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CLINICAL INVESTIGATIONS

Combined Medical and Surgical Treatment of Severe Vernal Keratoconjunctivitis

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Purpose: We report the efficacy of an alternative method of treatment for vernal keratoconjunctivitis (VKC) that consists of excision of the palpebral conjunctiva followed by supratarsal injection of corticosteroid and five times daily topical application of 0.05% cyclosporine A (CsA) and cromolyn sodium.

Methods: We evaluated 10 patients with severe treat-resistant VKC with corneal complications. The patients were evaluated for symptoms and for signs, including conjunctival changes, corneal limbal infiltrates, vascularization, reduction of epitheliopathy, meibomitis, visual acuity, intraocular pressure, and pathologic evaluation, before and after treatment.

Results: All patients showed marked improvement after 2 weeks of treatment. The symptoms ($P < .01$), signs ($P < .02$), and the visual acuity of all patients ($P < .01$) had significantly improved following treatment. Histological examination showed significant inflammatory cell decreases 4 weeks after surgery ($P < .05$).

Conclusion: Surgery plus topical drug therapy may be useful in treating patients with very severe VKC. **Jpn J Ophthalmol 2000;44:511–515** © 2000 Japanese Ophthalmological Society

Key Words: Corneal complications, cyclosporine A, inflammatory cells, surgical treatment, vernal keratoconjunctivitis.

Introduction

Various surgical procedures, including cryotherapy and mucous membrane grafting[1] have been used successfully to treat such cases, but patients with severe vernal keratoconjunctivitis (VKC) may experience early recurrence and fail to respond to the prolonged administration of steroids, especially when there are the complications of glaucoma or cataract. Cyclosporine A (CsA), a potent immunomodulator that inhibits the clonal expansion of interleukin (IL)-2 in lymphocytes,[2] is widely used to treat such inflammatory conditions of the eye as uveitis, corneal graft rejection, and VKC.[3] While several authors have previously shown topical CsA to be effective[3] and reported that supratarsal injection of corticosteroid is efficacious, these treatments are insufficient for treating patients with very severe active VKC. In the present study, we therefore combined excision of giant papillary formations and supratarsal injection of corticosteroid with long-term use of CsA and cromolyn sodium eyedrops for patients with severe active VKC.

Materials and Methods

Patients

The participants in this study consisted of 10 patients (10 eyes), 6 men and 4 women, aged 13 to 29 years (mean: 18.3 ± 5.1 years) with severe bilateral active VKC (Figures 1A,C) of 2 to 8 years duration,

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(mean: 5.4 ± 1.9 years), treated at the outpatient clinic of the Tokyo Dental College. All had been treated previously in another hospital with topical corticosteroid eyedrops, short courses of a systemic corticosteroid (maximal dose betamethasone, 3 mg/day), or cryotherapy. Each patient was treated with 0.05% CsA eyedrops five times/day for at least 4 weeks before we considered combined treatment in our hospital. All patients did not have atopic dermatitis or systemic diseases. We obtained the informed consent of all patients to undergo this combined treatment, which was approved for use by our institutional review board. All patients were observed for more than a 5-year follow-up. For the fellow eye, 8 patients received the same treatment; 2 patients were treated without the surgical treatment.

Surgical Procedure

Following the technique described by Tse et al[1] we made full-thickness horizontal incisions through the palpebral conjunctiva just posterior to the lid margin and 4–5 mm above the superior border of the tarsus.[1] After administration of a few drops of 4% lidocaine,

