

Case Report of Restoration of the Corneal Epithelium in a Patient with Atopic Keratoconjunctivitis Resulting in Amelioration of Ocular Allergic Inflammation

Ken Fukuda^{1,2}, Naoyuki Yamada¹ and Teruo Nishida¹

ABSTRACT

Background: Atopic and vernal keratoconjunctivitis are severe types of ocular allergic disease characterized not only by conjunctival inflammation but also by corneal involvement. In vitro studies have suggested that breakdown of corneal epithelial barrier function and subsequent activation of stromal fibroblasts may amplify ocular allergic inflammation.

Case Summary: A 27-year-old man with atopic dermatitis developed atopic keratoconjunctivitis including corneal ulcer with plaque deposition in his right eye. Conjunctival inflammation in the right eye was resistant to topical steroid therapy. Surgical removal of corneal plaque and administration of autologous fibronectin eye-drops resulted not only in resurfacing of the corneal epithelium but also in amelioration of conjunctival inflammation.

Discussion: This case suggests that loss of corneal epithelial integrity likely exacerbates conjunctival allergic inflammation and that restoration or maintenance of the barrier function of the corneal epithelium may be one of the important targets for the treatment of severe ocular allergic diseases.

KEY WORDS

allergic inflammation, atopic keratoconjunctivitis, conjunctiva, corneal ulcer, epithelium

INTRODUCTION

Atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) are severe types of ocular allergic disease that are characterized by chronic inflammation of the conjunctiva and various corneal epithelial disorders including superficial punctate keratopathy, epithelial defects, shield ulcer, and plaque.¹ Persistence of these corneal lesions can result in the development of complications such as scarring, corneal vascularization, amblyopia, and infectious keratitis and a consequent reduction in visual acuity. These corneal lesions are often resistant to therapy, however, and remain a challenge in the treatment of ocular allergy.²

The pathogenesis of corneal lesions is thought to involve a combination of toxic epitheliopathy due to eosinophil- and mast cell-derived inflammatory mediators as well as mechanical damage to the corneal epithelium by giant papillae. The fact that the severity of conjunctival inflammation and corneal lesions in individuals with AKC or VKC often differs between the right and left eyes and the difficulty of treatment for conjunctivitis with corneal lesions suggest that local factors and interaction between conjunctival inflammation and corneal lesions may contribute to the exaggeration of ocular allergic inflammation. We now report a case of AKC that was successfully treated by restoration of the corneal epithelium.

¹Department of Ophthalmology, Yamaguchi University Graduate School of Medicine, Yamaguchi and ²Present address: Department of Ophthalmology, Kochi Medical School, Kochi, Japan.
Correspondence: Ken Fukuda, MD, PhD, Department of Ophthalmology, Kochi Medical School, Kohasu, Oko-cho, Nankoku City,

Kochi 783-8505, Japan.

Email: k.fukuda@kochi-u.ac.jp

Received 25 January 2010. Accepted for publication 15 March 2010.

