Clinical Case Report

Medicine®

OPEN

Topical steroids eye drops in conjunctival reactive lymphoid hyperplasia

Case report

Bernardo Rodrigues Mendes Moraes, MD*, Micael Valtoni Dantas do Nascimento, MD, Epitácio Dias da Silva Neto, MD, Ruth Miyuki Santo, PhD

Abstract

Rationale: Conjunctival lymphoproliferative lesions constitute a significant diagnostic challenge and it is essential to exclude neoplastic lesions. Histopathological and immunohistochemical tests are very useful in establishing the correct diagnosis. Reactive lymphoid hyperplasia (RLH) is part of a spectrum of lymphocytic infiltrative disorders. Evidence is scarce regarding appropriate treatment of conjunctival RLH. We report a case treated with topical corticosteroid.

Patient concerns: A 40 year-old female presented with a 7-month history of a slow growth tumor in the superior conjunctiva of the right eye. Slit-lamp examination demonstrated salmon colored lesion in the upper conjunctiva, with little conjunctival injection, but no significant neovascularization. There was no eyelid involvement.

Diagnoses: Ultrasound biomicroscopy showed lesion depth (1.53 mm) and larger diameter (10.73 mm). Pathological examination revealed a chronic inflammatory process with conjunctival folicular hyperplasia. The immunohistochemistry examination showed predominance of CD20, CD23, and CD 3 e CD 5.

Intervention: We started topic prednisolone 1% 6 times daily.

Outcomes: Six months after starting treatment, the lesion completely resolved, without any side-effects or recurrence during three-year follow-up period.

Lessons: Conjunctival RLH can be managed in various ways, depending on patient symptonm, comorbities, and disease distribution. Surgical resection with cryotherapy, radiotherapy, systemic corticosteroids, subconjunctival triamcinolone, and rituximab are some options. There is no strong evidence in the literature of conjunctival RLH successfully treated with topical eye drops corticosteroid. In this report, we obtained completely resolution of conjunctival RLH with topical corticosteroid.

Conclusion: Topical eye drops corticosteroids are an alternative treatment for selected cases of conjuncitval RLH with no orbital or eyelid involvement.

Abbreviations: ALH = atypical lymphoid hyperplasia, IOP = intraocular pressure, LH = lymphoid hyperplasia, NHL = non-Hodgkin lymphoma, OALD = ocular adnexal lymphoproliferative disease, RLH = reactive lymphoid hyperplasia.

Keywords: conjunctiva, corticosteroid, eyelid, histopathology, immunohistochemistry, lymphoma, orbit, reactive lymphoid hyperplasia

1. Introduction

Lymphoproliferative lesions in the area of the conjunctiva and the ocular adnexa often constitute a significant diagnostic challenge, and it is essential to exclude neoplastic lesions (conjunctival lymphoma). Histopathological tests, combined obligatorily with immunohistochemical analysis, are very useful in establishing the correct diagnosis.[1]

Reactive lymphoid hyperplasia (RLH) is part of a spectrum of ocular adnexal lymphocytic infiltrative disorders.[2] It is believed to be a consequence of a chronic inflammatory response of lymphoid cells to irritating or antigenic stimuli, often affecting adults in the sixth or seventh decade of life.[3,4]

Evidence is scarce regarding appropriate treatment of conjunctival reactive lymphoid hyperplasia. Biological therapies and immune modulators have shown promising results but not without side effects.[5] We report a case treated with topical corticosteroids. A dramatic response was obtained, which may represent a good therapeutic option.

2. Case report

A 40-year old female presented with a 7-month history of a slow growth tumor in the superior conjunctiva of the right eye. Her main complaint was foreign body sensation. She had no systemic complaints and no past ophthalmologic or systemic history of relevance. Her best corrected visual acuity was 20/20 in both

Editor: Kaili Wu.

The authors have no funding and conflicts of interest to disclose.