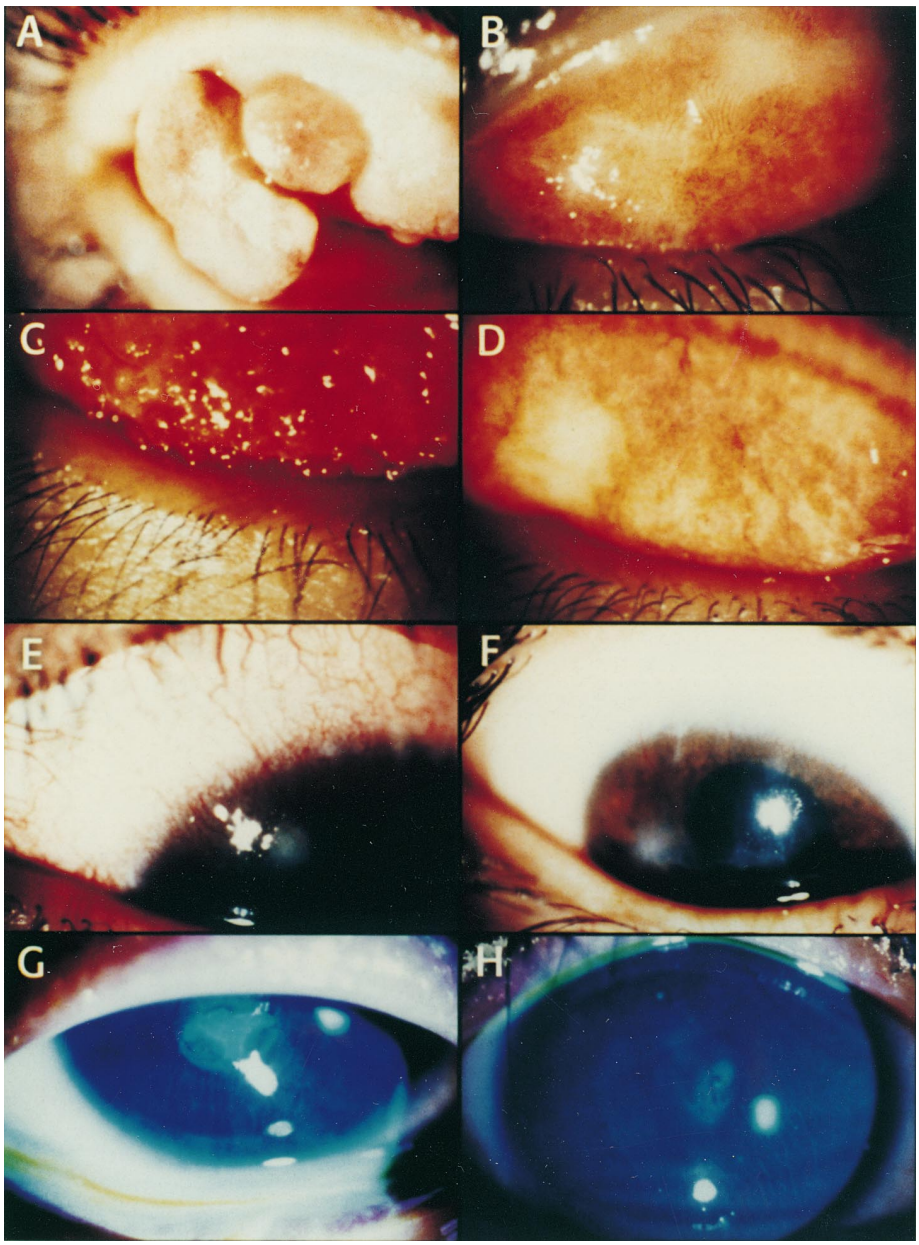

Figure 1. Clinical findings in representative vernal keratoconjunctivitis patients before (left) and after treatment (right). (**A**) Giant papillae (3 × 6 mm) were observed on upper tarsal conjunctiva. (**B**) Four weeks after treatment, healthy conjunctiva has no papillae. (**C**) Many giant papillae (2 × 2.5 mm) were observed. (**D**) Four weeks after treatment, healthy conjunctiva with no papillae. (**E**) Corneal ulcer, vascular invasion of cornea, and conjunctivitis before treatment. (**F**) Four weeks after treatment, corneal ulcer had healed, vascular invasion of cornea had subsided, and conjunctivitis had cleared. (**G**) Corneal ulcer and subepithelial opacity (fluorescein stain) before treatment. (**H**) Four weeks after treatment, corneal ulcer had healed, but subepithelial opacity was still present.