©2010 Japanese Society of Allergology

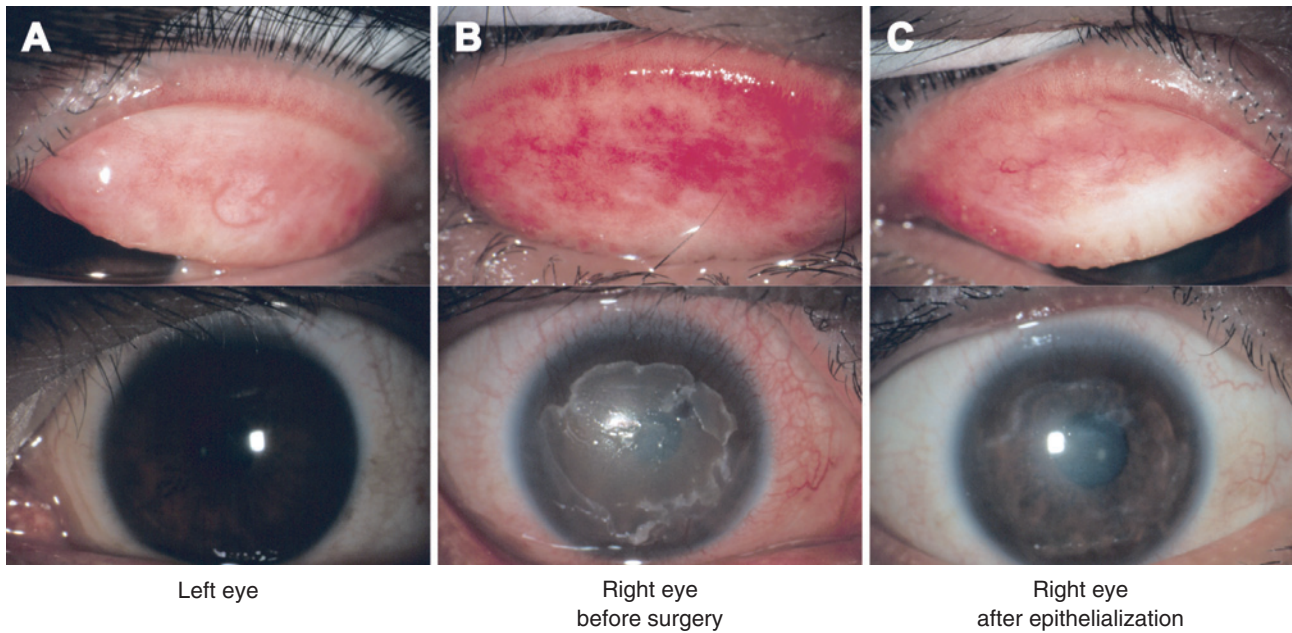


Fig. 1 Slitlamp photographs of the eyes of the patient. Whereas the left eye of the patient appeared normal (A), marked swelling and redness in the palpebral and bulbar conjunctiva as well as corneal epithelial defects with plaque deposition were observed in the right eye before surgery (B). Conjunctival redness and swelling in the right eye were diminished after corneal epithelial resurfacing (C).

CLINICAL SUMMARY

The patient was a 27-year-old Japanese man with corneal ulcer and plaque in his right eye. His AKC had been managed for several years at another eye clinic by application of topical corticosteroids and antibiotic eyedrops. On 13 April 2004, the patient was referred to our hospital because of the persistence of corneal plaque for 9 months despite the use of topical therapy. At his first visit to our hospital, his best corrected visual acuity was 0.4 in the right eye and 1.2 in the left eye. Slitlamp examination revealed lid swelling and redness in the bulbar and palpebral conjunctiva of the right eye. Corneal epithelial defects with plaque deposition and superficial vascular invasion were also apparent in the right cornea (Fig. 1). Conjunctival inflammation and corneal disorders were not observed in the left eye. The patient had also experienced atopic dermatitis for more than 15 years. He had a history of herpetic keratitis in both eyes dating back about 18 months.

PATHOLOGICAL FINDINGS

Laboratory analysis showed a high level of immunoglobulin E (5110 IU/ml) in the patient's serum (normal range, 0 to 120 IU/ml). Hansel staining also revealed the presence of eosinophils in discharge from his right eye. We diagnosed AKC with corneal ulcer and plaque deposition. We prescribed continued use of eyedrops containing betamethasone sodium phosphate four times a day and added subconjunctival in-

jection of dexamethasone twice a week. However, conjunctival inflammation and the corneal epithelial defects had not improved after 1 month, so we offered surgical intervention for removal of the persistent corneal plaque. Removal of the plaque with a spatula was performed with the patient under local anesthesia induced by xylocaine eyedrops. In addition to the betamethasone sodium phosphate eyedrops, we then prescribed administration four times a day of eyedrops containing fibronectin isolated from the patient's own blood³ in order to promote epithelial wound healing. Three weeks after surgery, complete epithelialization of the cornea had occurred and the lid swelling and redness in the bulbar and palpebral conjunctiva were also diminished (Fig. 1). Visual acuity of the right eye had improved to 0.6. Corneal erosion and conjunctival inflammation had not recurred within 2 months after epithelialization under treatment with fluorometholone and sodium cromoglicate eyedrops.

DISCUSSION

Corneal lesions are thought to be induced by the severe conjunctival inflammation in patients with AKC or VKC, with surgical removal of giant papillae at the palpebral conjunctiva having been found to be effective for treatment of corneal lesions in individuals with VKC.^{2,4} On the other hand, the effect of persistence of corneal epithelial defects on conjunctival inflammation has been unclear. We have now presented a case of AKC in which conjunctival inflamma-

tion was suppressed as a result of restoration of the corneal epithelium through surgical removal of plaque and the administration of fibronectin eye-drops. This case therefore suggests that loss of the integrity of the corneal epithelium may amplify allergic inflammation in severe ocular allergic diseases.

Corneal plaque formed at the base of a shield ulcer prevents epithelialization of the cornea, does not resolve spontaneously, and is not usually affected by pharmacological therapy. It is usually removed by surgery in order to promote epithelial resurfacing.^{2,5} Before surgical removal of the plaque, conjunctival inflammation should be adequately controlled in order to prevent plaque recurrence before epithelialization. The present case was not affected by topical corticosteroid therapy, however, and the patient was not a candidate for resection of the palpebral conjunctiva because of the lack of giant papillae. Oral corticosteroids might have been able to suppress the conjunctival inflammation in the patient, but he did not want to undergo such treatment because of the possible side effects. Although we were not able to use topical immunosuppressants because of their unavailability at the time, eyedrops containing cyclosporine A or tacrolimus are now available in Japan. Topical administration of these immunosuppressants has recently been found to be effective for the treatment of VKC or AKC, with such an approach now representing another therapeutic option.^{6,7}

