Ointment tacrolimus for steroid resistant adenoviral nummular keratitis

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SUMMARY

A 33-year-old man presented with a four-day history of redness and blurring of vision of the right eye. A clinical diagnosis of adenoviral keratitis was made with a differential of microsporidia epithelial keratitis. The patient subsequently developed nummular keratitis which was resistant to topical steroids. He continued to develop multiple recurrences of the condition. Treatment with tacrolimus ointment was started as the patient had an elevated intraocular pressure due to prolonged steroid use. Tacrolimus ointment showed a favourable outcome in the management of recurrent nummular keratitis.

KEY WORDS:

Punctate epithelial keratitis, adenoviral keratoconjunctivitis, tacrolimus

CASE STUDY

A 33-year-old Chinese man without any underlying medical illness, presented to the eye clinic of University Malaya Medical Centre, Kuala Lumpur, Malaysia with complaint of right eye (RE) redness for 4 days. This was associated with mild blurring of vision and watery discharge. He had a preceding history of soil exposure while playing football one week before the presentation. He had no contact with anyone having eye redness as well as no history of respiratory tract infection before the development of his symptoms. No history of trauma was noted. He was a contact lens user for 3 years with good contact lens care and hygiene.

On examination, his vision was 6/9 in the right eye (RE) and 6/6 in the left eye (LE). Both lids showed papillary reaction. The corneal sensation was intact in both eyes. In the RE there were multiple coarse whitish punctate epithelial infiltrates scattered throughout the cornea. In the LE, 2 to 3 infiltrates of similar morphology were seen. The infiltrates in both eyes stained with fluorescein. The cornea was otherwise clear. The conjunctiva was injected, more in the RE as compared to the LE and the corneal sensation was intact. The anterior chamber had occasional cells in the RE and deep and quiet in the LE. The intraocular pressure (IOP) in both eyes was 21

mm of Hg. Fundus examination showed a cup disc ratio of 0.8 in both eyes (BE), however optical coherence tomography (OCT) of retinal nerve fibre layer (RNFL) did not show any thinning.

A preliminary diagnosis of BE punctate epithelial keratitis (PEK) most likely secondary to Adenovirus was made with a differential diagnosis of microsporidia keratitis. The patient was started on guttae moxifloxacin 0.5% 2-hourly in the RE and four times a day in the LE. Corneal scrapings were sent to the laboratory for investigating the presence of Microsporidia along with routine microbiological cultures. Conjunctival swab testing for Microsporidia was also sent. However, none of the cultures yielded positive results. HIV screen was negative.

After 2 weeks of treatment, the corneal epithelium had healed completely, and the topical antibiotics were tapered accordingly. Approximately a week following complete resolution of corneal oedema and infiltrate, the RE cornea was noted to have subepithelial patchy opacities with ill-defined margins. Examination of the LE revealed these opacities were well defined and scarred at the nasal and superior part of the cornea. Thus, a diagnosis of BE adenoviral nummular keratitis was made and treatment with guttae fluorometholone 0.1% (FML) four times a day in BE was initiated and tapered slowly over 4 weeks.

The nummular keratitis recurred in the RE when the guttae FML dose was tapered to once-daily dosage. After 8 weeks of guttae FML therapy, the IOP of the RE started to rise and guttae timolol 0.5% twice daily was initiated along with FML. Approximately 3 months since the nummular keratitis was diagnosed, the patient had frequent recurrences in the RE and developed elevated IOP secondary to prolonged topical steroids. A decision was made to add the ointment tacrolimus to the RE while tapering off steroids because of persistent high IOP. His IOP returned to baseline 3 weeks after cessation of FML and he no longer required guttae timolol 0.5%.

Ointment tacrolimus (0.03%) was continued to be used once daily for 4 months and subsequently once every other day for 2 months in the RE. The patient continued to show improvement and achieved complete resolution at 5 months, and he achieved a good and favourable visual outcome of 6/6 despite having faint subepithelial scarring at central corneal (Figures 1 and 2). He has been stable in the follow-up period with no recurrences.

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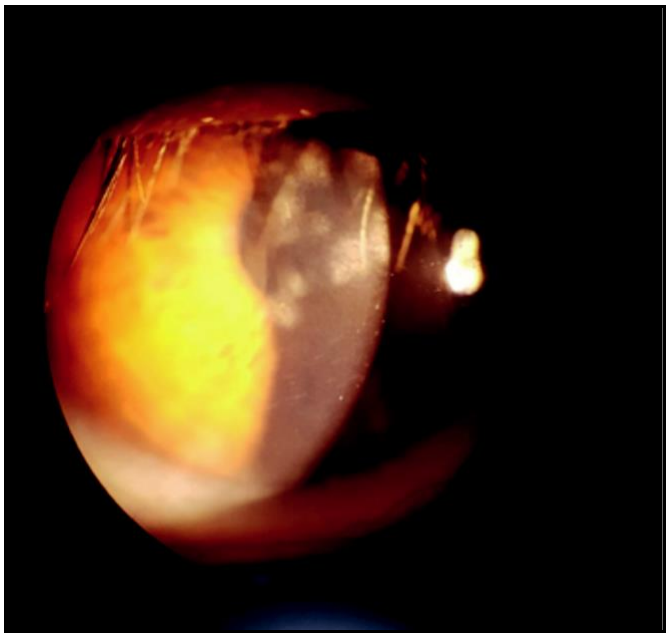

Fig. 1: RE showing scarring from nummular keratitis involving the centre of cornea.