the patient was instructed to look down and away from the quadrant of the eye to be injected; 0.5 mL of 2% lidocaine with diluted 1:80,000 epinephrine was injected with a 27-gauge cannula into the subconjunctival space just posterior to the lid margin. Sharp dissection of the tarsal conjunctiva and the giant (cobblestone-like) papillae from the tarsus was then performed until the surface was smooth, with no conjunctival tissue remaining (Figure 2). After conjunctival excision, 20 mg of methylprednisolone acetate (Depomedrol; Upjohn Japan, Tokyo) was injected into the supratarsal fornix of the subconjunctival space with a 27-gauge cannula, and antibiotic ointment was applied to the conjunctiva. Hemostasis was achieved by applying pressure to the eye for 5 minutes. A semipressure eye patch was applied for 1 day.

Postoperation Regimen

We dissolved CsA (0.05%) in alpha cyclodextrin as previously described[4] and prescribed the application of the solution as eyedrops[5] times per day for a minimum of 24 weeks. Patients also received the following topical medications: ofloxacin eyedrops and cromolyn sodium eyedrops, to be instilled five times daily, for at least 2 weeks. The eyedrops were discontinued when both clinical signs and symptoms had resolved.

Clinical Evaluation

We evaluated subjective symptoms by using the following 5-point grading system: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), and 4 (extremely severe), with a maximum total of 24 possible points.[3] Signs were each graded on a 4-point scale as follows: 0 = absent, 1 = mild, 2 = severe, and 3 = extremely severe, with a maximum total of 27 possible points.[3] Visual acuity and intraocular pressure were measured every 2 weeks.

Giemsa Staining and Immunocytochemistry

Conjunctival superficial samples were collected from the upper palpebral conjunctiva with a special brush (Cytobrush Small; Medscand, Malmo, Swe-