This manuscript was not founded by any sponsor or agency.

Department of Ophthalmology, University of São Paulo, São Paulo, Brazil.

** Correspondence: Bernardo Rodrigues Mendes Moraes, Department of Ophthalmology, University of São Paulo, São Paulo, Brazil, (e-mail: moraesbernardo@yahoo.com.br).*

Medicine (2017) 96:47(e8656)

Received: 7 August 2017 / Received in final form: 4 October 2017 / Accepted: 26 October 2017

http://dx.doi.org/10.1097/MD.0000000000008656

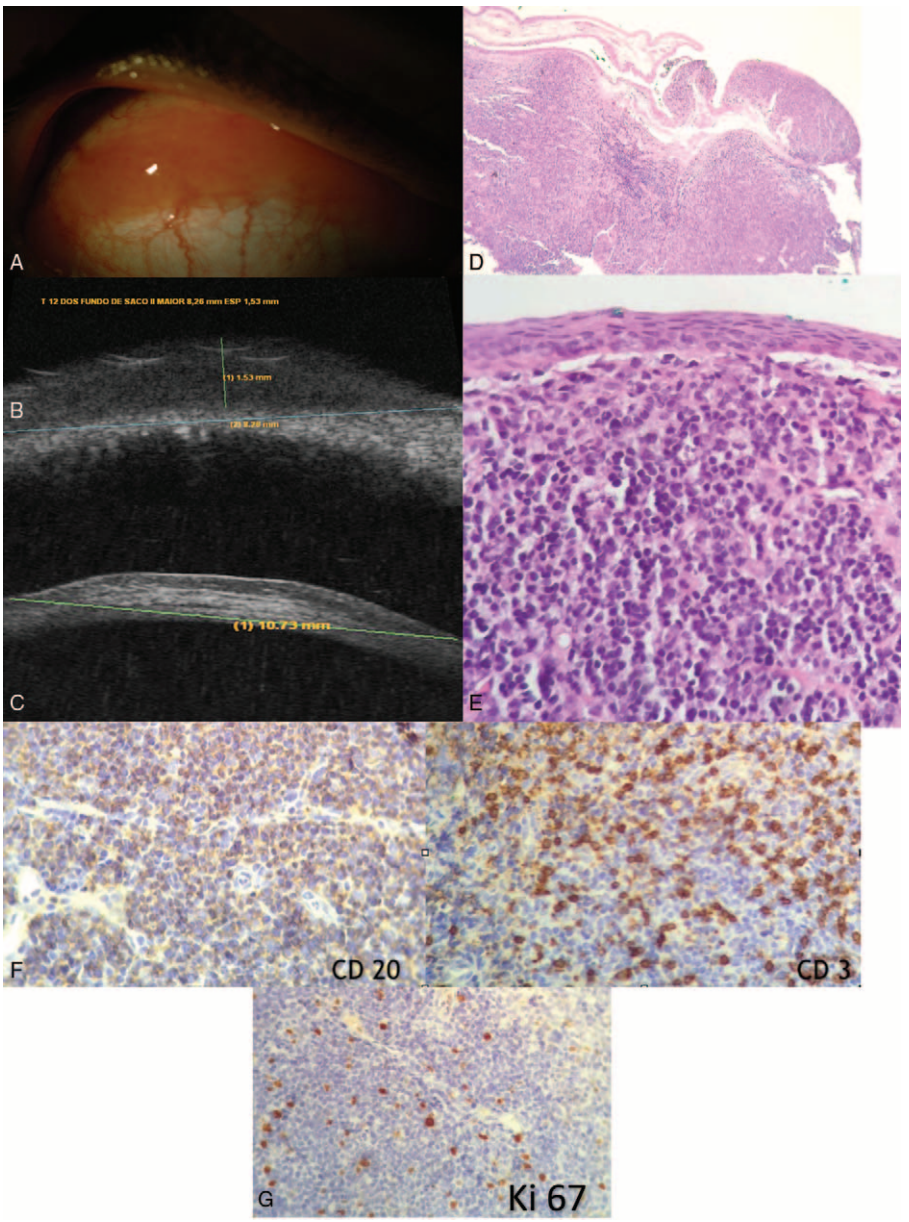

Figure 1. (A) Slit-lamp photograph of the patient right eye on initial presentation showed an elevated salmon colored lymphoid tumor in the upper bulbar conjunctiva of the right eye. (B) Ultrasound biomicroscopy of lesion depth (1.53 mm). (C) Ultrasound biomicroscopy of lesion large diameter (10.73 mm). (D) Histopathological section of the conjunctival biopsy showing chronic inflammatory infiltrate arranged in lymphoid follicules. Hematoxylin–Eosin stain, 100-fold magnification. (E) Hematoxylin–Eosin stain 400-fold magnification demonstrates that lymphocytes are small and show no atypic features. (F) Immunohistochemistry examination with predominance of CD20 B lymphocytes and CD 3 T lymphocytes, which shows polyclonality. (G) Immunohistochemistry examination demonstrates low levels of KI67, which is a marker of cell proliferation. This corroborates the diagnosis of RLH.

