports of its use in conjunctival LH cases, there are two cutaneous LH cases that were successfully treated with Protopic, further suggesting that this may play an important role in superficial disease, sparing patients from systemic side effects.[13,14]

We are not aware of ocular side effects other than ocular irritation with commercially available Tacrolimus (Protopic), but its use is not without risk. The theoretical increased risk of infection, conjunctival atrophy, and poor wound healing should be discussed.[15] In 2006, the FDA issued a black box warning for use of topical tacrolimus due to potential risk of cancer seen in case reports, animal studies, and organ transplant patients. However, a more recent review of data does not show any clear association between topical calcineurin inhibitors and cancer risk.[15] Despite this, patients should be made aware of the warning in addition to itsoff-label use prior to beginning treatment. Patients using topical tacrolimus in the eye should be carefully monitored, and the medication should be stopped if serious side effects occur.

4. Conclusions

Conjunctival LH is a rare entity without a well-defined treatment algorithm. Patients may prefer to avoid the consequences of topical steroids, systemic, or surgical treatments, therefore other treatment options should be explored. These two cases demonstrate the practical application of commercially available tacrolimus with variable, though overall positive, results.

CRediT authorship contribution statement

Angeline C. Rivkin: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Ashlie A. Bernhisel:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation, Conceptualization.

Patient consent

Both patients consented to publication of their cases.

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ACR: investigation, writing- original draft preparation, writing-reviewing and editing.

AAB: conceptualization, writing-reviewing and editing, supervision.

IRB approval was not required for this study.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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