

Successful treatment of allergic conjunctival granuloma by topical tacrolimus: A clinicopathologic case report

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Allergic conjunctival granuloma is a rare cause of conjunctival ocular lesions. The aim of this case report was to present a successful treatment of an allergic conjunctival granuloma with topical tacrolimus eye drops. A 20-year-old female presented with bilateral multiple yellow nodules of the bulbar conjunctival epithelium and conjunctival injection. The patient had tearing, photophobia, itching, foreign body sensation, and red eye. The patient's signs and symptoms progressed despite the use of topical steroids. The patient was treated by application of tacrolimus eye drop (0.005%) in her right eye every 6 h while the left eye was put on placebo. Her signs and symptoms were recorded at each visit. After 3 weeks' therapy with topical tacrolimus eye drop, the patient became asymptomatic in her right eye and conjunctival granulomas fully resolved. Topical tacrolimus seems to be an effective therapeutic option for the treatment of allergic conjunctival granulomas.

Key words: Allergic conjunctival granuloma, Splendore–Hoeppli phenomenon, Tacrolimus

Allergic conjunctival granuloma or Splendore–Hoeppli phenomenon was first described by Ashton and Cook.^[1] These are usually benign lesions with infectious or allergic origins. Without surgical intervention, these lesions can resolve spontaneously or after corticosteroid therapy in a few weeks or months.^[2] A case report of successful treatment of Splendore–Hoeppli reaction by cyclosporine has been reported recently.^[3] Tacrolimus is a macrolide lactone with immunosuppressive properties. It has been documented that tacrolimus eye drops can inhibit the infiltration of eosinophils and lymphocytes significantly in experimental animal models.^[4] This case report presents a complete resolution of an allergic conjunctival

granuloma after 3 weeks' administration of topical tacrolimus eye drop. To the best of our knowledge, this is the first case report of a patient with allergic conjunctival granuloma successfully treated with topical tacrolimus eye drops.

Case Report

A 20-year-old female, with bilateral multiple conjunctival granulomatous lesions and conjunctival injection, presented with tearing, photophobia, severe itching, foreign body sensation, and redness. Her problem was present for the past 9 months, and she underwent conjunctival biopsy sampling twice followed by topical corticosteroids with no response. The patient was given a questionnaire for the symptoms of itching, redness, and foreign body sensation with a grading scale of 0 or none, 1 or mild, 2 or moderate, and 3 or severe to report the severity of each individual symptom. In addition, she underwent a complete ophthalmic examination. Two weeks' before starting the study, all other medications including ophthalmic corticosteroids were discontinued. The informed consent was obtained before the start of the study.

Best-corrected visual acuity was 20/20 in both eyes. Systemic and laboratory assessments were all normal, except a moderate eosinophilia. Two biopsy samples were seen by two separate ophthalmologists and pathologists and infectious causes were ruled out by PAS and Ziehl–Neelsen staining. Epithelioid histiocytes, Langerhans giant cells, lymphocytes, a diffuse infiltration of eosinophils, moderate plasma cells, and few neutrophils in subepithelial stroma were found in the specimen.

A diagnosis of an allergic conjunctival granuloma was confirmed based on above and another finding known as Splendore–Hoeppli phenomenon [Figs. 1 and 2]. Tacrolimus eye drop was reconstituted by adding balanced salt solution to tacrolimus vial for injection under sterile condition in the local laboratory to achieve a 0.005% concentration.^[5] To evaluate the effectiveness of the drug, the patient was treated by application of tacrolimus eye drop (0.005%) in her right eye every 6 h while the left eye was put on vehicle control placebo (ophthalmic solution free of tacrolimus). The patient was followed up 3 days after starting the medication and every week in the 1st month and then every 2 weeks in the next 5 months. The signs and symptoms started to reduce dramatically and lesions disappeared in her right eye [Figs. 3–5] in 3 weeks while no improvements were observed in the left eye. After 1 month, the placebo was switched to tacrolimus eye drop, and in further follow-ups, a similar course was obtained in the left eye. The score of symptoms was reduced from 9 before treatment to 3 after the treatment in both eyes.