eyes. Slit-lamp examination demonstrated salmon colored lesion in the upper conjunctiva of the right eye, with little conjunctival injection, but no significant neovascularization (Fig. 1). There was no eyelid involvement. The slit-lamp examination of the left eye had no relevant findings. Intraocular pressures (IOP) of both eyes were 12. Extra-ocular muscle functions were normal bilaterally. Fundus examination of both eyes was normal. Ultrasound biomicroscopy was performed to confirm lesion depth (1.53 mm) and larger diameter (10.73 mm) (Fig. 1).

We hypothesized a lymphoproliferative lesion and an incisional biopsy was performed for definitive diagnosis. Pathological examination revealed a chronic inflammatory process with conjunctival folicular lymphoid hyperplasia. The immunohistochemistry examination showed predominance of CD20, CD23, CD 3 e CD 5. CD 10 was negative. KI-67 was positive in low index. There were no atypical cells (Fig. 1).

The patient subsequently underwent extensive investigation to rule-out systemic disease, including physical, hematologic, and radiology exams. These exams showed no abnormalities. With the diagnosis of RLH, we decided, with patient consent, to start topic prednisolone 1% six times a day.

On follow-up visits, one month and three months after starting treatment, a progressively reduction in tumor size was noted. Six months after starting treatment, the lesion completely resolved,