Fibronectin is a glycoprotein that is present in plasma and the extracellular matrix and is responsible for cellular adhesion and migration.⁸ We have previously shown that eyedrops containing fibronectin isolated from a patient's own plasma are effective for treatment of corneal epithelial erosion associated with various ocular surface diseases.⁹⁻¹¹ We have also demonstrated the effectiveness of fibronectin eye-drops for promotion of corneal epithelial wound healing after the removal of corneal plaque in patients with VKC.¹² Although conjunctival inflammation was not controlled before surgery in the present case, the epithelial defects disappeared completely without re-deposition of plaque after the administration of autologous fibronectin eyedrops and eyedrops containing betamethasone sodium phosphate. Betamethasone might have penetrated the corneal stroma after removal of the plaque and may have suppressed the function of corneal fibroblasts, including their expression of chemokines, thereby contributing to the amelioration of ocular allergic inflammation. This case also suggests that, although topical fibronectin by itself does not suppress inflammation, it might be effective for promoting corneal epithelial wound healing and consequent suppression of conjunctival inflammation.

On the basis of in vitro experiments, we and others have shown that fibroblasts of the corneal stroma, but not corneal epithelial cells, act as amplifiers of ocular

allergic inflammation by expressing chemokines and adhesion molecules.¹³⁻¹⁵ The barrier function of the corneal epithelium may suppress allergic inflammation by preventing the penetration of inflammatory mediators present in tear fluid into the corneal stroma. We have also recently shown that the conjunctiva and cornea interact in a reciprocal manner in a rat model of allergic conjunctivitis; the presence of corneal epithelial defects exacerbated conjunctival eosinophilia whereas conjunctival eosinophilic inflammation suppressed corneal epithelial wound healing, suggestive of the operation of a vicious cycle.¹⁶ Together with the present case, these observations suggest that restoration or maintenance of the corneal epithelial barrier may be one of the important targets for the treatment of severe ocular allergic diseases.

REFERENCES

1. Cameron JA. Shield ulcers and plaques of the cornea in vernal keratoconjunctivitis. *Ophthalmology* 1995;**102**:985-93.
2. Kumagai N, Fukuda K, Fujitsu Y, Seki K, Nishida T. Treatment of corneal lesions in individuals with vernal keratoconjunctivitis. *Allergol Int* 2005;**54**:51-9.
3. Nishida T, Nakagawa S, Awata T, Nishibayashi C, Manabe R. Rapid preparation of purified autologous fibronectin eyedrops from patient's plasma. *Jpn J Ophthalmol* 1982;**26**:416-24.
4. Fujishima H, Fukagawa K, Satake Y *et al.* Combined medical and surgical treatment of severe vernal keratoconjunctivitis. *Jpn J Ophthalmol* 2000;**44**:511-5.
5. Solomon A, Zamir E, Levartovsky S, Frucht-Pery J. Surgical management of corneal plaques in vernal keratoconjunctivitis: a clinicopathologic study. *Cornea* 2004;**23**:608-12.
6. Ebihara N, Ohashi Y, Uchio E *et al.* A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2009;**25**:365-72.
7. Miyazaki D, Tominaga T, Kakimaru-Hasegawa A, Nagata Y, Hasegawa J, Inoue Y. Therapeutic effects of tacrolimus ointment for refractory ocular surface inflammatory diseases. *Ophthalmology* 2008;**115**:988-92.
8. Nishida T, Nakagawa S, Awata T, Ohashi Y, Watanabe K, Manabe R. Fibronectin promotes epithelial migration of cultured rabbit cornea in situ. *J Cell Biol* 1983;**97**:1653-7.
9. Nishida T, Nakagawa S, Awata T, Tani Y, Manabe R. Fibronectin eyedrops for traumatic recurrent corneal erosion. *Lancet* 1983;**322**:521-2.
10. Nishida T, Nakagawa S, Manabe R. Clinical evaluation of fibronectin eyedrops on epithelial disorders after herpetic keratitis. *Ophthalmology* 1985;**92**:213-6.
11. Nishida T, Ohashi Y, Awata T, Manabe R. Fibronectin. A new therapy for corneal trophic ulcer. *Arch Ophthalmol* 1983;**101**:1046-8.
12. Yoshimura K, Chikama T, Nishida T. [Ablation of corneal plaque with topical fibronectin]. *Jpn J Clin Ophthalmol* 1998;**52**:1835-40 (in Japanese).
13. Fukagawa K, Okada N, Fujishima H *et al.* Corneal and conjunctival fibroblasts are major sources of eosinophil-recruiting chemokines. *Allergol Int* 2009;**58**:499-508.
14. Fukuda K, Fujitsu Y, Kumagai N, Nishida T. Fibroblasts as local immune modulators in ocular allergic disease. *Al-*

lergol Int 2006;**55**:121-9.

15. Kumagai N, Fukuda K, Fujitsu Y, Yamamoto K, Nishida T. Role of structural cells of the cornea and conjunctiva in the pathogenesis of vernal keratoconjunctivitis. *Prog Retin*
16. Fukuda K, Nishida T. Reciprocal interaction of the conjunctiva and cornea in ocular allergy. *J Allergy Clin Immunol* 2010;**125**:493-6.