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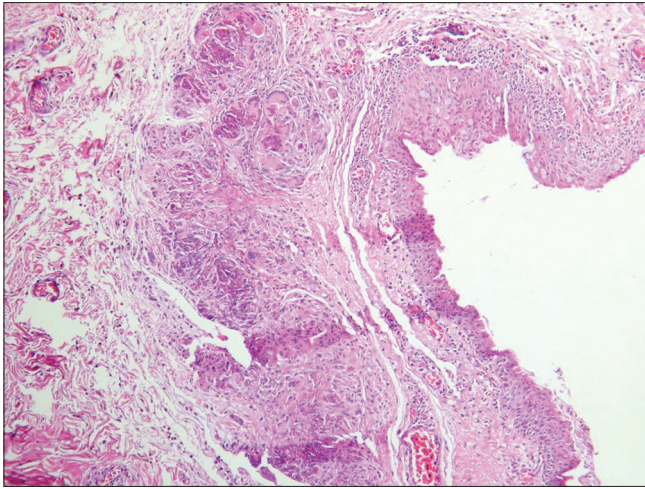


Figure 1: Conjunctival sections show subepithelial nodules with two or three

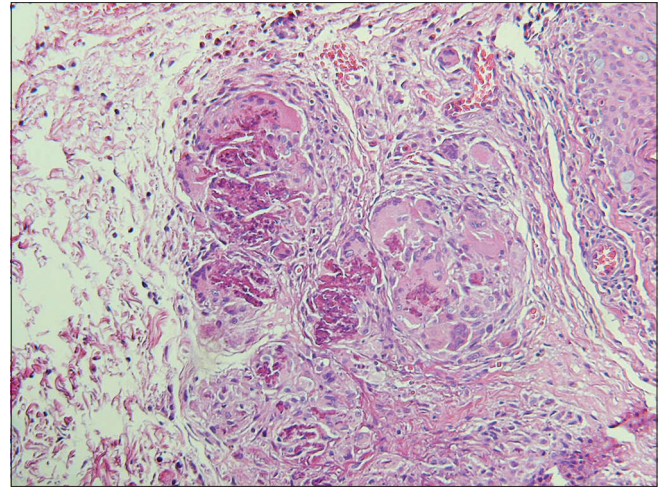


Figure 2: Splendore–Hoeppli phenomenon

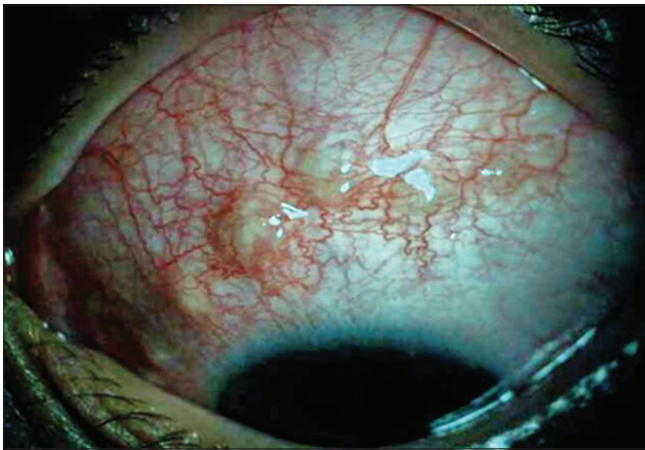


Figure 3: Patient's right eye, before treatment

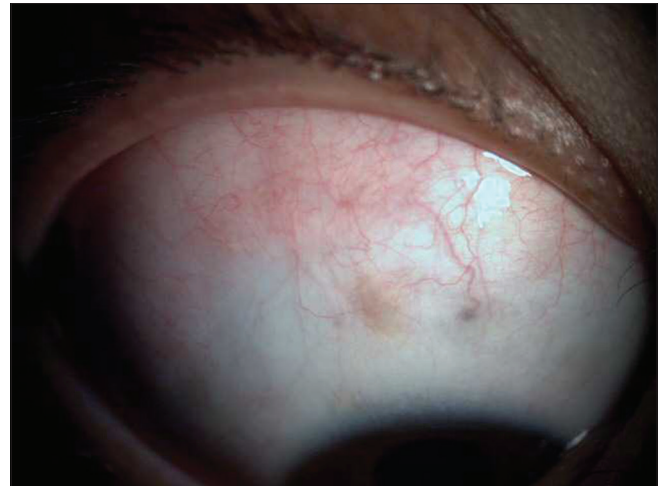


Figure 4: Patient's right eye, on day 9 after treatment by tacrolimus

Discussion

Splendore–Hoeppli phenomenon is described as a morphologically unique process consisting of an amorphous, eosinophilic material surrounded by epithelioid histiocytes, multinucleated giant cells, lymphocytes, and eosinophils.^[6] The nodules in patients with allergic conjunctival granuloma may regress spontaneously. Topical use of corticosteroid drops, however, may give relief of symptoms, and sometimes, excision of the granulomas will be necessary.^[7,8] Some studies have shown that topical corticosteroid therapy is ineffective, and therefore, the excisional biopsy of the granuloma is presented as the therapy of choice.^[9]