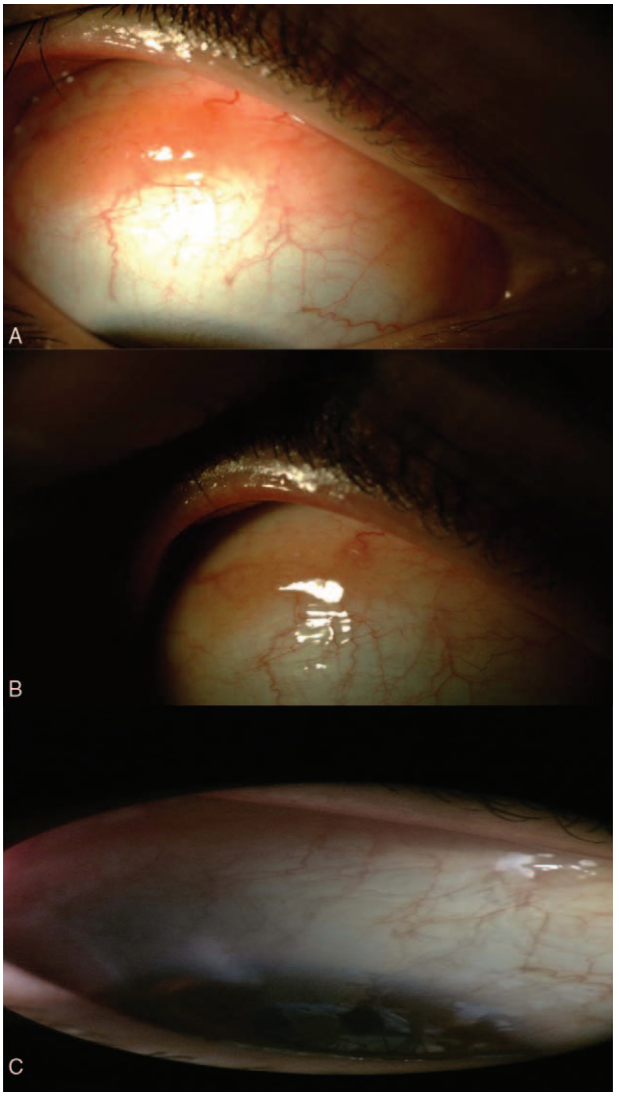

Figure 2. Lesion follow-up after topic steroid treatment. Progressive lesion reduction was observed. Six months after starting treatment, the lesion completely resolved, being no longer palpable or visible. (A) One-month follow-up. (B) Three-months follow-up. (C) Six-months follow-up.

being no longer palpable or visible (Fig. 2). At this point, a progressive reduction in prednisolone was started, with subtraction of one drop per week. The patient did not experience any side effects, recurrence, or other complications during three-year follow-up period.

3. Discussion

Ocular adnexal lymphoproliferative disease (OALD) encompasses the spectrum of lymphoid diseases affecting the tissues surrounding the eye. It is classified according to the presence or absence of malignant features assessed using histopathologic, immunophenotypic, and molecular genetic techniques. OALD includes both the malignant lymphomas—that is, monoclonal lymphoid proliferations with evidence of cytological atypia and malignant behavior—and lymphoid hyperplasia (LH)—that is, lymphoid proliferations, which are either polyclonal or occasionally oligoclonal. Thought to be an idiopathic lymphocytic cellular response to an inflammatory stimulus, most likely an endogenous or exogenous antigen, LH can also be subdivided into reactive (RLH), with completely benign morphology and immunophenotype, and atypical LH (ALH), borderline lesions between RLH and lymphoma.[6]

In 1990, Knowles et al[7] published a prognostic analysis of 108 cases of ocular adnexal lymphoid tumors. They found that the anatomic site of adnexal lymphoid tumor and its histopathologic features were important predictors of the development of systemic nonocular lymphoma. Patients with conjunctival infiltration showed a lower incidence of systemic lymphoma (20%) as compared with those with orbit (35%) or eyelid (70%) infiltration.[7,8] Non-Hodgkin lymphoma (NHL) may rarely arise concurrently or subsequent to LH, necessitating long-term patient follow-up.[6]

The OALD affects males and females equally.[1,6,8]. The mean age of onset of LH is from fifth to seventh decades, which is slightly lower than for ocular adnexal lymphoma.[6] In a study of 117 patients with conjunctival lymphoid tumors treated during the 25-year period, the mean patient age at diagnosis of the ocular tumor was 61 years. The quadrant location of main tumor was superior for 41% of patients, inferior for 21%, nasal for 14%, and temporal for 10%. At present, 62% of tumors were unilateral and 38% bilateral.[8]

Conjunctival LH appears as a circumscribed salmon-colored lesion that may be cystic, smooth, or nodular. Lesions arise in the conjunctival stroma, and the overlying conjunctival epithelium is normal, which helps to distinguish cases from ocular surface squamous neoplasia.[6] Although LH is considered to be benign, and ocular involvement represents only 2% of extra-nodal lymphoma,[9] there are no reliable features to distinguish LH and NHL clinically or radiologically, mandating tissue biopsy in all cases.[6,10]