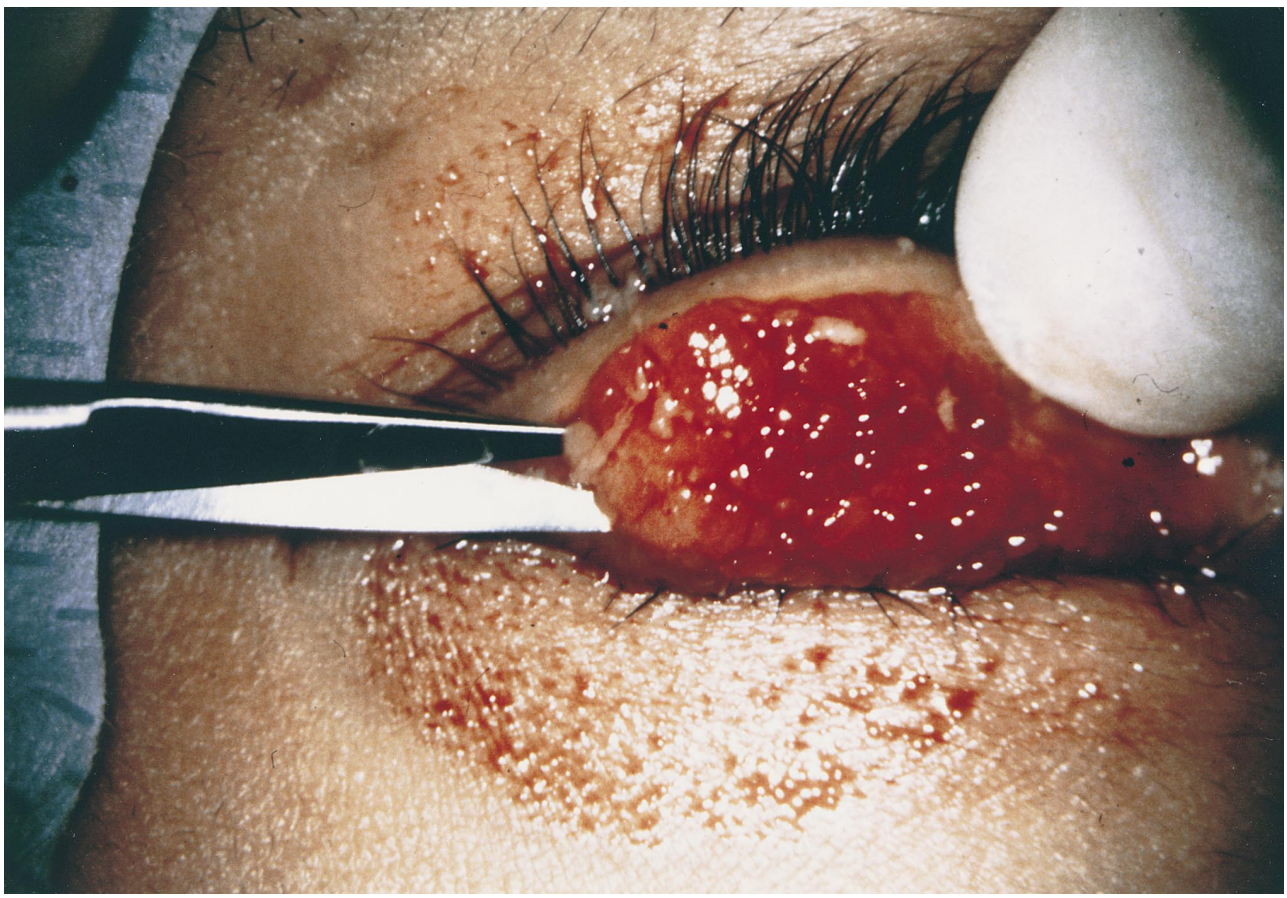

Figure 2. Removal of giant papillae from tarsus by sharp dissection. Papilla has been excised with small sharp scissors.

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den) before and 1 month after surgical treatment. Cells were stained and counted by two masked examiners.

Statistical Analysis

Data are expressed as mean ± SD. Statistical analysis was performed by using Wilcoxon signed rank test for symptoms, signs, and visual acuity, and the paired *t*-test was used for studies of intraocular pressure and pathological findings.

Results

Symptoms

The mean initial severity (scale is the same as explained in "Clinical Evaluation") of the symptoms observed in each patient was as follows: itching (3.5 ± 1.0), photophobia (3.1 ± 1.0), tearing (2.8 ± 1.2), foreign body sensation (3.2 ± 1.1), secretion (2.8 ± 1.1), and pain (3.0 ± 1.4). All scores had improved significantly after 2 weeks: itching (0.8 ± 0.6; $P = .004$), photophobia (0.8 ± 0.4; $P = .002$), tearing (0.3 ± 0.5; $P = .004$), foreign body sensation (0.9 ± 0.7; $P = .004$), secretion (0.4 ± 0.7; $P = .002$), and pain (0.4 ± 0.7; $P = .004$). No other notable findings were observed at the 24-week or later follow-up examinations after treatment, but one of the 10 patients experienced a recurrence 1 year later.

Clinical Examination

The mean initial scores were hyperemia (2.5 ± 0.5), chemosis (2.5 ± 0.5), papillae (2.6 ± 0.5), giant papillary conjunctivitis (GPC) (2.7 ± 0.5), secretions (2.7 ± 0.5), corneal limbal infiltration (2.5 ± 0.7), corneal vascularization (2.3 ± 0.7), corneal epitheliopathy (2.5 ± 0.5), and lid meibomitis (1.2 ± 0.6). All the scores had improved significantly after 2 weeks; hyperemia (1.0 ± 0.5; $P = .002$), chemosis (0.5 ± 0.5; $P = .002$), papillae (0.8 ± 0.4; $P = .002$), GPC (0.1 ± 0.3; $P = .002$), secretions (0.6 ± 0.5; $P = .002$), corneal limbal infiltration (0.5 ± 0.5; $P = .002$), corneal vascularization (1.6 ± 0.7; $P = .016$), corneal epitheliopathy (0.5 ± 0.4; $P = .002$), and lid meibomitis (0.6 ± 0.5; $P = .031$). After 4 weeks of treatment, all nine signs improved significantly ($P < .01$).