Tacrolimus, formerly known as FK506, is a macrolide lactone with immunosuppressive properties. Although structurally unrelated to cyclosporine A, its mode of action is similar. It exerts its effects principally through impairment of gene expression in target cells. Tacrolimus bonds to an immunophilin, FK506-binding protein. This complex inhibits calcineurin phosphatase. The drug inhibits calcium-dependent events, such as interleukin-2 gene transcription, nitric oxide synthase activation, cell degranulation, and apoptosis. The agent may enhance

expression of the transforming growth factor beta-1 gene in a fashion analogous to that demonstrated for cyclosporine A. T-cell proliferation in response to ligation of the T-cell receptor is inhibited by tacrolimus. Type 1 T-helper cells appear to be preferentially suppressed compared with Type 2 T-helper cells. T-cell-mediated cytotoxicity is impaired. B-cell growth and antibody production are affected indirectly by the suppression of T-cell-derived growth factors necessary for these functions. Antigen presentation appears to be spared. The molecular events affected by tacrolimus continue to be discovered.^[4] It has been documented that tacrolimus eye drops can inhibit the infiltration of eosinophils and lymphocytes significantly in experimental animal models.^[4] Recently, it was demonstrated that 3 weeks' treatment with cyclosporine A eye drop was effective in allergic conjunctival granuloma. This case report introduces cyclosporine A as a treatment option for the Splendore–Hoeppli phenomenon.^[3]

In the present study, to avoid the possible side effects of the drug, we use the lower dosage as we successfully used in another study in patients with vernal keratoconjunctivitis and we estimated that this dosage could be effective.^[10] After 3 weeks' administration of tacrolimus eye drop (0.005%), the



Figure 5: Patient's right eye, 1 month after treatment by tacrolimus

signs and symptoms of the patient, previously unresponsive to topical corticosteroid treatment, were completely resolved and the granulomatous lesions disappeared. This treatment was discontinued after 4 weeks. During 6-month follow-up, no relapse or recurrence was observed, and the patient was completely symptom-free. No adverse effects were seen during the treatment phase and follow-up.

Conclusion

Tacrolimus eye drop seems to be an effective therapeutic option in allergic conjunctival granuloma. However, further studies are required to evaluate the efficacy of the treatment and reveal the probable side effects and determine the minimal therapeutic dose and duration.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ashton N, Cook C. Allergic granulomatous nodules of the eyelid and conjunctiva. *Ophthalmology* 1979;86:8-42.
2. Dhermy P, Desjardins L, Limon S, Allart N, Haye C. Allergic granulomatous nodule of the conjunctiva. *J Fr Ophthalmol* 1984;7:451-6.
3. McGrath LA, Whitehead K, Lee GA. Topical ophthalmic use of cyclosporin A for Splendore-Hoepli phenomenon. *Clin Exp Optom* 2014;97:184-6.
4. Nishino K, Fukushima A, Okamoto S, Ohashi Y, Fukata K, Ozaki A, *et al.* Suppression of experimental immune-mediated blepharoconjunctivitis in brown Norway rats by topical application of FK506. *Graefes Arch Clin Exp Ophthalmol* 2002;240:137-43.
5. Kheirkhah A, Zavareh MK, Farzbod F, Mahbod M, Behrouz MJ. Topical 0.005% tacrolimus eye drop for refractory vernal keratoconjunctivitis. *Eye (Lond)* 2011;25:872-80.
6. Read RW, Zhang J, Albin T, Evans M, Rao NA. Splendore-Hoepli phenomenon in the conjunctiva: Immunohistochemical analysis. *Am J Ophthalmol* 2005;140:262-6.
7. Denk O, Rohrbach JM, Zierhut M, Thanos S. Allergic granuloma of the conjunctiva (Splendore-Hoepli phenomenon). *Klin Monbl Augenheilkd* 1995;206:478-9.
8. Stack RR, Weatherhead RG. Splendore-Hoepli phenomenon causing ptosis. *Clin Exp Ophthalmol* 2003;31:540-1.
9. Völcker HE, Enke P, Naumann GO. Eosinophilic, central necrotizing granuloma of the conjunctiva (Splendore-Hoepli phenomenon). Clinical-histopathological study. *Klin Monbl Augenheilkd* 1985;186:254-8.
10. Zanjani H, Aminifard MN, Ghafourian A, Pourazizi M, Maleki A, Arish M, *et al.* Comparative evaluation of tacrolimus versus interferon alpha-2b eye drops in the treatment of vernal keratoconjunctivitis: A Randomized, double-masked study. *Cornea* 2017;36:675-8.