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Case report

Syphilitic interstitial keratitis treated with topical tacrolimus

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ABSTRACT

Purpose: To report a case of syphilitic interstitial keratitis successfully managed with topical tacrolimus after the development of steroid-induced intraocular pressure elevation in a pediatric patient.

Observations: A 4-year-old female with a history of congenital syphilis that was reportedly treated after birth presented with bilateral conjunctival redness, tearing, and photosensitivity. Initial ophthalmic examination revealed corneal vascularization with diffuse haze of the right eye and circumferential vascularization with stromal infiltrates of the left eye. She was diagnosed with bilateral syphilitic interstitial keratitis and initially managed with topical steroids but developed steroid-induced elevation of her intraocular pressure. She experienced several recurrences of keratitis as steroids were tapered. After a recurrence in her right eye, she was treated with topical tacrolimus. Since then, she has remained recurrence-free for almost three years with normal intraocular pressure.

Conclusion and importance: Tacrolimus represents a novel alternative for the treatment of syphilitic interstitial keratitis, which is particularly useful in patients that develop elevated intraocular pressures in response to long-term treatment with steroid eye drops.

1. Introduction

Interstitial keratitis is a chronic, stromal inflammation mediated by an autoimmune reaction that may lead to permanent corneal scarring. Typical etiologies of interstitial keratitis include herpes simplex virus, varicella zoster virus, syphilis, and idiopathic.[1] Though the mechanism is poorly understood, laboratory studies have revealed changes to the corneal anatomy including vascularization of deep stromal lamellae, thickening of the Descemet membrane with an altered collagen profile, and retrocorneal scrolls.[2]

Cases are typically managed by treatment of the underlying condition, topical or systemic immunosuppression, and management of the side effects of treatments. Complications of management include recurrences of interstitial keratitis, corneal scarring, and glaucoma. Our case is an example of the common management and complications of management of this disease. We present a novel therapeutic modality for syphilitic interstitial keratitis, tacrolimus, which may avoid common treatment complications.

2. Case report

A 4-year-old female adopted at 15-months-old from South Korea presented with a six-week history of bilateral eyelid swelling associated with conjunctival redness, tearing, and photosensitivity. Her medical history included premature birth at 31 weeks and congenital syphilis, reportedly treated although the exact therapeutic regimen was unknown. After being adopted, RPR testing and skeletal X-rays were found to be negative and a Treponema particle agglutination (TP-PA) test was reactive, consistent with successfully treated congenital syphilis. However given the unknown therapeutic regimen, a course of IV penicillin was administered.

On presentation, the patient was noted to have a visual acuity of 20/60 in the right eye (OD) and 20/25 in the left eye (OS). Given difficulty with the office exam due to photosensitivity, an exam under anesthesia was performed. On portable slit lamp exam, there was extensive right corneal vascularization with diffuse haze and a dense S-shaped haze along the superior pupillary border. The left eye had circumferential vascularization with stromal infiltrates at the border of the vessels; however, the central portion of the left cornea was clear. Aside from 2+ bilateral conjunctival injection, the remainder of the ocular exam was

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normal. Her refractive error was noted to be +4.25 sphere OD and +3.25 sphere OS. Intraocular pressures were 20 mmHg OD and 15 mmHg OS.

In light of her history, her findings were consistent with bilateral interstitial keratitis secondary to congenital syphilis. She was treated with topical prednisolone acetate 1 % and cyclopentolate in both eyes (OU). Both her photosensitivity and conjunctival injection improved markedly on this therapy. Her refractive error was noted to decrease to +0.75 + 0.50 × 087 OD and +0.50 sphere OS. After one month of therapy, she was noted to have a visual acuity of 20/20 OU with stromal haze sparing the visual axis OD and resolution of corneal haze OS. Her drops were weaned over a period of one month.

Over the following three years, she developed several episodes of recurrent keratitis in both eyes, although this was typically asymmetric, with keratitis more often needing treatment in the right eye than the left eye. At her nadir, her visual acuity worsened to 20/80 in the right eye and 20/30 in the left eye. Additionally after a recurrence OD, she was noted to develop a large refractive shift over six months to −4.50 + 6.00 × 100 OD, while the left eye refraction remained relatively stable.