Visual Acuity and Intraocular Pressure

The visual acuity of all patients ranged from 0.05 to 1.0 before treatment. It significantly improved following treatment; from 0.2 to 1.0 ($P = .001$: 2 weeks; Wilcoxon's signed rank test), from 0.3 to 1.0 ($P = .009$: 4 weeks), and from 0.3 to 1.0 ($P = .001$: 24 weeks). Intraocular pressure before treatment was 13.8 ± 3.4 mm Hg and did not increase after treatment (13.2 ± 2.5, 12.6 ± 2.1, and 13.0 ± 3.0, at 2, 4, and 24 weeks, respectively).

Cytologic Study

May-Grunwald-Giemsa staining of cytocentrifuged preparations showed that epithelial cells increased significantly from 48.9 ± 21.4 to 97.7 ± 3.0 after treatment ($P = .0001$; paired *t*-test). The mean percentage of lymphocytes, neutrophils, eosinophils, and basophils before treatment were 6.8 ± 3.7%, 18.2 ± 9.9%, 25.3 ± 20.8%, and 0.8 ± 0.8%, respectively, and the values decreased significantly to 1.0 ± 1.0% ($P = .03$), 1.1 ± 1.9% ($P = .01$), 0.2 ± 0.7% ($P = .03$), and 0.1 ± 0.3% ($P = .0005$), respectively, by 4 weeks of treatment.

Discussion

This study demonstrated the safety and effectiveness of the combined treatment regimen for very severe active VKC. This regimen consisted of removal of the palpebral conjunctiva and supratarsal steroid injection, followed by the application of 0.05% CsA and cromolyn sodium eyedrops.

In a dose-dependent manner, CsA appears to suppress the lymphocyte proliferation response to mitogen by an apparent selectivity for T-cells[2] and also to act on mast cells and eosinophils. The clinical improvement in VKC after instillation of CsA eyedrops may be attributable to the inhibitory effect of CsA on the release of cytokines and on the clonal expansion of lymphocytes.[3] Although the blood level of CsA was below 30 ng/mL (the minimal level of detection of the radioimmunoassay) and patients have had no side effects, the safety in long-term use of CsA eyedrops needs to be confirmed, especially in a pediatric population.

The ideal surgical procedure for VKC cases that have been judged to be medically refractory and debilitating should accomplish the following objectives: (1) permanently remove the giant papillae, which can cause mechanical irritation of the cornea; (2) leave normal conjunctiva and subconjunctival tissue with intact lymphoid and granular cells, which produce cytokines or chemical mediators; (3) conserve the conjunctiva, which contains the basic secretors for tear production and the goblet cells for mucin production; and (4) remove eosinophilic cationic protein or eosinophilic granule major basic protein, which has been identified in the conjunctiva, tear film, contact lenses, and corneal ulcers[5] of VKC patients. The cytotoxic effects of ma-

jor basic protein has been well documented. The elimination of inflammatory cells in our study may have been responsible for the dramatic and rapid corneal improvement. The improvement in vision may have been due to either symptomatic relief or resolution of keratopathy.

Although the differential diagnosis between VKC and atopic keratoconjunctivitis is sometimes difficult, we believe these patients had severe VKC because the onset of illness was before 15 years of age and they did not have either atopic dermatitis or severe meibomitis. Atopic keratoconjunctivitis is still an uncontrollable disease, even when treated by this surgical method plus CsA eyedrops. This study did not include controls who received CsA alone for a long time. We did not observe any complications over the 5-year follow-up period. Further study is needed to clarify the side effects and indications for surgical treatment of such patients.

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