Stacy et al showed immunohistochemical features of patients with RLH and NHL. The follicles of RLH and follicular lymphoma stained positively for the B-cell marker CD20. In RLH, T cells were predominantly located in the interfollicular zones but also lightly throughout the center of the follicles, as demonstrated by the T cell marker CD3. CD5 stained T cells in the same pattern. T cells stained positively for CD3 and CD5 in follicular lymphoma and were located within the interfollicular zones as well, the latter with a more prominent stain of CD20 then in RLH. Follicles in both RLH and follicular lymphoma were positive for BCL-6. BCL-2 staining revealed that the follicular centers in RLH were negative and those in follicular lymphoma were positive. CD10 staining was positive for both RLH and follicular lymphoma but showed greater interfollicular staining in follicular lymphoma. Ki-67, a marker for cellular proliferation, showed dense positivity that was polarized within RLH follicles. In contrast, follicular lymphoma demonstrated a more diffuse, evenly distributed staining pattern within the follicular centers. Polyclonality was evident in RLH, with in situ hybridization revealing equal populations of both kappa and lambda light chains. In follicular lymphoma rare cells stained positive for kappa or lambda.[1]

Conjunctival LH can be managed in a number of ways, depending on patient symptoms, comorbidities, and disease distribution. If the patient shows no sign of systemic lymphoma after evaluation by the medical physician, the approach with complete tumor excision plus cryotherapy if the mass is small or incisional biopsy and low-dose radiotherapy if the mass is large has great success rates.[8]

However, new approaches, less invasive, have been emerged. Ahmed et al[5] reported a case of RLH treated with one

subconjunctival triamcinolone injection, with complete regression and no recurrence in three and half years of follow-up. Telander et al[11] had also similar results using single dose of subconjunctival triamcinolone for benign lymphoid hyperplasia, with complete resolution in two months after injection. Brazert et al published a case of a 14-year-old child with conjuctival RLH treated with 1.5 mg per 1 kg of body mass of methylprednisolone with a reduction scheme. The lesion had completely resolution for 45 days after starting treatment. The lesions had no recurrence or malignant transformation after 32 months of follow-up and the only side effect experimented was poststeroid acne.[12] Ho et al[13] showed completely resolution in two months of a RLH vascularized lesion treated with subconjunctival bevacizumab injection.

Witzig et al published a 11-cases series of orbit RLH treated with rituximab, 375 mg/m^2, intravenously each week for four doses, and 10 (91%) of the 11 responded. Seven patients were either treated with maintenance rituximab or successfully retreated with rituximab after relapse. None of the 10 responders has become refractory to rituximab.[14] Ho et al[13] reported successful treatment of two patients with benign lymphoid hyperplasia of the orbit with rituximab. Rituximab is a monoclonal antibody that targets the CD20 marker on B-cells inducing apoptosis in normal and pathogenic B-cells. The advantages of rituximab over long-term steroid therapy include lack of myelosuppression and better long-term side effect profile. Adverse effects include reactivation of latent infections, infusion reactions and, rarely, multifocal leukoencephalopathy.[6,13] However, there is no evidence embasing use of rituximab for conjunctival RLH.

There is scarce evidence in the literature of conjunctival RLH successfully treated with topical eye drops corticosteroid. In the case described, patient presented unilateral conjunctival RLH, no eyelid or orbital involvement, which made us try an even less invasive approach than subconjunctival triamcinolone, systemic corticosteroid, rituximab, surgical ressection with crioterapy, or radiotherapy. The decision was shared with patient that agreed after analyzing risks and benefits. The lesion regressed dramatically with prednisolone 1% six times a day, with completely resolution after 6 months of treatment and no ocular or systemic side effects. The patient was provided with regular follow-up visits and, during 24-month observation period, did not experienced local recurrence or systemic lymphoproliferative disease. We believe that topical eye drops corticosteroids are an alternative treatment for selected cases of conjuncitval RLH with no orbital or eyelid involvement, although further studies need to be performed.