The keratitis required treatment with multiple rounds of topical prednisolone acetate 1 % which remained effective in controlling the inflammation; however, the patient developed steroid-induced intraocular pressure (IOP) elevation, with eye pressure maximally elevated to 32 mmHg OD and 45 mmHg OS (Baseline IOP was 13 mmHg OU). Elevated IOP was lowered with the addition of topical dorzolamide, latanoprost and timolol. While elevation of IOP was not marked with prednisolone 0.12 % or the subsequent use of loteprednol, these medications were not adequate to maintain disease quiescence.

After the patient developed a severe recurrence of keratitis with extension into the visual axis in her left eye, treatment with oral systemic prednisone 0.5 mg/kg/day was initiated with resolution of keratitis. Following a two-month taper of systemic corticosteroids, the patient stayed in remission for several months with daily loteprednol; however, she then developed a keratitis relapse in her right eye with decrease of vision to 20/80 (Fig. 1). Treatment with systemic prednisone again restored quiescence and the patient was started on topical cyclosporine 0.05 % twice daily in the right eye one month into her oral steroid taper; however, cyclosporine also proved inadequate to maintain quiescence, with her exam exhibiting worsened stromal haze, vascularization of the cornea, and decline in best corrected visual acuity to 20/60.

Topical Tacrolimus ointment 0.03 % twice daily was then started in the right eye. Only Cosopt BID was concurrently used for treatment of the right eye. Within one month of instituting tacrolimus, her keratitis markedly improved with decrease in vascular precipitations without elevation of IOP. She was initially maintained on loteprednol daily OS but was transitioned to tacrolimus after one year of therapy OD. Over the following three years, she had no episodes of recurrence in either eye. On last exam, she was noted to have sustained improvement in corneal haze (Fig. 2), normal IOP, visual acuities of 20/25 OD and 20/20 OS, and refractive error measuring −2.75 + 3.25 × 118 OD and +0.50 + 0.50 × 135 OS.

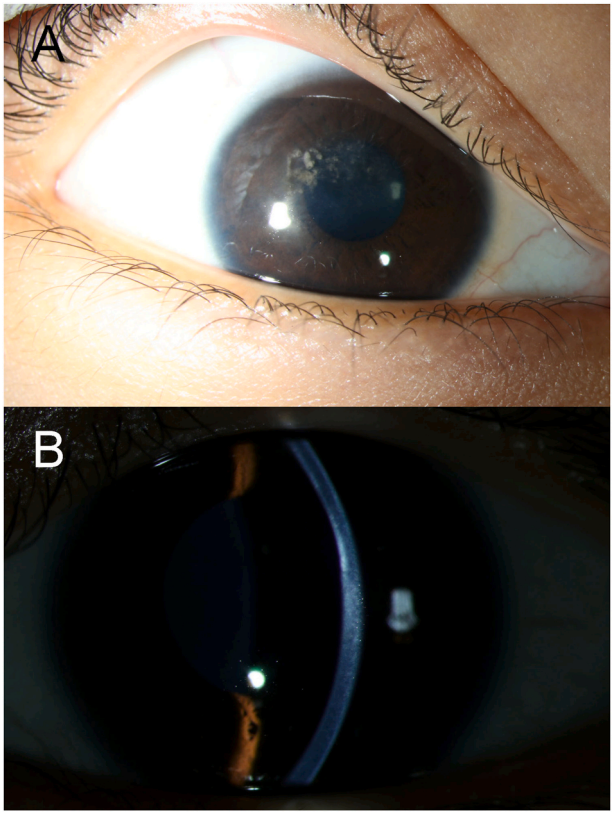

Fig. 1. Diffuse (1A) and slit beam (1B) photos of the right eye exhibiting recurrent interstitial keratitis with paracentral infiltrates with central haze.

3. Discussion

Interstitial keratitis is an autoimmune-mediated stromal inflammation that can lead to permanent, visually-significant scarring of the cornea.[1] In our patient, interstitial keratitis was secondary to congenital syphilis which developed despite having been treated with IV penicillin years prior to the development of ophthalmic complications. Her chronic, relapsing inflammation was initially managed with topical steroids, but this treatment resulted in the complication of steroid-induced IOP elevation that is often encountered when managing ocular inflammatory conditions. Low-dose topical steroids, oral prednisone, IOP lowering medications, and topical cyclosporine were tried without success. Prior to the consideration of glaucoma filtering surgery or systemic immunosuppression with steroid sparing agents, all of which have significant morbidity in the pediatric population, we attempted treatment with tacrolimus.