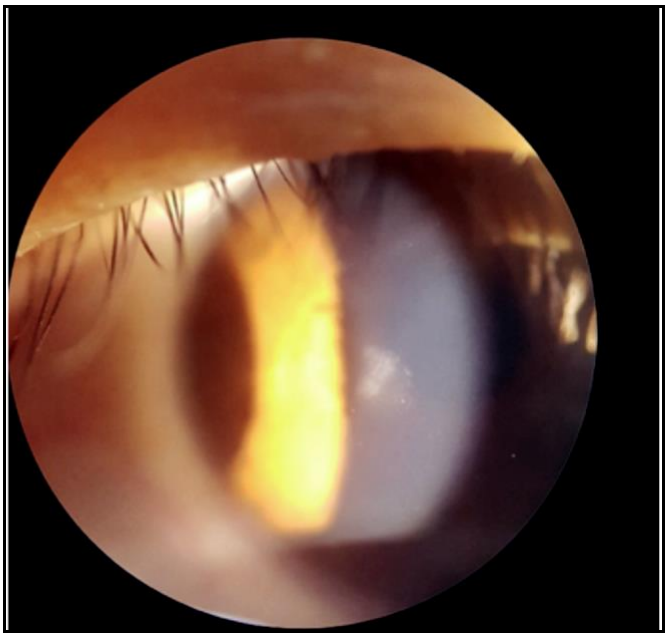

Fig. 2: LE showing minimal scarring paracentrally.

DISCUSSION

Histologically subepithelial lymphocytes, histiocytes and fibroblasts with disruption of collagen fibres of Bowman's layer[1] are present in nummular keratitis. This suggests that it may be due to viral replications subepithelially which usually resolves with topical steroids and recur if steroids are withheld.[2]

To date, there are no specific therapeutic guidelines for the treatment of adenoviral nummular keratitis although ocular formulations of cidofovir[3], cyclosporin A[4] and tacrolimus[5] have been studied in the condition.

In a study where a regimen of Cyclosporin A 2% four drops a day has been used to treat persistent nummular keratitis post adenoviral keratoconjunctivitis, more than half of the patients treated showed improvement while a small percentage showed no improvement. A small number of patients complained of burning sensation in the eye when being treated with gutt cyclosporin.[4] Restasis (cyclosporin A 0.05%) has also been tested for the treatment of subepithelial infiltrates and have shown promising results.[6]

Gutt Cyclosporin, however, is stable for only one week and patients are required to come weekly to collect medication which leads to compliance and logistic issues. Thus, other studies were referred to and the decision for tacrolimus treatment was chosen.

Tacrolimus has an immunomodulatory and anti-inflammatory activity which blocks with transcriptional activation of cytokines. It is isolated from *Streptomyces turubaensis*. It is a more potent immunosuppressive agent compared to cyclosporine.

The use of topical tacrolimus (0.03%) in steroid resistance adenoviral nummular keratitis has been previously documented to last for 8.8 months and follow up duration of slightly more than 10 months. In total, 80% of the eyes showed successful treatment with Occ Tacrolimus. This study showed that treatment with tacrolimus also lead to significant improvement of visual acuity in these patients.[2]

In a separate study, the use of Occ Tacrolimus 0.03% twice daily for 22 weeks on patients with subepithelial corneal infiltrates which did not respond to topical corticosteroids, resulted in significant clinical improvement with the majority of patients having no severe subepithelial infiltrates at the end of the study. Some of the side effects documented with the use of this medication include severe dizziness and discomfort however, our patient did not experience any of these symptoms.[5]

Our patient had multiple recurrences of the nummular keratitis over 3 months requiring long term corticosteroid eye drops with a resultant rise in intraocular pressure owing to prolonged corticosteroid use. The use of Occ Tacrolimus had significantly reduced recurrences and helped to normalise the IOP of the patient and preserve good vision despite minimal subepithelial scarring at the end of 6-month treatment.

CONCLUSION

The treatment for adenoviral nummular keratitis can be difficult especially when topical corticosteroid eye drops cannot be used for long duration due to increase in IOP or subsequently lead to recurrences after cessation of therapy. Topical Occ Tacrolimus therapy has shown a promising result in our patient and we recommend its use for recurrent adenoviral nummular keratitis.

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