4. Conclusion

In conclusion, benign reactive lymphoid hyperplasia should be considered in the differential diagnosis of lymphoproliferative lesions in the conjunctiva. Histopathologic evaluation and immunohistochemistry studies are necessary to exclude lymphoma and other malignant lesions. Long-term follow-up is advised because of the possibility of recurrence or malignancy development.

An ideal treatment for reactive lymphoid hyperplasia remains uncertain. In our case report, we found a dramatic response to topical eye drops corticosteroid without any ocular or systemic side effects. There was no recurrence of the local lesion or proliferative diseases of the hematopoietic system during follow-up. The corticosteroid close from the reactive follicle must have been sufficient to suppress lymphocyte proliferation.

We believe that topical eye drops corticosteroids are an alternative treatment for selected cases of conjuncitval RLH with no orbital or eyelid involvement, although larger studies are required.

References

[1] Stacy RC, Jakobiec FA, Schoenfield L, et al. Unifocal and multifocal reactive lymphoid hyperplasia vs follicular lymphoma of the ocular adnexa. Am J Ophthalmol 2010;150:412–26.
[2] Liesegang TJ. Ocular adnexal lymphoproliferative lesions lymphoid hyperplasia. Mayo Clin Proc 1993;68:1003–110.
[3] Kubota T, Moritani S. High incidence of autoimmune disease in Japanese patients with ocular adnexal reactive lymphoid hyperplasia. Am J Ophthalmol 2007;144:148–9.
[4] Sigelman J, Jakobiec FA. Lymphoid lesions of the conjunctiva: relation of histopathology to clinical outcome. Ophthalmology 1978;85:818–43.
[5] Ahmed TY, Agarwal PK, Roberts F, et al. Periocular steroids in conjunctival reactive lymphoid hyperplasia, a new approach? Clin Exp Ophthalmol 2011;39:576–7.
[6] Andrew NH, Coupland SE, Pirbhai A, et al. Lymphoid hyperplasia of the orbit and ocular adnexa: a clinical pathologic review. Surv Ophthalmol 2016;61:778–90.
[7] Knowles DM, Jakobiec FA, Mcnally L, et al. Lymphoid hyperplasia and malignant lymphoma occurring in the ocular adnexa (orbit, conjunctiva, and eyelids): a prospective multiparametric analysis of 108 cases during 1977 to 1987. Hum Pathol 1990;21:959–73.
[8] Shields CL, Shields JA, Carvalho C, et al. Conjunctival lymphoid tumors: clinical analysis of 117 cases and relationship to systemic lymphoma. Ophthalmology 2001;108:979–84.
[9] Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972;29:252–60.
[10] Westacott S, Garner A, Moseley IF, et al. Orbital lymphoma versus reactive lymphoid hyperplasia: an analysis of the use of computed tomography in differential diagnosis. Br J Ophthalmol 1991;75:722–5.
[11] Telander DG, Lee TZ, Pambuccian SE, et al. Subconjunctival corticosteroids for benign lymphoid hyperplasia. Br J Ophthalmol 2005;89:770–1.
[12] Agata Brazert & Anna Gotz-Wieckowska (2014): Positive Response to Methylprednisolone in a Child with Reactive Lymphoid Hyperplasia of the Conjunctiva, Seminars in Ophthalmology, DOI: 10.3109/08820538.2013.874476.
[13] Ho HH, Savar A, Samaniego F, et al. Treatment of benign lymphoid hyperplasia of the orbit with rituximab. Ophthal Plast Reconstr Surg 2010;26:11–3.
[14] Witzig TE, Inwards DJ, Habermann TM, et al. Treatment of benign orbital pseudolymphomas with the monoclonal anti-CD20 antibody rituximab. Mayo Clinic Proc 2007;82:692–9.