Tacrolimus is a macrolide produced from soil samples containing the bacteria *Streptomyces tsukubaensis* that inhibits calcineurin activity, leading to inhibition of T lymphocytes.[3] Tacrolimus has been used for the treatment of other inflammatory ocular diseases including vernal conjunctivitis,[4] acute graft rejection after penetrating keratoplasty,[5] anterior uveitis, scleritis, and graft versus host disease.[3] Side effects of topical tacrolimus are reportedly minimal, but include transient ocular irritation on administration and increased risk of corneal infection with prolonged use.[3,4] Systemic adverse effects from tacrolimus are unlikely to occur, as a study examining the blood concentrations of patients after topical administration of tacrolimus showed systemic exposure was minimal and transient.[6]

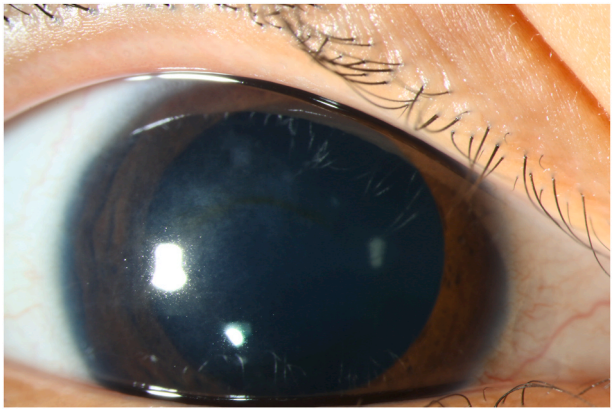

Fig. 2. Slit lamp photo of the right eye taken 9 months after starting treatment with topical tacrolimus. Corneal exudates have resolved with some residual patent vasculature and haze.

To our knowledge, topical tacrolimus has been used for the treatment of interstitial keratitis in two other reports.[1,7] The first paper involved the treatment of a 12 year-old-boy with a 3-year history of interstitial keratitis suspected to be secondary to zoster sine herpete. After failure of topical and systemic steroids, topical cyclosporine 0.5 % was initially instituted; however, this was abandoned in favor of topical tacrolimus 0.1 % after continued recurrence was noted. The improved response between the two topical therapies was thought to be secondary to tacrolimus' comparatively increased potency. Similarly, we observed a better therapeutic response to topical tacrolimus compared to topical cyclosporine.

The second paper details a randomized control trial in which patients diagnosed with suspected HSV stromal keratitis received either systemic acyclovir with topical prednisolone or 0.05 % tacrolimus eye drops four times daily in addition to systemic acyclovir and topical prednisolone. Throughout one month of therapy, the group receiving tacrolimus exhibited significantly faster improvement in best corrected visual acuity and faster resolution of both corneal edema and vascularization (as determined by masked observers using a grading scale designed for this study). There was no data following one month of therapy; so, it is unknown if these effects were sustained or how the investigators planned to manage patients' treatment regimens (i.e. tapering drops).

Despite the successful treatment of the patient's recurrent keratitis with tacrolimus, several questions remain regarding her future management. Presently, topical tacrolimus is prepared for dermatologic use but can be compounded through specialty pharmacies for ocular administration by dilution with balanced salt solution and repackaging for easier administration; however, the ideal dosage for the treatment of corneal disease has not been determined. Additionally, we do not have long term studies describing the effect of tacrolimus on the cornea, a particular concern in pediatric patients who may have to deal with complications of treatment throughout their lives. Additional questions include the length of proposed treatment with tacrolimus, the benefits of treatment of the patient's fellow eye despite current control with low dose steroids, and the future management of her marked refractive changes in her right eye.

4. Conclusions

Topical tacrolimus is an effective therapy for syphilitic interstitial keratitis.

Patient consent

The patient's legal guardian consented to publication of the case.

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Authorship

Jacob Martin: Writing-Original Draft; Laura Kopplin: Writing-Review & Editing, investigation, conceptualization; Deborah Costakos: Writing-Review & Editing, investigation, conceptualization.

Declaration of competing interest

No conflict of interest exists.

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